Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies[1–3]

*Yu Zhang,[4] Jingnan Chen,[4] Jieni Qiu,[5] Yingjun Li,[6] Jianbing Wang,[6] and Jingjing Jiao[5]**

[4]Department of Food Science and Nutrition, College of Biosystems Engineering and Food Science, Zhejiang University, Hangzhou, China; and [5]Department of Nutrition, and [6]Department of Epidemiology and Health Statistics, Zhejiang University School of Medicine, Hangzhou, China

ABSTRACT

Background: The intake of fish and polyunsaturated fatty acids (PUFAs) may benefit cognitive function. However, optimal intake recommendations for protection are unknown.

Objective: We systematically investigated associations between fish and PUFA intake and mild-to-severe cognitive impairment risk.

Design: Studies that reported risk estimates for mild cognitive impairment (MCI), cognitive decline, dementia, Alzheimer disease (AD), or Parkinson disease (PD) from fish, total PUFAs, total n–3 (ω-3) PUFAs, or at least one n–3 PUFA were included. Study characteristics and outcomes were extracted. The pooled RR was estimated with the use of a random-effects model meta-analysis. A dose-response analysis was conducted with the use of the 2-stage generalized least-squares trend program.

Results: We included 21 studies (181,580 participants) with 4438 cases identified during follow-up periods (2.1–21 y). A 1-serving/wk increment of dietary fish was associated with lower risks of dementia (RR: 0.95; 95% CI: 0.90, 0.99; $P = 0.042$, $I^2 = 63.4\%$) and AD (RR: 0.93; 95% CI: 0.90, 0.95; $P = 0.003$, $I^2 = 74.8\%$). Pooled RRs of MCI and PD were 0.71 (95% CI: 0.59, 0.82; $P = 0.733$, $I^2 = 0\%$) and 0.90 (95% CI: 0.80, 0.99; $P = 0.221$, $I^2 = 33.7\%$), respectively, for an 8-g/d increment of PUFA intake. As an important source of marine n–3 PUFAs, a 0.1-g/d increment of dietary docosahexaenoic acid (DHA) intake was associated with lower risks of dementia (RR: 0.86; 95% CI: 0.76, 0.96; $P < 0.001$, $I^2 = 92.7\%$) and AD (RR: 0.63; 95% CI: 0.51, 0.76; $P < 0.001$, $I^2 = 94.5\%$). Significant curvilinear relations between fish consumption and risk of AD and between total PUFAs and risk of MCI (both P-nonlinearity < 0.001) were observed.

Conclusions: Fishery products are recommended as dietary sources and are associated with lower risk of cognitive impairment. Marine-derived DHA was associated with lower risk of dementia and AD but without a linear dose-response relation. *Am J Clin Nutr* 2016;103:330–40.

Keywords: Alzheimer disease, cognitive impairment, dementia, fish, polyunsaturated fatty acids

INTRODUCTION

Cognitive impairment refers to a group of cognitive decline symptoms in intellectual performance. These mental, neurologic, and substance-use disorders constitute 13% of the global health burden and surpass both cardiovascular and cancer diseases (1). The benefits of PUFAs, especially of EPA and DHA, in preventing cognitive problems have been of public interest (2). In addition, n–3 PUFA–rich diets, such as the Mediterranean-style diet, may contribute to cognitive health (3, 4). Unfortunately, previous studies have reported inconsistent outcomes and induced extensive controversy. Some clinical trials have shown the cognitive-enhancing effects of n–3 PUFAs during infant development, childhood, and adulthood as well as in the elderly with neurodegenerative diseases such as Alzheimer disease (AD)[7] (5, 6). However, other trials have indicated that dietary DHA intake from the perinatal period to adulthood has not revealed a clear memory improvement in humans (7).

The daily n–3 PUFA intake could be from plant-derived α-linolenic acid (ALA), fish and marine n–3 PUFAs (EPA and DHA), and PUFA supplements. Both positive and null effects of n–3 PUFAs have been observed. In detail, some cohort studies have shown an inverse association between fish consumption and the prevalence of dementia or AD (8–11), but these findings were not supported by other studies (12, 13). Meta-analyses have also reported conflicting findings (14–17). Mild cognitive impairment (MCI), dementia, AD, or Parkinson disease (PD) may occur with the development of cognitive degradation (18). In addition to the continuous emergence of new evidence, reasons for confounding reports may be ascribed to the use of data

[1] Supported by the National Natural Science Foundation of China (grant 31201307), the Zhejiang Provincial Natural Science Foundation of China (grant LY14C200008), and the Fundamental Research Funds for the Central Universities (grant 2015QNA7014).

[2] The funders did not have a role in the study selection, quality assessment, data synthesis, or manuscript preparation.

[3] Supplemental Methods 1–3, Supplemental Tables 1–4, and Supplemental Figures 1–20 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

*To whom correspondence should be addressed. E-mail: jingjingjiao@zju.edu.cn.

[7] Abbreviations used: AD, Alzheimer disease; ALA, α-linolenic acid; apoE, apolipoprotein E; MCI, mild cognitive impairment; PD, Parkinson disease; RCT, randomized controlled trial; TFA, total fatty acid; V_E, vitamin E.

Received September 21, 2015. Accepted for publication November 30, 2015.
First published online December 30, 2015; doi: 10.3945/ajcn.115.124081.

from both randomized controlled trials (RCTs) and observational studies, the inclusion of studies with short follow-up durations or small populations, the exclusion of healthy individuals, or the inclusion of patients only. The aim of this study was to conduct a comprehensive dose-response meta-analysis of the association between fish and PUFA intake and cognitive problems spanning from mild impairment to severe diseases.

METHODS

Data sources and search strategy

We followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (19). Literature searches of the PubMed (http://www.ncbi.nlm.nih.gov/pmc/), Embase (http://www.embase.com), and Cochrane Library (http://www.thecochranelibrary.com/) databases were conducted through May 2015 without language restriction. All possible sources of PUFAs were considered including fish, marine n–3 PUFAs, dietary n–3 fatty acids, and concentrations of PUFAs in plasma, serum, or erythrocytes. Keywords used in the searches included synonyms and abbreviations of polyunsaturated fatty acid, docosahexaenoic acid, eicosapentaenoic acid, fish oil, cognition, cognitive decline, cognitive impairment, dementia, Alzheimer's disease, and Parkinson's disease. Details of search strategies are shown in **Supplemental Methods 1.**

Study selection

An initial screening was conducted for the exclusion of duplicate references and irrelevant articles. The relevant full-text articles were independently read by 2 groups of investigators (YZ and JC; JQ and JJ). Studies were included if *1*) the targeted association was investigated; *2*) fish consumption, total PUFAs (including both n–3 and n–6 PUFAs), total n–3 PUFAs, or at least one n–3 PUFA concentration was evaluated from the diet or measured as a blood biomarker; and *3*) at least one endpoint from MCI, cognitive decline, dementia, AD, or PD was investigated. Studies were excluded if *1*) cross-sectional studies were conducted, *2*) only 2 categories were considered, and *3*) the reference group was not the lowest category showing the amounts of fish consumption, dietary PUFA intake, or blood biomarker measurements. There was no restriction for age ranges and sample sizes of participants in eligible cohort studies. However, the duration of the follow-up time for all eligible studies should have been >2 y.

Data extraction and quality assessment

Two investigators (YZ and JC) independently performed the data extraction. The following data were recorded: first author's name, publication year, cohort region, sex, age, number of participants, follow-up duration, number of cases, person-years for each category, assessment method and categories of fish or PUFA intake, ascertainment of outcomes, and adjusted covariates. Discrepancies were resolved by consensus. The study quality was evaluated with the well-known Newcastle-Ottawa quality-assessment scale (20). We assigned a maximal score of 9 points (representing the highest quality) to each study including 4 points for selection, 2 points for comparability, and 3 points for the assessment of outcomes (for cohort studies) or exposures (for case-control studies). We regarded total scores of 0–6 and 7–9 as low and high quality, respectively.

