Effect of n−3 PUFA supplementation on cognitive function throughout the life span from infancy to old age: a systematic review and meta-analysis of randomized controlled trials1–4

Jingjing Jiao, Qingqing Li, Jingjing Chu, Weijiang Zeng, Min Yang, and Shankuan Zhu

ABSTRACT
Background: n−3 PUFAs play an important role in cognitive function. Objective: The objective was to investigate the effect of n−3 PUFA supplements on cognitive development, function, and decline throughout the life span. Design: The study included randomized controlled trials and provided ≥3 mo of treatment. Potential studies were independently screened in duplicate, and study characteristics and outcomes were extracted. A meta-analysis was performed by using fixed- or random-effects models. The results are presented as standardized mean differences (SMDs) with 95% CIs.

Results: Of the 3692 citations retrieved, 34 studies of a total of 12,999 participants (1031 infants, 1517 children, 3657 adults, and 6794 elderly individuals) were included. Compared with placebo, n−3 PUFA supplements significantly improved cognitive development in infants, including the Mental Development Index (SMD: 0.33; 95% CI: 0.15, 0.52), the Psychomotor Development Index (0.27; 95% CI: 0.09, 0.45), and language (0.27; 95% CI: 0.13, 0.42), motor (0.29; 95% CI: 0.14, 0.43), and cognitive (0.31; 95% CI: 0.16, 0.45) abilities. However, n−3 PUFAs did not promote cognitive function in terms of composite memory, executive function, and processing speed domains in children, adults, or the elderly, except for the attention domain. No association was found between n−3 PUFA intake and improvements in cognitive performance in terms of recognition, immediate and delayed word recall, digit span backward and forward tests, rapid visual information processing, verbal fluency, and simple and choice reaction times. In addition, n−3 PUFA supplements were not associated with improvements in cognitive decline or with any effects on Alzheimer disease in elderly people.

Conclusions: n−3 PUFA supplements may significantly improve cognitive development in infants but do not improve cognitive performance in children, adults, or the elderly. n−3 PUFA intake, especially that of DHA supplements, may benefit cognitive development during infancy.

Keywords: cognitive function, infancy, life span, meta-analysis, n−3 polyunsaturated fatty acid

INTRODUCTION

Cognition refers to a group of mental processes, including attention, working memory, language production and comprehension, learning, explanation, problem responses, and decision making. The global health burden of human cognitive decline and neurological disorders has surpassed that of both cardiovascular disease and cancer (1, 2). PUFAs are essential nutrients for humans and cannot be synthesized de novo in mammals (3). The Western diet has generally been low in fish and other sources of n−3 PUFAs, which leads to low blood concentrations of these fatty acids and an imbalance of dietary fatty acids during the past several decades (4). The n−3 PUFA supplements may become an alternative source for the dietary n−6/n−3 PUFA balance and health promotion. Thus, the role of n−3 PUFA supplementation in improving cognitive function has recently become a clinical focus (3, 5). However, related clinical trials have reported different outcomes at different age stages and have thus generated considerable controversy. Although there is conflicting clinical evidence regarding the benefits of n−3 PUFAs for the brain and cognitive function, it is thought that deficiencies in n−3 PUFAs have harmful effects on brain development; dietary supplementation of n−3 PUFAs may therefore be beneficial (6, 7). Clinical trials have suggested that n−3 PUFAs significantly affect prenatal neurodevelopment; however, such a cognitive-enhancing effect might diminish postnatally with maturation, because no research on child populations has clearly tied dietary n−3 PUFAs to improved cognitive skills (8, 9). Furthermore, evidence from clinical studies indicates that n−3 PUFAs may have therapeutic potential for mild cognitive impairment associated with neurodegenerative disorders such as Alzheimer disease (AD)5 (10).

Effect of n−3 PUFA intake and improvements in cognitive decline or with any effects on Alzheimer disease in elderly people.

Conclusions: n−3 PUFA supplements may significantly improve cognitive development in infants but do not improve cognitive performance in children, adults, or the elderly. n−3 PUFA intake, especially that of DHA supplements, may benefit cognitive development during infancy. Am J Clin Nutr 2014;100:1422–36.

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The controversial results have generated widespread confusion in everyday clinical practice regarding whether to use n−3 PUFA agents for cognitive protection in populations of different ages. Several epidemiologic studies have shown an explicit association between the intake of n−3 PUFA–supplemented formula and cognitive development in infants (11–13). Many randomized controlled trials (RCTs) have described the role of n−3 PUFAs in cognitive functions among children and adults (14–20). However, others have shown no effects on the prevention of cognitive decline and AD (21–23). Previous systematic reviews and meta-analyses did not fully address the overall effect of n−3 PUFAs on cognition and thus reported conflicting findings. Reasons may include the use of single outcome, data from both RCTs and observational findings, the use of n−6 PUFAs, inclusion of RCTs with a short intervention period, inclusion of populations only of a specific age, or exclusion of healthy individuals/inclusion of only patients with cognitive decline (24–28). In the current study, we set out to conduct a large-scale systematic review and meta-analysis of RCTs to summarize the effect of n−3 PUFAs on cognitive performance outcomes throughout the life span, extending from infants to the elderly.

MATERIALS AND METHODS

Literature search

A systematic literature search (1950–May 2014) of PubMed, Embase, and the Cochrane Library Central Register of Controlled Trials was performed to identify all published RCTs that studied the effect of n−3 PUFA supplementation, compared with placebo, on cognitive function. RCTs investigating the effect of n−3 PUFA–supplemented formula (compared with general formula feeding) on cognitive development in infants were also included. The search was not restricted to any language or publication date. Keywords used for the search comprised synonyms and abbreviations of n−3 polyunsaturated fatty acid, docosahexaenoic acid, eicosapentaenoic acid, cognition, cognitive decline, and Alzheimer’s disease (Supplemental Methods 1). Trials were eligible if they were RCTs and implemented in primary or secondary outcome settings; n−3 PUFAs could be administered via formula or supplements. We initially screened 3692 articles using the literature search strategy. A total of 1780 records were selected after removing 1912 duplicate records. Of these articles, 331 were identified for further review based on the exclusion of 1449 records, i.e., unrelated reports, reviews, and cell or animal studies. After 297 studies were excluded, a total of 34 RCTs fit our inclusion criteria and were used for the meta-analysis (Figure 1).

