A Meta-Analytic Review of Polyunsaturated Fatty Acid Compositions in Dementia

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ABSTRACT

Objective: To determine whether the levels of docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), arachidonic acid (AA), total n-3 polyunsaturated fatty acids (PUFAs), and total n-6 PUFAs were changed in patients with dementia or predementia syndrome.

Data Sources: PubMed was searched for studies from first date available to July 2011 using the following search terms: (*dementia* OR *cognitive impairment* OR *mild cognitive impairment*) AND (*omega-3* OR *omega-6* OR *polyunsaturated fatty acid* OR *docosahexaenoic acid* OR *DHA* OR *eicosapentaenoic acid* OR *EPA*). The search was limited to literature in English and to human studies. The references of relevant articles and review articles were searched for citations not indexed in PubMed.

Study Selection: Studies were included if they measured levels of EPA, DHA, AA, total n-3 PUFAs, or total n-6 PUFAs from peripheral blood tissues in subjects with cognitive deficits (dementia or predementia syndrome) and elderly controls and were published in peer-reviewed journals. The search yielded 10 articles including 2,280 subjects.

Data Extraction: The study design, sample size, PUFA levels for both patients and control subjects, sampling tissue, diagnoses and diagnostic criteria for cognitive deficits, and distribution of mean age and gender of included subjects were extracted for each study.

Results: In a random-effects model, we found that the levels of EPA (effect size [ES] = −0.47, $P < .0001$), DHA (ES = −0.33, $P = .017$), and total n-3 PUFAs (ES = −0.46, $P = .001$) were decreased in patients with dementia. However, the levels of EPA (ES = −0.44, $P = .002$), but not DHA or other PUFAs, were significantly lower in patients with predementia syndrome.

Conclusions: Our results support the important role of n-3 PUFAs in the pathophysiology of dementia. In addition, the analyses of predementia studies indicate that EPA might be not only a disease-state marker but also a risk factor for cognitive impairment.

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Dementia is a progressive, devastating, and fatal neurodegenerative disorder.[1] There are 24.3 million patients suffering from dementia, with an estimated 4.6 million increase in incidence every year throughout the world.[2] Although cognitive decline is an aging process, dementia is definitely a major clinical disorder and causes significant cognitive and memory deterioration, progressive impairment of daily living, and a variety of behavioral disturbances.[1] Predementia syndromes, including cognitive impairment with no dementia (CIND) and mild cognitive impairment (MCI), are in the continuum between age-related cognitive changes and dementia and are important risk factors for developing clinical dementia.[3,4] Dementia could be due to numerous medical conditions including vascular changes, head trauma, neurodegenerative diseases, human immunodeficiency virus infection, or Alzheimer's disease; however, the phenomenology defined by current diagnostic systems might not be distinguishable.[1] Indeed, reflecting the heterogeneity of dementia, several hypotheses have been proposed for its etiology, including genetic susceptibility, vascular risk factors, lifestyle in midlife, inflammatory process, oxidative stress, and, recently, deficiency of n-3 polyunsaturated fatty acids (PUFAs).[5–9]

Polyunsaturated fatty acids are classified into mainly omega-3 (n-3) and omega-6 (n-6) groups. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), the major bioactive components of n-3 PUFAs, are associated with neuronal membrane stability and fluidity, neurogenesis, neuroplasticity, neurotransmission, and anti-inflammation, which might all connect to the etiology of several neuropsychiatric diseases including depression and dementia.[10–15] On the other hand, arachidonic acid (AA), the major bioactive component of n-6 PUFA, is a precursor of eicosanoids with proinflammatory, vasoconstrictive, and platelet proaggregatory effects, which might also link to the pathogenesis of neuroinflammatory and neurodegenerative diseases like dementia.[16,17] Consistent with the theoretical relevance, supportive evidence linking PUFAs to dementia has been reported extensively from epidemiologic studies. For example, it has been observed that societies with a high consumption of fish, which is a good source of n-3 PUFAs, appear to have a lower prevalence of dementia[18–22] and MCI.[23] Although clinical studies until now have failed to demonstrate beneficial effects of n-3 PUFA supplementation in patients with moderate or severe Alzheimer's disease,[24,25] n-3 PUFA supplementation may benefit patients with mild Alzheimer's disease or MCI and those without the *APOE* ε4 allele.[24–26]

Abnormal fatty acid compositions in patients with dementia and predementia syndrome have been reported extensively,[27–36] while findings of the differences in individual PUFAs between patients and control groups are inconsistent. In 2000, Conquer and colleagues[35] reported that people with dementia or CIND had lower plasma levels of EPA, DHA, and total n-3 PUFAs; higher plasma levels of total n-6 PUFAs; and a lower n-3/n-6 ratio as compared with healthy elderly controls. The links between dementia and lower DHA were further

supported in other studies.[30,31,36] However, other groups did not replicate the finding of lower DHA levels in patients with dementia,[34] multi-infarct dementia,[28] or MCI,[33] but some did find lower plasma α-linolenic acid (ALA) and total n-3 PUFA levels in dementia,[34] lower serum EPA and higher AA levels in multi-infarct dementia,[28] and lower erythrocyte EPA, higher AA, and higher total n-6 PUFA levels in MCI.[33] In addition, serum DHA levels have been found to be significantly correlated to the severity of dementia.[31] However, a few studies[27,29,32] found no significant differences in levels of any n-3 or n-6 PUFAs in patients with dementia, MCI, or CIND as compared to the elderly controls.

The discrepancies among these studies may be caused by differences in the sampling process, characteristics of subjects, or selection of PUFA measurement. To test the hypothesis that the levels of n-3 PUFAs are lowered in patients with dementia or predementia, we performed a meta-analysis to examine whether individual PUFAs are changed in patients with dementia or predementia syndrome.

- Studies have shown an association between peripheral blood levels of polyunsaturated fatty acids (PUFAs) and dementia and predementia syndrome.
- Intervention with n-3 PUFAs might be beneficial for patients with dementia or predementia syndrome, but the outcomes are not consistent.
- The results of this meta-analysis suggest that patients with dementia and predementia syndrome have lower levels of n-3 PUFAs, supporting an important role of n-3 PUFAs in cognitive disorders.

Clinical Points

METHOD

Literature Search

To identify eligible studies, 3 independent investigators (P.-Y.L., C.-C.C., and K.-P.S.) searched for studies from first date available to July 2011 in the electronic databases of PubMed at the National Library of Medicine. The search was performed using the following search terms: (*dementia* OR *cognitive impairment* OR *mild cognitive impairment*) AND (*omega-3* OR *omega-6* OR *polyunsaturated fatty acid* OR *docosahexaenoic acid* OR *DHA* OR *eicosapentaenoic acid* OR *EPA*). The search was limited to literature in English and to human studies. The references of relevant articles and review articles were searched for citations not indexed in PubMed. The titles and abstracts of studies obtained by this search strategy were scrutinized by the independent investigators to determine whether the studies were potentially eligible for inclusion in this review. In cases of disagreement about eligibility, the investigators reached agreement through consensus.