Statistical methods

All statistical analyses were conducted with STATA v11.0 software (StataCorp LP). All types of associations were estimated as RRs and 95% CIs. Some studies reported the OR in each category. We calculated RRs with the use of the outcome incidence in the nonexposed group (21). Multiple PUFA-assessment methods (dietary intake and blood biomarkers) and intake categories (tertiles, quartiles, or quintiles) were reported. Results from multivariable models with the most-complete covariate adjustments were used. We derived a dose-response analysis with the use of a 2-stage generalized least-squares trend program (22, 23). To generate a linear dose-response profile, data on the amount of fish and PUFA intake, the distribution of cases and person-years, and RRs plus 95% CIs for ≥3 categories were extracted. One study presented the results separately for men and women (24). We separately recorded the cases and person-years from men and women as 2 studies. We assigned the median or mean amount in each category to corresponding RRs for each study. The midpoint of lower and upper bounds was regarded as the dose of each category if the study only reported the range. The difference from the lowest range to the median was equivalent to the same difference in the preceding category if the highest category was open ended. The lowest bound was set to zero if it was open ended. If the fish consumption was reported as grams per day, we converted intake into the standard serving defined as 105 g/serving (25). Overall RRs and 95% CIs were one-by-one investigated for an increment of fish (1 serving/wk), total PUFAs [8 g/d for the diet or 10% of total fatty acids (TFAs) for the blood biomarker measurement], n–3 PUFAs (0.6 g/d or 2% of TFAs), DHA (0.1 g/d or 1% of TFAs), EPA (0.05 g/d or 0.5% of TFAs), and ALA (0.5 g/d or 0.5% of TFAs) intakes. For study comparability, n–3 PUFA increments were chosen to be ∼1 SD of the mean on the basis of recommendations from the WHO and the Global Organization for EPA and DHA Omega-3s (26). Pooled RRs from each included study, which were weighted by inverse variances, were estimated via a random-effects model (27), whereby MCI, cognitive decline, dementia, AD, and PD were considered different endpoints. Detailed STATA software commands and examples regarding the 2-stage generalized least-squares trend program, the increment analysis, and the final dose-response meta-analysis are shown in **Supplemental Methods 2**. In addition, a restricted cubic spline model with 4 knots at fixed centiles (5%, 35%, 65%, and 95%) of the distribution was used to estimate the curvilinear association. Detailed STATA commands regarding the establishment of cubic spline models are shown in **Supplemental Methods 3**.

Study heterogeneity was assessed with the use of Cochran's Q statistic, and the impact was evaluated with an I^2 statistic (28). Subgroup, meta-regression, and sensitivity analyses were conducted to investigate heterogeneity sources. Risk of publication bias was assessed by the visualization of contour-enhanced funnel plots as well as Egger's and Begg's tests at the $P < 0.05$ significance level.

RESULTS

Literature search

Figure 1 shows search results and overall selection processes. We initially identified 2008 articles after duplicate exclusion and

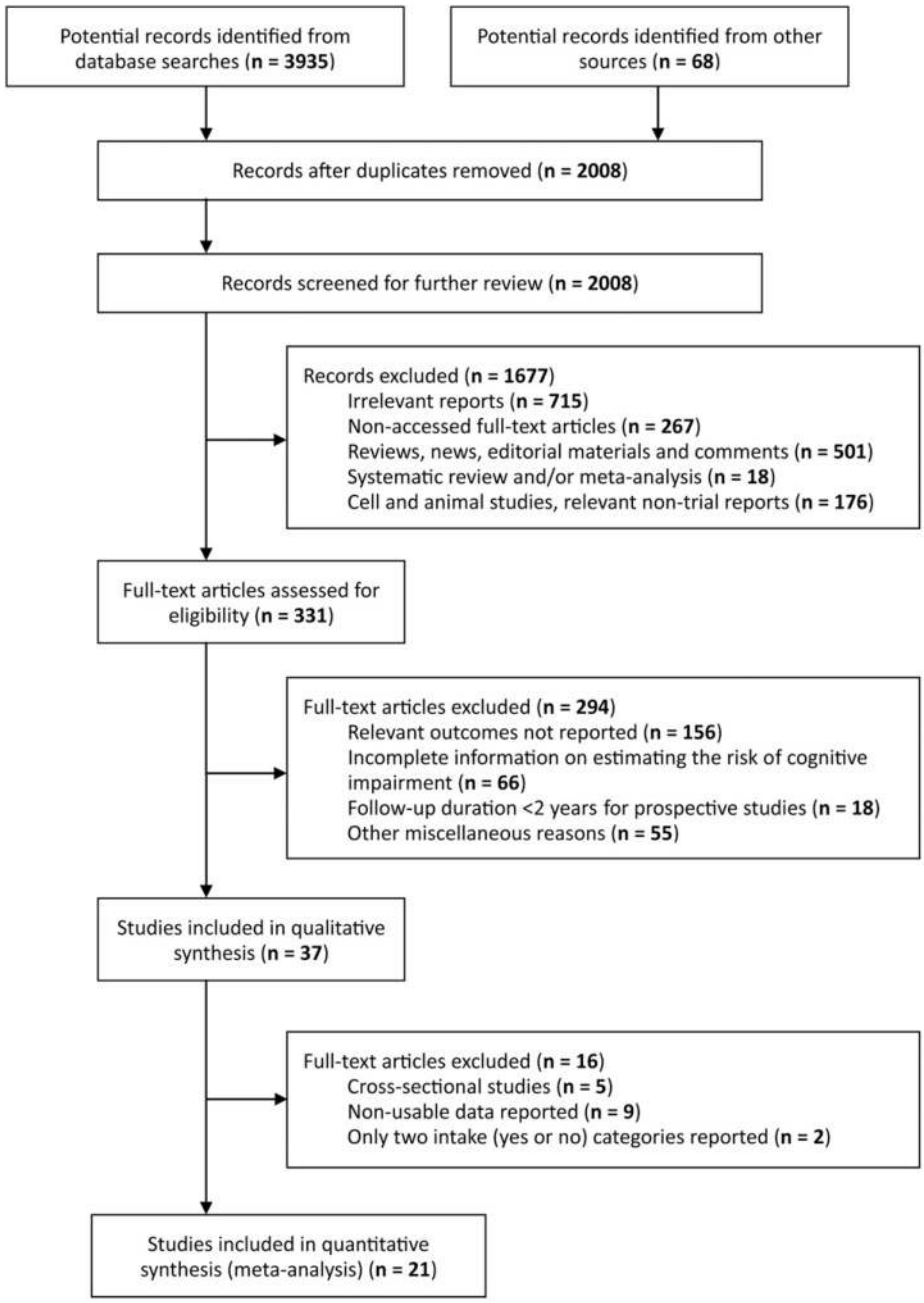

FIGURE 1 Study selection for investigating the association between fish consumption or n–3 PUFA intake and risk of cognitive impairment and related diseases.

obtained 37 relevant articles from 331 full-text articles. Sixteen of the articles were excluded, including 4 cross-sectional studies (8, 29–32), 9 articles that reported insufficient data or no relative ORs or RRs (33–41), and 2 articles that reported only 2 categories (42, 43). Finally, 21 eligible articles that reported 4438 cases (263 cases of MCI, 320 cases of cognitive decline, 1864 cases of dementia, 1332 cases of AD, and 659 cases of PD) in 181,580 participants from 17 independent cohorts were included (9–13, 24, 44–58). Of these articles, 4 case-control studies were included (50, 53–55).

Study characteristics

Table 1 and **Supplemental Table 1** show the characteristics of included studies. Of these studies, 6 trials reported the association between fish consumption and various risk of adverse cognitive outcomes (9–13, 55), 11 trials described the correlation between total PUFAs and risk of adverse cognitive outcomes (24, 44–48, 50, 52, 55–57), 12 trials investigated the association between n–3 PUFAs and risk of adverse cognitive outcomes (11, 24, 44–46, 48–51, 54–56), and 13 trials described the correlation between representative n–3 PUFAs (ALA, EPA, and DHA) and risk of adverse cognitive outcomes (11, 12, 24, 44, 45, 48, 50, 51, 53–56, 58). Overall, 7 studies were from the United States (11, 13, 24, 44, 53, 55, 58), 11 studies were from Europe (9, 10, 12, 45–49, 52, 56, 57), 2 studies were from Asia (50, 54), and one study was from Canada (51). One study only included men (49), and the other studies

TABLE 1
Characteristics of included studies in current meta-analysis[1]

Reference	Source (country)	Cohort study name	Participants, *n*	Age at baseline, y	Follow-up duration, y	Endpoints (cases, *n*)
Barberger-Gateau et al., 2007 (9)	France	Three-City Cohort Study	8085	65	3.48	Dementia (281), AD (183)
Beydoun et al., 2007 (44)	United States	The ARIC Study	2251	52–62	12	Cognitive decline (140)
Chen et al., 2003 (24)						
Men	United States	The Health Professionals Follow-Up Study	47,331	40–75	15	PD (191)
Women	United States	The Health Professionals Follow-Up Study	88,563	30–55	15	PD (168)
de Lau et al., 2005 (45)	Netherlands	The Rotterdam Study	5289	55	6	PD (51)
Devore et al., 2009 (12)	Netherlands	The Ommoord Study	5395	55	9.6	Dementia (465), AD (365)
Engelhart et al., 2002 (46)	Netherlands	The Rotterdam Study	5395	55	6	Dementia (197), AD (146)
Eskelinen et al., 2008 (47)	Finland	The CAIDE Study	1449	65–80	21	MCI (82)
Heude et al., 2003 (48)	France	The EVA Study	1188	63–74	4	Cognitive decline (27)
Huang et al., 2005 (13)	United States	Cardiovascular Health Cognition Study	2233	65	5.4	Dementia (378), AD (190)
Kalmijn et al., 1997 (49)	Netherlands	The Zuphen Elderly Study	476	69–89	8	Cognitive decline (153)
Kalmijn et al., 1997 (10)	Netherlands	The Rotterdam Study	5386	55	2.1	Dementia (58), AD (37)
Kim et al., 2010 (50)	Korea	Korean Kuri Area Study	57	65	2.5	Dementia (33)
Kröger et al., 2009 (51)	Canada	Canadian Study of Health and Aging	663	65	4.9	Dementia (149), AD (105)
Laitinen et al., 2006 (52)	Finland	The CAIDE Study	2000	65–79	21	Dementia (117), AD (76)
Lopez et al., 2011 (53)	United States	The Rancho Bernardo Study	402	67–100	3	Dementia (42), AD (30)
Miyake et al., 2010 (54)	Japan	Fukuoka Prefecture Study	617	58–77	6	PD (249)
Morris et al., 2003 (11)	United States	Chicago Health and Aging Project	842	65–94	3.9	AD (140)
Roberts et al., 2010 (55)	United States	The Mayo Clinic Study of Aging	1567	70	2.7	MCI (163)
Samieri et al., 2008 (56)	France	Three-City Cohort Study	1214	65	4	Dementia (65)
Solfrizzi et al., 2006 (57)	Italy	The Italian Longitudinal Study on Aging	278	65–84	2.6	MCI (18)
Schaefer et al., 2006 (58)	United States	The Framingham Heart Study	899	76	9.1	Dementia (79), AD (60)

