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Seafood consumption, toenail mercury and selenium with cognitive function among American adults -- 25 years of follow-up

Xuanxia Mao, MS[1,2,†], **Cheng Chen, PhD**[3,†], **Pengcheng Xun, PhD**[3], **Martha Daviglus, MD,PhD**[4], **Lyn M. Steffen, PhD**[5], **David R. Jacobs Jr, PhD**[5], **Linda Van Horn, PhD**[6,7], **Stephen Sidney, MD**[7], **Na Zhu, MD,PhD**[8], and **Ka He, MD, ScD**[3]

[1]Department of Clinical Nutrition, School of Medicine, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China.

[2]Department of Nutrition, School of Medicine, Shanghai Jiao Tong University, Shanghai, China.

[3]Department of Epidemiology and Biostatistics, School of Public Health-Bloomington, Indiana University, Bloomington, Indiana, USA.

[4]Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA.

[5]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA.

[6]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA.

[7]Division of Research, Kaiser Permanente Northern California, Oakland, California, USA.

[8]Indiana University Health Arnett Hospital, Lafayette, Indiana, USA.

Abstract

Objectives: To examine the longitudinal association between seafood as well as long-chain omega-3 polyunsaturated fatty acids (LCω−3PUFA) intake and cognitive function and to explore the possible effect modifications by mercury (Hg) and selenium (Se) levels.

Methods: Participants (*n*=3,231) from the Coronary Artery Risk Development in Young Adults Study underwent baseline examination and were re-examined in 8 follow-ups. Diet was assessed at baseline, exam years 7 and 20. Toenail Hg and Se were measured at exam year 2. Cognitive function was measured at exam year 25 using 3 tests: Rey Auditory Verbal Learning Test

Correspondence to Dr. Ka He, Department of Epidemiology and Biostatistics, School of Public Health -- Bloomington, Indiana University, 1025 E. Seventh Street, SPH C042, Bloomington, Indiana 47405, USA (Phone: 812-856-2260; Fax: 812-855-9107; kahe@indiana.edu).

†Co-first author.

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(RAVLT), Digit Symbol Substitution Test (DSST), and the Stroop Test. The general linear regression model was used to examine cumulative average intakes of LCω−3PUFA and seafood in relation to the cognitive test scores; and to explore the possible effect modifications by Hg and Se.

Results: LCω−3PUFA intake was significantly associated with better performance in the DSST test [quintile 5 *vs.* quintile 1; mean difference = 1.74; 95% CI = (0.19, 3.29); *P* for trend = 0.048], but not in the RAVLT and Stroop tests. Similar results were observed for intakes of EPA, DHA, and non-fried seafood. The observed associations were more pronounced in participants with body mass index ≥25 kg/m^2, but not materially modified by toenail Hg or Se.

Conclusion: This longitudinal study supports the hypothesis that LCω−3PUFA or non-fried seafood intake is associated with better cognitive performance in psychomotor speed among American adults, especially in overweight and obese individuals.

Keywords

LCω−3PUFA; seafood consumption; Hg; Se; cognitive function

INTRODUCTION

Cognitive dysfunction is a common outcome of aging that may lead to dementia, which is an irreversible disorder. Since cognitive decline begins in middle age and progresses slowly during the decades before a diagnosis of clinical dementia [1], the prevention of cognitive decline at early stages is of great medical and economic importance.

Long-chain omega-3 polyunsaturated fatty acids (LCω−3PUFA) from seafood may play important roles in maintaining cognitive function through the reduction of inflammation [2]. However, epidemiological data are inconsistent and non-conclusive. Two systematic reviews among randomized clinical trials (RCT) concluded that no sufficient evidence supports the beneficial effects of LCω−3PUFA supplementation on cognitive decline. But, most of the RCTs included in the systematic reviews had small sample sizes (<100 participants) with short intervention durations (<5 months) [3, 4]. On the other hand, observational studies supported benefits of long-term intakes of LCω−3PUFA and seafood on age-related cognitive decline [5, 6]. Of note, most of the previous studies focused on older adults and those of young adults are limited. Since cognition declines with aging and young adults are under the risk development stage, following-up a cohort of young adults to midlife or later will provide insight on the natural history or etiology of cognitive decline.