Inclusion Criteria for Studies Chosen for the Meta-Analysis

The inclusion criteria for this meta-analysis were as follows: the studies (1) measured levels of EPA, DHA, AA, total n-3 PUFAs, or total n-6 PUFAs; (2) used samples from erythrocyte membrane, blood phospholipids, or cholesteryl esters; (3) included subjects with cognitive deficits (dementia or predementia syndrome) and elderly control subjects; and (4) were published in peer-reviewed journals. Studies that analyzed the same data set with overlapping subjects were not considered as independent, and we included only the study with the larger sample size among these studies. When the reports provided data from different sample tissues from the same subjects, we first used data from erythrocyte membrane, followed by blood phospholipids and then blood cholesteryl esters.

Data Extraction

The study design, sample size, PUFA levels for both patients and control subjects, sampling tissue, diagnoses and diagnostic criteria for cognitive deficits, and distribution of mean age and gender of included subjects were extracted for each study.

Meta-Analytic Methods

The primary outcomes were comparisons of EPA, DHA, AA, total n-3 PUFA, and total n-6 PUFA levels and the ratio of total n-3/total n-6 PUFA levels between patients with dementia and controls for all included studies. The secondary outcomes were comparisons of levels of these PUFA indices between patients with predementia syndrome and controls. The diagnoses of dementia and predementia syndromes were based on criteria provided in individual articles.

For each identified study, the effect size (ES) expressing the difference in PUFA levels between patients with cognitive deficits and controls was described as the standardized mean difference based on Hedges adjusted *g*, for which values greater than 0 indicated that the PUFA levels were higher in patients. The means and standard deviations of each PUFA index for both patients and controls were used to derive the ES from each included study. When these data were not available from the articles, we contacted the authors to acquire the data, or we derived the ES from other statistical parameters. One included study did not present data for age and sex for subjects with dementia and controls.[27] The data were provided upon request. The ESs for the individual studies were synthesized by the random-effects model.[37] The significance of the pooled ES was determined by the *Z* test. Sensitivity analyses were performed for any analysis that resulted in a significant difference to determine whether any individual study was responsible for the significant result. Each study was individually removed, and the significance was retested.

Heterogeneity was examined to determine whether the group of ESs came from a homogeneous source—and assessed by the *Q* statistic, the related *P* value, and the I^2

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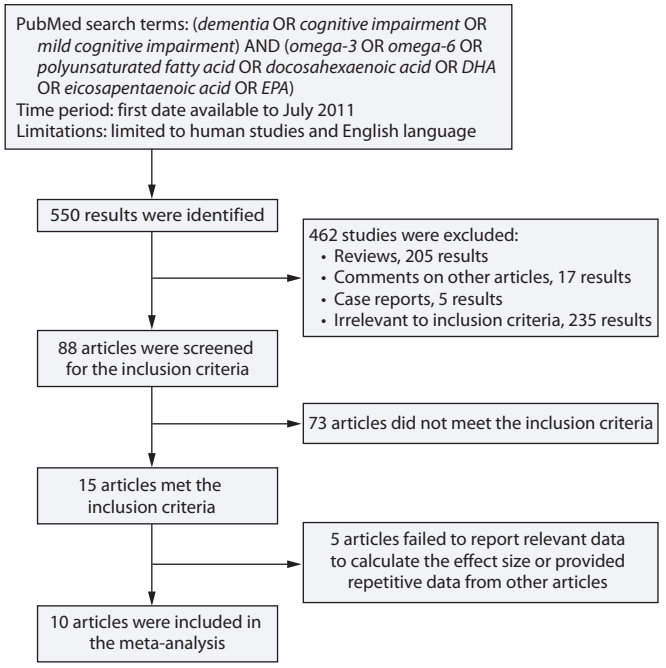
Figure 1. Flowchart of Article Search and Study Selection for the Meta-Analysis



statistic, which is the percentage of the variability in the estimate of effects that is due to heterogeneity rather than random error.[37] A larger value for the I^2 statistic indicates higher heterogeneity. A rejection of homogeneity suggests that there may be systemic differences existing among the included studies. In addition, publication bias was assessed by plotting the ES against the precision (inverse of the standard error) for each study in a funnel plot, and then the symmetry of the dots in the funnel plot was visually examined. We used the Egger regression to statistically test for evidence of publication bias.[38] To examine whether distribution of age and gender (percentage of men) of included subjects moderated the ES, we performed meta-regression by using the unrestricted maximum likelihood method.

Meta-analyses were conducted using Comprehensive Meta-Analysis software, Version 2 (Biostat, Englewood, New Jersey). Two-sided P values < .05 were considered statistically significant. We reported the methods and results of our meta-analysis by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[39]

RESULTS

Our initial computerized search identified 550 articles. Of these, 462 articles were excluded because they were irrelevant to the inclusion criteria or were not research articles. Of the remaining 88 articles, 15 met the inclusion criteria. Of these 15 articles, 5 were excluded because they analyzed the same dataset with overlapping subjects or did not present relevant data to calculate effect size. Finally, 10 articles covering 2,280 participants were included in the current meta-analysis.[27–36] The selection process is shown in Figure 1. The characteristics of the included studies are described in Table 1.

For the primary outcomes, we compared the PUFA levels between patients with dementia (n = 481) and controls (n = 1409); the data were extracted from 10 articles.[27–36] Among these articles, the study by Conquer and colleagues[35] provided data for both Alzheimer's disease and other dementias, so it was analyzed as 2 studies. Our analyses showed a significant decrease for the patient group in levels of EPA (ES = −0.47, P < .0001) (Figure 2A), DHA (ES = −0.33, P = .017) (Figure 2B), and total n-3 PUFAs (ES = −0.46, P = .001) (Figure 2C). The levels of AA (ES = 0.40, P = .157) (Figure 3A) and total n-6 PUFAs (ES = −0.29, P = .059) (Figure 3B) and the ratio of total n-3/total n-6 PUFAs (ES = −0.48, P = .069) (Figure 3C) were not significantly different for patients compared with controls. However, significant heterogeneity existed among the studies for EPA (Q_8 = 20.84, I^2 = 61.6%, P = .008), DHA (Q_8 = 32.07, I^2 = 75.1%, P < .001), AA (Q_6 = 61.78, I^2 = 90.3%, P < .001), total n-6 PUFAs (Q_5 = 20.55, I^2 = 75.7%, P = .001), and the ratio of total n-3/total n-6 PUFAs (Q_3 = 13.84, I^2 = 78.3%, P = .003), but not for total n-3 PUFAs. Sensitivity analyses showed that the significant differences in the levels of EPA, DHA, and total n-3 PUFAs were not influenced by any single study. However, in meta-regression, we found that the age factor significantly moderated the effect size (point estimate of slope = 0.08; P = .04) in the comparison of total n-6 PUFA levels. Specifically, the higher the age of the patients, the larger the differences in total n-6 PUFAs between patients with dementia and control subjects. Neither age nor gender distribution significantly influenced the effect size for comparison of other PUFA measurements.

