**Supplemental Table 1: Characteristics and fi****ndings of cross-sectional studies identified for the systematic literature review of the association of fish consumption and dementia risk**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **First Author; Publication year; Study type; Study location**  | **Participants’ characteristics; recruitment strategy** | **Sample size**  | **Baseline measure of frequency of fish consumption; categories of comparison** | **Endpoint outcomes: Number of dementia cases; diagnosis criteria**  | **Data analysis method; confounders adjusted** | **Findings** |
| Albanese (2009)(1): Cross-sectional studyLatin America, China and India | Age ≥65 years. Recruited by door knocking between Jan 2003 and Nov 2007 from 11 sites across Peru, Mexico, China and India, Cuba, Dominican Republic and Venezuela.   | Total 14,956:Cuba 2,934; Dominican Rep 1,999; Peru 1927; Venezuela 1,939; Mexico 1,997; China 2,162; India 1,998.  | Standardised questionnaires from 10/66 protocol using face-to-face interviews.Never; some days; most days; and every day. The fish intakes of "most days" and "every day" were combined as one category. | 1,345 prevalent dementia cases: Cuba 316 Dominican Republic 235 Peru 165 Venezuela 140 Mexico 171 China 137India 181 Dementia was assessed by 10/66 diagnostic algorithm. | PR estimated using Poisson regression. Adjustment for age, sex, educational level and family history of dementia, self-reported chronic diseases (stroke, diabetes, and CHD), ICD-10 depression, smoking habits, living arrangements and number of assets, daily intake of fruits/ vegetables, meat intake, and alcohol intake. | PRadj (95% CIs) of dementia for each increase in fish consumption category:Cuba 0.81 (0.65-1.02) Dominican Rep 0.80 (0.65-1.00) Peru 0.76 (0.56-1.05) Venezuela 0.87 (0.56-1.34)Mexico 0.81 (0.62-1.08) China 0.58 (0.39-0.85)India 1.47 (0.92-2.35)   |
| Conquer 2000(2): Case control Canada | Aged 77.5-83.3 years.Recruited96 eligible participants from a large urban center.  | 84 gave blood samples. | GLC analyzed fatty acid methyl esters in blood plasma. Fatty acids composition: EPA (20:5n-3), 24:0, DHA (22:6 n-3), total n-3 fatty acids, and n-3/n-6 ratio was assessed in 4 different fractions of plasma lipids [total phospholipid (PL), phosphatidylcholine (PC), phosphatidylethanolamine (PE), and lysophosphatidylcholine (lysoPC)]. | 29 cases (19 AD, 10 other dementia [OD]); 36 CIND; 19 controls. CT scan,Neuropsychological assessment performed by a geriatricianDiagnosis made using NINCD-ADRDA criteria and DSM-IV criteria. | ANOVA and ANCOVA used to estimate the multifactorial data of the fatty acid composition. Adjustment for age and education  | In plasma PL and PC, the levels of EPA, DHA, total n-3 fatty acids and the n-3/n-6 ratio were lower in the AD, OD and CIND groups compared to the control group. In plasma PE, the levels of EPA, DHA, and the total n-3 fatty acid except n-3/n-6 ratio, were significantly lower in the AD, OD and the CIND groups. Plasma PL (24:0) was lower in the AD, OD, and the CIND compared to normal group. Total n-6 fatty acid levels were lower in the AD and CIND groups only.(p≤0.05; effect sizes not given) |
| Kim 2010(3): Case-control studyKorea | Age ≥ 65 years. Recruited from the Kuri Area between Dec 2008 and Jan 2009. |  57 | FFQ GLC analyzed fatty acid methyl esters in blood samples. Erythrocyte fatty acid composition as biomarker of n-3 PUFA were categorized into tertiles. | 33 cases; 24 controls.Dementia detected by Korean Mini-Mental Status Examination (MMSE-K;controls score > 21, cases score ≤ 21). | OR estimated using a logistic regression model. Adjustment for age, sex, height, and energy intake.  | ORadj (95% CIs) of dementia:Highest tertile 0.68 (0.12-3.77)Middle tertile 0.53 (0.09-3.18)Lowest tertile REF. |
| Tully 2003(4):Case control studyIreland | Cases recruited from community dwellers registered with Mercer Institute for Research and Aging aged 49-92 years; mean CDR of 1 (SD 0.62) and mean MMSE 19.5 (SD 4.8). Controls recruited from active elderly retirement group aged 53-81 years. | 193 | GLC analyzed fatty acid methyl esters of cholesteryl esters in blood plasma. Plasma cholesteryl ester-fatty acid composition as biomarker of n-3 PUFA.  | 148 cases (108 probable AD, 16 possible AD, 13 mixed AD and 11 vascular dementia); 45 controls. Screening with MMSE (controls score ≥24, cases score <24);Neuropsychological examination and neuroimaging. Diagnosis made using NINCDS-ADRDA and ICD-10 criteria.  | ANOVA was used to describe differences between cases and controls. Step-wise multiple regression analysis used to ascertain relative importance of age, sex and fatty acid composition on MMSE scores. . | Cases had significant lower levels (p<0.001) of n-3 PUFA compared to control (effect size not given). Fatty acid levels predicted MMSE and CDR scores independently of age and sex.  |

