Review

Omega-3 fatty acids intake and risks of dementia and Alzheimer's disease: A meta-analysis

Shunquan Wu, Yingying Ding, Fuquan Wu, Ruisheng Li, Jun Hou, Panyong Mao

A R T I C L E   I N F O

Article history:
Received 18 August 2014
Received in revised form 14 October 2014
Accepted 13 November 2014
Available online 21 November 2014

Keywords:
Omega-3 fatty acids
Dementia
Alzheimer's disease

A B S T R A C T

Background: We systematically reviewed the association of omega-3 fatty acids intake with the incidence of dementia and Alzheimer's disease (AD) in this meta-analysis of prospective cohort studies, as evidence from previous studies suggests inconsistent results.

Methods: We identified relevant studies by searching PubMed, Embase, and Web of Science databases up to June 2013. Prospective cohort studies reporting on associations of dietary intake of long-chain omega-3 fatty acids or fish with the incidence of dementia and AD were eligible.

Results: Comparing the highest to lowest category of long-chain omega-3 fatty acids intake and fish intake, the pooled relative risks (RRs) for dementia were 0.97 (95% CI 0.85–1.10) and 0.84 (95% CI 0.71–1.01), respectively. Evidence synthesis for AD risk did not show a statistically significant association with long-chain omega-3 fatty acids intake (RR = 0.89, 95% CI 0.74–1.08). However, a higher intake of fish was associated with a 36% (95% CI 8–56%) lower risk of AD. Dose–response meta-analysis showed that an increment of 100 g per week of fish intake was associated with an 11% lower risk of AD (RR = 0.89, 95% CI 0.79–0.99). There was limited evidence of heterogeneity across studies or within subgroups.

Conclusion: A higher intake of fish was associated with a lower risk of AD. However, there was no statistical evidence for similar inverse association between long-chain omega-3 fatty acids intake and risk of dementia or AD, nor was there inverse association between fish intake and risk of dementia.

© 2014 Elsevier Ltd. All rights reserved.

Contents

1. Introduction .............................................................. 2
2. Methods ........................................................................ 2
   2.1. Study selection .......................................................... 2
   2.2. Study quality evaluation .............................................. 2
   2.3. Statistical analysis and data synthesis ......................... 2
3. Results ........................................................................ 3
   3.1. Search results .......................................................... 3
   3.2. Meta-analysis: dietary intake of omega-3 fatty acids and risk of dementia ........................................... 3
   3.3. Meta-analysis: dietary intake of omega-3 fatty acids and risk of AD .................................................. 3
   3.4. Dose–response meta-analysis ...................................... 5

* Corresponding author at: Research and Technology Service Center, 302 Hospital of PLA, No. 100 of West Fourth Ring Middle Road, Beijing 100039, China.
Tel.: +86 10 63879156; fax: +86 10 63879156.
E-mail addresses: houj302@163.com (J. Hou), maopy302@163.com (P. Mao).

** Corresponding author at: Research and Technology Service Center, 302 Hospital of PLA, No. 100 of West Fourth Ring Middle Road, Beijing 100039, China.
Tel.: +86 10 88240980; fax: +86 10 88240980.

http://dx.doi.org/10.1016/j.neubiorev.2014.11.008
0149-7634/© 2014 Elsevier Ltd. All rights reserved.
1. Introduction