Study selection and data extraction

Two investigators (JJ and QL) reviewed the literature and independently identified studies for possible inclusion. Disagreements were resolved by negotiation and consensus. To ensure efficacy in terms of cognitive function, we excluded studies with the following characteristics: 1) an intervention duration of <3 mo—a(n) insufficient time for n−3 PUFA treatment; 2) inclusion of a multinutrient intervention besides n−3 PUFAs (e.g., vitamins and phytochemicals); 3) a treatment mixed by n−6 PUFAs; and 4) inclusion of an effect of an n−3 PUFAs–rich diet (e.g., a fish-heavy diet). The selected studies fulfilled the following criteria: 1) an intervention group that received at least one dose level of n−3 PUFA treatment and 2) a control group that received appropriate placebo treatment. Populations from selected studies were not permitted to have exposure to similar PUFA treatments before the investigation, unless an adequate washout period was clearly specified. We then extracted information about the characteristics of the included studies, such as authors, publication year, countries from which the study populations originated, population age and female ratio, n−3 PUFA treatment, type of placebo control, treatment duration, outcome measures of cognitive performance, number of participants, funding sources, and information about potential sources of bias. The standardized mean differences (SMDs) and 95% CIs of outcomes were finally extracted for further data synthesis.

Outcome measures

The primary outcome of this systematic review was cognitive function throughout the life span. However, such an analysis should include measures of cognitive development in infants, cognitive performance in children, adults, the elderly, and possible cognitive decline in the elderly.

1) The Mental Development Index (MDI) and the Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development were taken as the primary outcomes during infancy (27, 29). To further evaluate cognition, language, motor, and cognitive abilities were considered as secondary outcomes.

2) Composite memory, executive function, attention, and processing speed were used as the representative cognitive domains and were regarded as the primary outcomes during the child, adult and the elderly stages of the life span (15, 26, 30). To further describe these domains, we also included other secondary outcomes, including recognition, immediate word recall, delayed word recall, digit span backward, digit span forward, the Stroop effect, rapid visual information processing, verbal fluency, simple reaction time, and choice reaction time (14–17, 31, 32).

3) The Mini-Mental State Examination (MMSE) result was used as a primary outcome to screen for cognitive decline in elderly people (4, 25, 33–35). Considering the prevalence of AD in cognitive decline, we chose the score of the Cognitive Subscale of the Alzheimer Disease Assessment Scale (ADAS-Cog) as an additional secondary outcome (21, 23, 36).

Explanations and details of all above outcomes are available in Supplemental Methods 2. Data about the primary and secondary outcomes in all of the n−3 PUFA groups were included if multiple dose levels or multiple types of n−3 PUFAs were considered as the intervention. Whenever clinical trials referred to the same populations at different follow-up periods, we used only the population with the longest follow-up period to avoid data duplication.

Assessment of methodologic quality

Two authors (JJ and JC) independently assessed the risk of bias in included RCTs using the Cochrane Risk of Bias Tool (37). The
domains used in the current systematic review pertained to randomization and allocation concealment (selection bias), blinding (performance and measurement bias), loss to follow-up and adherence to the intent-to-treat principle (attrition bias), and selective outcome publication (reporting bias). An acknowledged study quality score for evaluating RCTs (Jadad score) was also applied with a score of ≥3 indicating high quality.

**Statistical analysis**

SMDs were calculated as the mean difference in the change of cognitive function between the n-3 PUFA group and the placebo group, divided by the pooled SD, with an adjustment for small sample bias (Hedges g) (38). Hedges g provides a standardized estimate of effect size that is suitable for merging multiple cognitive tests in populations of varying sample sizes and has been widely used in a meta-analysis (26, 39). Of the included studies, several provided means (m_{treatment} and m_{placebo}) and SDs (SD_{treatment} and SD_{placebo}) at baseline and follow-up, but did not report the within-subject change in SD, which was required for the meta-analysis. Initially, we tried to contact the corresponding authors of these studies to obtain this unpublished data. However, we could not obtain responses from the authors in some cases and thus considered an imputation approach. In such situations, the SD_{baseline} of SMDs of the selected outcomes were estimated by merging the SDs reported at baseline and at the follow-up endpoint with the weighted mean correlation (Cor) between baseline and follow-up visits reported by other reports, thus weighted by the sample size of each trial, as expressed in the following equation (38, 40).
To check the imputation effect on the precision of the current meta-analysis, we performed a sensitive analysis and compared the results of n–3 PUFA treatment effects using the above imputation with corresponding results using directly reported data without imputation. To investigate variances in cognitive function at different ages that may have been affected by n–3 PUFA treatment, we conducted a planned subgroup analysis to examine the effect of n–3 PUFA treatment on the following domains: 1) primary outcomes, including composite memory, attention, and processing speed and 2) secondary outcomes, including recognition, immediate word recall, delayed word recall, digit span forward, digit span backward, Stroop effect, and verbal fluency. When more than one treatment group (e.g., multiple treatment levels of n–3 PUFAs or multiple types of n–3 PUFA treatments) was used in an included study, the effect sizes for each group were individually evaluated and regarded as multiple treatment effects.

Study heterogeneity regarding comparisons of each cognitive function domain was assessed by using a Q statistic in the chi-square test, whereas the effect of heterogeneity was evaluated with an I² statistic (41). A significant Q statistic (P ≤ 0.05 and/or I² > 55%) indicates differences in study characteristics and high heterogeneity. In this situation, a meta-analysis using the random-effects model would be used to combine the study outcomes, assuming that studies were drawn from unequal populations and therefore accounting for variable underlying effects in the estimates of uncertainty (38). Otherwise, the fixed-effects model was used for the meta-analysis. Heterogeneity was also investigated by using subgroup analyses of outcomes in both children and adult groups and the elderly group. To investigate whether various study characteristics could explain the observed heterogeneity, meta-regression analyses (summarized as a β coefficient) were conducted by comparing effect sizes with selected study characteristics such as duration of n–3 PUFA treatment, dose levels of n–3 PUFAs, mean age, and percentage of female participants. The risk of small study effects was assessed by visualization of funnel plots (42), followed by the Egger’s test (43). All statistical analyses and meta-analyses were performed with Stata software (version 11.0; StataCorp).

