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THIRTEEN-YEAR PROSPECTIVE STUDY BETWEEN FISH CONSUMPTION, LONG-CHAIN N-3 FATTY ACIDS INTAKES AND COGNITIVE FUNCTION

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Abstract: *Objectives:* Because of their structural, anti-inflammatory and antithrombic properties, long-chain n-3 fatty acids may be key factors in the aging process. We sought to elucidate the association between intake of long-chain n-3 fatty acids and/or fish and cognitive function evaluated 13 years after dietary assessment. *Design:* Prospective population-based study. *Participants/Setting:* 3,294 adults from the SU.VI.MAX study (Supplementation with Antioxidant Vitamins and Minerals study). *Measurements/Statistical analysis:* Subjects underwent a standardized clinical examination which included cognitive tests and self-reported cognitive difficulties scale (2007-2009). Poor scores were defined using percentiles as cut-off. Dietary data were assessed through repeated 24-h dietary records. Odd ratio (OR), comparing the fourth (Q4) to the first quartile (Q1), of having a poor score were calculated using adjusted logistic regression. *Results:* Self-reported cognitive difficulties were less frequent among subjects with higher intakes of total n-3 long chain fatty acids (OR = 0.72, CI 95%=0.56-0.92) and eicosapentaenoic acid (OR Q4 versus Q1 = 0.74, CI 95%=0.58-0.95), even after adjustment for depressive symptoms. A borderline significant association was also found with high fish consumption (OR Q4 versus Q1 = 0.80, CI 95%=0.63-1.01). *Conclusion:* Cognitive complaints, which may be an early indicator of cognitive decline, are less frequent among the elderly who have a high long-chain n-3 acids intake, as assessed 13 years earlier.

Key words: Cognition, cognitive difficulties, fish, omega-3 fatty acids.

Introduction

In a context of increasing life span, it is of major public health importance to enhance the quality of aging, to optimize the health status of the elderly and to delay loss of autonomy. As modifiable factors, nutritional aspects are of particular interest as preventive goals.

In France, diet has been shown to be rich in n-6 fatty acids and poor in n-3 fatty acids (FA) (1). Nutritional guidelines have been recently developed to improve the health status of the general population via nutrition (2). In particular, these guidelines advise eating fish at least twice a week. It would be of major interest to estimate whether promoting long chain n-3 fatty acids, notably through fish consumption, can improve cognitive aging.

As essential structural components of the neuronal membrane, and through their anti-thrombotic and anti-inflammatory properties (3), long-chain n-3 fatty acids are presumed to be key factors involved in the aging process, especially affecting cognitive functions (4).

However, observational epidemiologic studies evaluating the association between long-chain n-3 FA and/or fish and cognitive performance, cognitive decline and dementia, have produced inconsistent results according to recent reviews (5;6). Some studies suggested that long-chain n-3 FA intake and/or fish consumption may prevent dementia, and particularly Alzheimer diseases (7-10), while others did not (11, 12). Findings concerning cognitive performances (13-16) and decline (17-20) are even more inconsistent.

Most studies focusing on aging and nutritional factors included older populations. Studies are lacking on the consequences of nutrition, as assessed during middle age, upon the quality of cognitive ageing.

The aim of the present study was to investigate the association between fish consumption, long-chain n-3 FA, in particular EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), and markers of cognitive function and subjective cognitive difficulties evaluated 13 years after dietary assessment, in men and women participating in the SU.VI.MAX 2 study.

Materials and methods

Population and data collection

The SUVIMAX study

The SU.VIMAX study was initially a randomized double-blind, placebo-controlled, primary prevention trial that began in 1994 and ended in 2002. Design and methods have been reported elsewhere (21, 22).

This study was initially designed to evaluate the effect of 8-year daily antioxidant supplementation at nutritional doses (vitamin C, vitamin E, beta-carotene, selenium, zinc) on the incidence of cardiovascular disease and cancer. A total of 13,017 individuals (5,141 men aged 45–60 y and 7,876 women

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aged 35–60 y) were included and followed for an average of 7.5 years. During that period, participants were invited to a yearly check-up consisting of blood sampling alternating with a clinical examination. Subjects were also invited to complete a 24 h record every 2 months for a total of 6 records per year covering all days of the week and all seasons. Data were collected through computerized questionnaires using the Minitel, a small terminal used in France as an adjunct to the telephone. Participants were assisted by an instruction manual for coding food portions including validated photographs of more than 250 foods represented in three different portion sizes. Subjects could also choose from two intermediate or two extreme portions, for a total of seven different possible portion sizes (23).