Alzheimer’s disease (AD), accounting for more than 70% of all cases of dementia, is the most dreaded disease and the fifth leading cause of death in persons aged 65 and older (Brookmeyer et al., 1998; Alzheimer’s Association, 2008). The role of nutrition in prevention of dementia and AD arises increasing hope with particular interest in dietary intake of omega-3 fatty acids, for brain tissue membranes are rich in omega-3 fatty acids, including docosahexaenoic acid (DHA) (Youdin et al., 2000). Eicosapentaenoic acid (EPA) also plays a protective role for nervous system (Kou et al., 2008). Experimental evidence indicates that a DHA-enriched diet can protect the brain from cognitive decline and reduce neurodegenerative pathology in aged rats (Calon and Cole, 2007; Lim and Suzuki, 2000). However, evidence from observational and epidemiological studies suggests an inconsistent relationship between dietary intake of omega-3 fatty acids and risk of dementia and AD. Some human studies suggest that higher intakes of omega-3 fatty acids from dietary sources are related to reduced risk of dementia and AD (Barberger-Gateau et al., 2002; Morris et al., 2003), while other studies failed to find this association (Schaefer et al., 2006; Engelhart et al., 2002).

Given the inconsistency in the literature on the role of omega-3 fatty acids and risk of dementia and AD, we conducted a meta-analysis to review current evidence on the associations of dietary intake of long-chain omega-3 fatty acids or fish (an important source of omega-3 fatty acids) and the incidence of dementia and AD. We restricted the meta-analysis to prospective cohort studies, because case-control studies may be biased by recall of past dietary habits after disease has been diagnosed, especially for patients with dementia or AD, and heterogeneity between study results may be assumed to be smaller by focusing on one study design.

2. Methods

We followed the guidelines published by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group to complete the meta-analysis (Stroup et al., 2000) (see Table S1). Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2014.11.008.

2.1. Study selection

Prospective cohort studies on dementia and AD that included data on the exposure to “omega-3 fatty acids” or “fish” were considered eligible for meta-analysis. A systematic literature search of PubMed, Embase, and Web of Science for identification of articles published between 1965 and June 2013 was performed by two investigators (Wu and Ding). No language restriction was imposed. In addition, we also manually reviewed the references of all retrieved articles and recent reviews to identify relevant studies.

The eligible studies should meet the following inclusion criteria: (1) use of prospective cohort design; (2) examination of dietary intake of omega-3 fatty acids or fish as the variable of interest; (3) determination of incidence of dementia or AD as the outcome of interest; (4) at least one year of follow-up and involved general populations or people at high risk of dementia or AD (e.g. the elderly); and (5) reporting the relative risks (RRs) of dementia or AD calculated according to the highest category with the lowest category of dietary intake of omega-3 fatty acids or fish, and their 95% confidence intervals (CIs). The studies about animal experiment, review research and mechanistic research were excluded.

2.2. Study quality evaluation

The quality of each study was assessed by two investigators (Wu and Mao), using the Newcastle-Ottawa Scale (Wells et al., 2000). This scale judges each study on three broad categories: selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. It ranges from 1 to 9 stars based on the quality of the study, and we considered a study awarded 7 or more stars as a high-quality study in current study, as no standard criteria has been established.

2.3. Statistical analysis and data synthesis

We performed meta-analyses of risk estimates comparing the highest category of exposure with the lowest category. As dietary intake of fish is a major source of omega-3 fatty acids but not the final form of omega-3 fatty acids intake, we pooled the data on dietary intake of long-chain omega-3 fatty acids (including total long-chain omega-3 fatty acids, DHA, and EPA) and fish separately. Dose–response meta-analyses of fish intake and risks of dementia and AD were then conducted using methods previously reported (Larsson and Orsini, 2011; Greenland and Longnecker, 1992), which facilitated the calculation of a pooled relative risk across studies with a common unit of comparison with studies, assuming a linear dose–response relation. In this study, we estimated the relative risk per unit of 100 g increment of fish intake per week for each study and then pooled them together. For studies that reported results for fish intake in servings only, we derived grams by assuming that one serving equals 100 g (Bouzan et al., 2005; Guevel et al., 2008). We converted the level of fish intake categories based on the calculated midpoint of fish intake if the study did not report the median of exposure category. Table S2 shows the definition of fish intake and the means of conversion of categories within each study. These analyses were carried out for fish intake and risks of dementia and AD only, as there was insufficient data for total long-chain omega-3 fatty acids, DHA, and EPA.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2014.11.008.