Abbreviations: AD Diagnostic and treatment Center criteria -ADDTC; Alzheimer’s-Disease-AD; Apolipoprotein E-APOE-e4; Analysis of Covariance-ANCOVA; Analysis of Variance-ANOVA; Blood Pressure-BP; Body Mass Index-BMI; Cambridge Mental Disorders of the Elderly Examination-CAMDEX; Cognitively Impaired No Dementia-CIND; Clinical Dementia Rating-CDR; Coronary Heart Disease-CHD; 95% Confidence Interval-95%CI; Computerised Tomography-CT; Diagnostic and Statistical Manual of Mental Disorders-III-Revised-DSM-III-R; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-DSM-IV; Docosahexaenoic acid-DHA; Eicosapentaenoic acid-EPA; Food-frequency questionnaire-FFQ; Gas Liquid Chromatography-GLC; Geriatric Mental State schedule-GMS; Hazard Ratio-HR; Informant Questionnaire for Cognitive Decline in the Elderly-IQCoDE; International Classification of Diseases, 10th revision-ICD-10; Lysophosphatidylcholine-lysoPC; Magnetic Resonance Imaging-MRI; Mini-Mental State Examination-MMSE; Myocardial Infarction-MI; omega-3 Poly-unsaturated fatty acids- n-3PUFA; National Institute of Neurological and Communicative Diseases and Stroke AD and Related Disorders Association-NINCDS-ADRDA; National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences NINDS-AIREN; Other dementia-OD; Odd Ratio-OR; Plasma phosphatidylcholine-PC; Phosphatidylethanolamine-PE; Prevalence ratio-PR; Relative Risk-RR; Semi-quantitative food-frequency questionnaire -SFFQ; Telephone Interview for Cognitive Status-TICS; Total phospholipid-PL; Vascular Dementia- VaD.