RESULTS

Literature search results and study characteristics

Of the 34 RCT articles retrieved, 7 articles investigated cognitive development in infants (567 in a treatment group compared with 464 in a control group) (11–13, 44–47); 15 articles investigated cognitive function in children and adults (2642 in a treatment group compared with 2532 in a control group) (9, 14, 16–19, 31, 48–55); and 12 articles investigated cognitive function, decline, and related diseases (e.g., AD) in elderly people (4213 in a treatment group compared with 2581 in a control group) (15, 20–23, 32, 36, 56–60). The demographic features and other characteristics of all the included trials are summarized in Tables 1 and 2. Of the 34 trials that were included in this analysis, 5 used DHA-supplemented infant formulas as the treatment, 7 used single n–3 PUFA supplements (DHA or ethyl-EPA) as the treatment, and 22 used combined mixed n–3 PUFA supplements as the treatment. Regarding the controls, 5 studies used commercial infant formula, 10 used olive oil, 4 used corn oil, 3 used mixed corn and soy oils, 8 used other oils, and 3 did not report details of the control group. The age of the participants throughout all of the trials ranged from birth to 86 y, which covers nearly the entire scale of the human life span. The duration of n–3 PUFA treatment ranged from 12 wk to 4 y. Of 11,968 individuals (infants not included), 6855 received a median intervention dose of 1 g/d (IQR: 0.6–1.74 g/d). Overall, 12,999 participants (52.5% female) were treated and followed up, for a median treatment duration of 6 mo (IQR: 4–11.1 mo).

Six trials were graded as having a low risk of bias in all domains of the Cochrane Risk of Bias tool (Supplemental Figures 1–3) (14, 19, 20, 23, 46, 58). We realized that selective reporting was the most frequent deficiency in trials because one or more outcomes of interest in these trials were reported incompletely and could not be entered in a meta-analysis. The

\[
SD_{\text{follow-up} - \text{baseline}} = \sqrt{SD_{\text{baseline}}^2 + SD_{\text{follow-up}}^2 - (2 \times Cor_{\text{baseline, follow-up}} \times SD_{\text{baseline}} \times SD_{\text{follow-up}})}
\]  

\(1\)

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>Summary of the characteristics of eligible RCTs¹</td>
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<tr>
<td>Characteristics</td>
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<tr>
<td>No. of RCTs</td>
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<tr>
<td>No. of participants</td>
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<tr>
<td>Age</td>
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<tr>
<td>Female sex, %</td>
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<tr>
<td>Treatment duration, mo</td>
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<tr>
<td>n–3 PUFA dose³</td>
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</tbody>
</table>

¹There was a total of 34 RCTs and a total of 12,999 participants. RCT, randomized controlled trial.
²Median; IQR in parentheses (all such values).
³The n–3 PUFA dose in infant RCT studies is presented as the percentage of total fatty acids supplemented in formula. The n–3 PUFA dose in all other categories is expressed as grams per day. Two studies were excluded because n–3 PUFAs were administered as a capsule supplement (46, 47).