When examining LCω−3PUFA intake and cognitive decline, mercury (Hg) and selenium (Se) are two elements should be considered since they often coexist with LCω−3PUFA in seafood. Hg has potential neurotoxicity [7], while Se may be neuroprotective due to its anti-oxidative and anti-inflammatory properties [8] or by modulating the neurotoxicity effect of Hg [9]. It has been hypothesized that the benefit of LCω−3PUFA or seafood on cognitive function may be more pronounced in the setting of high Se and low Hg concentrations. However, no study has examined the potential three-way interaction.

We therefore analyzed the data from a cohort of young adults with 25 years of follow-up to prospectively examine the long-term associations between LCω−3PUFA intake and seafood

consumption with cognitive performance. We hypothesize that higher intakes of LCω−3PUFA and seafood are associated with better cognitive function, especially in the setting of high Se and low Hg levels.

METHODS

Study population

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a multicenter, ongoing longitudinal cohort study that recruited 5,115 biracial male and female young adults initially aged 18–30 years in 1985–1986 from 4 study centers. The participants underwent baseline examination and were re-examined in 8 follow-ups at exam years 2, 5, 7, 10, 15, 20, 25, and 30. The detailed design and methods of the CARDIA project are published elsewhere [10].

Among the 3,499 participants who remained at exam year 25, 3,316 had information available on cognitive function measurements. Of them, 85 participants were sequentially excluded because of missing data on baseline LCω−3PUFA or seafood (n=2), report of an extreme energy intake (<600 or >6000 kcal/day for women; <800 or >8000 kcal/day for men) (n=13), and experience of a stroke event during the follow-up (n=70). Thus, the final database included 3,231 participants. Written informed consent was provided by all of the participants. The study design, data collection and analyses were approved by the institutional review boards of the CARDIA participating institutions.

Seafood consumption and LCω−3PUFA intake

Dietary intake information was collected using the interviewer-administered CARDIA Diet History questionnaire at baseline, exam years 7 and 20. The CARDIA questionnaire has been evaluated and discussed elsewhere [11, 12]. In brief, participants were asked about their diet habits in the prior 30 days, including frequency, amount and food preparation methods. Since preparation method, particularly frying, may substantially alter the fatty acids content of a seafood meal [13], seafood consumption was divided into fried and non-fried seafood intake groups. Fried seafood consumption included intakes of fried fish and fried shellfish from commercial and fast food. Non-fried seafood consumption was the sum of fresh fish, smoked fish, lean fish, and shellfish intakes. Because the distribution of fried seafood consumption was extremely skewed and relatively narrow, it was considered as a covariate when examining non-fried seafood, but not as an exposure of interest. Nutrient intake was estimated using an adaptively updated nutrient database from the Nutrition Coordinating Center at the University of Minnesota. Information on supplementation use was also collected. In this study, LCω−3PUFA intake was defined as the sum of eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) intakes from diet and supplementation. Because of the relatively small amount and the narrow distribution, DPA was not analyzed as a separate exposure in the analysis. To reduce the measurement errors caused by within-person variation and to best represent the long-term dietary intakes, cumulative average daily intakes of LCω−3PUFA and seafood, which were calculated by averaging the corresponding measurements at baseline and exam years 7 and 20, were used in the analyses. A modified A Priori Diet Quality Score was

calculated to measure the quality of diet based on other food groups at baseline and exam years 7 and 20 [14]. The average of the three measurements were used in the analyses.

Cognitive function assessments

Cognitive function was measured at exam year 25 using 3 tests, including Rey Auditory Verbal Learning Test (RAVLT), Digit Symbol Substitution Test (DSST), and the Stroop Test. All tests were administered by trained and certified CARDIA research technicians following a standardized protocol. RAVLT examined verbal learning and memory by assessing the ability to correctly memorize and recall 15 words after a 10-minute delay. A greater number of words recalled (corresponds to a higher score; possible range: 0–15) indicated better cognitive performance. DSST from the Wechsler Adult Intelligence Scale–III measured psychomotor speed, sustained attention, and working memory [15]. The possible scores ranged from 0 to 133, with a higher score indicating better cognitive performance. The Stroop Test evaluated executive function by assessing the ability to view a complex visual stimulus and to respond while suppressing the responses to another dimension [16, 17]. The test was scored by the time to complete the trials plus the number of errors, thus a higher score indicated worse cognitive performance.