At baseline, data on gender, date of birth, smoking status, education level, physical activity and medication uses were collected by a self-administered questionnaire. Blood samples were obtained after a 12-h fast; all biochemical measurements were centralized in a single laboratory. Fasting blood glucose and total cholesterol were measured by using an enzymatic method (Advia 1650; Bayer Diagnostic, New York, NY). Blood pressure (BP) was measured using a standardized procedure with a mercury sphygmomanometer. It was taken twice from each arm in subjects who had been lying down for 10 min. The mean between the lowest right and left measures was retained.

The SUVIMAX 2 study

In 2006, 8,330 SU.VI.MAX participants from among the 11,141 who ended the SU.VI.MAX trial accepted an invitation to undergo a new check-up in view of a future specific study. Among them, 7,180 subjects agreed to enroll in the SU.VI.MAX. 2 study. The aim of that study was to investigate the impact of nutrition on quality of aging.

All participants were invited to undergo a clinical examination in one of the medical centers participating in the study. Examination included a self-reported questionnaire completed by the participants and a clinical examination performed by trained technicians and geriatricians. The self-reported questionnaire included data on sociodemographic characteristics, lifestyle, personal medical history, family medical history, instrumental activities of daily living, depressive symptoms by means of a French version of the Center for Epidemiologic Studies Depression Scale (CES-D) (24) and self-reported memory complaint using McNair's Cognitive Difficulties Scale (CDS) (25).

The assessment of cognitive functions included a French version of the MMSE which evaluates overall cognitive functions (26), a 5-word test which is an immediate and delayed verbal memory test including free and cued recall (27).

In case of suspected health event (cardiovascular diseases and cancer), investigations were conducted to obtain relevant medical data (clinical, biochemical, histological, radiological reports) from participants, physicians and/or hospital. All reported cardio- and cerebrovascular events were reviewed and validated by an independent expert committee.

The SU.VI.MAX and SU.VI.MAX 2 studies were approved by the Ethical Committee for Studies with Human Subjects of Paris-Cochin Hospital (CCPPRB n° 706 and n° 2364, respectively) and the Comité National Informatique et Liberté (CNIL n° 334641 and n° 907094, respectively).

Inclusion criteria

Among the 7,180 potential participants, 6,850 subjects were able to come to the specific centers for the check-up. Among them, and for this specific analysis, we selected the 3,611 subjects who were older than 45 at baseline and who had completed at least six 24-h dietary records during the first two years of the SU.VI.MAX follow-up to better account for intra individual variability in intakes. In addition, a total of 317 subjects were excluded because of a missing value for at least one covariable (except for hypertension: a missing category was created because of more than 5% of missing value) (28), leaving 3,294 subjects for this specific analysis.

Statistical analysis

Dietary nutrient intakes were calculated based on the average daily food intakes of each subject using a food composition table (29). Fish (and seafood) from composite dishes were taken into account for fish consumption estimation. N-3 long-chain FA intakes were calculated as the sum of EPA eicosapentaenoic acid), DHA (docosahexaenoic acid) and DPA (docosapentaenoic acid). Total n-3 FA intake was calculated as the sum of alpha-linolenic acid and n-3 long-chain FA intake. Energy adjustment was performed using the residual method (30).

Scores for McNair CDS (range 0-148, lower is better) and MMSE (range 0-30, higher is better) were calculated. For the 5-word test, a weighted score was calculated as the sum of immediate and delayed recall (31, 32). Two points were attributed to immediate recall and one point to cued recall for a total of 20 points (higher is better).

For clinical cognitive assessment, poor score were identified according to the 10th percentile (15) of the test score (MMSE<27, 5-words test<18). For Mc Nair CDS, we used the 4th quartile as cut-off (CDS McNair>39).

Body mass index (BMI) was calculated by dividing weight by height-squared (kg/m²). Hypertension at baseline was defined as SBP≥140 mmHg or a DBP≥ 90mmHg or reporting antihypertensive drugs use. Diabetes mellitus at baseline was defined as glycemia≥7mmol/L or reporting oral hypoglycaemic agents use. Hypercholesterolemia was defined as serum total-cholestestol≥6.5 mmol/L or reporting lipid lowering drugs use.