A fixed effects model was used to estimate the pooled RRs and 95% CIs if there was no evidence of heterogeneity; otherwise, a random effect model was used. The chi-square ($\chi^2$) test and I-squared ($I^2$) statistic were used to explore the heterogeneity among studies. Publication bias was assessed by Egger’s regression test and Begg–Mazumdar test (Egger et al., 1997; Begg and Mazumdar, 1994). Subgroup analyses were performed on fish intake and risk of dementia and AD, according to follow-up duration, geographic location, study quality, and difference between highest intake categories, to test the possible impact factors.

Statistical analyses were conducted using Stata Version 12.0 software (Stata Corp, College Station, TX). All statistical tests were two sided and used a significance level of $p < 0.05$. 

4. Discussion

4.1. Conflicts of interest

4.2. Acknowledgments

References
3. Results

3.1. Search results

The search strategy identified 1361 citations. After removing the duplicate articles, 1232 articles remained for further evaluation. Following detailed assessments, 1214 articles were excluded (Fig. 1). Overall, 6 cohort studies conducted in the US (n = 3) (Morris et al., 2003; Schaefer et al., 2006; Huang et al., 2005) or Europe (n = 3) (Devore et al., 2009; Barberer-Gateau et al., 2007; Kalmijn et al., 1997) met the inclusion criteria and were included in the meta-analysis, with a total of 22,402 participants. Table S3 shows the details of the excluded studies and reasons for exclusion. All relevant studies identified were published in the English language. Of these studies, five reported on dementia incidence and all the six on AD incidence. Dietary intake of omega-3 fatty acids and/or fish was recorded using either semiquantitative food-frequency questionnaire (SFFQ) or food-frequency questionnaire (FFQ) in the included studies. Frequency of consumption was recorded in different categories from the least frequent intake to the most frequent intake. Different types of omega-3 fatty acids were recorded separately (such as total long-chain omega-3 fatty acids, DHA, and EPA). We recorded relative risks of dementia and AD according to the highest vs. lowest category long-chain omega-3 fatty acids intake and fish intake. All reported RRs with 95% CIs of dementia or AD in each study were adjusted for multiple covariates. The quality of studies included in the analysis was relatively higher in four studies, with two studies scoring 8 stars on the Newcastle-Ottawa Scale and two scoring 7 stars. Characteristics of these six studies are provided in Table 1, and Table S4 presents the quality assessment of the included studies in detail.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2014.11.008.

3.2. Meta-analysis: dietary intake of omega-3 fatty acids and risk of dementia

Four cohorts from two independent studies evaluated the association between dietary intake of long-chain omega-3 fatty acids (including total long-chain omega-3 fatty acids in one cohort (Devore et al., 2009), DHA in two (Schaefer et al., 2006; Devore et al., 2009), and EPA in one (Devore et al., 2009)) and risk of dementia. In the pooled analysis, a higher intake of long-chain omega-3 fatty acids was not associated with risk of dementia (RR = 0.97, 95% CI 0.85–1.10) compared with the lowest category of long-chain omega-3 fatty acids intake (Fig. 2A), and there was no evidence of significant heterogeneity among individual cohorts ($I^2 = 0.0\%$, $p = 0.694$). We found no evidence of publication bias using Begg–Mazumdar test ($p = 0.090$), but the result of Egger’s regression test had shown that there was potential publication bias ($p = 0.007$). After using the trim and fill approach, one study was filled and the pooled result did not reverse (RR = 0.95, 95% CI 0.85–1.07).