For the secondary outcomes, we compared PUFA levels between patients with predementia syndrome (n = 363) and controls (n = 979); the data were extracted from 5 studies.[29,32–35] The levels were significantly lower in patients for EPA (ES = −0.44, P = .002) (Figure 2A), but not for DHA (ES = −0.13, P = .306) (Figure 2B), total n-3 PUFAs (ES = −0.32, P = .066) (Figure 2C), AA (ES = 0.26, P = .227) (Figure 3A), or total n-6 PUFAs (ES = 0.03, P = .871) (Figure 3B). Only 1 study (Conquer et al[35]) showed a significant decrease in the ratio of total n-3/total n-6 PUFAs in patients with predementia syndrome (ES = −1.10, P = .0002) (Figure 3C). As with the primary outcomes, the sensitivity analysis showed that the significant difference in EPA was not contributed by any single study. In addition, significant heterogeneity existed among the studies for EPA (Q_4 = 14.10, I^2 = 71.6%, P = .007), DHA (Q_4 = 10.76, I^2 = 62.8%, P = .029), AA (Q_2 = 6.67, I^2 = 70.0%, P = .036), and total n-3 PUFAs (Q_3 = 10.30, I^2 = 70.9%, P = .016), but not for total n-6 PUFAs. In meta-regression, age and gender distribution of subjects did not significantly moderate the effect sizes in secondary analysis.

Table 1. Summary of Characteristics of Studies Included in the Meta-Analysis

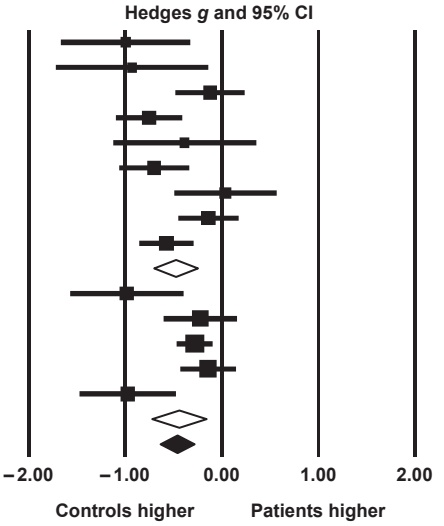
Study	Study Design	Country	Patients by Group, n	Controls, n	Diagnosis of Cognitive Deficits	Mean Age by Group, y	Male Sex by Group, %	Sampling Tissue
Conquer et al, 2000[35]	Case-control	Canada	AD, 19 OD, 10 CIND, 36	19	Dementia and OD (*DSM-IV*) AD (NINCDS-ADRDA) CIND (*DSM-IV* and neuropsychological examination)	AD, 82.7 OD, 79.4 CIND, 83.3 Controls, 77.5	AD, 32 OD, 50 CIND, 25 Controls, 37	Plasma
Laurin et al, 2003[29]	Cross-sectional	Canada	Dementia, 52 CIND, 43	79	Dementia (*DSM-IV*) AD (NINCDS-ADRDA) Vascular dementia (*ICD-10*) CIND (modified Zaudig criteria)	Dementia, 81.4 CIND, 79.2 Controls, 76.9	Dementia, 25 CIND, 40 Controls, 34	Plasma
Tully et al, 2003[31]	Case-control	Ireland	AD, 137 Vascular dementia, 11	45	AD (NINCDS-ADRDA) Mixed dementia and vascular dementia (*ICD-10*)	Dementia, 76.5 Controls, 70.0	Dementia, 20 Controls, 20	Serum
Boston et al, 2004[27]	Baseline data from open trial of ethyl-EPA	United Kingdom	AD, 22	10	AD (*ICD-10*)	AD, 81.1 Controls, 72.5	AD, 46 Controls, 50	Erythrocyte
Hirai et al, 2005[28]	Case-control	Japan	MID, 40	152	MID (Clinical evaluation, brain imaging, and cognitive tests)	MID, 69.0 Controls, 68.2	MID, 38 Controls, 50	Serum
Cherubini et al, 2007[34]	Case-control, community-dwelling	Italy	Dementia, 57 CIND, 153	725	Dementia (*DSM-III-R*) CIND (no dementia, MMSE < 23 and/or any disability related to cognitive impairment)	Dementia, 84.8 CIND, 80.6 Controls, 73.8	Dementia, 42 CIND, 29 Controls, 48	Plasma
Selley, 2007[36]	Case-control	Australia	AD, 29	26	AD (NINCDS-ADRDA and *DSM-IV*)	AD, 71.9 Controls, 71.3	AD, 52 Controls, 54	Erythrocyte
Arsenault et al, 2009[32]	Cross-sectional, observational	United States	Dementia, 62 MCI, 82	129	AD (NINCDS-ADRDA) Vascular dementia (NINDS-AIREN) OD (*DSM-IV*)	Dementia, 76.3 MCI, 72.5 Controls, 72.6	Dementia, 32 MCI, 28 Controls, 22	Plasma
Lopez et al, 2011[30]	Case-control in cohort	United States	Dementia, 42	224	AD (NINCDS-ADRDA) Dementia (clinical evaluation, brain imaging, and cognitive tests)	Dementia, 84.1 Controls, 79.5	Dementia, 50 Controls, 58	Plasma
Milte et al, 2011[33]	Baseline data from randomized placebo-controlled trial of EPA and DHA	Australia	MCI, 49	27	International Working Group on MCI	MCI, 74.1 Controls, 69.0	MCI, 67 Controls, 52	Erythrocyte

Abbreviations: AD = Alzheimer's disease, CIND = cognitive impairment nondemented, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, MCI = mild cognitive impairment, MID = multi-infarct dementia, MMSE = Mini-Mental State Examination, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association, NINDS-AIREN = National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherché et l'Enseignement en Neurosciences, OD = other dementia.

Figure 2. Forest Plots Showing Effect Sizes (Hedges *g*) and 95% CIs From Individual Studies and Pooled Results Comparing (A) Eicosapentaenoic Acid (EPA), (B) Docosahexaenoic Acid (DHA), and (C) Total n-3 Polyunsaturated Fatty Acid (PUFA) Levels Between Patients With Dementia or Predementia Syndrome and Control Subjects

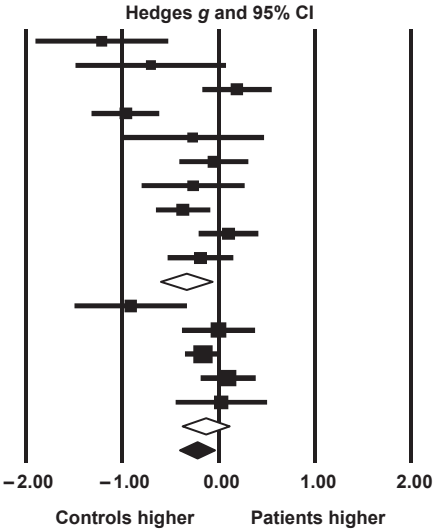
A. EPA

		Statistics			
Group	**Study**	**Hedges *g***	**95% CI**	***Z* Value**	***P* Value**
Dementia	Conquer et al, 2000[35] (AD)	–0.994	–1.656 to –0.333	–2.946	.0032
Dementia	Conquer et al, 2000[35] (OD)	–0.927	–1.709 to –0.145	–2.325	.0201
Dementia	Laurin et al, 2003[29]	–0.117	–0.465 to 0.231	–0.659	.5098
Dementia	Tully et al, 2003[31]	–0.750	–1.085 to –0.414	–4.380	.0000
Dementia	Boston et al, 2004[27]	–0.379	–1.114 to 0.355	–1.012	.3116
Dementia	Hirai et al, 2005[28]	–0.694	–1.048 to –0.341	–3.847	.0001
Dementia	Selley, 2007[36]	0.042	–0.480 to 0.564	0.158	.8748
Dementia	Arsenault et al, 2009[32]	–0.134	–0.436 to 0.168	–0.872	.3832
Dementia	Cherubini et al, 2007[34]	–0.568	–0.839 to –0.297	–4.110	.0000
Dementia pooled		**–0.467**	**–0.693** to **–0.241**	**–4.057**	**.0000**
Predementia	Conquer et al, 2000[35]	–0.981	–1.559 to –0.403	–3.328	.0009
Predementia	Laurin et al, 2003[29]	–0.219	–0.589 to 0.151	–1.158	.2468
Predementia	Cherubini et al, 2007[34]	–0.278	–0.453 to –0.103	–3.121	.0018
Predementia	Arsenault et al, 2009[32]	–0.138	–0.414 to 0.138	–0.981	.3267
Predementia	Milte et al, 2011[33]	–0.972	–1.462 to –0.482	–3.888	.0001
Predementia pooled		**–0.437**	**–0.719** to **–0.155**	**–3.041**	**.0024**
Overall		**–0.455**	**–0.631** to **–0.279**	**–5.068**	**.0000**