[1]AD, Alzheimer disease; ARIC, Atherosclerosis Risk in Communities; CAIDE, Cardiovascular Disease Risk Factors, Aging and Dementia; EVA, Etude du Vieillissement Artériel; MCI, mild cognitive impairment; PD, Parkinson disease.

included both men and women. The total number of participants, which ranged from 57 to 135,894, and the number of cases, which ranged from 18 to 830, varied widely across different studies. The average follow-up duration reported in eligible studies ranged from 2.1 to 21 y (Table 1). Quality-assessment scores ranged from 5 to 9 points (**Supplemental Table 2**).

Fish consumption and risk of adverse cognitive outcomes

Six eligible studies investigated the association between fish consumption and MCI (55), dementia (9, 10, 12, 13), or AD (9–13), which comprised 23,508 participants and 2260 cases. Four studies investigated both dementia and AD events (9, 10, 12, 13). A dose-response meta-analysis showed that the pooled RR of dementia was 0.95 (95% CI: 0.90, 0.99; $P = 0.042$, $I^2 = 63.4\%$) for an increment of 1 serving/wk with no publication bias (Begg's $P = 0.308$; Egger's $P = 0.105$). Similarly, such an increment was associated with 7% lower risk of AD (RR: 0.93; 95% CI: 0.90, 0.95; $P = 0.003$, $I^2 = 74.8\%$) with no publication bias (Begg's $P = 0.086$; Egger's $P = 0.174$) (**Figure 2**A). No missing studies were imputed in the contour-enhanced funnel plot of the associations (**Supplemental Figure 1**). With the use of a restricted cubic splines model, we observed evidence of a curvilinear association between fish consumption and risk of AD ($P < 0.001$; Figure 2B). In comparison with subjects who had no fish consumption, RRs of AD were 0.79 (95% CI: 0.66, 0.95), 0.74 (95% CI: 0.62, 0.89), and 0.71 (95% CI: 0.62, 0.81) for 2–4 servings fish/wk, respectively. However, no significant curvilinear association with risk of dementia was observed ($P = 0.176$; Figure 2C).

Total PUFA and n–3 PUFA intakes and risk of adverse cognitive outcomes

Eleven studies investigated the association between total PUFA intake and MCI (47, 55, 57), cognitive decline (44, 48), dementia (46, 50, 52, 56), AD (46, 52), or PD (24, 45) with 156,582 participants and 1474 cases. Two studies investigated both dementia and AD events (46, 52). Overall, an 8-g/d increment of dietary PUFAs was significantly associated with lower risks of both MCI (RR: 0.71; 95% CI: 0.59, 0.82; $P = 0.733$, $I^2 = 0\%$) and PD (RR: 0.90; 95% CI: 0.80, 0.99; $P = 0.221$, $I^2 = 33.7\%$) but was not associated with lower risks of dementia (RR: 0.96; 95% CI: 0.71, 1.21) or AD (RR: 0.96; 95% CI: 0.65, 1.27) (**Figure 3**A). Furthermore, no significant publication bias was detected for associations with MCI (Egger's $P = 0.698$) or PD (Egger's $P = 0.421$). We showed evidence of a curvilinear association for dietary PUFAs with risk of MCI ($P < 0.001$;

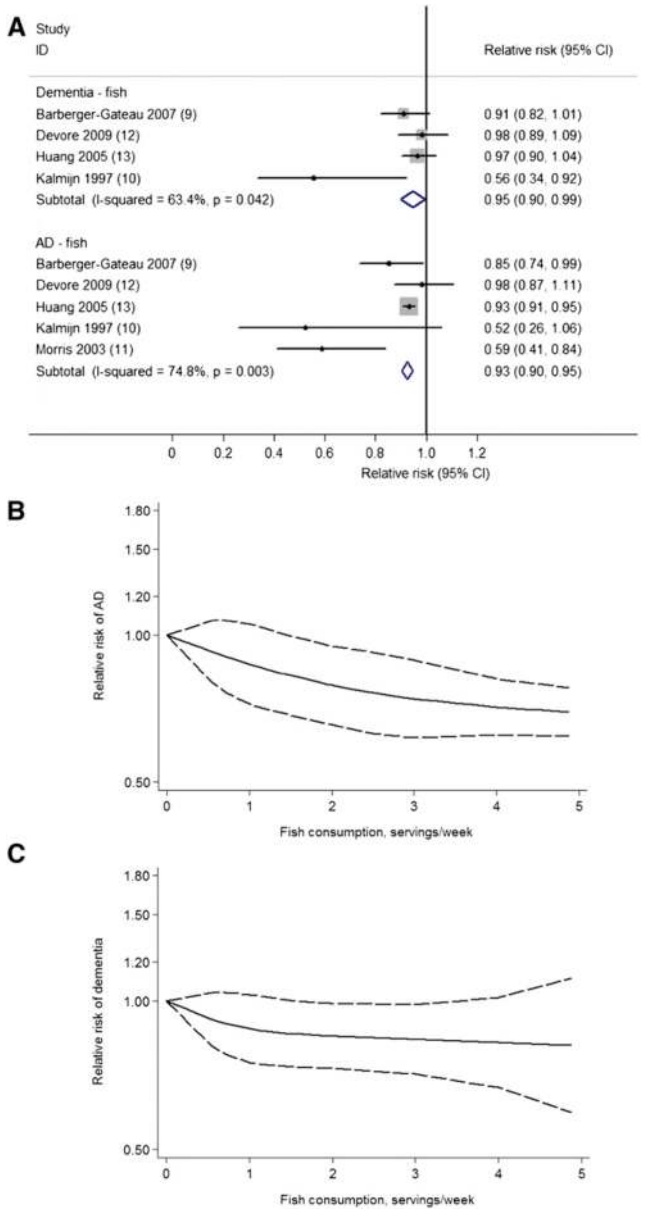

FIGURE 2 Associations between fish consumption and risk of mild-to-severe cognitive impairment and related diseases. (A) A meta-analysis showed that the RRs of dementia and AD were associated with a 1-serving/wk increment of fish consumption. Black-dot data markers represent RRs, and horizontal lines represent 95% CIs with the gray box size reflecting the statistical weight of the study in the meta-analysis. Diamond-data markers represent RRs and 95% CIs for the outcome of interest. Four studies investigated both dementia and AD events linked to fish consumption (9, 10, 12, 13). Dose-response analyses for curvilinear associations between fish consumption (servings/wk) and RRs of dementia (B) and AD (C) are shown. Solid lines represent best-fitting cubic spline models. Areas between dashed lines represent 95% CIs. AD, Alzheimer disease; ID, identifier.