A total of five studies (Schaefer et al., 2006; Huang et al., 2005; Devore et al., 2009; Barberer-Gateau et al., 2007; Kalmijn et al., 1997) evaluated the association between dietary intake of fish and risk of dementia. Compared to the lowest category of fish intake, there was a 16% lower risk of dementia in the highest category of fish intake in the pooled analysis, however, it did not quite reach statistical significance (95% CI –1% to 29%) (Fig. 2B). There was no statistically significant evidence for heterogeneity among studies ($I^2 = 29.1\%$, $p = 0.227$) and no evidence for publication bias (Egger’s regression test ($p = 0.051$), and Begg–Mazumdar test ($p = 0.142$)). The overall associations observed in prospective studies for fish intake and risk of dementia remained broadly consistent when these studies were grouped by several characteristics at study level (Table 2).

3.3. Meta-analysis: dietary intake of omega-3 fatty acids and risk of AD

Ten cohorts from three independent studies reported on dietary intake of long-chain omega-3 fatty acids (including total long-chain omega-3 fatty acids in three cohorts (Morris et al., 2003; Devore et al., 2009), DHA in four (Morris et al., 2003; Schaefer et al., 2006; Devore et al., 2009), and EPA in three (Morris et al., 2003; Devore et al., 2009)) and risk of AD. Evidence synthesis for AD risk did not show a statistically significant association with long-chain omega-3 fatty acids intake (RR = 0.89, 95% CI 0.74–1.08) (Fig. 3A), and there was no evidence for the presence of significant heterogeneity among the 10 cohorts ($I^2 = 36.6\%$, $p = 0.116$). There was potential publication bias in these included studies (Egger’s regression test ($p = 0.011$), and Begg–Mazumdar test ($p = 0.020$)), however, the result of the trim and fill approach had shown that no trimming was performed and the pooled result had not been changed.

Seven cohorts from all the six included studies (Morris et al., 2003; Schaefer et al., 2006; Huang et al., 2005; Devore et al., 2009; Barberer-Gateau et al., 2007; Kalmijn et al., 1997) examined the association between dietary intake of fish and incident AD. In the pooled analysis, we observed a potential protective effect of higher intake of fish against AD incidence. Compared with the lowest category of fish intake, a higher intake of fish was associated with a 36% (95% CI 8%–56%) lower risk of AD (Fig. 3B). Because there was significant heterogeneity among different studies ($I^2 = 59\%$, $p = 0.023$), we removed the cohort from Devore et al’s study with follow up duration of 9–14 years, which had a point estimate over 1, and pooled...
Table 1
Summary characteristics of the eligible cohort studies in the meta-analysis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Sample size</th>
<th>Disease type, number of cases</th>
<th>Age (years), mean/range</th>
<th>Follow-up duration (years), mean/range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devore et al. (2009)</td>
<td>The Netherlands</td>
<td>5395</td>
<td>Dementia, 465 AD (follow-up 0–8 years), 168 AD (follow-up 9–14 years), 197 AD</td>
<td>68±55</td>
<td>9.6/0–8, 9–14</td>
</tr>
<tr>
<td>Barberer-Gateau et al. (2007)</td>
<td>France</td>
<td>8085</td>
<td>Dementia, 281 AD, 183 Dementia, 378 AD, 190 AD</td>
<td>NR/65</td>
<td>3.48/NR</td>
</tr>
<tr>
<td>Huang et al. (2005)</td>
<td>US</td>
<td>2233</td>
<td>Dementia, 58 AD</td>
<td>72±65</td>
<td>5.4/0.1–8.4</td>
</tr>
<tr>
<td>Morris et al. (2003)</td>
<td>US, The Netherlands</td>
<td>815, 5386</td>
<td>Dementia, 131 AD, 58 AD, 37 AD</td>
<td>68±55</td>
<td>3.9/NR</td>
</tr>
</tbody>
</table>