**Supplemental Table 2:** **Characteristics and findings of longitudinal studies identified for the systematic literature review of the association of fish consumption and dementia risk**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **First Author; Publication year; Study type (Study name); Study location**  | **Participant characteristics at baseline and recruitment strategy** | **Sample size at follow up (% of baseline sample); Study duration**  | **Baseline measure of fish consumption; Categories of frequency** | **Number of new dementia cases;****Dementia diagnosis criteria**  | **Data analysis;****Adjustment for confounders** | **Findings** |
| Barberger-Gateau et al 2007(5)Cohort study (Three-City)France | 9,471 eligible community dwellers aged ≥65 years were recruited at baseline between 1999 and 2000.  | 8,085 participants (85.4%) were followed up at least once over a mean period of 3.48 years.  | A short FFQ.Daily; 4-6 times a week; 2-3 times weekly; once a week; less than once a week; and never. | 281 (including 183 AD).Psychological and neurological examination and reassessment by neurologist was performed using the DSM-IV and NINCDS- ADRDA criteria.   | HR estimated using a proportional hazard model with delayed entry. Adjustment for age, sex, education, city, income, marital status. Analysis of AD additionally adjusted for APOE-e4, BMI and diabetes. | HRadj (95% CI) dementia: ≥4 times/week 0.81 (0.45-1.46)2-3 times/week 0.68 (0.48-0.98)Once/week 0.81 (0.57-1.17)Never or <1/week REFHRadj (95% CI) AD: ≥4 times/week 0.58 (0.25-1.34) 2-3 times/week 0.59 (0.37-0.94) Once/week 0.74 (0.46-1.17)Never or <1/week REFHRadj (95% CI) dementia in APOE-e4 non-carriers: ≥ 4 times/week 0.78 (0.39-1.58) 2-3 times/week 0.54 (0.35-0.85) once /week 0.64 (0.41-1.00)Never or <1/week REFHRadj (95%CI) dementia in APOE-e4 carriers: ≥4 times/week 0.36 (0.04-2.91) 2-3 times/week 1.24 (0.53-2.90) once/week 1.66 (0.72-3.83). Never or <1/week REF |
| Barberger-Gateau et al 2002(6)Cohort study (Personnes Agees QUID [PAQUID])France\* | 1,674 eligible community dwellers aged ≥68 years were visited during the 3rd wave of the study between 1991 and 1992. | 1,416 participants (84.6%) took part in at least one of the follow up visits after 2, 5 and 7 years.  | FFQ.Daily; at least once weekly (but not every day); from time to time (but not every week); never. | 170 (including 135 AD).Screening with MMSE (decline ≥3 points from previous visit) and review using DSM-III-R with further confirmation by a neurologist.  | HR estimated using a Cox proportional hazard model with delayed entry. Adjustment for age, sex and education (at least primary school diploma vs less education). | HRadj (95% CI) of dementia ≥once/week 0.73 (0.52-1.03) <once/week REF |
| Larrieu et al 2004(7)\* | The same as above | The same as above | Once a week or more; lessthan once a week |   | RR estimated using a Cox proportional hazard model with delayed entry. Adjustment for age, sex and education (at least primary school diploma vs less education). | RRadj (95% CI) AD≥once/week 0.77 (0.52-1.14)<once/week REF |
| Devore et al 2009(8):Cohort study (Rotterdam) Netherlands | 7,983 community dwellers aged ≥55 years were recruited at baseline in 1990 (78% of eligible sample). | 5,395 participants (67.6%) were followed up over a mean period of 9.6 years. | A meal-based check list to inform semi-quantitative SFFQ.Times per day, week, or month (categorized as none, low [8.2g/day] and high [29.6g/day]). Fish type was classified as “no”, “lean” and “fatty fish”. | 465 (including 365 AD).Screening with MMSE <26 or GMS scores >0; CAMDEX and evaluation by a neurologist and neuropsychologist with neuroimaging and computerized linkage of dataset and digitalized medical records. Diagnosis made using DSM-III-R NINCDS-ADRDA and NINDS-AIREN criteria.  | HR estimated using Cox proportional hazard models.Adjustment for age, sex, education, total energy intake, alcohol intake, smoking, BMI, high total cholesterol, baseline hypertension, intake of vitamin E, supplement use, history of stroke, Myocardial infarction (MI) and type 2 diabetes. | HRadj (95% CI) dementia: High 0.95 (0.76-1.19)Low 0.94 (0.75-1.17)None REFHRadj (95% CI) AD: High 0.99 (0.76-1.29)Low 1.07 (0.83-1.37)None REF |
| Huang et al 2005(9):Cohort study(Cardiovascular Health Cognitive Study [CHCS])USA | 2,798 eligible participants aged ≥65 years recruited between 1989 and 1994 from a randomised Medicare eligibility lists.  | 2,233 (79.8%) participants were followed- up between 0.1-8.4 years (mean 5.4 years). | A modified National Cancer Institute FFQTuna and other fish: <0.25; 0.25-2; 2-4; ≥4 servings per week.Fried fish: <0.25; 0.25-2; ≥2 servings per week. | 378 (including 190 AD and 50 VaD).80-point cutoff and/or decline of ≥5 points on the 3MSE, TICS score < 28, IQCoDE score >3.6. Further assessment was performed by a neurologist using DSM-IV, NINCDS-ADRDA and ADDTC criteria.  | HR estimated using Cox proportional hazard regression models. Adjustment for baseline age, minority status, gender, APOE-e4, energy intake, baseline BMI and region, education and income. | Tuna and other fishHRadj (95% CI) dementia: ≥4/week 0.79 (0.53-1.20)2-4/week 0.83 (0.59-1.18)0.25-2/week 0.85 (0.61-1.19)<0.25/week REFHRadj (95% CI) AD: ≥4/week 0.69(0.91-1.22) 2-4/week 0.72(0.44-1.17) 0.25-2/week 0.85 (0.54-1.33)<0.25/week REFFried fish:HRadj (95% CI) dementia: ≥2/week 0.97 (0.69-1.35)0.25-2/week 1.12 (0.87-1.44)<0.25/week REFHRadj (95% CI) AD: ≥2/week 0.95 (0.60-1.52) 0.25-2/week 0.97 (0.67-1.40)<0.25/week REF |
| Lopez 2011(10): Case-Cohort study (Rancho Bernardo) USA | 1692 community dwellers aged ≥55 years participated in a clinic research visit in 1988-91. Of the 1349 participants aged ≥ 65 years, available between 1991-93, 402 partook in all the clinic visits.  | 242 (90.9%) participants who had data for dietary DHA and fish consumption were followed up for approximately 3 years.  | SFFQRarely or never; 1-3 times/month; 1 time/week; 2-4 times per week; 5-6 times per week; daily and 2 times/day. | 42 (including 30 AD). Screening with MMSE, neuropsychological test battery by a psychometrist and neurologist and CT examination. Diagnosis made using NINCDS-ADRDA criteria.  | OR estimated using a logistic regression model. Adjustment for age, sex, education, APOE-e4 status, stroke, systolic B.P, smoking, alcohol intake, exercise, diabetes and BMI. | ORadj (95% CI) all-cause dementia: ≥1 serving/week 0.51 (0.20-1.32). REF (not specified)ORadj (95% CI) AD: ≥1 serving/week 0.55 (0.20-1.48).REF (not specified) |
| Morris et al 2003(11):Cohort study (Chicago Health and Aging Project [CHAP])USA | 6,158 participants aged ≥65 years recruited at baseline identified from that 1993-1997 south-side Chicago census programme (78.8% of eligible sample). 1140 randomly selected from survivors at follow-up. | 815 participants (71.5%) were followed up over a mean period of 3.9 years. | FFQ. Never; 1-3 times/month; once/week; ≥ twice/week. .  | 131 cases of AD.Assessment by neuropsychological technician, nurse practitioner, phlebotomist and neurologist using the NINCDS- ADRDA criteria.  | OR as estimates of RR estimated using a logistic regression model. Adjustment for race, sex, age, total energy intake, APOE-e4 status, education, race\*APOE-e4 interaction,period of observation, and indicator variables for fish consumption levels. | RRadj (95% CI) AD: ≥ twice/week 0.4 (0.2-0.9) once/week 0.4 (0.2-0.9)1-3 times/month 0.6 (0.3-1.3)Never REF |
| Schaefer et al 2006(12):Cohort study (Framingham Heart Study)USA | 1,208 participants aged 55-88 years examined at the 20th biennial examination cycle 1986/1988 (62.9% of eligible sample). 899 selected based upon availability of plasma sample.  | 488 participants who provided dietary information (54.3%) were followed up over a period of 16 years (mean 9.1 years). | A semi-quantitative SFFQ.>twice/week; ≤twice/week.  | 99 (including 71 AD).Screening with MMSE (score less than education-based cut-offs or lost ≥3 points) with neurological and neuropsychological examination using DSM-IV and NINCDS-ADRDA criteria. | RR estimated using a Cox proportional hazards regression analysis.Adjustment for age, sex, APOE-e4, homocysteine concentration, educational level, BMI, hypertension, diabetes mellitus, smoking status, alcohol intake, history of stroke, daily calorie intake.  | HRadj (95% CI) Dementia: >twice/week 0.61 (0.28-1.33)≤twice/week REFHRadj (95% CI) AD: >twice/week 0.50 (0.20-1.27)≤twice/week REF  |