Other Variables

Toenail clippings from all 10 toes were collected at exam year 2 and shipped to a central laboratory at the University of Missouri Research Reactor [18]. Toenail Hg and Se were measured by using instrumental neutron-activation analysis [19]. Plasma HDL-cholesterol, and triglyceride concentrations were measured through baseline to exam year 30 by enzymatic methods at Northwest Lipids Research Laboratory (Seattle, WA). Plasma LDL-cholesterol concentration was estimated by the Friedewald equation. Fasting glucose was measured at baseline and exam years 7, 10, 15, 20, 25, and 30 by using hexokinase coupled to glucose-6-phosphate dehydrogenase (Millipore, Inc, Bellerica, MA; later at the University of Minnesota) [10]. The cumulative average of repeated measurements across all available examinations of HDL-cholesterol, LDL-cholesterol, triglyceride and fasting glucose by exam year 25 when cognitive function was examined were used in the analyses. The cumulative average daily intakes of total energy, B_6, B_{12}, and folate were calculated by using the repeated measurements at baseline and exam years 7 and 20 through CARDIA questionnaire. In addition, some other important covariates were collected at each follow-up. Demographic and lifestyle information, including age, sex (female or male), race (black or white), study center, education levels, smoking status, alcohol consumption, and physical activity were collected through a self-administered questionnaire and were verified in clinic examinations. Education attained through exam year 25 has 3 levels (<12.0, 12.0–15.9, or ≥16.0 years). Smoking status at exam year 25 was classified into 3 groups: never-, former or current smokers. Alcohol consumption was presented as milliliters of alcohol per day. Physical activity was assessed using the CARDIA Physical Activity History Questionnaire. Body weight and height were measured to calculate body mass index (BMI). Blood pressure was measured by using a random zero sphygmanometer from baseline to exam year 15 and the Omron HEM907XL sphygmomanometer (Omron Corporation, Kyota, Japan) at exam years 20, 25, and 30 [20]. A calibration study was performed at exam year 20 in a subgroup

of participants. Cumulative average alcohol intake, physical activity, BMI, and blood pressure by exam year 25 were calculated by averaging the repeated measurements.

Statistical analysis

Characteristics of participants were summarized using mean values with standard deviations or medians with inter-quartile ranges for continuous variables and proportions for categorical variables. Analysis of variance (ANOVA), the Kruskal-Wallis test, or the chi-squared test, as appropriate, were used to test for the differences across quintiles of LCω−3PUFA intake. Covariates related to cognitive function and associated with LCω−3PUFA intake were considered in the main analyses.

The general linear regression model was used to examine the associations between intake of LCω−3PUFA, DHA, EPA or non-fried seafood and cognitive test scores. The mean differences of each cognitive test score with the corresponding 95% confidence intervals (CIs) using the lowest quintile of each exposure as the referent were estimated with adjustment for potential confounders (model 1 and 2). Linear trends were tested by using the continuous variable of the exposure with values over 99th percentile excluded.

Several sensitivity analyses were conducted to test the robustness of our findings. First, only participants with all repeated measurements of LCω−3PUFA, DHA, EPA, and non-fried seafood were included in the analysis. Second, shellfish was excluded from seafood consumption due to its relatively low levels of LCω−3PUFA. Third, model 2 was further adjusted for toenail Hg and Se levels as well as the dietary intakes of total energy, B_6, B_{12}, and folate to explore possible confounding effects from other nutrients and contaminants in seafood. Fourth, model 2 was additionally adjusted for the modified A Priori Diet Quality Score to reduce the influence of the diet quality based on other food groups.