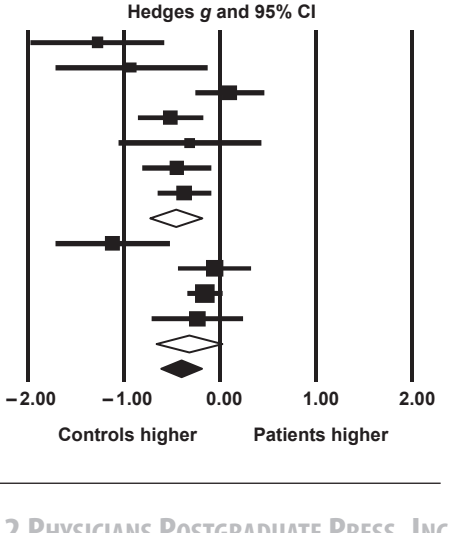
B. DHA

		Statistics			
Group	**Study**	**Hedges *g***	**95% CI**	***Z* Value**	***P* Value**
Dementia	Conquer et al, 2000[35] (AD)	–1.210	–1.889 to –0.531	–3.490	.0005
Dementia	Conquer et al, 2000[35] (OD)	–0.702	–1.468 to 0.064	–1.797	.0724
Dementia	Laurin et al, 2003[29]	0.190	–0.159 to 0.538	1.066	.2863
Dementia	Tully et al, 2003[31]	–0.962	–1.303 to –0.622	–5.542	.0000
Dementia	Boston et al, 2004[27]	–0.270	–1.001 to 0.462	–0.723	.4699
Dementia	Hirai et al, 2005[28]	–0.047	–0.394 to 0.300	–0.265	.7911
Dementia	Selley, 2007[36]	–0.263	–0.787 to 0.262	–0.982	.3261
Dementia	Cherubini et al, 2007[34]	–0.368	–0.638 to –0.098	–2.675	.0075
Dementia	Arsenault et al, 2009[32]	0.103	–0.199 to 0.404	0.666	.5052
Dementia	Lopez et al, 2011[30]	–0.185	–0.514 to 0.144	–1.105	.2693
Dementia pooled		**–0.327**	**–0.595** to **–0.058**	**–2.387**	**.0170**
Predementia	Conquer et al, 2000[35]	–0.911	–1.485 to –0.337	–3.112	.0019
Predementia	Laurin et al, 2003[29]	0.000	–0.369 to 0.369	0.000	1.0000
Predementia	Cherubini et al, 2007[34]	–0.162	–0.337 to 0.012	–1.823	.0683
Predementia	Arsenault et al, 2009[32]	0.100	–0.176 to 0.376	0.711	.4769
Predementia	Milte et al, 2011[33]	0.029	–0.436 to 0.494	0.124	.9013
Predementia pooled		**–0.128**	**–0.372** to **0.117**	**–1.023**	**.3062**
Overall		**–0.218**	**–0.398** to **–0.037**	**–2.364**	**.0181**



C. Total n-3 PUFAs

		Statistics			
Group	**Study**	**Hedges *g***	**95% CI**	***Z* Value**	***P* Value**
Dementia	Conquer et al, 2000[35] (AD)	–1.276	–1.962 to –0.591	–3.649	.0003
Dementia	Conquer et al, 2000[35] (OD)	–0.924	–1.706 to –0.143	–2.318	.0204
Dementia	Laurin et al, 2003[29]	0.100	–0.248 to 0.448	0.562	.5739
Dementia	Tully et al, 2003[31]	–0.517	–0.848 to –0.185	–3.054	.0023
Dementia	Boston et al, 2004[27]	–0.316	–1.049 to 0.417	–0.846	.3977
Dementia	Hirai et al, 2005[28]	–0.449	–0.799 to –0.100	–2.518	.0118
Dementia	Cherubini et al, 2007[34]	–0.371	–0.641 to –0.101	–2.697	.0070
Dementia pooled		**–0.455**	**–0.727** to **–0.184**	**–3.287**	**.0010**
Predementia	Conquer et al, 2000[35]	–1.119	–1.705 to –0.532	–3.740	.0002
Predementia	Laurin et al, 2003[29]	–0.058	–0.427 to 0.312	–0.306	.7595
Predementia	Cherubini et al, 2007[34]	–0.157	–0.331 to 0.017	–1.765	.0776
Predementia	Milte et al, 2011[33]	–0.236	–0.703 to 0.230	–0.993	.3205
Predementia pooled		**–0.320**	**–0.661** to **0.022**	**–1.836**	**.0663**
Overall		**–0.403**	**–0.615** to **–0.190**	**–3.715**	**.0002**

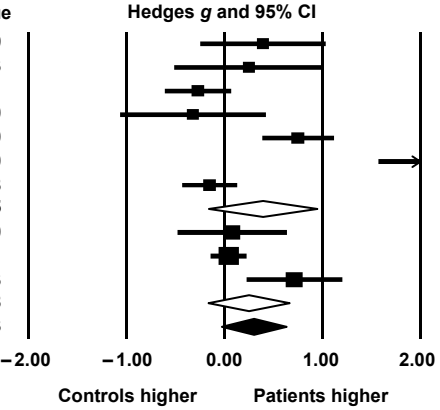


Abbreviations: AD = Alzheimer's disease, OD = other dementias.