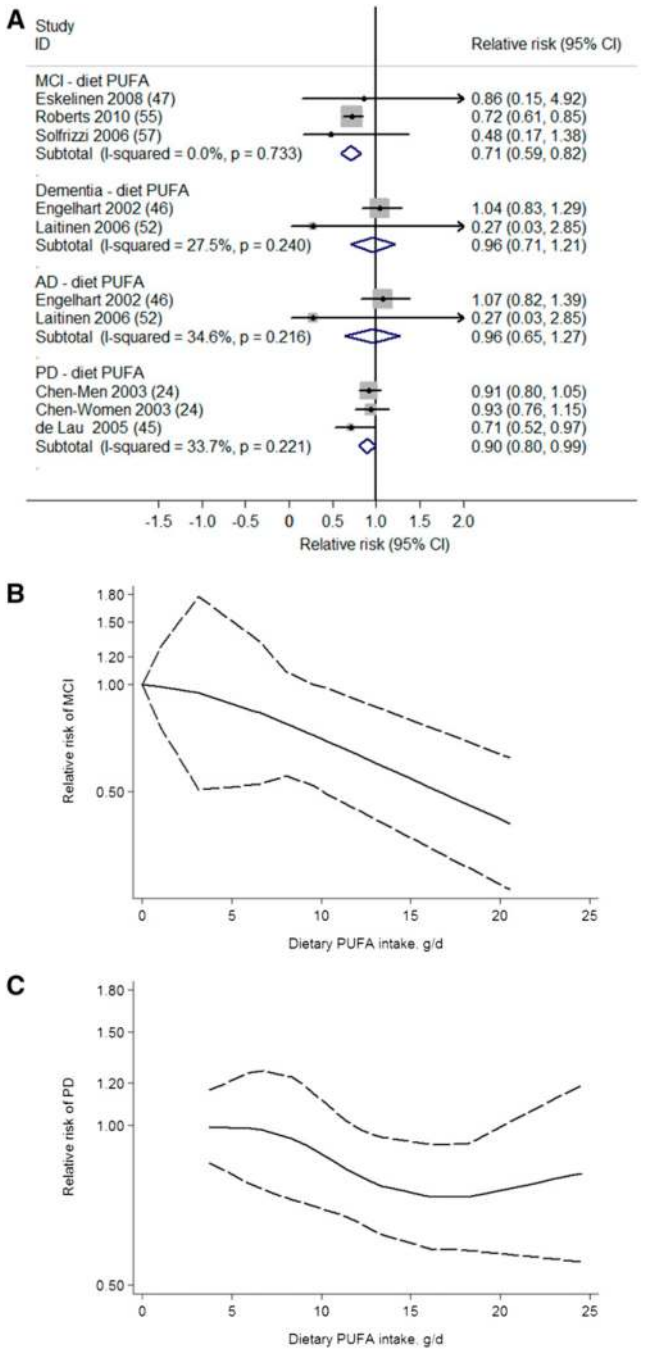

FIGURE 3 Associations between dietary total PUFA intake and risk of mild-to-severe cognitive impairment and related diseases. (A) A meta-analysis showed that the RRs of MCI, dementia, AD, and PD were associated with dietary PUFA intake. Black-dot data markers represent RRs, and horizontal lines represent 95% CIs with the gray box size reflecting the statistical weight of the study in the meta-analysis. Diamond-data markers represent RRs and 95% CIs for the outcome of interest. Two studies investigated both dementia and AD events linked to PUFA intake (46, 52). Dose-response analyses for curvilinear associations between dietary PUFA intake (g/d) and RRs of MCI (B) and PD (C) are shown. Solid lines represent best-fitting cubic spline models. Areas between 2 dashed lines represent the 95% CIs. AD, Alzheimer disease; ID, identifier; MCI, mild cognitive impairment; PD, Parkinson disease.

Figure 3B) but not of PD (P = 0.063; Figure 3C). The total concentration of PUFAs in blood could be alternatively evaluated as blood biomarkers via their percentages of TFAs. A dose-response analysis showed that a 10% increment of blood PUFA concentrations was not associated with lower risk of either cognitive decline (RR: 1.00; 95% CI: 0.97, 1.02) or dementia (RR: 0.98; 95% CI: 0.89, 1.08) (**Supplemental Figure 2**).

The associations of n–3 PUFA intake with risk of adverse cognitive outcomes were investigated and compared with the previous PUFA-related results. Twelve studies investigated the

association between n–3 PUFA intake and MCI (55), cognitive decline (44, 48, 49), dementia (46, 50, 51, 56), AD (11, 46, 51), and PD (24, 45, 54) with 155,453 participants and 1977 cases. Two studies investigated both dementia and AD events (46, 51). An increment of dietary n–3 PUFAs was not associated with lower risk of either AD (RR: 0.99; 95% CI: 0.85, 1.12) or PD (RR: 0.99; 95% CI: 0.94, 1.04) (**Supplemental Figure 3**). For concentrations in blood, the dose-response relation between increments of n–3 PUFA concentrations and lower risks of cognitive decline (RR: 1.03; 95% CI: 0.96, 1.11) or dementia (RR: 0.99; 95% CI: 0.94, 1.04) did not seem significant (**Supplemental Figure 4**). We showed no evidence of curvilinear associations between dietary n–3 PUFAs and risk of AD ($P = 0.162$) and PD ($P = 0.627$) or between blood n–3 PUFA concentrations and risk of dementia ($P = 0.796$) (**Supplemental Figures 5–7**).

DHA, EPA, and ALA intakes and risk of adverse cognitive outcomes

For comparison with the associations with n–3 PUFA intake, the dose-response relation between intakes of 3 main n–3 PUFA nutrients and risk of adverse cognitive outcomes was observed. Dietary intake and concentrations of DHA in blood were alternatively investigated in 12 studies with 154,711 participants and 2359 cases. EPA intake was examined in 10 studies with 153,410 participants and 2148 cases, and ALA intake was examined in 8 studies with 147,731 participants and 1200 cases.

Overall, a 0.1-g/d increment of dietary DHA was significantly associated with lower risks of both dementia (RR: 0.86; 95% CI: 0.76, 0.96; $P < 0.001$, $I^2 = 92.7\%$) and AD (RR: 0.63; 95% CI: 0.51, 0.76; $P < 0.001$, $I^2 = 94.5\%$) but was not associated with lower risk of PD (RR: 1.00; 95% CI: 0.97, 1.03; $P = 0.891$, $I^2 = 0\%$) with no publication bias (Begg's $P = 0.175$; Egger's $P = 0.103$) (**Figure 4**A). However, for the blood biomarker, a 1% increment of blood DHA concentrations was not associated with lower risks of cognitive decline, dementia, or AD (Figure 4B). There were no significant curvilinear associations between dietary DHA and risk of AD ($P = 0.136$) or PD ($P = 0.880$). Moreover, no significant curvilinear association was observed between blood biomarker concentrations of DHA intake and risk of dementia ($P = 0.196$) (**Supplemental Figures 8–10**).

As another important n–3 PUFA nutrient, a 0.05-g/d increment of dietary EPA intake was not associated with risk of AD (RR: 1.04; 95% CI: 0.85, 1.23) or PD (RR: 1.01; 95% CI: 0.98, 1.04) (**Supplemental Figure 11**). In addition, a 0.5% increment of blood EPA concentrations was not associated with risk of cognitive decline (RR: 0.96; 95% CI: 0.86, 1.07) or dementia (RR: 0.96; 95% CI: 0.83, 1.10) (**Supplemental Figure 12**). Similarly, there was no significant association between the increment of dietary ALA intake and lower risk of PD (RR: 0.98; 95% CI: 0.93, 1.03) and no observed association between blood ALA concentration increments and lower risk of dementia (RR: 1.02; 95% CI: 0.97, 1.07) (**Supplemental Figure 13**). Null results were observed not only for curvilinear associations of risk of PD linked to dietary EPA and ALA intake ($P = 0.858$ and $P = 0.279$, respectively) but also for the curvilinear association of risk of dementia linked to concentrations of ALA in blood ($P = 0.060$) (**Supplemental Figures 14–16**).

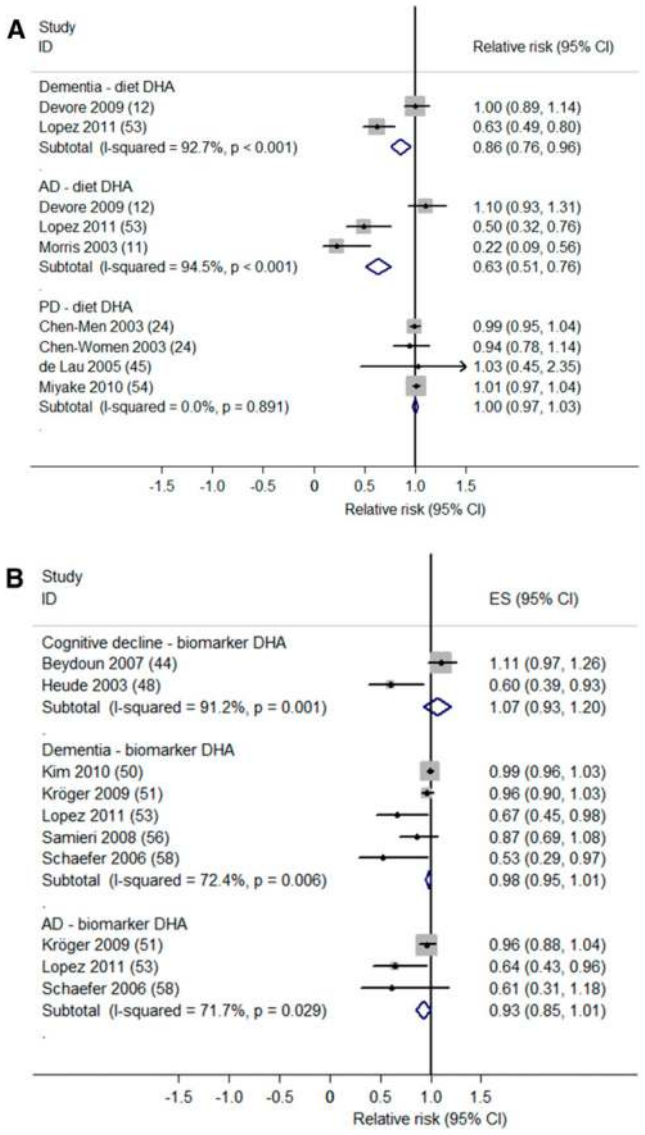

FIGURE 4 Associations between DHA intake and risk of mild-to-severe cognitive impairment and related diseases. A meta-analysis showed that the RRs of dementia, AD, and PD were associated with dietary DHA intake (A) and that the RRs of cognitive decline, dementia, and AD were associated with blood DHA biomarker concentrations (B). Black-dot data markers represent RRs; horizontal lines represent 95% CIs with the gray box size reflecting the statistical weight of the study in the meta-analysis. Diamond-data markers represent RRs and 95% CIs for the outcome of interest. Three studies investigated both dementia and AD events linked to DHA intake (12, 51, 53). AD, Alzheimer disease; ID, identifier; MCI, mild cognitive impairment; PD, Parkinson disease.