Reference | Disease ascertainment | Type of omega-3 fatty acids intake determination | Adjustment | Study qualitya |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Devore et al. (2009)</td>
<td>MMSE, GMS, DSM-III-R, neurological exam, and NINCDS-ADRDA</td>
<td>Total long-chain omega-3 fatty acids, DHA, EPA, and fish</td>
<td>SFFQ</td>
<td>8</td>
</tr>
<tr>
<td>Barberer-Gateau et al. (2007)</td>
<td>DSM-III-R, neurological exam, and NINCDS-ADRDA</td>
<td>Fish</td>
<td>FFQ</td>
<td>8</td>
</tr>
<tr>
<td>Schaefer et al. (2006)</td>
<td>MMSE, neurological exam, DSM-IV, and NINCDS-ADRDA</td>
<td>DHA and fish</td>
<td>SFFQ</td>
<td>7</td>
</tr>
<tr>
<td>Huang et al. (2005)</td>
<td>MMSE, neurological exam, DSM-IV, and NINCDS-ADRDA</td>
<td>Fish</td>
<td>FFQ</td>
<td>6</td>
</tr>
<tr>
<td>Morris et al. (2003)</td>
<td>NINCDS-ADRDA, and neurological exam</td>
<td>Total long-chain omega-3 fatty acids, DHA, EPA, and fish</td>
<td>FFQ</td>
<td>7</td>
</tr>
<tr>
<td>Kalmijn et al. (1997)</td>
<td>MMSE, GMS, CAMDEX, neurological exam, and NINCDS-ADRDA</td>
<td>Fish</td>
<td>SFFQ</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; NR, not reported; MMSE, Mini-Mental State Examination; GMS, Geriatric Mental State schedule; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders-III-Revised; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders Association; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SFFQ, semiquantitative food-frequency questionnaire; APOE, apolipoprotein E; BMI, body mass index; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; CAMDEX, Cambridge Mental Disorders of the Elderly Examination.

a Study quality was judged based on the Newcastle-Ottawa Scale (range, 1–9 stars).

The remaining six cohorts again. Heterogeneity disappeared after removing this cohort (I² = 0.0%, p = 0.460) and the pooled relative risk of AD did not reversed (RR = 0.59, 95% CI 0.46–0.77), suggesting this cohort was the main source of heterogeneity in the original pooled analysis. No evidence of publication bias was found using Begg–Mazumdar test (p = 0.099), but the result of Egger’s regression test had shown that there was potential publication bias (p = 0.014). However, after using the trim and fill approach, no trimming was performed and the pooled result had not been changed. For subgroup analyses, we excluded the cohort from Devore et al’s study with follow up duration of 9–14 years, because it caused large heterogeneity in the pooled analyses. Similarly, the associations between fish intake and risk of AD did not change in all the subgroups (Table 2). However, longer follow-up duration yielded a stronger protective effect of higher intake of fish against risk of AD. A 47% (95% CI 15–67%) reduction in the risk of AD were observed in the studies followed up at least five years versus 38% (95% CI 15–54%) in the studies followed up below five years. In addition, the magnitude of the relative risks of AD for the highest category of 500 g or more per week seemed lower than those for the highest
Fig. 2. Adjusted relative risks of dementia according to the highest vs. lowest category long-chain omega-3 fatty acids intake (A) and fish intake (B). In the pooled analysis, a higher intake of long-chain omega-3 fatty acids was not associated with risk of dementia (RR = 0.97, 95% CI 0.85–1.10) compared with the lowest category of long-chain omega-3 fatty acids intake. In addition, there was a 16% lower risk of dementia in the highest category of fish intake compared with the lowest category of fish intake in the pooled analysis, but it did not reach statistical significance (95% CI −1% to 29%).

category of less than 500 g per week (RR = 0.55, 95% CI 0.35–0.88 vs. RR = 0.61, 95% CI 0.45–0.84). The relative risks were also different when grouped by geographic location and study quality, but all with statistical significances.

3.4. Dose–response meta-analysis

Dose–response meta-analysis was conducted for fish intake and risk of dementia and AD only, as there was insufficient data for other types of omega-3 fatty acids. The Schaefer et al’s study was excluded for dose–response meta-analysis, because there were only two categories of fish intake in this study, and dose–response meta-analysis requires data for the distribution of cases and person-time across at least three categories of exposure (Alexander et al., 2009).