\(\text{Cor}_{\text{baseline, follow-up}}\)
<table>
<thead>
<tr>
<th>Source (study name), year, country (ref)</th>
<th>Infants (cognitive development)</th>
<th>Children and adults (cognitive function)</th>
<th>Treatment duration</th>
<th>Outcome measures of cognitive performance</th>
<th>No. of RCT participants</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birch et al., 2000, US (11)^3</td>
<td>2.1 ± 1.0 d; T: 59%/C: 55%</td>
<td></td>
<td>17 wk</td>
<td>MDI, PDI, BRS, cognition, language, motor</td>
<td>T: 26/C: 26</td>
<td>Academy</td>
</tr>
<tr>
<td>Birch et al., 2007, US (44)^3,4</td>
<td>2.1 ± 1.0 d; T: 59%/C: 55%</td>
<td></td>
<td>17 wk</td>
<td>Performance IQ, verbal IQ, full-scale IQ</td>
<td>T: 26/C: 26</td>
<td>Academy</td>
</tr>
<tr>
<td>Drover et al. (DIAMOND),2011, US (12)</td>
<td>T1: 18.1 ± 0.2 mo/T2: 18.1 ± 0.2 mo/T3: 18.1 ± 0.2 mo/C: 18.1 ± 0.2 mo/T1: 45%/T2: 38%/T3: 46%/C: 50%</td>
<td>DHA (T1: 0.32% of total fatty acids; T2: 0.64% of total fatty acids; T3: 0.96% of total fatty acids)</td>
<td>12 mo</td>
<td>MDI, PDI, BRS, cognition, language, motor</td>
<td>T1: 45/T2: 44/T3: 46/C: 46</td>
<td>Industry</td>
</tr>
<tr>
<td>Makrides et al., 2000, Australia (45)^3</td>
<td>Birth; T: 48%; C: 48%</td>
<td>DHA (0.35% of total fatty acids)</td>
<td>34 wk</td>
<td>MDI, PDI</td>
<td>T: 27/C: 28</td>
<td>Academy and industry</td>
</tr>
<tr>
<td>Meldrum et al., 2012, Australia (46)</td>
<td>Birth; T: 48.4%; C: 48.5%</td>
<td>EPA (0.06 g/d); DHA (0.25 g/d)</td>
<td>6 mo</td>
<td>Cognition, language, motor, social emotion, adaptive behavior</td>
<td>T: 218/C: 202</td>
<td>Academy</td>
</tr>
<tr>
<td>Scott et al., 1998, US (13)^3</td>
<td>T: 2.6 ± 1.9 d; C: 3.2 ± 2.5 d; T: 18.1 ± 0.2 mo/C: 18.1 ± 0.2 mo; T: 49%/C: 42%</td>
<td>EPA (0.20% of total fatty acids)</td>
<td>12 mo</td>
<td>MDI, PDI</td>
<td>T1: 43/C: 45</td>
<td>Academy and industry</td>
</tr>
<tr>
<td>Van der Merwe et al., 2013, Gambia (47)</td>
<td>T: 92.3 ± 4.25 d/C: 93.2 ± 4.22 d; T: 18.1 ± 0.2 mo/C: 18.1 ± 0.2 mo; C: 44%; C: 41%</td>
<td>Commercial infant formula</td>
<td>6 mo</td>
<td>Total intention, intentional solutions, inattention rate, mean look duration</td>
<td>T: 92/C: 91</td>
<td>Academy</td>
</tr>
<tr>
<td>Baumgartner et al., 2012, South Africa (14)^3</td>
<td>T: 8.9 ± 1.3 y/C: 9.1 ± 1.4 y; T: 18.1 ± 0.2 mo/C: 18.1 ± 0.2 mo; T: 49%/C: 42%</td>
<td>EPA (0.046 g/d); DHA (0.24 g/d); Medium-chain triglycerides</td>
<td>8.5 mo</td>
<td>Recognition, immediate word recall, delayed word recall, discrimination index</td>
<td>T: 81/C: 80</td>
<td>Academy</td>
</tr>
<tr>
<td>Cheatham et al., 2011, Denmark (48)^3</td>
<td>T: 7.4 ± 1.5 y/C: 7.4 ± 1.5 y; T: 33.3%; C: 57.1%</td>
<td>EPA (0.62 g/d); DHA (0.79 g/d); others (0.09 g/d)</td>
<td>4 mo</td>
<td>Processing speed, Stroop effect, SDQ scores</td>
<td>T: 36/28</td>
<td>Academy</td>
</tr>
<tr>
<td>Dunstan et al., 2008, Australia (49)</td>
<td>T: 30.9 ± 3.7 y/C: 32.6 ± 3.6 y; T: 100% C: 100%</td>
<td>EPA (1.1 g/d); DHA (2.2 g/d)</td>
<td>20 wk</td>
<td>Griffiths Mental Development Scale scores, Peabody Picture Vocabulary Test IIIA scores, Child Behavior Checklist scores</td>
<td>T: 52/C: 46</td>
<td>Academy</td>
</tr>
<tr>
<td>Helland et al., 2008, Norway (50)^3</td>
<td>T: 29.7± 3.3 y/C: 28.6 ± 2.6 y; T: 100% C: 100%</td>
<td>EPA (0.803 g/d); DHA (1.183 g/d); others (0.508 g/d)</td>
<td>8 mo</td>
<td>Kaufman Assessment Battery for Children scores</td>
<td>T: 175/C: 166</td>
<td>Academy</td>
</tr>
<tr>
<td>Jackson et al., 2012, UK (16)</td>
<td>T: 22.7± 4.1 y/C: 21.9 ± 3.6 y; T: 60.9%; T: 21.94 ± 3.6 y/C: 63.0%; T: 77.1%</td>
<td>EPA (0.3 g/d) + DHA (0.2 g/d); T2: EPA (0.09 g/d) + DHA (0.45 g/d)</td>
<td>12 wk</td>
<td>Immediate word recall, delayed word recall, simple word recognition, Stroop effect, verbal fluency, RT of working memory, Corsi blocks span, RT of 3-back task, recognition, Stroop effect</td>
<td>T1: 46/T2: 46/C: 48</td>
<td>Industry</td>
</tr>
<tr>
<td>Kirby et al., 2010, UK (51)</td>
<td>T: 9.17 ± 0.5 y/C: 9.08 ± 0.56 y; T: 52.6%; C: 50.8%</td>
<td>EPA (0.056 g/d); DHA (0.4 g/d)</td>
<td>16 wk</td>
<td>Digit span forward, digit span backward, word reading, spelling, SDQ scores</td>
<td>T: 22/C: 22</td>
<td>Industry</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Source (study name), year, country (ref)</th>
<th>Age; female per treatment group, %</th>
<th>n−3 PUFA dose</th>
<th>Control</th>
<th>Treatment duration</th>
<th>Outcome measures of cognitive performance</th>
<th>No. of RCT participants</th>
<th>Funding source</th>
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<tr>
<td>Makrides et al., (DOMInO), 2010, Australia (9)</td>
<td>T: 28.9 ± 5.7 y/C: 28.9 ± 5.6 y; T: 100%/C: 100%</td>
<td>EPA (0.1 g/d); DHA (0.8 g/d)</td>
<td>Vegetable oil</td>
<td>19–40 wk</td>
<td>Cognition, language, motor, social emotion, adaptive behavior</td>
<td>T: 1197/C: 1202</td>
<td>Academy</td>
</tr>
<tr>
<td>Mille et al., 2012, Australia (52)</td>
<td>T: 8.7 ± 3.6 y/T2: 28.9 ± 5.6 y; T: 28.9 ± 5.6 y; T: 100%/C: 100%</td>
<td>EPA (0.109 g/d) + DHA (0.108 g/d); T2: EPA (0.264 g/d) + DHA (1.032 g/d)</td>
<td>Safflower oil</td>
<td>4 mo</td>
<td>Word reading, spelling, vocabulary, CPRS</td>
<td>T1: 31/T2: 29/C: 30</td>
<td>Academy</td>
</tr>
<tr>
<td>Ockendarp et al., 2007, Australia and Indonesia (18)</td>
<td>T (Australia)/T (Indonesia): 8.8 ± 1.1 y; T (Australia): 8.1 ± 1.1 y; T: 52%/C: 50% (Indonesia)</td>
<td>EPA (0.022 g/d) + DHA (0.088 g/d)</td>
<td>NR</td>
<td>12 mo</td>
<td>Composite memory, attention</td>
<td>T: 115/C: 113</td>
<td>Academy</td>
</tr>
<tr>
<td>Purui et al., 2005, UK, US, Canada, and Australia (53)</td>
<td>T: 50 ± 9.3 y/C: 49 ± 9.0 y; T: 43%/C: 56%</td>
<td>Ethyl-EPA (2 g/d)</td>
<td>Liquid paraffin</td>
<td>12 mo</td>
<td>Total motor score 4 of UHDRS, verbal fluency, symbol digit, Stroop effect</td>
<td>T: 67/C: 68</td>
<td>Industry</td>
</tr>
<tr>
<td>Richardson et al., 2012, UK (31)</td>
<td>T: 103.7 ± 100 mo/C: 104.8 ± 10.1 mo; T: 46.7%/C: 47.3%</td>
<td>DHA (0.6 g/d)</td>
<td>Corn/soybean oil</td>
<td>16 wk</td>
<td>Digit span forward, digit span backward, word reading, CPRS, CTRS</td>
<td>T: 180/C: 182</td>
<td>Academy</td>
</tr>
<tr>
<td>Rogers et al., 2008, UK (54)</td>
<td>T: 38.0 ± 13.5 y/C: 38.2 ± 13.7 y; T: 78%/C: 76%</td>
<td>EPA (0.63 g/d); DHA (0.85 g/d)</td>
<td>Olive oil</td>
<td>12 wk</td>
<td>Simple RT, RT of lexical decision, RT of digit-symbol &amp; symbol digit, Attention, processing speed, RT of attention, RT of working memory</td>
<td>T: 109/C: 109</td>
<td>Academy</td>
</tr>
<tr>
<td>Stonehouse et al., 2013, New Zealand (19)</td>
<td>T: 33.4 ± 7.6 y/C: 33.2 ± 7.90 y; T: 63%/C: 65%</td>
<td>DHA (1.16 g/d)</td>
<td>Sunflower oil</td>
<td>6 mo</td>
<td>Composite memory, executive function, attention, processing speed, immediate word recall, delayed word recall, digit span forward, digit span backward, verbal fluency, simple RT, choice RT</td>
<td>T: 115/C: 113</td>
<td>Academy</td>
</tr>
<tr>
<td>Yiet al., 2011, US (55)</td>
<td>T: 24.4 ± 10.6 y/C: 25.6 ± 10.7 y; T: 100%/C: 100%</td>
<td>DHA (10 mg · kg$^{-1}$ · d$^{-1}$)</td>
<td>Mixture of soy and corn oils</td>
<td>4.5 mo</td>
<td>Processing speed, verbal ability, cognitive inhibition, cognitive flexibility</td>
<td>T: 17/C: 16</td>
<td>Academy</td>
</tr>
</tbody>
</table>