Overall associations between fish and PUFAs and cognitive impairment risks

Overall, the current dose-response analysis showed significant associations between dietary intakes of fish and PUFAs and various cognitive impairment risks. First, a 1-serving/wk increment of dietary fish was associated with lower risks of dementia and AD, respectively (Figure 2A). Second, an 8-g/d increment of PUFA intake was associated with lower risks of MCI and PD, respectively (Figure 3A). As an important source of marine n–3 PUFAs, a 0.1-g/d increment of DHA intake was associated with lower risks of dementia and AD, respectively (Figure 4A).

Cubic spline models that exhibited all nonlinear investigated associations are shown in **Supplemental Table 3**. Significant curvilinear relations between fish consumption and risk of AD and between total PUFAs and risk of MCI (both *P*-nonlinearity < 0.001) were observed. A network for elucidating the significance of all investigated associations is summarized in **Supplemental Figure 17**.

Subgroup and sensitivity analyses

For fish consumption, subgroup analyses stratified by location, education, energy intake, apoE (apolipoprotein E) ϵ4 status, and intakes of other nutrients did not show significant changes in risks of adverse cognitive outcomes. Significant evidence was shown in the heterogeneity from subgroups stratified by follow-up duration, publication year, and the adjustment covariates BMI and study quality (**Table 2**). Changes in RRs of cognitive impairment and related diseases affected by total PUFA intake were shown only in subgroup analyses stratified by dietary intake (RR: 0.89; 95% CI: 0.81, 0.96), and no association was observed in studies stratified by blood biomarker measurements (RR: 1.00; 95% CI: 0.98, 1.02) (Table 2). For n–3 PUFA intake, subgroup analyses stratified by any factor did not show any significant change. For DHA intake, significant evidence was shown for the heterogeneity from subgroups stratified by location, BMI, education, apoE ϵ4 status, and intakes of other nutrients (**Table 3**). For EPA intake, subgroup analyses stratified by any factor did not show any significant change. For ALA intake, significant evidence was shown for the heterogeneity from subgroups stratified by intake measurement, age, and intakes of other nutrients.

The meta-regression analysis was conducted to examine study characteristics such as the publication year, mean age, mean BMI, percentage of apoE ϵ4 carriers, follow-up duration, percentage of education above the primary school level, total energy intake, incident rate of cognitive impairment, study quality, and

TABLE 2
Stratified analyses of associations between fish, total PUFA, or n–3 PUFA intake and risk of cognitive impairment and related diseases[1]

	Fish intake				Total PUFA intake				n–3 PUFA intake			
	n	RR (95% CI)	I^2, %	*P*	*n*	RR (95% CI)	I^2, %	*P*	*n*	RR (95% CI)	I^2, %	*P*
Location												
Europe	6	0.94 (0.88, 0.99)	64.3	0.862	9	0.99 (0.93, 1.05)	28.1	0.980	6	0.98 (0.90, 1.06)	71.5	0.745
United States and Canada	4	0.94 (0.91, 0.96)	74.6		4	0.99 (0.96, 1.01)	86.5		7	1.00 (0.96, 1.05)	71.5	
Asia and others	—	—	—		1	1.00 (0.89, 1.11)	—		2	0.99 (0.95, 1.03)	0.0	
Duration[2]												
Less than the mean	6	0.89 (0.82, 0.96)	72.2	0.022	8	0.97 (0.92, 1.02)	74.4	0.091	11	0.99 (0.96, 1.02)	71.9	0.094
At least the mean	4	0.94 (0.92, 0.96)	0.0		6	0.99 (0.97, 1.02)	0.0		4	1.04 (0.97, 1.11)	0.0	
Year[3]												
<2005	3	0.57 (0.41, 0.73)	0.0	<0.001	5	0.99 (0.93, 1.05)	0.0	0.841	7	1.02 (0.94, 1.11)	68.4	0.377
≥2005	7	0.94 (0.92, 0.96)	0.0		9	0.99 (0.96, 1.01)	74.0		8	0.99 (0.96, 1.02)	66.8	
Intake measurement												
Diet	10	0.94 (0.92, 0.96)	65.1	—	10	0.89 (0.81, 0.96)	45.3	<0.001	9	0.98 (0.94, 1.03)	68.5	0.315
Blood biomarker	—	—	—		4	1.00 (0.98, 1.02)	0.0		6	1.00 (0.97, 1.04)	61.0	
Adjustment for confounding factors												
Age												
Yes	10	0.94 (0.92, 0.96)	65.1	—	13	0.99 (0.97, 1.01)	63.8	0.718	12	0.99 (0.96, 1.03)	69.3	0.718
No	—	—	—		1	0.95 (0.80, 1.11)	—		3	1.00 (0.94, 1.06)	39.6	
BMI												
Yes	7	0.94 (0.92, 0.96)	0.0	<0.001	5	0.99 (0.97, 1.02)	81.6	0.617	5	1.00 (0.97, 1.03)	67.4	0.288
No	3	0.57 (0.41, 0.73)	0.0		9	0.98 (0.93, 1.03)	29.1		10	0.98 (0.93, 1.03)	65.2	
Education												
Yes	8	0.94 (0.89, 0.99)	71.8	1.000	10	0.99 (0.97, 1.02)	64.9	0.147	11	1.00 (0.97, 1.03)	69.9	0.578
No	2	0.94 (0.92, 0.96)	0.0		4	0.95 (0.87, 1.02)	46.0		4	0.98 (0.91, 1.04)	47.3	
Energy intake												
Yes	8	0.94 (0.92, 0.96)	70.9	0.275	6	0.99 (0.96, 1.01)	78.1	0.862	8	1.01 (0.96, 1.06)	69.7	0.572
No	2	0.89 (0.82, 0.97)	0.0		8	0.99 (0.93, 1.04)	33.2		7	0.99 (0.96, 1.02)	63.5	
apoE ϵ4 status												
Yes	5	0.93 (0.91, 0.95)	66.6	0.572	6	0.99 (0.97, 1.02)	77.2	0.718	6	0.99 (0.95, 1.04)	78.7	0.920
No	5	0.95 (0.88, 1.01)	71.7		8	0.98 (0.93, 1.03)	37.8		9	1.00 (0.96, 1.03)	49.3	
Other nutrients												
Yes	2	0.98 (0.91, 1.06)	0.0	0.144	5	1.00 (0.97, 1.02)	44.7	0.045	6	1.01 (0.97, 1.05)	61.7	0.108
No	8	0.93 (0.91, 0.95)	70.4		9	0.96 (0.91, 1.01)	63.7		9	0.97 (0.93, 1.02)	66.1	
Study quality[4]												
Score ≥7	8	0.94 (0.92, 0.96)	54.6	0.001	13	0.99 (0.97, 1.01)	63.9	0.752	13	1.00 (0.96, 1.04)	69.6	0.584
Score <7	2	0.55 (0.31, 0.78)	0.0		1	1.00 (0.89, 1.11)	—		2	0.99 (0.95, 1.03)	0.0	

[1] *n* denotes the number of studies included. *P* values are for the heterogeneity between strata. apoE, apolipoprotein E.
[2] Mean follow-up durations for fish, total PUFA, and n–3 PUFA intakes were 4.5, 8.8, and 6.3 y, respectively.
[3] The year 2005 was regarded as the time threshold for recent studies (≤10 y).
[4] The quality of each study was assessed with the use of the Newcastle-Ottawa quality-assessment scale (20).