In stratified analyses, the associations between intakes of LCω−3PUFA and cognitive test scores using tertiles or the continuous variable for LCω−3PUFA were estimated by stratifying age at exam year 25 (<median 51 years *vs.* ≥median 51 years), sex (female *vs.* male), race (black *vs.* white), BMI (<25 *vs.* ≥25 kg/m^2), smoking status (never- *vs.* ever-smokers), toenail Se levels (<median 0.85 ppm *vs.* ≥median 0.85 ppm), and toenail Hg levels (<median 0.22 ppm *vs.* ≥median 0.22 ppm) with adjustment for all covariates in model 2 except the potential effect modifier. To further explore the possible joint modification by Hg and Se, we examined the association of interest in 4 subgroups defined by the median levels of Hg (0.22 ppm) and Se (0.85 ppm). Interaction was tested using the continuous variable of LCω−3PUFA with values over 99th percentile excluded.

All analyses were performed by using SAS version 9.4 (SAS Institute, Cary, NC, USA). Two-sided *P* values ≤0.05 (main effect) and *P* values ≤0.10 (interaction) were considered statistically significant.

RESULTS

In the study population (n=3,231), 56% of participants were female and 45% were blacks with an average age of 50 years at exam year 25. Table 1 shows the characteristics of the

study population across quintiles of LCω−3PUFA intake. Participants with higher LCω−3PUFA intake were more likely to be older, males, blacks, have higher total energy intake, education level, have higher alcohol consumption, be physically active, and have higher levels of fasting glucose and toenail Hg but lower levels of toenail Se. They were less likely to be current smokers.

Higher LCω−3PUFA intake was significantly associated with a better cognitive performance measured by DSST (Table 2). Compared with participants in the lowest quintile (Q1) of LCω−3PUFA intake, those in the highest quintile (Q5) had 2.79 more points in DSST [95% CI: 1.19, 4.40; *P* for trend<0.01; model 1], and 1.42 less points in the Stroop Test [95% CI: −2.53, −0.31; *P* for trend = 0.013; model 1]. The observed associations were attenuated to some extent after further adjustment for other confounding variables in model 2, but remained statistically significant for DSST [Q5 *vs.* Q1; mean difference: 1.74; 95% CI: 0.19, 3.29; *P* for trend = 0.048]. No statistically significant association was found between LCω−3PUFA intake and RAVLT score. The findings persisted when examining DHA and EPA separately (Table 2).

Similar results were observed for non-fried seafood consumption (Table 2). Higher non-fried seafood consumption was associated with better performances in DSST [Q5 *vs.* Q1; mean difference: 2.87; 95% CI: 1.29, 4.45; *P* for trend <0.01; model 1] and the Stroop test [Q5 *vs.* Q1; mean difference: −1.72; 95% CI: −2.81, −0.62; *P* for trend <0.01; model 1]. After adjusting for other confounding variables in model 2, the significant findings remained for DSST [Q5 *vs.* Q1; mean difference: 1.48; 95% CI: −0.05, 3.01; *P* for trend = 0.04]. Non-fried seafood consumption was not associated with performance measured by RAVLT.

In a sensitivity analysis, when only including participants who have data in all repeated measurements of LCω−3PUFA, DHA, EPA, and non-fried seafood, the results were not materially changed. In addition, the results were generally consistent when excluding shellfish from seafood consumption or further adjusting for toenail Hg and Se levels. The observed associations were not materially changed when additionally adjusting for total energy intake and other nutrients in seafood. The associations were attenuated when adjusting for the modified A Priori Diet Quality Score (Data not shown).

Because intakes of LCω−3PUFA and non-fried seafood were consistently associated with cognitive performance measured by DSST, we conducted stratified analyses based on DSST by a few pre-specified factors (Table 3). A significant interaction was observed between LCω−3PUFA intake and BMI (*P* for interaction <0.01); the association of interest was more pronounced in participants with BMI ≥25 kg/m^2 [tertile 3 *vs.* tertile 1; mean difference: 1.50; 95% CI: −0.08, 3.09; *P* for trend <0.01].

We also examine the main effects of toenail Se and Hg on cognitive function tests, but no significant associations were found after adjustment for potential confounders (Supplemental Table 1). Although the interaction was not statistically significant (*P* for interaction = 0.25), the association between LCω−3PUFA intake and DSST score was more profound in participants with higher toenail Se levels [tertile 3 *vs.* tertile 1; Se ≥median 0.85 ppm: mean difference: 2.06; 95% CI: 0.30, 3.82; *P* for trend = 0.04; Se <median 0.85 ppm:

mean difference: 0.25; 95% CI: −1.59, 2.09; *P* for trend = 0.43]. However, Hg levels did not appreciably modify the association (*P* for interaction = 0.54). We further explored the joint modification of Se and Hg on LCω−3PUFA intake, a three-way interaction. When participants were jointly classified according to median levels of Se (0.85 ppm) and Hg (0.22 ppm), the association between LCω−3PUFA intake and DSST score was not materially modified (*P* for interaction = 0.60).