Elderly people (cognitive function and decline) |
| Andreva et al. (SU.FOL.OM3), 2011, France (56) | T: 60.1 ± 8.7 y/C: 60.9 ± 8.9 y; T: 20.0%/C: 22.6% | EPA (0.4 g/d); DHA (0.2 g/d) | NR | 48 mo | Composite memory | T: 633/C: 626 | Academy and industry |
| Chiu et al., 2008, Chinese Taiwan (36) | T: 74.0 ± 8.9 y/C: 76.5 ± 9.3 y; T: 65.0%/C: 46.7% | EPA (1.08 g/d); DHA (0.72 g/d) | Olive oil esters | 24 wk | MMSE, ADAS-Cog | T: 24/C: 22 | Academy |
| Dangour et al. (OPAL), 2010, UK (15) | T: 74.7 ± 5.5 y/C: 74.6 ± 2.7 y; T: 46.6%/C: 43.4% | EPA (0.2 g/d); DHA (0.5 g/d) | Olive oil | 24 mo | Composite memory, executive function, attention, processing speed, immediate word recall, delayed word recall, digit span forward, digit span backward, verbal fluency, simple RT, choice RT | T: 434/C: 433 | Academy |
| Freund-Levi et al. (OmegAD), 2008, Sweden (57) | T: 72.6 ± 9.0 y/C: 72.9 ± 9.6 y; T: 55%/C: 46% | EPA (0.6 g/d); DHA (1.72 g/d) | Corn oil | 6 mo | Neuropsychiatric inventory | T: 103/C: 101 | Academy and industry |
| Freund-Levi et al. (OmegAD), 2006, Sweden (21) | T: 72.6 ± 9.0 y/C: 72.9 ± 9.6 y; T: 55%/C: 46% | EPA (0.6 g/d); DHA (1.72 g/d) | Corn oil | 6 mo | MMSE, ADAS-Cog, CDR sum of boxes | T: 103/C: 101 | Academy and industry |

(Continued)
<table>
<thead>
<tr>
<th>Source (study name), year, country (ref)</th>
<th>Age; female per treatment group, %</th>
<th>n – 3 PUFA dose</th>
<th>Control</th>
<th>Treatment duration</th>
<th>Outcome measures of cognitive performance</th>
<th>No. of RCT participants</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geleijnse et al., 2012, The Netherlands (58)</td>
<td>T1: 69.2 ± 5.4 y/T2: 69.1 ± 5.6 y/T3: 69.2 ± 5.6 y; T1: 3.6%/T2: 22.8%/T3: 21.8%; C: 5.4%</td>
<td>T1: EPA (0.24 g/d) + DHA (0.16 g/d); T2: ALA (2 g/d); T3: EPA (0.24 g/d) + DHA (0.16 g/d) + ALA (2 g/d)</td>
<td>Margarine</td>
<td>40 mo</td>
<td>MMSE</td>
<td>T1: 726/T2: 727/T3: 719/C: 739</td>
<td>Acadmy and industry</td>
</tr>
<tr>
<td>Johnson et al., 2008, US (59)</td>
<td>T: 68.5 ± 4.9 y; T: 100%; C: 100%</td>
<td>DHA (0.8 g/d)</td>
<td>NR</td>
<td>4 mo</td>
<td>Recognition, digit span forward, digit span backward, Stroop effect</td>
<td>T: 14/C: 10</td>
<td>Acadmy</td>
</tr>
<tr>
<td>Lee et al., 2013, Malaysia (22)</td>
<td>T: 66.4 ± 5.1 y; T: 82.4%; C: 72.2%</td>
<td>EPA (0.45 g/d); DHA (1.29 g/d)</td>
<td>Corn oil</td>
<td>12 mo</td>
<td>Composite memory, executive function, attention, processing speed, MMSE, immediate word recall, delayed word recall</td>
<td>T: 18/C: 18</td>
<td>Acadmy</td>
</tr>
<tr>
<td>Quinn et al., 2010, US (23)</td>
<td>T: 76 ± 9.3 y; T: 47.1%; C: 59.8%</td>
<td>DHA (0.9–1.1 g/d)</td>
<td>Corn or soy oil</td>
<td>18 mo</td>
<td>MMSE, ADAS-Cog, CDR sum of boxes, neuropsychiatric inventory</td>
<td>T: 238/164</td>
<td>Acadmy</td>
</tr>
<tr>
<td>Sinn et al., 2012, Australia (32)</td>
<td>T1: 74.88 ± 5.06 y/T2: 74.22 ± 7.00 y/C: 73 ± 3.96 y; T1: 18%/T2: 28%; C: 53%</td>
<td>T1: EPA (1.67 g/d) + DHA (0.16 g/d); T2: EPA (0.40 g/d) + DHA (1.55 g/d)</td>
<td>Safflower oil</td>
<td>6 mo</td>
<td>Recognition, immediate word recall, delayed word recall, digit span forward, digit span backward, Stroop effect, verbal fluency</td>
<td>T1: 18/T2: 18/C: 18</td>
<td>Acadmy</td>
</tr>
<tr>
<td>van de Rest et al., 2008, The Netherlands (22)</td>
<td>T1: 69.5 ± 3.2 y/T2: 69.9 ± 3.4 y/C: 70.1 ± 3.7 y; T1: 45%/T2: 45%; C: 44%</td>
<td>T1: EPA (0.226 g/d) + DHA (0.176 g/d); T2: EPA (1.093 g/d) + DHA (0.847 g/d)</td>
<td>High-oleic acid sunflower oil</td>
<td>26 wk</td>
<td>Composite memory, executive function, attention, processing speed, recognition, immediate word recall, delayed word recall, digit span forward, digit span backward, Stroop effect, verbal fluency</td>
<td>100/96/106</td>
<td>Acadmy</td>
</tr>
<tr>
<td>Yurko-Mauro et al., 2010, US (60)</td>
<td>T: 70 ± 9.3 y; T: 56%/C: 60%</td>
<td>DHA (0.9 g/d)</td>
<td>Corn and soy oil</td>
<td>24 wk</td>
<td>Composite memory, MMSE, recognition, immediate word recall, delayed word recall</td>
<td>T: 242/C: 243</td>
<td>Industry</td>
</tr>
</tbody>
</table>