Figure 3. Forest Plots Showing Effect Sizes (Hedges *g*) and 95% CIs From Individual Studies and Pooled Results Comparing (A) Arachidonic Acid, (B) Total n-6 Polyunsaturated Fatty Acid (PUFA), and (C) Ratio of Total n-3/Total n-6 PUFA Levels Between Patients With Dementia or Predementia Syndrome and Control Subjects

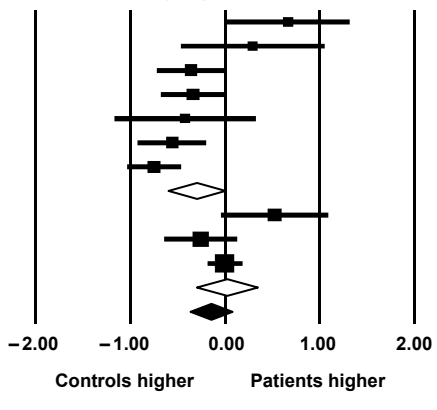
A. Arachidonic Acid

Group	Study	Statistics: Hedges *g*	95% CI	*Z* Value	*P* Value
Dementia	Conquer et al, 2000[35] (AD)	0.397	–0.232 to 1.026	1.238	.2159
Dementia	Conquer et al, 2000[35] (OD)	0.253	–0.494 to 1.000	0.663	.5073
Dementia	Tully et al, 2003[31]	–0.264	–0.593 to 0.064	–1.576	.1151
Dementia	Boston et al, 2004[27]	–0.317	–1.049 to 0.416	–0.847	.3970
Dementia	Hirai et al, 2005[28]	0.753	0.398 to 1.108	4.160	.0000
Dementia	Selley, 2007[36]	2.255	1.585 to 2.926	6.590	.0000
Dementia	Cherubini et al, 2007[34]	–0.146	–0.416 to 0.123	–1.063	.2878
Dementia pooled		**0.400**	**–0.153** to **0.953**	**1.417**	**.1565**
Predementia	Conquer et al, 2000[35]	0.085	–0.463 to 0.633	0.303	.7620
Predementia	Cherubini et al, 2007[34]	0.049	–0.125 to 0.223	0.553	.5801
Predementia	Milte et al, 2011[33]	0.718	0.239 to 1.197	2.940	.0033
Predementia pooled		**0.255**	**–0.158** to **0.668**	**1.209**	**.2268**
Overall		**0.307**	**–0.024** to **0.637**	**1.816**	**.0693**



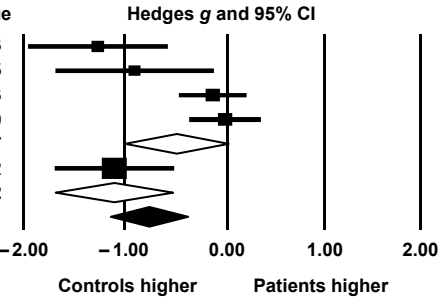
B. Total n-6 PUFAs

Group	Study	Statistics: Hedges *g*	95% CI	*Z* Value	*P* Value
Dementia	Conquer et al, 2000[35] (AD)	0.665	0.025 to 1.305	2.035	.0418
Dementia	Conquer et al, 2000[35] (OD)	0.293	–0.455 to 1.041	0.768	.4426
Dementia	Laurin et al, 2003[29]	–0.360	–0.710 to –0.009	–2.010	.0445
Dementia	Tully et al, 2003[31]	–0.337	–0.666 to –0.007	–2.002	.0452
Dementia	Boston et al, 2004[27]	–0.419	–1.155 to 0.316	–1.117	.2640
Dementia	Hirai et al, 2005[28]	–0.559	–0.910 to –0.207	–3.116	.0018
Dementia	Cherubini et al, 2007[34]	–0.748	–1.019 to –0.476	–5.389	.0000
Dementia pooled		**–0.292**	**–0.596** to **0.011**	**–1.891**	**.0586**
Predementia	Conquer et al, 2000[35]	0.523	–0.034 to 1.080	1.842	.0655
Predementia	Laurin et al, 2003[29]	–0.257	–0.627 to 0.114	–1.358	.1743
Predementia	Cherubini et al, 2007[34]	–0.001	–0.175 to 0.173	–0.012	.9905
Predementia pooled		**0.027**	**–0.296** to **0.350**	**0.163**	**.8708**
Overall		**–0.143**	**–0.364** to **0.078**	**–1.267**	**.2050**



C. Ratio of Total n-3/Total n-6 PUFAs

Group	Study	Statistics: Hedges *g*	95% CI	*Z* Value	*P* Value
Dementia	Conquer et al, 2000[35] (AD)	–1.265	–1.950 to –0.581	–3.623	.0003
Dementia	Conquer et al, 2000[35] (OD)	–0.901	–1.681 to –0.122	–2.266	.0235
Dementia	Tully et al, 2003[31]	–0.121	–0.449 to 0.207	–0.725	.4683
Dementia	Hirai et al, 2005[28]	0.000	–0.347 to 0.347	0.000	.0000
Dementia pooled		**–0.479**	**–0.994** to **0.037**	**–1.820**	**.0687**
Predementia	Conquer et al, 2000[35]	–1.101	–1.686 to –0.516	–3.688	.0002
Predementia pooled		**–1.101**	**–1.686** to **–0.516**	**–3.688**	**.0002**
Overall		**–0.750**	**–1.137** to **–0.364**	**–3.803**	**.0001**



Abbreviations: AD = Alzheimer's disease, OD = other dementias.

Finally, when we pooled patients with dementia and predementia syndrome together, the levels were significantly lower in patients for EPA (ES = –0.46, $P < .0001$) (Figure 2A), DHA (ES = –0.22, $P = .018$) (Figure 2B), total n-3 PUFAs (ES = –0.40, $P = .0002$) (Figure 2C), and ratio of total n-3/total n-6 PUFAs (ES = –0.75, $P = .0001$) (Figure 3C), but not for AA (ES = 0.31, $P = .069$) (Figure 3A) or total n-6 PUFAs (ES = –0.14, $P = .205$) (Figure 3B). The heterogeneity tests did not reach significant levels for meta-analysis of any of these PUFAs (data not shown). Also, no publication bias was detected for meta-analysis of any of these PUFAs (see funnel plots in Figure 4), evidenced by linear regression analysis (EPA, $P = .108$; DHA, $P = .205$; total n-3 PUFAs, $P = .052$; AA, $P = .207$; and total n-6 PUFAs, $P = .690$), except for the ratio of total n-3/total n-6 PUFAs ($P = .026$).

DISCUSSION

To our knowledge, this meta-analysis is the first to demonstrate PUFA abnormalities in dementia. The main finding