TABLE 3
Stratified analyses of associations between DHA, EPA, or ALA intake and risk of cognitive impairment and related diseases[1]

	DHA intake				EPA intake				ALA intake			
	n	RR (95% CI)	I^2, %	*P*	*n*	RR (95% CI)	I^2, %	*P*	*n*	RR (95% CI)	I^2, %	*P*
Location												
Europe	5	0.99 (0.90, 1.08)	63.2	0.019	5	0.99 (0.90, 1.09)	65.3	0.691	2	1.02 (0.97, 1.07)	90.3	0.192
United States and Canada	12	0.97 (0.94, 1.00)	89.0		6	0.99 (0.95, 1.04)	0.0		5	0.95 (0.90, 1.01)	52.0	
Asia and others	2	1.00 (0.98, 1.03)	0.0		2	1.01 (0.97, 1.05)	0.0		2	0.98 (0.90, 1.05)	71.0	
Duration[2]												
Less than the mean	12	0.98 (0.96, 1.01)	89.3	0.204	8	1.00 (0.97, 1.04)	48.1	1.000	6	0.98 (0.95, 1.02)	79.7	0.458
At least the mean	7	1.01 (0.97, 1.05)	57.9		5	1.00 (0.96, 1.05)	0.0		3	1.00 (0.93, 1.07)	0.0	
Year[3]												
<2005	4	0.99 (0.94, 1.03)	93.9	0.527	4	1.00 (0.94, 1.06)	49.5	0.806	3	0.99 (0.91, 1.06)	0.0	0.841
≥2005	15	0.99 (0.97, 1.01)	80.0		9	1.00 (0.97, 1.04)	3.4		6	0.99 (0.95, 1.03)	79.5	
Intake measurement												
Diet	9	1.00 (0.97, 1.02)	90.6	0.560	7	1.01 (0.98, 1.04)	0.0	0.132	6	0.96 (0.91, 1.00)	67.6	0.017
Blood biomarker	10	0.98 (0.96, 1.01)	73.6		6	0.97 (0.89, 1.04)	52.9		3	1.03 (0.97, 1.08)	53.0	
Adjustment for confounding factors												
Age												
Yes	16	1.00 (0.97, 1.02)	87.3	0.699	10	1.01 (0.98, 1.03)	0.0	0.173	8	0.96 (0.92, 1.00)	64.1	0.015
No	3	0.96 (0.91, 1.01)	0.0		3	0.95 (0.83, 1.06)	56.4		1	1.03 (0.97, 1.08)	—	
BMI												
Yes	6	1.00 (0.97, 1.03)	10.3	0.027	6	1.01 (0.97, 1.04)	0.0	0.647	3	0.95 (0.89, 1.01)	71.4	0.093
No	13	0.98 (0.95, 1.00)	89.0		7	1.00 (0.94, 1.05)	53.8		6	1.01 (0.97, 1.05)	67.8	
Education												
Yes	16	0.97 (0.94, 1.00)	86.5	0.006	6	1.01 (0.97, 1.04)	0.0	0.647	6	1.00 (0.96, 1.03)	61.9	0.306
No	3	1.00 (0.98, 1.03)	0.0		7	1.00 (0.94, 1.05)	53.8		3	0.97 (0.90, 1.04)	82.1	
Energy intake												
Yes	6	1.01 (0.97, 1.05)	89.4	0.689	6	1.00 (0.96, 1.05)	0.0	0.920	5	0.95 (0.90, 1.01)	52.0	0.118
No	13	0.98 (0.96, 1.01)	83.3		7	1.00 (0.97, 1.04)	52.7		4	1.01 (0.96, 1.05)	79.5	
apoE ϵ4 status												
Yes	11	0.95 (0.90, 0.99)	89.1	<0.001	5	0.96 (0.88, 1.04)	29.4	0.173	4	1.00 (0.95, 1.04)	77.0	0.647
No	8	1.00 (0.98, 1.02)	30.6		8	1.01 (0.98, 1.04)	0.0		5	0.98 (0.93, 1.03)	67.1	
Other nutrients												
Yes	6	1.01 (0.98, 1.05)	0.0	0.007	6	1.01 (0.97, 1.04)	30.2	0.777	4	1.01 (0.97, 1.05)	72.3	0.034
No	13	0.98 (0.95, 1.00)	88.8		7	1.00 (0.95, 1.05)	14.7		5	0.94 (0.88, 1.00)	60.2	
Study quality[4]												
Score ≥7	13	0.98 (0.95, 1.02)	81.5	0.467	11	0.99 (0.95, 1.04)	21.6	0.413	7	0.99 (0.95, 1.03)	72.6	0.920
Score <7	6	0.99 (0.97, 1.02)	90.7		2	1.01 (0.97, 1.05)	0.0		2	0.98 (0.90, 1.05)	71.0	

[1] *n* denotes the number of studies included. *P* values are for the heterogeneity between strata. ALA, α-linolenic acid; apoE, apolipoprotein E.
[2] Mean follow-up durations for DHA, EPA, and ALA intake were 6.5, 6.8, and 7.1 y, respectively.
[3] The year 2005 was regarded as the time threshold for recent studies (≤10 y).
[4] The quality of each study was assessed with the use of the Newcastle-Ottawa quality-assessment scale (20).

vitamin E (V_E) intake underlying the heterogeneity in RRs of mild-to-severe cognitive impairment and related diseases. Our results indicated that there were no associations between RRs affected by fish, total PUFA, or n–3 PUFA intakes with any of the study characteristics previously noted except for the significant association between the RR affected by fish intake with the publication year of studies (**Supplemental Table 4**). In the sensitivity analyses, which excluded one study from each analysis in each iteration, most of the results appeared to be robust to the influence of individual studies (**Supplemental Figures 18–20**).

DISCUSSION

In this meta-analysis, we systematically investigated associations between intakes of fish and PUFAs and mild-to-severe cognitive impairment risk. Our previous study showed that n–3 PUFA supplements could significantly improve cognitive development in infants but not in other age ranges (59), which attracted our concern for the associations in observational studies.

To reveal the role of fish and PUFA intakes, we investigated their associations with the use of a 2-step dose-response meta-analysis. First, the mild-to-severe cognitive problems were classified into MCI, cognitive decline, dementia, AD, and PD. Second, measurements were divided into diet amounts and blood biomarker concentrations. The enhancement of dietary fish consumption (a 1-serving/wk increment) significantly reduced risks of dementia (RR: 0.95; 95% CI: 0.90, 0.99) and AD (RR: 0.93; 95% CI: 0.90, 0.95). DHA intake was also inversely associated with risks of dementia (RR: 0.86; 95% CI: 0.76, 0.96) and AD (RR: 0.63; 95% CI: 0.51, 0.76). As a severe neurodegenerative disease, AD is the most prevalent and disabling cause of dementia worldwide (60). Mechanistic studies, epidemiologic analyses, and RCTs have provided insights into the positive effects of DHA in helping neurons to treat neurodegenerative diseases (61–63). However, benefits of an n–3 PUFA–rich diet

on the improvement of dementia and AD still attract wide debate. Our additional curvilinear meta-analysis revealed a significant nonlinear relation between fish consumption and AD instead of dementia. However, such a curvilinear association was not significantly observed when DHA was investigated. Overall, the current study highlighted the protective role of fishery products instead of marine n–3 PUFAs against pathologic cognitive impairment in the elderly, which was consistent with previous reports (64, 65). Meanwhile, we showed that lower RRs of MCI (0.71; 95% CI: 0.59, 0.82) and PD (0.90; 95% CI: 0.80, 0.99) were inversely associated with the increase of total PUFA intake instead of n–3 PUFA intake. Recent studies have suggested that MCI is frequent in PD even in early disease stages (66, 67). Combined with curvilinear correlation results, the increment of total PUFA intake was significantly associated with lower risk of MCI than of PD, which indicated that PUFAs may protect against early stage cognitive pathology.

To investigate residual confounding factors, we conducted related subgroup and meta-regression analyses. V_E consumption was regarded as the most influential confounding factor that contributed to the current associations. V_E has been studied in patients with MCI and AD, but both positive and negative findings were observed (68–72). Mild-to-moderate AD patients who were given V_E supplements had a slower decline than did patients who received placebos (68, 69). An additional comprehensive review provided a scientific rationale on the basis of cellular, animal, observational, and intervention studies for incorporating the combination of n–3 PUFAs and tocotrienol-rich V_E as complementary nutritional recipes for improving neurodevelopmental disorders (70). However, a negative trial reported that V_E had no benefit in patients with MCI (71). And additional RCT work showed that the long-term use of V_E supplements did not provide cognitive benefits in healthy people (72). Thus, it is still unclear whether V_E could synergize with PUFAs and protect against cognitive pathology. apoE plays an important role in the transport of cholesterol and other lipids involved in brain functionality. The percentage of apoE ϵ4 carriers is regarded as an effect modifier because the effect of n–3 PUFAs on cognitive outcomes can differ across levels of apoE carrier status. A previous study has shown a close relation between dietary n–3 PUFA and AD with consideration of the interaction with the apoE genotype (73). The mechanisms that underlie this gene-by-nutrient interaction may involve impaired transports for fatty acids and cholesterols, the altered metabolism of n–3 PUFAs, glucose, or ketones, or the modification of other risk factors (73–75). In our meta-analysis that was modulated by apoE ϵ4 status, significant changes were observed for the association between fish and DHA intakes and risk of adverse cognitive outcomes. More research is needed to explain the differential effect of n–3 PUFAs on cognitive impairment by the apoE genotype. The follow-up duration varied across a broad range (2.1–21 y) and might have influenced changes in the development of cognitive issues. Nevertheless, our meta-regression analyses showed that all of the associations between fish and n–3 PUFA intakes and risk of adverse cognitive outcomes did not change with the variation of the follow-up duration. Few studies have focused on the mechanisms in terms of the role of n–3 PUFAs on brain functions. For instance, a study mechanistically revealed that major facilitator super family domain containing 2a acts as a transporter for DHA uptake in the brain (76). Additional clinical and mechanistic investigations are needed to determine the role of PUFAs in cognitive protection.