Interaction between gender and nutritional factors on outcome were tested.

Descriptive results are reported as percentage or mean ± standard deviation, as appropriate. Differences between men and women were tested using the chi-square test or Wilcoxon-Mann-Whitney test, as appropriate.

Logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI 95%) of having a poor score

on one of the test score according to the gender-specific quartile of fish consumption or of fatty acid intake. Tests for linear trend were performed using the ordinal score.

Based on previous literature and on exploratory analyses, the first adjusted model included gender, age at baseline (years), BMI (kg/m²), physical activity (irregular, <1 h walking/day, ≥ 1 h walking/day), tobacco status (never, former, current), education level (primary, secondary or university level), energy intake (Kcal/day) and alcohol consumption (g/day). In a second model, we also accounted for energy-adjusted saturated FA, energy-adjusted n-6 FA, fruit and vegetable consumption, baseline hypertension, mellitus diabetes and hypercholesterolemia and stroke and coronary heart diseases history. We performed a final model adjusted for depressive symptoms (using CES-D scale score).

Additional adjustments for cholesterol intake and vitamin E intake were also done. As they did not substantially modify the findings, these factors were not considered in the final model.

The supplementation group (intervention versus placebo) during the SU.VI.MAX trial (1994-2002) was not related to any markers of cognitive performances, assessed in the SU.VI.MAX 2 study. This cofactor was therefore not taken into account in the analyses.

All statistical analyses were performed using SAS software (version 9.1, SAS Institute Inc, Cary, NC, USA).

Results

A total of the 1,772 men and 1,522 women were retained for the present analysis (table 1).

Women reported stronger depressive symptoms, but had a better score on the MMSE and 5-word test than men.

Table 2 shows the association between cognitive function and intake of fish and related fatty acids. We did not observed significant association between poor scores on the MMSE and 5-word cognitive tests and intake of fish and related fatty acids. Nevertheless, subjects with high intake in total n-3 fatty acids showed less frequently a poor score on MMSE but the association was not significant.

Table 3 shows the association between self-administered cognitive difficulties and intake of fish and related fatty acids.

A poor score on the McNair CDS was negatively associated with increasing intake of EPA, DHA and long-chain n-3 FA (model 2). High consumption of fish was also associated with less frequent cognitive complaints but the association was only borderline significant after adjustment for depressive symptoms.

Table 1
Characteristics (mean ± SD or %) of men (N = 1,772) and women (N = 1,522) in the SU.VI.MAX 2 study, 2007-2009

	Men	Women	P[1]
N	1,772	1,522	
Age at clinical exam (years)	64.7 ± 4.7	63.7 ± 4.6	<0.0001
Body mass index (kg/m²) (baseline)	24.9 ± 2.7	22.9 ± 3.1	<0.0001
Intervention group during the trial phase	53.72	52.96	0.66
Hypertension (13.5% missing values) (baseline)	40.89	24.79	<0.0001
Diabetes Mellitus (baseline)	5.81	2.56	<0.0001
Hypercholesterolemia (baseline)	34.99	31.41	0.03
Physical activity (baseline)			
Irregular	23.31	23.32	<0.0001
< 1 h walking/d	23.14	36.14	
≥ 1 h walking/d	53.56	40.54	
Smoking status(baseline)			
Non-smoker	38.09	64.72	<0.0001
Former smoker	50.68	25.56	
Current smoker	11.23	9.72	
Education level(baseline)			
Primary school	22.91	20.57	0.0002
High school	36.46	43.5	
University or equivalent	40.63	35.94	
Cognitive markers and CES-D			
McNair CDS (self-reported) (0-148, 0 is better)	29.2 ± 15.6	30.3 ± 15.8	0.05
MMSE (0-30, 30 is better)	28.56 ± 1.44	28.63 ± 1.46	0.04
5-words (0-20, 20 is better)	18.9 ± 1.4	19.3 ± 1.2	<0.0001
CES-D scale score (0-60, 0 is better)	7.2 ± 6.5	10.2 ± 8.0	<0.0001
Intake (baseline)			
Energy[2] (Kcal/d)	2316.6 ± 506.0	1766.5 ± 428.6	<0.0001
Ethanol (g/d)	28.9 ± 22.7	11.5 ± 13.1	<0.0001
Carbohydrates[3]	42.2 ± 6.1	41.8 ± 5.6	0.02
Lipids[3]	40.0 ± 5.0	40.3 ± 4.8	0.05
Proteins[3]	17.8 ± 2.6	17.9 ± 2.7	0.40
Fish and seafood (g/d)	51.3 ± 35.8	42.3 ± 29.8	<0.0001
EPA[4] (g/d)	0.15 ± 0.13	0.15 ± 0.10	0.33
DHA[4] (g/d)	0.28 ± 0.23	0.28 ± 0.18	0.18
Long-chain n-3 fatty acids[4] (g/d)	0.50 ± 0.38	0.49 ± 0.31	0.47
Total n-3 fatty acids[4] (g/d)	1.37 ± 0.46	1.38 ± 0.37	0.01

EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; 1. P of chi-square test for categorical variables and of Wilcoxon-Mann-Whitney test for continuous variables; 2. Excluding energy from alcohol; 3. Values are percentage of total daily energy intake (without alcohol); 4. Energy-adjusted intake using residual (see methods section)

Discussion

In a large population-based study of French elderly, we observed that subjects with high intake of long-chain n-3 fatty acids at the onset of the study less frequently had a poor score on the McNair CDS evaluating cognitive difficulties, assessed 13 years later.

To our knowledge, no other studies have evaluated a potential link between diet and cognitive difficulties using a self-administered scale, which may be considered as an early indicator of cognitive impairment (33).

After accounting for depressive symptoms, results were partly attenuated but remained significant. This attenuation is not surprising. Indeed, McNair CDS and depression have been previously associated (25). In addition, n-3 PUFA are suspected to be associated with depression or mood despite a lack of consistent findings in epidemiological and clinical trials (34, 35).

Table 2

Adjusted OR (95%CI) for poor score on cognitive test across gender-specific quartile of intake of fish and related fatty acids assessed 13 years before

Global cognitive test (poor<27)		**Q1**	**Q2**	**Q3**	**Q4**	**P[1]**
EPA[2]	Model 1[3]	1 [-]	1.08 [0.77-1.52]	0.84 [0.59-1.19]	0.98 [0.69-1.39]	0.57
	Model 2[4]	1 [-]	1.09 [0.78-1.53]	0.85 [0.60-1.22]	0.98 [0.69-1.39]	0.58
	Model 3[5]	1 [-]	1.11 [0.79-1.57]	0.82 [0.57-1.18]	0.96 [0.68-1.37]	0.47
DHA[2]	Model 1[3]	1 [-]	0.85 [0.61-1.20]	0.91 [0.65-1.28]	0.87 [0.62-1.23]	0.52
	Model 2[4]	1 [-]	0.86 [0.61-1.22]	0.93 [0.66-1.31]	0.87 [0.62-1.23]	0.55
	Model 3[5]	1 [-]	0.87 [0.62-1.23]	0.89 [0.63-1.26]	0.85 [0.60-1.21]	0.41
Long-chain n-3 fatty acids[2]	Model 1[3]	1 [-]	0.96 [0.68-1.34]	0.88 [0.62-1.24]	0.88 [0.62-1.24]	0.40
	Model 2[4]	1 [-]	0.97 [0.69-1.36]	0.89 [0.63-1.27]	0.88 [0.62-1.25]	0.41
	Model 3[5]	1 [-]	0.98 [0.70-1.39]	0.86 [0.60-1.22]	0.86 [0.61-1.23]	0.31
Total n-3 fatty acids[2]	Model 1[3]	1 [-]	0.95 [0.68-1.32]	0.89 [0.63-1.25]	0.79 [0.56-1.12]	0.18
	Model 2[4]	1 [-]	0.97 [0.69-1.36]	0.92 [0.65-1.31]	0.79 [0.55-1.14]	0.21
	Model 3[5]	1 [-]	0.95 [0.67-1.34]	0.91 [0.64-1.30]	0.75 [0.52-1.09]	0.14
Fish	Model 1[3]	1 [-]	1.10 [0.78-1.53]	0.98 [0.69-1.39]	0.84 [0.59-1.21]	0.29
	Model 2[4]	1 [-]	1.13 [0.80-1.58]	0.99 [0.70-1.41]	0.83 [0.58-1.20]	0.26
	Model 3[5]	1 [-]	1.10 [0.79-1.53]	0.97 [0.68-1.37]	0.85 [0.60-1.21]	0.29
Verbal Memory (poor<18)		**Q1**	**Q2**	**Q3**	**Q4**	**P[1]**
EPA[2]	Model 1[3]	1 [-]	0.78 [0.55-1.10]	1.00 [0.72-1.40]	1.00 [0.72-1.40]	0.63
	Model 2[4]	1 [-]	0.78 [0.55-1.11]	1.01 [0.72-1.41]	1.01 [0.72-1.41]	0.61
	Model 3[5]	1 [-]	0.79 [0.55-1.13]	0.97 [0.69-1.36]	1.01 [0.72-1.42]	0.67
DHA[2]	Model 1[3]	1 [-]	0.89 [0.63-1.27]	1.02 [0.72-1.43]	1.13 [0.81-1.57]	0.36
	Model 2[4]	1 [-]	0.87 [0.61-1.23]	0.99 [0.71-1.40]	1.13 [0.80-1.57]	0.36
	Model 3[5]	1 [-]	0.87 [0.61-1.23]	0.94 [0.66-1.33]	1.13 [0.81-1.59]	0.39
Long-chain n-3 fatty acids[2]	Model 1[3]	1 [-]	0.75 [0.53-1.07]	0.89 [0.63-1.24]	1.01 [0.73-1.40]	0.73
	Model 2[4]	1 [-]	0.75 [0.53-1.07]	0.88 [0.63-1.24]	1.02 [0.73-1.42]	0.70
	Model 1[3]	1 [-]	0.76 [0.53-1.07]	0.84 [0.60-1.19]	1.02 [0.73-1.41]	0.77
Total n-3 fatty acids[2]	Model 1[3]	1 [-]	0.95 [0.68-1.33]	0.82 [0.58-1.16]	1.06 [0.76-1.47]	0.94
	Model 2[4]	1 [-]	0.93 [0.66-1.31]	0.79 [0.55-1.13]	1.03 [0.73-1.46]	0.94
	Model 3[5]	1 [-]	0.89 [0.63-1.26]	0.77 [0.54-1.11]	1.03 [0.72-1.46]	0.97
Fish	Model 1[3]	1 [-]	0.76 [0.54-1.08]	0.92 [0.66-1.29]	1.10 [0.79-1.54]	0.38
	Model 2[4]	1 [-]	0.78 [0.55-1.11]	0.92 [0.65-1.29]	1.09 [0.78-1.52]	0.45
	Model 3[5]	1 [-]	0.76 [0.53-1.07]	0.92 [0.66-1.29]	1.09 [0.78-1.51]	0.41

EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; 1. P for trend (all such values); 2. Energy-adjusted intake using residual (see methods section); 3. Model 1: adjusted for gender, age, BMI, physical activity, tobacco status, education, energy intake, alcohol; 4. Model 2: model 1 + baseline saturated fatty acids intake, n-6 fatty acids intake and fruit and vegetables consumption, baseline diabetes mellitus, hypercholesterolemia and hypertension and stroke and coronary heart diseases history; 5. Model 3: model 2 + CES-D scale score

Table 3

Adjusted OR (95%CI) for self-reported cognitive difficulties across gender-specific quartile of intake of fish and related fatty acids assessed 13 years before

Cognitive difficulties (poor>39)		**Q1**	**Q2**	**Q3**	**Q4**	**P[1]**
EPA[2]	Model 1[3]	1 [-]	0.88 [0.70-1.10]	0.94 [0.75-1.18]	0.69 [0.55-0.88]	0.01
	Model 2[4]	1 [-]	0.89 [0.71-1.12]	0.96 [0.76-1.20]	0.69 [0.55-0.87]	0.01
	Model 3[5]	1 [-]	0.93 [0.73-1.19]	1.02 [0.80-1.29]	0.74 [0.58-0.95]	0.05
DHA[2]	Model 1[3]	1 [-]	1.00 [0.80-1.26]	0.84 [0.67-1.05]	0.76 [0.60-0.96]	0.01
	Model 2[4]	1 [-]	1.01 [0.81-1.27]	0.84 [0.67-1.06]	0.75 [0.60-0.95]	0.01
	Model 3[5]	1 [-]	1.09 [0.86-1.39]	0.92 [0.72-1.17]	0.81 [0.63-1.03]	0.04
Long-chain n-3 fatty acids[2]	Model 1[3]	1 [-]	0.84 [0.67-1.05]	0.86 [0.68-1.08]	0.68 [0.54-0.85]	0.002
	Model 2[4]	1 [-]	0.86 [0.68-1.08]	0.87 [0.70-1.10]	0.68 [0.53-0.85]	0.002
	Model 3[5]	1 [-]	0.88 [0.69-1.12]	0.96 [0.75-1.21]	0.72 [0.56-0.92]	0.02
Total n-3 fatty acids[2]	Model 1[3]	1 [-]	1.04 [0.83-1.30]	0.89 [0.71-1.12]	0.81 [0.64-1.03]	0.04
	Model 2[4]	1 [-]	1.01 [0.80-1.27]	0.85 [0.67-1.08]	0.75 [0.59-0.96]	0.01
	Model 3[5]	1 [-]	1.09 [0.85-1.39]	0.91 [0.71-1.17]	0.80 [0.62-1.03]	0.04
Fish	Model 1[3]	1 [-]	0.88 [0.70-1.11]	0.93 [0.74-1.17]	0.79 [0.62-1.00]	0.08
	Model 2[4]	1 [-]	0.95 [0.75-1.21]	0.94 [0.73-1.19]	0.85 [0.66-1.09]	0.20
	Model 3[5]	1 [-]	0.89 [0.70-1.11]	0.94 [0.75-1.18]	0.80 [0.63-1.01]	0.10

EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; 1. P for trend (all such values); 2. Energy-adjusted intake using residual (see methods section); 3. Model 1: adjusted for gender, age, BMI, physical activity, tobacco status, education, energy intake, alcohol; 4. Model 2: model 1 + baseline saturated fatty acids intake, n-6 fatty acids intake and fruit and vegetables consumption, baseline diabetes mellitus, hypercholesterolemia and hypertension and stroke and coronary heart diseases history; 5. Model 3: model 2 + CES-D score

In our study, we observed only a trend towards an association between poor score on MMSE and total n-3 fatty acids while a recent study observed a lower 5-year cognitive decline (assessed through a decrease in the MMSE score) among 70-89-year-old subjects having a high intake of EPA+DHA or fish (20). The absence of significant association between clinical cognitive tests and intakes of fish and n-3 FA may be due to a lack of power resulting from a reduced variability for cognitive performances evaluated through tests subjected to a ceiling effect. The MMSE has proven to be a reliable and valid indicator of cognitive impairment (36) but dietary factors may be associated with small effects on cognitive impairment, which may not be detected with the MMSE especially in a relatively young population with preserved cognitive function. In addition, it had previously been reported that, although variability between subjects is substantial, intake in long-chain n-3 FA in the SU.VI.MAX population is relatively high compared to that of other countries (1). If only very low intakes of n-3 FA are related to cognitive impairment, then it is possible that we would have been unable to detect such an effect because of the low proportion of the population presenting a very low intake. Evaluations of the relationship between cognitive performances or decline and intake of fish and n-3 FA have become increasingly frequent over the last few years. In observational studies, fish consumption has been relatively regularly associated with risk of dementia (7-10), cognitive impairment (14, 15, 19) and decline (17, 19, 20), apart from three studies (11, 12, 16). In contrast, findings on long-chain n-3 FA intake have been less consistent, as some prospective and cross-sectional studies found an association with dementia (7), cognitive decline (20) and cognitive impairment (14), while other prospective studies did not find such an association (12, 17, 19). In addition, the hypothesis of an association between cognition and intake of long-chain n-3 FA was strengthened by findings from studies focusing on plasma or erythrocyte concentrations (37-39), although one recently published study on erythrocyte membrane concentration did not observe this association (40). Disparities between these findings may be at least partly attributed to differences in study design (e.g. age of subjects, follow-up duration), the types of tests performed (e.g. specific or global cognitive test, self-administered or clinical exam) and the quality of dietary assessment, especially regarding food composition tables.

Some limitations in our study have to be emphasized. First, a lack of power may occur resulting from limited variability for cognitive performances as explained above. Second, generalizability of our findings may be discussed as our cohort was based on healthy volunteers participating initially in a nutritional intervention study who generally had a higher education level and occupational status, along with a healthier diet, than the general population (22). Third, there is a lack of cognitive evaluation assessment at baseline preventing us from evaluating cognitive decline. However, when participants were asked to report memory difficulties and attention trouble at baseline, we observed no differences in dietary intakes according to their answers.