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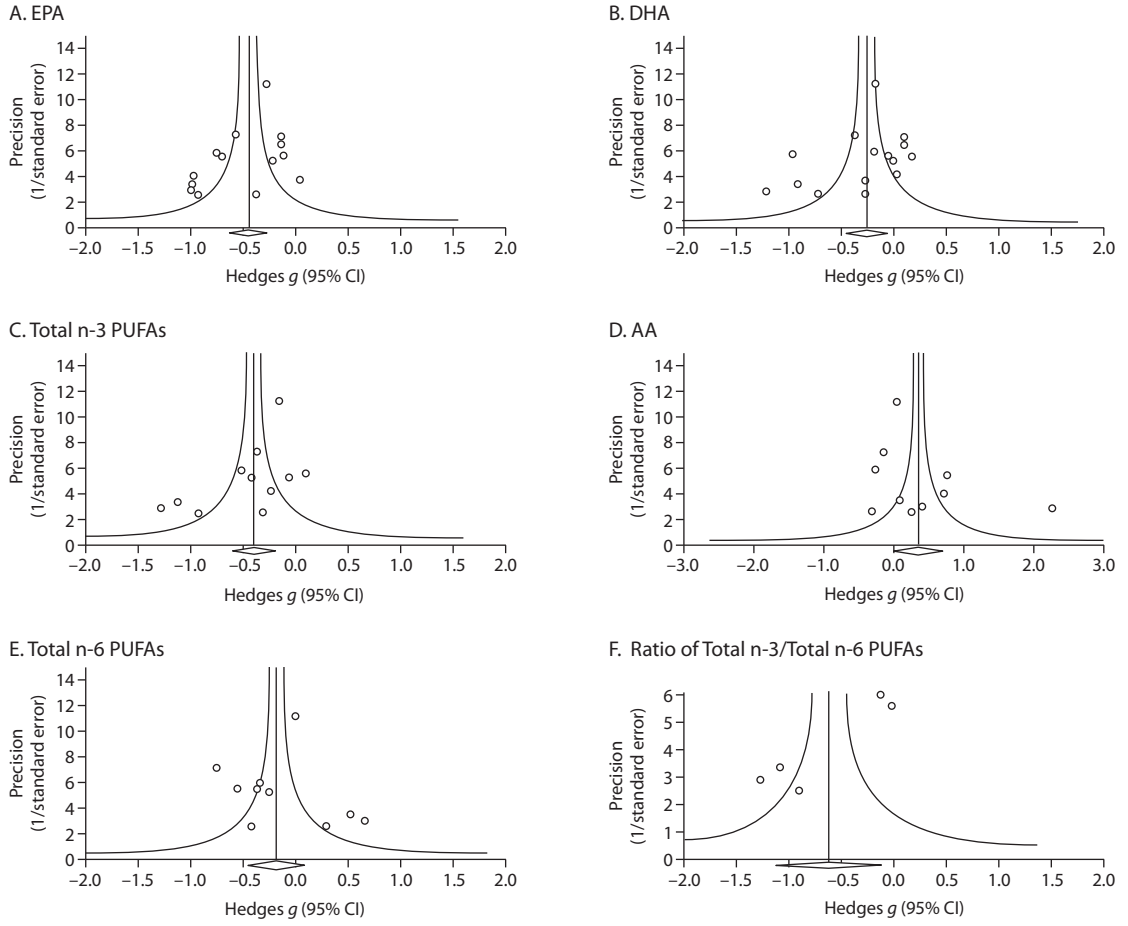
Figure 4. Funnel Plots (effect sizes [Hedges *g*] of studies vs their precision [inverse of standard error]) Examining Publication Bias in Studies Comparing (A) Eicosapentaenoic Acid (EPA), (B) Docosahexaenoic Acid (DHA), (C) Total n-3 Polyunsaturated Fatty Acid (PUFA), (D) Arachidonic Acid (AA), (E) Total n-6 PUFA, and (F) Ratio of Total n-3/Total n-6 PUFA Levels Between Patients With Dementia or Predementia Syndrome and Control Subjects[a]



[a]The diamonds represent 95% CIs of pooled effect sizes in each meta-analysis.

of this meta-analysis confirms that dementia is associated with lower levels of total n-3 PUFAs and both major types of n-3 PUFAs, EPA and DHA. In spite of some negative findings,[27,29,32,40,41] several studies have revealed that patients with dementia had n-3 PUFA deficit in blood,[28,30,31,34–36] liver,[42] and brain tissues.[42,43] In addition, a negative association between intake of fish or n-3 PUFAs and the risk of dementia or Alzheimer's disease has been shown in epidemiologic observations.[19–22] Furthermore, placebo-controlled clinical trials seem to support n-3 PUFA supplementation as beneficial for cognitive function in subjects with MCI or mild dementia[24,26,44] but not in subjects with moderate or severe dementia.[24,25] Our results extend the findings of these clinical observational and interventional studies that n-3 PUFA deficits play an important role in the risk of dementia.

Theories have been hypothesized about the mechanisms of n-3 PUFA deficits in dementia. First, n-3 PUFA supplementation may decrease amyloid-β deposition (a theory supported by some animal models[45,46]), thus reducing the consequences of amyloid-β deposition, such as oxidation and lipid peroxidation, glutamatergic excitotoxicity, inflammation, and activation of biochemical cascades underlying apoptotic cell death.[1] Second, the association may result from the microvascular protective effects of n-3 PUFAs.[47–49] EPA or DHA may exert antithrombotic properties via inhibition of platelet aggregation and further increased blood flow and supply of nutrients, as well as increased removal of toxic metabolites and proteins from the brain.[50] Third, n-3 PUFAs are anti-inflammatory by way of inhibiting production of AA-derived proinflammatory eicosanoids.[51] For example, a new family of EPA- and DHA-derived lipid mediators, resolvins, has been reported to have potent anti-inflammatory and inflammation-resolving properties.[52]

The second main finding of this meta-analysis is that subjects with predementia syndrome had significantly lower levels of EPA, but not DHA or total n-3 PUFAs. Selectively lower levels of EPA, rather than DHA, in predementia patients may have a specific biological meaning. Specifically, DHA is a major structural component of phospholipids in neuronal cell membranes, while EPA is present in a very small amount in neuronal cell membranes.[53] It

has been proposed that DHA is the important n-3 PUFA in brain functioning.[14,15,54,55] In subjects with predementia syndrome, the cognitive impairment is not as severe as in dementia. Therefore, the deficit of DHA might not be profound enough to be detectable. EPA, on the other hand, is important in balancing inflammatory and microcirculatory dysfunctionings,[51,56] which are all risk factors contributing to dementia.[51,57,58] Interestingly, our meta-analysis was able to demonstrate that EPA is already lower in predementia syndrome, supporting the concept that low EPA might act as a risk factor for development of dementia.

Previous work examining DHA and EPA treatment of major depression has found mixed results with regard to whether the ratio of total n-3/total n-6 PUFAs may be associated with antidepressant response.[59,60] A lower ratio of total n-3/total n-6 PUFAs has also been found to be associated with risk of dementia.[6] In addition, a specific total n-3/total n-6 PUFA ratio has been suggested to be the most effective in learning performance.[61] Although the ratio of total n-3/total n-6 PUFAs was significantly lower in patients when we pooled dementia and predementia syndrome studies together in our meta-analysis, the role of total n-3/total n-6 PUFA ratio in dementia needs more investigation considering that only 3 studies[28,31,35] in our analysis reported the ratio of total n-3/total n-6 PUFAs. Higher AA and n-6 PUFA levels have been reported to be associated with cognitive decline,[62,63] cognitive impairment,[35] and dementia.[35] However, this meta-analysis did not detect any significant difference in levels of AA or n-6 PUFAs. Considering that the relationship between blood levels (erythrocyte or plasma) and brain levels is less correlated for AA and n-6 PUFAs than for n-3 PUFAs,[64,65] the negative findings from this present meta-analysis should be interpreted with caution.