Abbreviations: AD Diagnostic and treatment Center criteria -ADDTC; Alzheimer’s Disease-AD; Apolipoprotein E-APOE-e4; Analysis of Covariance-ANCOVA; Analysis of Variance-ANOVA; Blood Pressure-BP; Body Mass Index-BMI; Cambridge Mental Disorders of the Elderly Examination-CAMDEX; Cognitively Impaired No Dementia-CIND; Clinical Dementia Rating-CDR; Coronary Heart Disease-CHD; 95% Confidence Interval-95%CI; Diagnostic and Statistical Manual of Mental Disorders-III-Revised-DSM-III-R; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-DSM-IV; Docosahexaenoic acid-DHA; Eicosapentaenoic acid-EPA; Food-frequency questionnaire-FFQ; Gas Liquid Chromatography-GLC; Geriatric Mental State schedule-GMS; Hazard Ratio-HR; Informant Questionnaire for Cognitive Decline in the Elderly-IQCoDE; International Classification of Diseases, 10th revision-ICD-10; Lysophosphatidylcholine-lysoPC; Magnetic Resonance Imaging-MRI; Mini-Mental State Examination-MMSE; Modified Mini-Mental State Examination-3MSE; Myocardial Infarction-MI; omega 3 Poly-unsaturated fatty acids-n-3PUFA; National Institute of Neurological and Communicative Diseases and Stroke AD and Related Disorders Association-NINCDS-ADRDA; National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences NINDS-AIREN; Other dementia-OD; Odd Ratio-OR; Plasma phosphatidylcholine-PC; Phosphatidylethanolamine-PE; Prevalence ratio-PR; Relative Risk-RR; Semi-quantitative food-frequency questionnaire -SFFQ; Telephone Interview for Cognitive Status-TICS; Total phospholipid-PL; Vascular Dementia-VaD.