In the dose–response meta-analysis, the reduced risk of dementia by an increment of 100 g per week of fish intake was only observed in Kalmijn et al’s study, and there was no statistical significance in the pooled result (RR = 0.96, 95% CI 0.91–1.01) (Fig. 4A). However, the pooled result showed that an increment of 100 g per week of fish intake was associated with a 11% lower risk of AD (RR = 0.89, 95% CI 0.79–0.99) (Fig. 4B), and three individual studies (Morris et al., 2003; Huang et al., 2005; Kalmijn et al., 1997) showed significant protective effect. Although there were potential heterogeneity among studies ($\chi^2 = 52.3$, $p = 0.063$), after we removed the cohort from Devore et al’s study with follow up duration of 9–14
years, the heterogeneity disappeared ($I^2 = 20.2\%$, $p = 0.286$) and the relative risk of AD did not change significantly (RR = 0.87, 95% CI 0.81–0.93).

### 4. Discussion

To the best of our knowledge, this is the first meta-analysis of prospective cohort studies that specifically addressed the dietary intake of omega-3 fatty acids and the risks of dementia and AD. The prospective study designs minimized recall bias and selection bias. Although randomized placebo-controlled trials are the most effective method for evaluation of the causality of diet–disease relations, it would be difficult to conduct a long-term, large-scale and randomized trial on omega-3 fatty acids intake and risks of dementia and AD.

In this meta-analysis, we found that a higher dietary intake of long-chain omega-3 fatty acids was not associated with lower risk of dementia or AD compared with the respective lower exposure category. A previous randomized trial indicated that supplementation with DHA compared with placebo did not slow the rate of cognitive and functional decline in patients with mild to moderate AD (Quinn et al., 2010). This conclusion has been further strengthened with the evidence from our study. Nevertheless, most of the individual studies evaluating the relationships between long-chain omega-3 fatty acids intake and risk of dementia or AD had a RR below one, suggesting that there was maybe potential protective effect of long-chain omega-3 fatty acids on incidence of dementia and AD, although no significant statistical differences were identified in the pooled analyses. The biological mechanisms could support beneficial effects of long-chain omega-3 fatty acids on the risks of dementia and AD. Indeed, long-chain omega-3 fatty acids are major components of neuron membranes, and they have vascular and anti-inflammatory properties which have a protective effect against dementia and AD (Barberger-Gateau et al., 2007; Yehuda et al., 2002; Ringbom et al., 2001; Combs et al., 2000; Horrocks and Yeo, 1999). Anyway, we did not find significant evidence on this protective effect in our meta-analysis.

We also found that there was a 16% lower risk of dementia by a higher intake of fish, but this protective effect did not reach statistical significance. However, we found a borderline significant 36% lower risk of AD for those in the highest fish intake category compared with those in the lowest intake category. The association was more pronounced in the studies in which the follow-up duration was at least five years, and the highest category of fish intake was 500 g or more. Other subgroup analyses showed the association was a little weaker in studies from Europe than those in the United States, and in studies with higher quality than those with lower quality. Dose–response meta-analysis showed that each 100 g per week higher intake of fish was associated with an 11% lower risk of AD. The protective effect of fish intake was mainly attributed to its high content in long-chain omega-3 fatty acids, in particular DHA (Barberger-Gateau et al., 2007), and the biological mechanisms are similar as we mentioned above. However, this protective effect may have several alternative explanations. Firstly, fish is also a good source of other nutrients, such as vitamins, essential amino acids and trace elements, and these nutrients may also contribute to cognitive function improvement (Chandra, 2001; Ortega et al., 1997). Secondly, a higher fish intake may simply be an indicator of a healthier dietary pattern or higher socioeconomic status, which themselves are associated with better cognitive performance (Kesse-Guyot et al., 2012; Evans et al., 1997). Thirdly, a higher fish intake may associate with a lower intake of other type of fat such as saturated fat. A previous study has shown that a high saturated fat intake increases the risk of dementia (Kalmijn et al., 1997). Thus, the protective effect of fish intake may also due to the lower intake of other type of fat.