1ADAS-Cog, Cognitive Subscale of the Alzheimer’s Disease Assessment Scale; ALA, α-linoleic acid; BRS, Behavior Rating Scale; C, control; CDR, Clinical Dementia Rating; CPRS, Conners’ Parent Rating Scale; CTRS, Conners’ Teacher Rating Scale; DIAMOND, DHA Intake And Measurement Of Neural Development; DOMInO, DHA to Optimize Mother Infant Outcome; IQ, intelligence quotient; LCPUFA, long-chain PUFA; MDI, Mental Development Index; MMSE, Mini-Mental State Examination; NR, not reported; OmegAD, Omega-3 and Alzheimer’s Disease; OPAL, the Older People And n-3 Long-chain polyunsaturated fatty acids; PDI, Psychomotor Development Index; RCT, randomized controlled trial; RT, reaction time; SDQ, Strengths and Difficulties Questionnaire; SU.FOL.OM3, SUpplementation with FOLate, vitamins B-6 and B-12 and/or OMega-3 fatty acids; T, treatment; UHDRS, Unified Huntington’s Disease Rating Scale.

2All studies used n-3 PUFA supplements, except for some studies in infants that administered n-3 PUFA–supplemented formula.

3Participants from the irrelevant or other mixed-nutrient supplement treatment groups were excluded.

4Participants from the breast milk–fed groups were excluded.

5Participants were singleton pregnant women, and cognitive outcomes were measured in their children.
Jadad quality evaluation of included RCTs showed that the low quality was mainly ascribed to lack of adequate randomization and blind method details, although both methods were clearly mentioned in most of the trials (Supplemental Table 1).

Primary outcome measures of cognitive function

The meta-analysis of 7 infant trials showed that n-3 PUFAs supplementation could significantly improve MDI and PDI, which are important outcome indexes of cognitive development in infants. The treatment effects on MDI and PDI between the n-3 PUFAs treatment and control groups were SMDs of 0.33 (95% CI: 0.15, 0.52) and 0.27 (95% CI: 0.09, 0.45), respectively (Figure 2). Meanwhile, both effects were acceptably heterogeneous across trials (MDI: $I^2 = 7.8\%$, $P = 0.366$; PDI: $I^2 = 54.7\%$, $P = 0.050$; Supplemental Table 2).

For estimating cognitive performance in children, adults, and the elderly, we chose 4 acknowledged cognitive domains, including composite memory, executive function, attention, and processing speed as our primary outcomes, which are consistent with expert recommendations (30, 61). Our results showed that n-3 PUFAs supplementation significantly improved the attention domain as a whole (SMD: 0.13; 95% CI: 0.01, 0.25). Considering the differences among population groups, we then conducted a subgroup analysis and observed the treatment effect, classified by age. Subgroup analysis showed that improvements in the attention domain were significant in the elderly (0.29; 95% CI: 0.10, 0.47), but not in children or adults (0.02; 95% CI: −0.14, 0.18) (Figure 3A). Furthermore, the treatment effect was significantly heterogeneous across studies ($I^2 = 59.0\%$, $P = 0.032$), which may be generated by the differential effects in the subgroup of elderly people ($I^2 = 68.5\%$, $P = 0.042$; Supplemental Table 2). Our results also indicated that n-3 PUFAs did not significantly improve the domains of composite memory (0.01; 95% CI: −0.06, 0.07), executive function (−0.03; 95% CI: −0.14, 0.08), and processing speed (−0.07; 95% CI: −0.16, 0.03) in either the overall or subgroup meta-analyses (Figure 3B and Figure 4A, B). To evaluate potential cognitive declines in the elderly, we investigated the results of the MMSE, which were not significantly affected by n-3 PUFAs supplementation (0.04; 95% CI: −0.02, 0.10) with no heterogeneity across trials ($I^2 = 0.0\%$, $P = 0.882$; Figure 5 and Supplemental Table 2).

Secondary outcome measures of cognitive function

To further demonstrate the positive treatment effect of n-3 PUFAs in infant growth, we investigated the development of language, motor, and cognitive abilities by comparing brain PUFAs in infant growth, we investigated the development of

Sensitivity analysis, evaluation of small study effects, and meta-regression

No significant heterogeneity was found for treatment effect in terms of the primary cognitive function outcomes, except for the attention domain in primary cognitive function outcomes. To further confirm such positive results for the attention domain and investigate the imputation effect on this statement, a relative sensitivity analysis was conducted. The reported data were directly used to generate SMDs of each primary and secondary outcome in children, adults, and the elderly (Supplemental Tables 4 and 5). The results indicated that all of the outcomes agreed with previously corresponding outcome measures, except the attention outcome. No significant amelioration effect of n-3 PUFAs on the attention domain was found in this sensitivity analysis, which indicated that an imputation effect may interfere with the meta-analysis results (Supplemental Table 4). To identify the source of heterogeneity across trials, a sensitivity analysis was performed by using the random-effects model and indicated no significant differences in treatment effect on the attention domain after individual removal of each included trial, except the last included trial (22). In detail, the treatment effect changed considerably (0.10; 95% CI: −0.03, 0.22), and the heterogeneity across trials for the attention domain was significantly reduced ($I^2 = 2.5\%$, $P = 0.392$) after the removal of data from Lee et al. (22) (Supplemental Table 5). Furthermore, we tested for asymmetry using funnel plots to investigate small study effects and to visually identify possible bias (Supplemental Figure 12). However, the
results of Egger’s test showed that no significant small study effects for the attention domain (bias coefficient = 4.50; 95% CI: −0.43, 9.43; \( P = 0.064 \)) were detected across these studies (Supplemental Table 7). In addition, we tested the treatment effects of MDI and PDI in infants, which showed a significant difference compared with controls. Finally, both the effects of MDI and PDI as estimated by sensitivity analysis and Egger’s test showed little change and no small study bias, respectively. Details about the treatment effects of all primary outcomes as shown by Egger’s test are shown in Supplemental Table 7.