There are some limitations. First, the diagnoses and definitions for dementia and predementia syndrome for this meta-analysis were different across pooled studies. Dementia is heterogeneous. Individuals with clinical or subclinical cognitive impairments could have distinguishable phenotypes and etiologies. However, the 10 articles meeting our study criteria for the current meta-analysis either did not provide or provided insufficient subtyping information for predementia and dementia. There would be a significant loss of statistical power to carry out our meta-analysis by stratifying subtypes of dementia. Although we applied more conservative approaches (ie, a random-effects model) for the analyses, one should still interpret the results with consideration of the heterogeneity of studies. Second, PUFA levels from the pooled studies were not directly from central nervous system tissues; hence, these results could not be applied to brain PUFA levels. Nonetheless, n-3 PUFA levels from peripheral blood tissues of red blood cells and plasma might strongly reflect brain levels of n-3 PUFAs in mammals.[64–67] For example, in a study[64] that gave piglets assigned diets and measured PUFA levels in tissues from blood plasma, erythrocytes, liver, muscle, adipose tissue, retina, and brain, the levels of EPA and DHA in both plasma and erythrocytes were highly correlated to the levels in brain tissue. Specifically, the coefficients (r) of EPA and DHA in plasma in correlation with brain tissue were 0.78 ($P<.001$) and 0.80 ($P<.001$), respectively. Meanwhile, the r values of EPA and DHA in erythrocyte in correlation with brain tissue were 0.78 ($P<.001$) and 0.80 ($P<.001$), respectively.[64] Although data from human subjects are not yet available, similar findings of high brain-plasma-erythrocyte correlations of EPA and DHA have been reported in rhesus monkeys[65] and rats.[67] Third, we combined the different blood measurements for fatty acid levels together. Although the levels of n-3 and n-6 PUFA levels are highly correlated in peripheral blood plasma and erythrocyte, the reliability of combining plasma and erythrocyte levels of PUFAs is uncertain. In this study and in our previous meta-analytic review of PUFA compositions in depression,[15] we expect that the use of "percentage" (individual PUFAs from the obtained tissues) as the unit of measure might have offered better reliability in combining PUFA concentration for data analysis.[67] Fourth, only 10 articles met study criteria from a total of 88 relevant articles in the literature. The results from the current meta-analysis should be interpreted with caution regarding its representability. Finally, as with all retrospective case-control studies, the association that was found does not necessarily mean that lower n-3 PUFA levels are involved in the predisposition to cognitive impairment. For instance, it is possible that lower EPA levels in patients with dementia and predementia syndromes reflect an effect of the disease on dietary intake. Therapeutic trials to study the symptomatic and presymptomatic stages of the disorder are needed to clarify this issue further.

Our current analysis might have important clinical implications. Patients with dementia have lower levels of total n-3 PUFAs, EPA, and DHA—findings that support an important role of n-3 PUFAs in dementia. Since only EPA is lower in patients with predementia, EPA might be a potential biomarker and a candidate preventive treatment for populations at risk for dementia. Further investigations are highly recommended for the possible use of n-3 PUFAs in subtyping predementia and dementia and for determining the biological mechanisms of the effects of EPA or DHA in human and animal models with dementia or predementia syndrome.

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Author contributions: Drs Lin and Chiu contributed equally as first authors of this study.

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REFERENCES

1. Cummings JL. Alzheimer's disease. *N Engl J Med*. 2004;351(1):56–67.
2. Ferri CP, Prince M, Brayne C, et al; Alzheimer's Disease International. Global prevalence of dementia: a Delphi consensus study. *Lancet*. 2005; 366(9503):2112–2117.
3. O'Brien JT. Mild cognitive impairment. In: Jacoby R, Oppenheimer C, Dening T, et al, eds. *Oxford Textbook of Old Age Psychiatry*. 3rd ed. New York, NY: Oxford University Press; 2008:407–415.
4. Bruscoli M, Lovestone S. Is MCI really just early dementia? a systematic review of conversion studies. *Int Psychogeriatr*. 2004;16(2):129–140.
5. Fratiglioni L, Strauss E, Qiu C. Epidemiology of the dementia of old age. In: Jacoby R, Oppenheimer C, Dening T, et al, eds. *Oxford Textbook of Old Age Psychiatry*. 3rd ed. New York, NY: Oxford University Press; 2008: 391–406.
6. Samieri C, Féart C, Letenneur L, et al. Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk. *Am J Clin Nutr*. 2008;88(3):714–721.
7. Cole GM, Frautschy SA. DHA may prevent age-related dementia. *J Nutr*. 2010;140(4):869–874.
8. Mucke L, Pitas RE. Food for thought: essential fatty acid protects against neuronal deficits in transgenic mouse model of AD. *Neuron*. 2004;43(5): 596–599.
9. Gomez-Pinilla F. The influences of diet and exercise on mental health through hormesis. *Ageing Res Rev*. 2008;7(1):49–62.
10. Horrobin DF, Bennett CN. Depression and bipolar disorder: relationships to impaired fatty acid and phospholipid metabolism and to diabetes, cardiovascular disease, immunological abnormalities, cancer, ageing and osteoporosis: possible candidate genes. *Prostaglandins Leukot Essent Fatty Acids*. 1999;60(4):217–234.
11. Su KP, Shen WW, Huang SY. Effects of polyunsaturated fatty acids on psychiatric disorders. *Am J Clin Nutr*. 2000;72(5):1241.
12. Chalon S. Omega-3 fatty acids and monoamine neurotransmission. *Prostaglandins Leukot Essent Fatty Acids*. 2006;75(4–5):259–269.
13. Lukiw WJ, Bazan NG. Survival signalling in Alzheimer's disease. *Biochem Soc Trans*. 2006;34(pt 6):1277–1282.
14. Su KP. Biological mechanism of antidepressant effect of omega-3 fatty acids: how does fish oil act as a "mind-body interface"? *Neurosignals*. 2009;17(2):144–152.
15. Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biol Psychiatry*. 2010;68(2):140–147.
16. Sanchez-Mejia RO, Mucke L. Phospholipase A2 and arachidonic acid in Alzheimer's disease. *Biochim Biophys Acta*. 2010;1801(8):784–790.
17. Lukiw WJ, Bazan NG. Inflammatory, apoptotic, and survival gene signaling in Alzheimer's disease: a review on the bioactivity of neuroprotectin D1 and apoptosis. *Mol Neurobiol*. 2010;42(1):10–16.
18. Kalmijn S, Launer LJ, Ott A, et al. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. *Ann Neurol*. 1997;42(5): 776–782.
19. Barberger-Gateau P, Letenneur L, Deschamps V, et al. Fish, meat, and risk of dementia: cohort study. *BMJ*. 2002;325(7370):932–933.
20. Barberger-Gateau P, Raffaitin C, Letenneur L, et al. Dietary patterns and risk of dementia: the Three-City cohort study. *Neurology*. 2007;69(20): 1921–1930.
21. Morris MC, Evans DA, Bienias JL, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol*. 2003; 60(7):940–946.
22. Huang TL, Zandi PP, Tucker KL, et al. Benefits of fatty fish on dementia risk are stronger for those without *APOE* ε4. *Neurology*. 2005;65(9): 1409–1414.
23. Roberts RO, Cerhan JR, Geda YE, et al. Polyunsaturated fatty acids and reduced odds of MCI: the Mayo Clinic Study of Aging. *J Alzheimers Dis*. 2010;21(3):853–865.
24. Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study, a randomized double-blind trial. *Arch Neurol*. 2006;63(10):1402–1408.
25. Quinn JF, Raman R, Thomas RG, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. *JAMA*. 2010;304(17):1903–1911.
26. Chiu CC, Su KP, Cheng TC, et al. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(6):1538–1544.
27. Boston PF, Bennett A, Horrobin DF, et al. Ethyl-EPA in Alzheimer's disease: a pilot study. *Prostaglandins Leukot Essent Fatty Acids*. 2004;71(5):341–346.
28. Hirai K, Kozuki M, Miyanaga K, et al. Lower levels of eicosapentaenoic acid and the ratio of docosahexaenoic acid to arachidonic acid in sera of patients with multi-infarct dementia. *J Clin Biochem Nutr*. 2005; 36(3):83–89.
29. Laurin D, Verreault R, Lindsay J, et al. Omega-3 fatty acids and risk of cognitive impairment and dementia. *J Alzheimers Dis*. 2003;5(4): 315–322.
30. 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(1):25–31.
31. Tully AM, Roche HM, Doyle R, et al. Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: a case-control study. *Br J Nutr*. 2003;89(4):483–489.
32. Arsenault LN, Matthan N, Scott TM, et al. Validity of estimated dietary eicosapentaenoic acid and docosahexaenoic acid intakes determined by interviewer-administered food frequency questionnaire among older adults with mild-to-moderate cognitive impairment or dementia. *Am J Epidemiol*. 2009;170(1):95–103.
33. Milte CM, Sinn N, Street SJ, et al. Erythrocyte polyunsaturated fatty acid status, memory, cognition and mood in older adults with mild cognitive impairment and healthy controls. *Prostaglandins Leukot Essent Fatty Acids*. 2011;84(5–6):153–161.
34. Cherubini A, Andres-Lacueva C, Martin A, et al. Low plasma N-3 fatty acids and dementia in older persons: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci*. 2007;62(10):1120–1126.
35. Conquer JA, Tierney MC, Zecevic J, et al. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. *Lipids*. 2000;35(12):1305–1312.
36. Selley ML. A metabolic link between *S*-adenosylhomocysteine and polyunsaturated fatty acid metabolism in Alzheimer's disease. *Neurobiol Aging*. 2007;28(12):1834–1839.
37. Shadish WR, Haddock CK. Combining estimates of effect size. In: Cooper H, Hedges LV, eds. *The Handbook of Research Synthesis*. New York, NY: Russell Sage Foundation; 1994:261–281.
38. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.
39. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1–e34.
40. Skinner ER, Watt C, Besson JA, et al. Differences in the fatty acid composition of the grey and white matter of different regions of the brains of patients with Alzheimer's disease and control subjects. *Brain*. 1993;116(pt 3):717–725.
41. Fraser T, Tayler H, Love S. Fatty acid composition of frontal, temporal and parietal neocortex in the normal human brain and in Alzheimer's disease. *Neurochem Res*. 2010;35(3):503–513.
42. Astarita G, Jung KM, Berchtold NC, et al. Deficient liver biosynthesis of docosahexaenoic acid correlates with cognitive impairment in Alzheimer's disease. *PLoS ONE*. 2010;5(9):e12538.
43. Corrigan FM, Horrobin DF, Skinner ER, et al. Abnormal content of n-6 and n-3 long-chain unsaturated fatty acids in the phosphoglycerides and cholesterol esters of parahippocampal cortex from Alzheimer's disease patients and its relationship to acetyl CoA content. *Int J Biochem Cell Biol*. 1998;30(2):197–207.
44. Kotani S, Sakaguchi E, Warashina S, et al. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. *Neurosci Res*. 2006;56(2):159–164.
45. Hashimoto M, Hossain S, Agdul H, et al. Docosahexaenoic acid–induced amelioration on impairment of memory learning in amyloid β–infused rats relates to the decreases of amyloid β and cholesterol levels in detergent-insoluble membrane fractions. *Biochim Biophys Acta*. 2005;1738:91–98.
46. Green KN, Martinez-Coria H, Khashwji H, et al. Dietary docosahexaenoic acid and docosapentaenoic acid ameliorate amyloid-β