The discordant results observed for long-chain omega-3 fatty acids intake compared with fish intake may also have several potential explanations. Firstly, it is not well-known about what foods

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Study</th>
<th>RR (95% CI)</th>
<th>$p$ value</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up duration Dementia</td>
<td></td>
<td></td>
<td>$\chi^2$</td>
<td>$I^2$</td>
</tr>
<tr>
<td>Below 5 years</td>
<td>21, 22</td>
<td>0.59 (0.30–1.18)</td>
<td>0.136</td>
<td>2.10</td>
</tr>
<tr>
<td>5 years or above</td>
<td>9, 19, 20</td>
<td>0.89 (0.73–1.08)</td>
<td>0.225</td>
<td>1.56</td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 5 years</td>
<td>8, 20–22</td>
<td>0.62 (0.46–0.85)</td>
<td>0.002</td>
<td>4.33</td>
</tr>
<tr>
<td>5 years or above</td>
<td>9, 19</td>
<td>0.53 (0.33–0.85)</td>
<td>0.009</td>
<td>0.02</td>
</tr>
<tr>
<td>Geographic location Dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>9, 19</td>
<td>0.75 (0.52–1.07)</td>
<td>0.114</td>
<td>0.33</td>
</tr>
<tr>
<td>Europe</td>
<td>20–22</td>
<td>0.75 (0.48–1.17)</td>
<td>0.210</td>
<td>4.74</td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>8, 9, 19</td>
<td>0.49 (0.33–0.73)</td>
<td>&lt;0.001</td>
<td>0.40</td>
</tr>
<tr>
<td>Europe</td>
<td>20–22</td>
<td>0.68 (0.48–0.95)</td>
<td>0.025</td>
<td>2.74</td>
</tr>
<tr>
<td>Study quality Dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 7 stars</td>
<td>19, 22</td>
<td>0.61 (0.32–1.16)</td>
<td>0.132</td>
<td>2.43</td>
</tr>
<tr>
<td>7 stars or more</td>
<td>9, 20, 21</td>
<td>0.90 (0.74–1.11)</td>
<td>0.333</td>
<td>1.30</td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 7 stars</td>
<td>19, 22</td>
<td>0.49 (0.31–0.76)</td>
<td>0.002</td>
<td>0.39</td>
</tr>
<tr>
<td>7 stars or more</td>
<td>8, 9, 20, 21</td>
<td>0.64 (0.47–0.87)</td>
<td>0.004</td>
<td>2.81</td>
</tr>
<tr>
<td>Highest intake category*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 500 g per week</td>
<td>9, 20, 22</td>
<td>0.68 (0.39–1.17)</td>
<td>0.161</td>
<td>5.48</td>
</tr>
<tr>
<td>500 g per week or more</td>
<td>19, 21</td>
<td>0.80 (0.57–1.11)</td>
<td>0.184</td>
<td>0.00</td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 500 g per week</td>
<td>8, 9, 20, 22</td>
<td>0.61 (0.45–0.84)</td>
<td>0.002</td>
<td>4.50</td>
</tr>
<tr>
<td>500 g per week or more</td>
<td>19, 21</td>
<td>0.55 (0.35–0.88)</td>
<td>0.012</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* If the original study expressed fish intake in serving, we assume that one serving is 100 g. We converted the level of the highest intake category based on the calculated midpoint of fish intake if the study did not report the median of highest exposure category.
contain long-chain omega-3 fatty acids and the food composition tables are often incomplete, and this would lead to an underestimation of the true long-chain omega-3 fatty acids intake. Secondly, dietary intake of long-chain omega-3 fatty acids may also be accompanied by the intake of other nutrients simultaneously such as saturated fat, which may attenuate the associations between long-chain omega-3 fatty acids and risk of dementia or AD. Thirdly, the categories of long-chain omega-3 fatty acids intake and fish intake are quite different, and this may also be responsible for the inconsistent results in studies concerning long-chain omega-3 fatty acids intake and in those concerning fish intake.