Similarly, no significant heterogeneity was found in terms of treatment effect on the secondary outcomes, except for language, motor, and cognitive abilities in infants. To visually inspect the asymmetry in funnel plots and found a possible small study bias for the treatment effects on language and cognitive abilities in a statistical view via the Egger’s test (Supplemental Figure 13 and Supplemental Table 8), which may be attributable to the publication of Birch et al. (11). This RCT reported fewer participants and a much more promising effect of n−3 PUFAs on the improvement of cognitive development in infants than did the other included trials, which was probably regarded as the source of publication bias. However, such a bias could probably be excluded because the estimation of all treatment effects on language, motor, and cognitive abilities in the sensitivity analysis always showed positive results, with little change regardless of whether the publication of Birch et al. (11) was removed (Supplemental Table 9).
A meta-regression analysis was conducted to examine RCT characteristics such as treatment duration, \( n^{-3} \) PUFA dose, mean age, female ratio, and number of participants underlying the heterogeneity in all the investigated primary and secondary outcomes of cognitive function throughout the life span from infancy to old age. In detail, the regression models for investigating the association of every selected outcome with each of the above 5 RCT characteristics were established and statistically evaluated. Our results indicated no associations between any of the treatment effects or outcomes with either of the above RCT characteristics (Supplemental Table 10).

**DISCUSSION**

Long-chain PUFAs (LCPUFAs) may be responsible for the potential gaps in cognitive development observed between

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**FIGURE 3** Treatment effects of \( n^{-3} \) PUFA supplementation on attention (A) and composite memory (B) of cognitive domains in children, adults, and the elderly. The black dot data markers represent SMDs; the horizontal lines represent the 95% CIs, with the marker size reflecting the statistical weight of the study in the meta-analysis. The diamond data markers represent each subgroup and overall SMDs and 95% CIs for the outcome of interest. This evaluation used the fixed-effects model. The Osendarp et al. and Van De Rest et al. trials (18, 20) reported 2 dose levels in the \( n^{-3} \) PUFA treatment groups. AUS, Australia; ID, identification; IDN, Indonesia; SMD, standardized mean difference.
breastfed and formula-fed infants. The n-3 LCPUFAs, especially EPA and DHA, play a crucial role in fetal development and infant growth (62). Previous studies have shown that infants who were fed formula deficient in LCPUFAs had significantly lower concentrations of EPA and DHA in plasma and red blood cells than did infants fed LCPUFA-supplemented formula (11, 63). We concluded that n-3 PUFA supplements, in the form of either capsules or formula, could benefit cognitive development in infants, based on promising improvements in MDI and PDI and significant promotion in language, motor, and cognitive abilities. Several RCTs have reported the effects of both EPA + DHA and arachidonic acid (an n-6 PUFA) on cognitive development but had controversial outcomes (64–68). Previous meta-analyses concluded that simultaneous n-3 and n-6 PUFA supplementation during pregnancy failed to show a significant effect on infant cognition or growth (8, 27). Nutritional evidence has shown that long-term n-3 PUFA deficiency reduces DHA concentrations and enhances n-6 PUFA concentrations, especially those of docosapentaenoic acid [22:5, n-6 (ω-6)] in brain (2, 6). Unfortunately, high concentrations of docosapentaenoic acid instead of DHA may have negative effects on cognitive development (6). Some included studies, such as that of Makrides et al. (9), reported that infants receiving DHA-only supplemented formula had higher MDI and PDI scores than did infants

**FIGURE 4** Treatment effects of n-3 PUFA supplementation on executive function (A) and processing speed (B) of cognitive domains in children, adults, and the elderly. The black dot data markers represent SMDs; the horizontal lines represent the 95% CIs, with the marker size reflecting the statistical weight of the study in the meta-analysis. The diamond data markers represent each subgroup and overall SMDs and 95% CIs for the outcome of interest. This evaluation used the fixed-effects model. The Van de Rest et al. trial (20) reported 2 dose levels in the n-3 PUFA treatment groups. ID, identification; SMD, standardized mean difference.
receiving DHA + arachidonic acid–supplemented formula (45). Furthermore, the inclusion of trials that used formulas providing close to the worldwide mean level of DHA in breast milk (0.32% DHA) was more likely to yield functional benefits attributable to DHA (69). The beneficial effects of DHA supplementation in infants were supported by several mechanistic investigations, which indicated that DHA supplementation can affect many specific processes and structures during development of the central nervous system. DHA is capable of influencing gene transcription and modifying the fluidity and thickness of neuronal membranes, thereby affecting receptor function, which is important for the developing brain and cognitive functionalities (2).