\*These two papers report on the same studied population but have different findings for AD as the earlier study did not adjust for education in its estimate for AD. Thus, the earlier study was used for its estimate for all-cause dementia and the second study was used for its estimate for AD.

**Supplemental Table 3: Quality assessment for the 11 articles identified that studied the association between fish consumption and the risk of dementia.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** |  **1** |  |  **2** |  |  **3** |  |  **4** |  |  **5** |  |  **6** |  | 7 |  |  **8** |  |  **9** |  |  **10** |
| Albanese et al(1) | ★  |  | ★  |  | ★  |  |   |  | ★  |  | ★  |  | ★  |  | ★  |  | ★  |  | ★  |
| Conquer et al(2) | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  |  |  |  |  | ★ |  | ★ |  |   |
| Kim et al(3) |  |  |  |  | ★ |  |  |  | ★ |  |  |  | ★ |  | ★ |  | ★ |  | ★ |
| Tully et al(4) | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  |  |  |  |  | ★ |  | ★ |  |   |
| Barberger-Gateau et al(5)  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |
| Barberger-Gateau et al (6)  | ★ |  | ★ |  |  |  | ★ |  | ★ |  | ★ |  |  |  | ★ |  |  |  | ★ |
| Devore et al(8)  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |
| Huangs et al (9) | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |
| Lopez et al(10) |  |  | ★  |  | ★  |  |  |  | ★  |  | ★  |  | ★ |  | ★  |  | ★  |  | ★  |
| Morris et al(11) | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |
| Schaefer et al(12) | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |  | ★ |

**Cross-sectional Studies**

1– Aims/objectives of the study clear and study design appropriate for the stated aim(s)

2 –The sample size justified

3 – Sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation.