Several strengths were highlighted in this study such as the association network built via the evaluation of mild-to-severe cognitive impairment risks, dose-response and curvilinear meta-analyses, 2-step classifications for dose-response analyses, a complete quality assessment, and large populations. Compared with previous meta-analyses in this field (14–17), the current dose-response meta-analysis covered broader classifications of PUFAs (total PUFAs, n–3 PUFAs, DHA, EPA, and ALA), and more-comprehensive adverse cognitive outcomes (MCI, general cognitive decline, dementia, AD, and PD). Besides, the current study fully considered PUFA measurements from both dietary intake (external source) and the blood biomarker (internal dose). Thus, such a comprehensive investigation might provide objective evidence-based support for the effect of PUFA on the cognitive performance and improvements. The combined use of dose-response and curvilinear analyses could provide substantial evidence of promising associations (25, 77). The positive associations appeared to be independent of confounding factors. The 2-step classifications fully considered both mild-to-severe cognitive impairments and categorical measurements. The large sample size provided sufficient statistical power to detect significance. We also performed subgroup, meta-regression, and sensitivity analyses to examine heterogeneity sources and to assess potential residual confounding.

This meta-analysis also had some limitations. Heterogeneity was high in some of the dose-response meta-analyses, but this appeared to be highly related to obvious differences in the size of effect estimates in studies rather than to a lack of association. Some associations (e.g., fish consumption and risk of PD) were not a concern because, to our knowledge, no related study has previously been reported. Some associations (e.g., dietary n–3 PUFA intake and risk of MCI) were not investigated via the meta-analysis because not enough dose-response studies were included. Some associations (e.g., dietary n–3 PUFA intake and risk of AD; Supplemental Figure 5) appeared to have a steepening tendency via the curvilinear relation estimation that was due to the limited number of dose-response observations reported in included studies. Some studies (10, 54) collected information by self-reported questionnaires that might have led to information bias, which might have weakened true associations. V_E intake appeared as the most-frequent confounding factor, and its impact was investigated during the subgroup analysis. However, few studies adjusted for other dietary factors such as other nutrients, saturated fat intake, fruit and vegetable intake, and meat consumption. Moreover, current associations may also have been related to physical activity, tobacco and alcohol use, and unique dietary practices such as vegetarianism, which were not considered in this study. In addition, most of the included studies with large populations were from Europe and North America. Thus, large-scale prospective cohort studies from Asia, Africa, and South America need to be considered in the future. Nevertheless, subgroup analyses reveal no significant differences in the direction of these associations on the basis of the geographic location.

In conclusion, current dose-response meta-analyses provide systematic evidence that higher consumption of fish and marine-derived DHA may be associated with lower risks of dementia and AD. Higher total PUFA intake may be associated with

lower risks of MCI and PD. However, total n–3 PUFAs are not inversely associated with all investigated cognitive risks. Overall, fishery products are recommended as dietary sources and are associated with lower risks of cognitive impairment. Marine-derived DHA was associated with lower risks of dementia and AD but not without a linear dose-response relation.

The authors' responsibilities were as follows—YZ, JC, JQ, and JJ: acquired, assembled, analyzed, collected, and interpreted the data; YZ, YL, and JW: performed the statistical analysis; YZ and JJ: drafted the manuscript, designed the research, and provided the final approval of the manuscript; and all authors: critically revised the manuscript for important intellectual content. None of the authors reported a conflict of interest related to the study.

REFERENCES

1. Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, Scientific Advisory Board and the Executive Committee of the Grand Challenges on Global Mental Health, Anderson W, Dhansay MA, Phillips A, et al. Grand challenges in global mental health. Nature 2011;475:27–30.
2. Karr JE, Alexander JE, Winningham RG. Omega-3 polyunsaturated fatty acids and cognition throughout the lifespan: a review. Nutr Neurosci 2011;14:216–25.
3. Féart C, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues JF, Scarmeas N, Barberger-Gateau P. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA 2009;302:638–48.
4. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martínez-González MÁ, Martínez-Lapiscina EH, Fitó M, Pérez-Heras A, Salas-Salvadó J, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern Med 2015;175:1094–103.
5. Luchtman DW, Song C. Cognitive enhancement by omega-3 fatty acids from child-hood to old age: findings from animal and clinical studies. Neuropharmacology 2013;64:550–65.
6. Huang TL. Omega-3 fatty acids, cognitive decline, and Alzheimer's disease: a critical review and evaluation of the literature. J Alzheimers Dis 2010;21:673–90.
7. Joffre C, Nadjar A, Lebbadi M, Calon F, Laye S. n-3 LCPUFA improves cognition: the young, the old and the sick. Prostaglandins Leukot Essent Fatty Acids 2014;91:1–20.
8. Albanese E, Dangour AD, Uauy R, Acosta D, Guerra M, Guerra SS, Huang Y, Jacob KS, de Rodriguez JL, Noriega LH, et al. Dietary fish and meat intake and dementia in Latin America, China, and India: a 10/66 Dementia Research Group population-based study. Am J Clin Nutr 2009;90:392–400.
9. Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, Alpérovitch A. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology 2007;69:1921–30.
10. Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM. Dietary fat intake and the risk of incident dementia in the Rotterdam study. Ann Neurol 1997;42:776–82.
11. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol 2003;60:940–6.
12. Devore EE, Grodstein F, van Rooij FJA, Hofman A, Rosner B, Stampfer MJ, Witteman JC, Breteler MM. Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. Am J Clin Nutr 2009;90:170–6.
13. Huang TL, Zandi PP, Tucker KL, Fitzpatrick AL, Kuller LH, Fried LP, Burke GL, Carlson MC. Benefits of fatty fish on dementia risk are stronger for those without APOE ϵ4. Neurology 2005;65:1409–14.
14. Lin P-Y, Chiu C-C, Huang S-Y, Su K-P. A meta-analytic review of polyunsaturated fatty acid compositions in dementia. J Clin Psychiatry 2012;73:1245–54.
15. Mazereeuw G, Lanctôt KL, Chau SA, Swardfager W, Herrmann N. Effects of ω-3 fatty acids on cognitive performance: a meta-analysis. Neurobiol Aging 2012;33:1482.e17–29.
16. Sydenham E, Dangour AD, Lim WS. Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database Syst Rev 2012;6:CD005379.
17. Wu S, Ding Y, Wu F, Li R, Hou J, Mao P. Omega-3 fatty acids intake and risks of dementia and Alzheimer's disease: a meta-analysis. Neurosci Biobehav Rev 2015;48:1–9.
18. Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. Nature 2010;464:529–35.
19. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
20. Wells GA, Shea G, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ottawa (Canada): The Ottawa Hospital Research Institute. [cited 2013 Oct 26]. The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
21. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690–1.
22. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata J 2006;6:40–57.
23. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012;175:66–73.
24. Chen H, Zhang SM, Hernán MA, Willett WC, Ascherio A. Dietary intakes of fat and risk of Parkinson's disease. Am J Epidemiol 2003;157:1007–14.
25. He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation 2004;109:2705–11.
26. Global Organization for EPA and DHA Omega-3s (GOED). Global recommendations for EPA and DHA intake [Internet]. [cited 2014 Apr 16]. GOED, Salt Lake City, UT, USA. Available from: http://www.goedomega3.com/index.php/files/download/304.
27. Jackson D, White IR, Thompson SG. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. Stat Med 2010;29:1282–97.
28. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
29. González S, Huerta JM, Fernández S, Patterson ÁM, Lasheras C. The relationship between dietary lipids and cognitive performance in an elderly population. Int J Food Sci Nutr 2010;61:217–25.
30. Kesse-Guyot E, Péneau S, Ferry M, Jeandel C, Hercberg S, Galan P, SU.VI.MAX 2 Research Group. Thirteen-year prospective study between fish consumption, long-chain n-3 fatty acids intakes and cognitive function. J Nutr Health Aging 2011;15:115–20.
31. Nurk E, Drevon CA, Refsum H, Solvoll K, Vollset SE, Nygård O, Nygaard HA, Engedal K, Tell GS, Smith AD. Cognitive performance among the elderly and dietary fish intake: the Hordaland Health Study. Am J Clin Nutr 2007;86:1470–8.
32. Roberts RO, Geda YE, Cerhan JR. Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment. Dement Geriatr Cogn Disord 2010;29:413–23.
33. Ammann EM, Pottala JV, Harris WS, Espeland MA, Wallace R, Denburg NL, Carnahan RM, Robinson JG. ω-3 fatty acids and domain-specific cognitive aging: secondary analyses of data from WHISCA. Neurology 2013;81:1484–91.
34. Beydoun MA, Kaufman JS, Sloane PD, Heiss G, Ibrahim J. n-3 Fatty acids, hypertension and risk of cognitive decline among older adults in the Atherosclerosis Risk in Communities (ARIC) study. Public Health Nutr 2008;11:17–29.
35. Cherubini A, Andres-Lacueva C, Martin A, Lauretani F, Iorio AD, Bartali B, Corsi A, Bandinelli S, Mattson MP, Ferrucci L. Low plasma N-3 fatty acids and dementia in older persons: the InCHIANTI study. J Gerontol A Biol Sci Med Sci 2007;62:1120–6.
36. Okereke OI, Rosner BA, Kim DH. Dietary fat types and 4-year cognitive change in community-dwelling older women. Ann Neurol 2012;72:124–34.
37. Solfrizzi V, Panza F, Torres F, Mastroianni F, Del Parigi A, Venezia A, Capurso A. High monounsaturated fatty acids intake protects against age-related cognitive decline. Neurology 1999;52:1563–9.
38. Velho S, Marques-Vidal P, Baptista F, Camilo ME. Dietary intake adequacy and cognitive function in free-living active elderly: a cross-sectional and short-term prospective study. Clin Nutr 2008;27:77–86.