The prospective design of the current study, where diet was assessed several years before the assessment of cognitive functions, is an important strength. In addition, diet assessment through repeated 24 h records led to obtaining comprehensive and accurate dietary data, especially for n–3 FA intake. Fish consumption and long-chain n-3 FA intake may be a marker of a healthy diet (41), also characterized by high consumption of fruit and vegetables and thus high intake of antioxidants or folates, which may confound potential associations (6). Although we cannot exclude the possibility that specific confounders were not taken into account, a wide variety of cofactors, including diet and vascular factors, were assessed during the survey follow-up, thereby accounting for multiple confounding factors.

Conclusion

In conclusion, our study provides support that cognitive complaints may be less frequent among the elderly who had a high intake of long-chain n-3 fatty acids and fish consumption, even after adjustment for other markers of healthy lifestyle and depressive symptoms. As memory complaints may be an early sign of cognitive impairment, nutritional recommendations regarding long-chain n-3 fatty acids may help to prevent aged-related cognitive decline.

Appendix 1

Members (City) of the Research SU.VI.MAX 2 Study Group

Luc Vogt (Agen); Michèle Escande (Allauch); Jean-Marie Sérot (Amiens); Emmanuel Vasseur (Angers); Matthieu Debray (Annecy); Chantal Hussonnois (Auxerre); Martine Iehl-Robert (Besançon); Myriam le Sommer (Bordeaux); Thierry Boge (Bourg en Bresse); Josiane Rajaonarivo (Bourges); Jean Jouseau (Bourges); Monique Frison (Brest); Armelle Gentric (Brest); Fabienne Leenaert (Caen); Bernard Bascou (Carcassonne); Jean-Paul Lemaire (Cavaillon); Nathalie Baptiste (Champcueil); Marie-France Maugourd (Champcueil); Anne Gibelain (Chartres); Roland Lopitaux (Clermont-Ferrand); Jacques Hild (Colmar); Henri Nachar (Avignon); Géraldine Soulié (Dax); Francine Clémenti (Dax); Patrick Friocourt (Blois); Alain Sagnier (Chambéry); Philippe Schiano (Hyères); Andréa Collet (Port-Louis Riantec); Dominique Richard (Dijon); Françoise Zandi (Gradignan); Pascal Couturier (Grenoble); Agathe Raynaud-Simon (Ivry); Pierre Lermite (La Roche sur Yon); Michel Alix (La Rochelle); Emmanuel Alix (Le Mans); François Puisieux (Lille); Cédric Gaxatte (Lille); Thierry Dantoine (Limoges); Pierre livet (Lyon); Gilles Albrand (Lyon); Pierre Haond (Lyon); Pascal Ménecier (Macon); François Pinoche (Malestroit); Sylvie Bonin Guillaume (Marseille); Marc Heim (Marseille); André Wang (Metz); Claude Jeandel (Montpellier); Yves Passadori (Mulhouse); Athanase Benetos (Nancy); Catherine Couturier (Nantes); Gilles Berrut (Nantes); Sylvie Sacher-Huvelin (Nantes); Henri Patouraux (Nevers); Patrice Brocker (Nice); Olivier Guérin (Nice); Denise Strubel (Nîmes); Florence Dupriez (Orléans); Jean-Bernard Gauvain (Orléans); Yves Wolmark (Paris); Olivier Hanon (Paris); Bernard Cassou (Paris); Philippe Déjardin (Paris, Troyes); François de la Fournière (Pau); Frédéric Woné (Périgueux); Claudine Buj-Hardy (Perpignan); Marc Paccalin (Poitiers); Bertrand Placines (Pontacq-Nay); Jean-Luc Novella (Reims); Pierre Jouanny (Rennes); Florence Martin (Rodez, Toulouse); Philippe Chassagne (Rouen); Isabelle Landrin (Rouen); Chantal Girtanner (Saint-Etienne); Régis Gonthier (Saint-Etienne); Claudie Troadec (Saint-Brieuc); Christophe Dourthe (Saintes); Eric Bonnin (Saintes); Jean-Paul Marot

(Saint-Nazaire); Sylvie Rossignol (Sens); Georges Sebbane (Sevran); Pierre-Yves Cornu (Sevran); Jean-Jacques Monsuez (Sevran); Isabelle Périllat (Sevran); Robert Ratiney (Sevran); Georges Kaltenbach (Strasbourg); Yves Rolland (Toulouse); Thierry Constans (Tours); Gisèle Coz (Tréguier); Monique Ferry (Valence); Jean Pierre Aquino (Versailles); Odile Cézard (Voiron).

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