4 – Selection process likely to select subjects/participants that were representative of the target/reference population under investigation.

5 – The exposure and outcome variables measured correctly using instruments/ measurements that had been trialed, piloted or published previously.

6 – Data analysis controlled for age, sex and education

7 – Data analysis controlled for other confounders

8 –Findings interpreted well

9 – Weakness mentioned and explained clearly

10 – Paper written well

**Cohort Study**

1 – Cohort truly representative
2 – Controls derived from the same cohort
3 – Clear measurement of fish consumption at baseline

4 – Adequacy Follow-up duration (≥12 months)

5 – Reliable methods of dementia and AD diagnosis (ie, Quality of outcome)

6 – Cohort data analysis controlled for age, sex and educational level
7 – Cohort data analysis controlled for other confounders
8 – Findings interpreted well

9 – Weakness mentioned and explained clearly

10 – Paper written well

N/A = Not applicable

**Case-Control Study**

1 – Is the case definition adequate? (yes, with independent validation)

2 – Representativeness of the cases

3 – Selection of controls (community controls)

4 – Definition of controls (No history of the disease)

5 – Clear measurement of fish consumption (clear records or structured interview and with same for both cases/controls)

6 – Data analysis controlled for age, sex and educational level

7 – Data analysis controlled for other confounders

8 – Findings interpreted well

9 – Weakness mentioned and explained clearly

10 – Paper written well

**Supplemental Table 4: The pooled analysis of AD risk in people with fish consumption versus those with no or lower level of fish consumption, by study design, by** **data analysis of level of fish consumption and by country of study in terms of income**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable for subgroup data analysis** |  | **Nos of studies\*** |  | **Participants** |  | **Nos of Alzheimer’s Dis** |  | **RR (95% CI)** |
| **By study design**  |  |  |  |  |  |  |  |  |
| Prospective cohort studies(follow up ≤ 5 years) (5, 10, 11) |  |  3 |  | 9,142 |  | 344 |  | 0.49 (0.30-0.80) |
| Prospective cohort studies(follow up year >5 years)(7-9, 12) |  |  4 |  | 9,532 |  | 761 |  | 0.75 (0.66-0.84) |
| **By fish consumption level** |  |  |  |  |  |  |  |  |
| Continuous(5, 7-12)  |  |  7 |  | 18,674 |  | 1105 |  | 0.73 (0.65-0.82) |
| Only 2 levels(7, 12) |  |  2 |  |  1,904 |  | 206 |  | 0.72 (0.50-1.03) |
| Only 3 levels(8, 10) |  |  2 |  |  5,637 |  | 395 |  | 0.95 (0.74-1.23) |
| 4 levels(5, 9, 11) |  |  3 |  | 11,133 |  | 504 |  | 0.67 (0.58-0.78) |
| **By country of study in terms of income** |  |  |  |  |  |  |  |  |
| High income countries (5, 7-12) |  |  7 |  | 18,674 |  | 1105 |  | 0.73 (0.65-0.82) |
| LMICs |  |  0 |  | NA |  | NA |  | NA |

 Abbreviations: Confidence Interval-CI; Relative Risk-RR.

\*The same number of studied populations

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Supplemental Fig.1: Funnel plot for the publication bias in the analysis of all dementia cases



Supplemental Fig. 2: Forest plot showing the association of the combination of all the fish consumption levels and dementia risk

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