We found that n−3 PUFAs did not improve the memory, executive function, attention, and processing speed domains of human cognitive function after combining the results of imputation effect–related sensitivity analyses. Although most of the included studies used doses of DHA that exceeded the above recommendation, the results of the meta-regression indicated that the n−3 PUFA dose was not related to the treatment effect. Many of the included trials reported a statistically significant increase in plasma n−3 PUFA concentrations (15, 19, 32, 51, 60). However, the current meta-analysis showed no significant improvements in memory function in any of the selected outcomes. Previous meta-analyses of the cognitive benefits of n−3 PUFAs supplementation in both cognitively impaired and intact subjects also concluded that there were no substantial beneficial effects in healthy subjects (26). Also, one important aspect of adult cognitive performance is the possible presence of underlying psychiatric disorders, such as attention-deficit disorders and depression, which may be present in children and adults and could affect cognitive performance. Furthermore, the possible mechanism relevant to the clinical cognitive benefits of n−3 PUFAs remains unclear, and the future mode of action elucidation would be informative. In terms of the attention domain in the current study, subgroup analyses showed significant improvements with n−3 PUFA treatment and observed differences in the Stroop effect—a secondary endpoint. Despite the acknowledged view that an age-related decrease in the efficiency of inhibitory processes accounted for age-related increases in the Stroop effect (70), a previous meta-analysis argued that Stroop interference effects possess apparent age-sensitivity (71). Although no association between the Stroop effect outcome and participant age was found in current meta-regression analysis ($\beta = -0.005$; 95% CI: $-0.012$, 0.002; $P = 0.111$), more clinical trials regarding the effect of n−3 PUFAs on the Stroop effect in age-dependent groups need to be conducted. Combined with the imputation effect–related sensitivity analysis and presence of confirmed heterogeneity source, the positive effect of n−3 PUFAs on the attention domain and on the Stroop effect (secondary endpoint) remains debatable.

On the basis of the analysis of MMSE and ADAS-Cog outcomes, our study indicated that n−3 PUFAs had no effect on cognitive decline or AD. The treatment effects of these outcomes were consistent across studies; neither heterogeneity nor small study bias were observed in any of the included studies. Animal studies have provided considerable evidence that n−3 PUFAs, especially DHA, are capable of protecting against cognitive decline, AD, and related pathological disorders (35, 72). In human studies, it might be valuable to conduct further clinical trials of long-term n−3 PUFA supplementation in patients with mild cognitive impairment and AD. To fully understand the benefits of n−3 PUFAs on cognitive function, other cognitive diseases—such as Huntington disease and Parkinson disease—should be studied. Furthermore, possible interactions with apolipoprotein E4, antioxidants, environmental hazards, and dietary intake of n−6 PUFAs should be investigated further (35).

The strengths of the current study included the identification and systematic review of all RCTs that studied the effect of n−3 PUFA supplementation on cognition from the major medical literature databases. All 34 of the included clinical trials were
RCTs and were identified by using a comprehensive search strategy, which included many terms and phrases related to n−3 PUFAs and cognition. Moreover, we included in the pooled analysis only RCTs that had a treatment duration of ≥3 mo (or 12 wk) and used an n−3 PUFAs supplement intervention with a certain daily n−3 PUFAs ingredient intake. The current study investigated the benefits of n−3 PUFAs on human cognition throughout the whole life span and ultimately showed a substantial application of n−3 PUFAs for cognitive protection in infants but not in all people. Furthermore, the primary and secondary outcomes were considered in the meta-analysis only when data extraction and synthesis could be generated from ≥3 pooled studies with consolidated methods for outcome measures. In addition, we successfully identified possible sources of heterogeneity across the studies via the combined use of sensitivity and subgroup analyses, funnel plots, and Egger’s test for the evaluation of small study bias and meta-regression.

The current study also had limitations regarding the design of the included trials, nonpooled cognitive outcomes, incomplete outcome measures, and geographic distribution of the populations. Using the Cochrane Risk of Bias Tool, several studies presented design concerns leading to potential bias from vague allocation concealment and blinding methods, which can negatively affect the identification of the benefits of n−3 PUFAs on cognitive function. Some other outcomes could not be pooled for the meta-analysis because of limited data reported in different trials and the lack of measurement criteria or baseline data. These outcomes included, but were not limited to, the following: 1) behavior rating scale and intelligence quotient of infants; 2) scores of strengths and difficulties questionnaire, scores of Kaufman Assessment Battery for Children, and word reading of children, adults, or the elderly; and 3) the clinical dementia rating sum-of-boxes and the neuropsychiatric inventory of the elderly. Also, incompletely reported outcome measures resulted in fewer included studies than expected, which limited the power of the Q and I² statistic tests for the presence of heterogeneity in the current meta-analysis (73, 74).

Finally, most of the trials included populations from developed countries, such as the United States, the United Kingdom, and Australia. Populations from Asia, Africa, and South America should be considered because economic conditions and the social burden of poverty may impede cognitive function (75). Overall, n−3 PUFAs supplementation may provide some benefits on the selected domains of cognition in infants. The findings of the current study have considerable implications for clinical recommendations regarding cognition and mental health in age-specific populations. For instance, the n−3 PUFAs ingredients in formula and related clinical nutritional observations for serving the infants should be considered. However, clinical trials on the intervention effect of n−3 PUFAs on cognitive behaviors in children and adults should be carefully evaluated before execution. Also, the high degree of heterogeneity for secondary outcomes among the included infant studies should be taken into consideration, although promising pooled analysis for these outcomes was reported.

In conclusion, in infants, n−3 PUFAs supplementation could significantly benefit cognitive development based on comprehensive improvements in MDI and PDI and in language, motor, and cognitive abilities. However, n−3 PUFAs supplementation was not associated with significant improvements in cognitive function in older children, adults, and the elderly and did not prevent cognitive decline or related neuropathological diseases in the elderly. Over the entire life span from infancy to old age, an appropriate intake of n−3 PUFAs supplements is recommended during infancy. However, such supplements do not appear to benefit cognitive performance during the remaining life span. To improve the quality of RCTs for future perspectives, the presentation of details about adequate randomization and blinding methods is strongly recommended. In addition, incomplete outcome data and selective reporting should be avoided as much as possible so that more eligible and high-quality RCTs can be included in meta-analyses. Finally, it would be of interest to investigate the effects of n−3 PUFAs-rich diets—such as a fish-heavy diet and a Mediterranean diet—on cognitive function.

The authors’ responsibilities were as follows—JJ, QL, and SZ: designed the research; JJ and QL: conducted the library search and wrote the manuscript; JJ, QL, and JC: extracted and controlled the data and assumed primary responsibility for the final content; JJ, QL, JC, WZ, and MY: controlled and analyzed the data; and JJ and SZ: contributed to the writing of the manuscript. All of the authors read and approved the final manuscript. None of the authors, or their close relatives, has a financial interest in or serves as an employee, officer, member, owner, trustee, or agent for an organization that has a financial interest in the outcome of this study. JJ received funding for the submitted work from the National Natural Science Foundation of China and Zhejiang Provincial Natural Science Foundation of China, which have no financial interest in the outcome of this study. The funders had no role in the study design, implementation, analysis, or interpretation of the data.

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