Findings of this meta-analysis are in line with three cross-sectional studies (Kalmijn et al., 2004; Barberger-Gateau et al., 2005; Nurk et al., 2007), which described better cognitive

---

Fig. 3. Adjusted relative risks of AD according to the highest vs. lowest category long-chain omega-3 fatty acids intake (A) and fish intake (B). Evidence synthesis for AD risk did not show a statistically significant association with long-chain omega-3 fatty acids intake (RR = 0.89, 95% CI 0.74-1.08). However, a higher intake of fish was associated with a 36% (95% CI 8-56%) lower risk of AD, compared with the lowest category of fish intake.
performance on various neuropsychological tests in middle-aged and older persons who regularly consumed fish. Despite the association between higher fish intake and better cognitive performance was reported in these cross-sectional studies, this type of study cannot ascertain causality. In contrast, in prospective studies, long-chain omega-3 fatty acids and fish intake was monitored in a cohort that was followed-up to determine which subjects developed dementia or AD. Thus, the results in our meta-analysis could be used to identify a causal relationship between dietary intake of omega-3 fatty acids and risks of dementia and AD. Since we found that a higher fish intake could reduce the risk of AD, mechanistic researches are essential to explain this protective effect. Well designed randomized controlled trials that address a specific mechanism of fish intake and reduced risk of AD are urgently needed.

The possibility of publication bias is always a concern in a meta-analysis. In our study, there was potential publication bias when assessing the relationship between long-chain fatty acids intake and risk of dementia, fish intake and risk of dementia, and fish intake and risk of AD. We further applied trim and fill method to adjust for publication bias. Nevertheless, results showed that meta-analyses with or without the trim and fill did not draw different effect estimates. More importantly, the inverse associations between dietary intake of omega-3 fatty acids and risk of dementia and AD appeared to be consistent across most studies. Thus, the likelihood that these findings are largely a result of selective publication seems to be minimal. Taken together, the results of this meta-analysis are sound and reliable.

Our findings have some limitations that merit additional comments. Firstly, our inference is based on observational studies, although all the included studies adjusted for known risk factors for dementia and AD, we cannot exclude chance, residual or unmeasured confounding as alternative explanation for our results.

---

**Fig. 4.** Relative risks of dementia (A) and AD (B) for an increment of 100 g per week of fish intake. In the dose–response meta-analysis, the reduced risk of dementia by an increment of 100 g per week of fish intake didn't show statistical significance (RR = 0.96, 95% CI 0.91–1.01). However, the pooled result showed that an increment of 100 g per week of fish intake was associated with an 11% lower risk of AD (RR = 0.89, 95% CI 0.79–0.99).
Secondly, because of the prospective design, any misclassification of omega-3 fatty acids is most likely random and leads to underestimation of the true relation between omega-3 fatty acids intake and risks of dementia and AD. Thirdly, considering the different amounts of long-chain omega-3 fatty acids in different types of fish, one would expect to observe more benefit by eating fatty fish rich in long-chain omega-3 fatty acids as the beneficial effect of fish intake on risks of dementia and AD is largely attributable to its content of long-chain omega-3 fatty acids. However, data are very limited regarding the effect of intake of different types of fish on risks of dementia and AD. Finally, there were limited studies in several subgroup analyses, which may lead to low statistical power in these analyses.

Conflicts of interest

The authors declare no financial or other conflicts of interest.

Acknowledgments

We thank Zhichao Jin, Qi Chen, and Chun Xiang for their generous assistance with this study.

References