and tau pathology via a mechanism involving presenilin 1 levels. *J Neurosci*. 2007;27(16):4385–4395.
47. He K, Song Y, Daviglus ML, et al. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. *Stroke*. 2004;35(7):1538–1542.
48. Lavie CJ, Milani RV, Mehra MR, et al. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. *J Am Coll Cardiol*. 2009;54(7): 585–594.
49. Chang JP, Chen YT, Su KP. Omega-3 polyunsaturated fatty acids (n-3 PUFAs) in cardiovascular diseases (CVDs) and depression: the missing link? *Cardiovasc Psychiatry Neurol*. 2009;2009:725310.
50. Jicha GA, Markesbery WR. Omega-3 fatty acids: potential role in the management of early Alzheimer's disease. *Clin Interv Aging*. 2010;5: 45–61.
51. Calder PC. Polyunsaturated fatty acids and inflammatory processes: new twists in an old tale. *Biochimie*. 2009;91(6):791–795.
52. Seki H, Tani Y, Arita M. Omega-3 PUFA derived anti-inflammatory lipid mediator resolvin E1. *Prostaglandins Other Lipid Mediat*. 2009; 89(3–4):126–130.
53. Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. *J Am Coll Nutr*. 2009;28(5):525–542.
54. Peet M, Stokes C. Omega-3 fatty acids in the treatment of psychiatric disorders. *Drugs*. 2005;65(8):1051–1059.
55. Bazan NG. Cell survival matters: docosahexaenoic acid signaling, neuroprotection and photoreceptors. *Trends Neurosci*. 2006;29(5): 263–271.
56. Sijben JW, Calder PC. Differential immunomodulation with long-chain n-3 PUFA in health and chronic disease. *Proc Nutr Soc*. 2007;66(2): 237–259.
57. Bazan NG, Colangelo V, Lukiw WJ. Prostaglandins and other lipid mediators in Alzheimer's disease. *Prostaglandins Other Lipid Mediat*. 2002;68–69:197–210.
58. Fotuhi M, Mohassel P, Yaffe K. Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association. *Nat Clin Pract Neurol*. 2009;5(3):140–152.
59. Mischoulon D, Best-Popescu C, Laposata M, et al. A double-blind dose-finding pilot study of docosahexaenoic acid (DHA) for major depressive disorder. *Eur Neuropsychopharmacol*. 2008;18(9):639–645.
60. Mischoulon D, Papakostas GI, Dording CM, et al. A double-blind, randomized controlled trial of ethyl-eicosapentaenoate for major depressive disorder. *J Clin Psychiatry*. 2009;70(12):1636–1644.
61. Yehuda S, Rabinovitz S, Carasso RL, et al. The role of polyunsaturated fatty acids in restoring the aging neuronal membrane. *Neurobiol Aging*. 2002;23(5):843–853.
62. Beydoun MA, Kaufman JS, Satia JA, et al. 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(4):1103–1111.
63. Heude B, Ducimetière P, Berr C; EVA Study. Cognitive decline and fatty acid composition of erythrocyte membranes: the EVA Study. *Am J Clin Nutr*. 2003;77(4):803–808.
64. Lapillonne A, DeMar JC, Nannegari V, et al. The fatty acid profile of buccal cheek cell phospholipids is a noninvasive marker of long-chain polyunsaturated fatty acid status in piglets. *J Nutr*. 2002;132(8): 2319–2323.
65. Connor WE, Neuringer M, Lin DS. Dietary effects on brain fatty acid composition: the reversibility of n-3 fatty acid deficiency and turnover of docosahexaenoic acid in the brain, erythrocytes, and plasma of rhesus monkeys. *J Lipid Res*. 1990;31(2):237–247.
66. Makrides M, Neumann MA, Byard RW, et al. Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. *Am J Clin Nutr*. 1994;60(2):189–194.
67. Stark KD. The percentage of n-3 highly unsaturated fatty acids in total HUFA as a biomarker for omega-3 fatty acid status in tissues. *Lipids*. 2008;43(1):45–53.

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