39. Wang W, Shinto L, Connor WE, Quinn JF. Nutritional biomarkers in Alzheimer's disease: the association between carotenoids, n-3 fatty acids, and dementia severity. J Alzheimers Dis 2008;13:31–8.
40. Whalley LJ, Deary IJ, Starr JM, Wahle KW, Rance KA, Bourne VJ, Fox HC. n-3 Fatty acid erythrocyte membrane content, APOE ϵ4, and cognitive variation: an observational follow-up study in late adulthood. Am J Clin Nutr 2008;87:449–54.
41. Zhang J, Hebert JR, Muldoon MF. Dietary fat intake is associated with psychosocial and cognitive functioning of school-aged children in the United States. J Nutr 2005;135:1967–73.
42. Gao Q, Niti M, Feng L, Yap KB, Ng T-P. Omega-3 polyunsaturated fatty acid supplements and cognitive decline: Singapore Longitudinal Aging Studies. J Nutr Health Aging 2011;15:32–5.
43. Laurin D, Verreault R, Lindsay J, Dewailly É, Holub BJ. Omega-3 fatty acids and risk of cognitive impairment and dementia. J Alzheimers Dis 2003;5:315–22.
44. Beydoun MA, Kaufman JS, Satia JA, Rosamond W, Folsom AR. Plasma n-3 fatty acids and the risk of cognitive decline in older adults: the Atherosclerosis Risk in Communities Study. Am J Clin Nutr 2007; 85:1103–11.
45. de Lau LML, Bornebroek M, Witteman JCM, Hofman A, Koudstaal PJ, Breteler MMB. Dietary fatty acids and the risk of Parkinson disease: the Rotterdam Study. Neurology 2005;64:2040–5.
46. Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A, Witteman JC, Breteler MM. Diet and risk of dementia: does fat matter? The Rotterdam Study. Neurology 2002;59:1915–21.
47. Eskelinen MH, Ngandu T, Helkala E-L, Tuomilehto J, Nissinen A, Soininen H, Kivipelto M. Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study. Int J Geriatr Psychiatry 2008;23:741–7.
48. Heude B, Ducimetière P, Berr C. Cognitive decline and fatty acid composition of erythrocyte membranes—the EVA Study. Am J Clin Nutr 2003;77:803–8.
49. Kalmijn S, Feskens EJM, Launer LJ, Kromhout D. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol 1997;145:33–41.
50. Kim M, Nam JH, Oh DH, Park Y. Erythrocyte α-linolenic acid is associated with the risk for mild dementia in Korean elderly. Nutr Res 2010;30:756–61.
51. Kröger E, Verreault R, Carmichael P-H, Lindsay J, Julien P, Dewailly E, Ayotte P, Laurin D. Omega-3 fatty acids and risk of dementia: the Canadian Study of Health and Aging. Am J Clin Nutr 2009;90:184–92.
52. Laitinen MH, Ngandu T, Rovio S, Helkala EL, Uusitalo U, Viitanen M, Nissinen A, Tuomilehto J, Soininen H, Kivipelto M. Fat intake at midlife and risk of dementia and Alzheimer's disease: a population-based study. Dement Geriatr Cogn Disord 2006;22:99–107.
53. Lopez LB, Kritz-Silverstein D, Barrett-Connor E. High dietary and plasma levels of the omega-3 fatty acid docosahexaenoic acid are associated with decreased dementia risk: the Rancho Bernardo Study. J Nutr Health Aging 2011;15:25–31.
54. Miyake Y, Sasaki S, Tanaka K, Fukushima W, Kiyohara C, Tsuboi Y, Yamada T, Oeda T, Miki T, Kawamura N, et al. Dietary fat intake and risk of Parkinson's disease: a case-control study in Japan. J Neurol Sci 2010;288:117–22.
55. Roberts RO, Cerhan JR, Geda YE, Knopman DS, Cha RH, Christianson TJ, Pankratz VS, Ivnik RJ, O'Connor HM, Petersen RC. Polyunsaturated fatty acids and reduced odds of MCI: the Mayo Clinic Study of Aging. J Alzheimers Dis 2010;21:853–65.
56. Samieri C, Féart C, Letenneur L, Dartigues JF, Pérès K, Auriacombe S, Peuchant E, Delcourt C, Barberger-Gateau P. Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk. Am J Clin Nutr 2008;88:714–21.
57. Solfrizzi V, Colacicco AM, D'Introno A, Capurso C, Del Parigi A, Capurso SA, Argentieri G, Capurso A, Panza F. Dietary fatty acids intakes and rate of mild cognitive impairment. The Italian Longitudinal Study on Aging. Exp Gerontol 2006;41:619–27.
58. Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker KL, Kyle DJ, Wilson PW, Wolf PA. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. Arch Neurol 2006;63:1545–50.
59. Jiao J, Li Q, Chu J, Zeng W, Yang M, Zhu S. 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 trials. Am J Clin Nutr 2014;100:1422–36.
60. Mohajeri MH, Troesch B, Weber P. Inadequate supply of vitamins and DHA in the elderly: implications for brain aging and Alzheimer-type dementia. Nutrition 2015;31:261–75.
61. Bateman RJ, Xiong CJ, Benzinger TLS, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2012;367:795–804.
62. Bazan NG, Molina MF, Gordon WC. Docosahexaenoic acid signalolipidomics in nutrition: significance in aging, neuroinflammation, macular degeneration, Alzheimer's, and other neurodegenerative diseases. Annu Rev Nutr 2011;31:321–51.
63. Chan KY, Wang W, Wu JJ, Liu L, Theodoratou E, Car J, Middleton L, Russ TC, Deary IJ, Campbell H, et al. Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990-2010: a systematic review and analysis. Lancet 2013;381:2016–23.
64. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, Galvin JE, Emond J, Jack CR Jr., Weiner M, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA 2010;304:1903–11.
65. Bégin ME, Plourde M, Pifferi F, Cunnane SC. What is the link between docosahexaenoic acid, cognitive impairment, and Alzheimer's disease in the elderly? In: Montmayeur JP, le Coutre J, editors. Fat detection: taste, texture, and post ingestive effects. Frontiers in Neuroscience. Boca Raton (FL): CRC Press/Taylor & Francis; 2010.
66. Amboni M, Tessitore A, Esposito F, Santangelo G, Picillo M, Vitale C, Giordano A, Erro R, de Micco R, Corbo D, et al. Resting-state functional connectivity associated with mild cognitive impairment in Parkinson's disease. J Neurol 2015;262:425–34.
67. Pedersen KF, Larsen JP, Tysnes O-B, Alves G. Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. JAMA Neurol 2013;70:580–6.
68. Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, Love S, Schellenberg GD, McCarten JR, Malphurs J, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease. The TEAM-AD VA Cooperative Randomized Trial. JAMA 2014;311: 33–44.
69. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, Woodbury P, Growdon J, Cotman CW, Pfeiffer E, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997;336:1216–22.
70. Gumpricht E, Rockway S. Can ω-3 fatty acids and tocotrienol-rich vitamin E reduce symptoms of neurodevelopmental disorders? Nutrition 2014;30:733–8.
71. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005; 352:2379–88.
72. Kang JH, Cook N, Manson J, Buring JE, Grodstein F. A randomized trial of vitamin E supplementation and cognitive function in women. Arch Intern Med 2006;166:2462–8.
73. Barberger-Gateau P, Samieri C, Féart C, Plourde M. Dietary omega 3 polyunsaturated fatty acids and Alzheimer's disease: interaction with apolipoprotein E genotype. Curr Alzheimer Res 2011;8:479–91.
74. Deary IJ, Whitman MC, Pattie A, Starr JM, Hayward C, Wright AF, Carothers A, Whalley LJ. Cognitive change and the APOE ϵ4 allele. Nature 2002;418:932.
75. Raber J, Wong D, Yu G-Q, Buttini M, Mahley RW, Pitas RE, Mucke L. Apolipoprotein E and cognitive performance. Nature 2000;404:352–4.
76. Nguyen LN, Ma D, Shui G, Wong P, Cazenave-Gassiot A, Zhang X, Wenk MR, Goh EL, Silver DL. Mfsd2a is a transporter for the essential omega-3 fatty acid docosahexaenoic acid. Nature 2014; 509:503–6.
77. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135:1301–9.