DISCUSSION

Over 25 years of follow-up, we found that higher LCω−3PUFA intake and non-fried seafood consumption were associated with better cognitive performance particularly measured by DSST, but not RAVLT and the Stroop test. The observed associations were more pronounced in overweight and/or obese individuals. While DSST score mainly reflects psychomotor speed indicating the overall efficiency of brain operations [21], RAVLT and the Stroop test measure verbal memory and executive functions, respectively. Since slow psychomotor speed appears far prior to the onset of mild cognitive impairment [22, 23], DSST score is considered a more sensitive index reflecting cognitive decline [21, 24].

Although the beneficial effects of LCω−3PUFA on cognitive function is supported by evidence from laboratory studies [25–27], epidemiological studies yielded inconsistent findings. Two recent systematic reviews of RCTs did not find a significant improvement of cognitive function with respect to LCω−3PUFA supplementation. However, most of the RCTs included in the reviews were conducted in less than 100 participants with an intervention period shorter than 5 months [3, 4]. Of note, some RCTs suggested a potential beneficial effect with a relatively long-term supplementation of LCω−3PUFA [28, 29]. Observational studies also suggested that long-term intakes of LCω−3PUFA and seafood were associated with a slower age-related cognitive decline [5, 6].

One important contribution of this study is that it recruited young adults and followed them up for more than 25 years, while most of the previous studies focused on older adults. Middle-aged or older men and women are more likely to already have onset of diseases, so their lifestyle choice and health conditions may be affected by perceived ill health or treatment for existing disease. Follow-up of a cohort of young adults for 25 years provides insight on the natural history or early etiology of cognitive decline. Since long-term randomized clinical trials may not be feasible, a longitudinal study such as the present one certainly provides important data to the literature. In addition, we used cumulative average intake to reflect the usual diet as well as took cooking methods into account, which has not been considered in previous studies due to lack of data.

When examining LCω−3PUFA and seafood, Se and Hg are two elements warrant consideration because they often coexist with LCω−3PUFA in seafood. Se is an element with antioxidant capacity and may protect against cognitive decline alone or by interacting with LCω−3PUFA [30]. Se can also modulate the neurotoxicity effect of Hg [9, 31, 32]. In the present study, the findings are consistent with a recent report of US adults that failed to observe a significant interaction between LCω−3PUFA and Hg with neurobehavioral

outcomes [33]. The association appeared to be more pronounced at higher toenail Se levels, though the interaction was not statistically significant.

In the present study, overweight or obese individuals seemed to have a better response to intake of LCω−3PUFA in terms of cognitive decline. Since obesity is characterized by chronic inflammation [34], it is possible that the influence of LCω−3PUFA on inflammation, and consequently cognitive function, is more evident in overweight and obese individuals who have a higher inflammation level [35]. This hypothesis is supported by previous studies that found associations between LCω−3PUFA and inflammatory biomarkers [36, 37]. It is also possible that having more adipose tissues protects against fat soluble pollutants, which are suggested to be associated with the risk of cognitive impairment [38].

Some limitations of the present study need to be acknowledged. First, cognitive function was assessed only once and not at baseline. Thus, we were not able to evaluate the association with changes in cognitive function. The inclusion of cognitive impaired individuals at baseline is unlikely given the young age of the participants at study enrollment and the fact that they remained in the study for 25 years. Second, other nutrients in seafood may confound the association between LCω−3PUFA and cognitive function. We adjusted for some nutrients in a sensitivity analysis and found the results were not materially changed, but the concern still remains. The fact that the associations were attenuated after adjustment for the diet quality based on other food groups suggests that seafood intake may be a part of healthy diet [39]. Third, objective measurements of LCω−3PUFA were not available. However, the diet history used in the present study has been validated [11, 12]. The use of food frequency questionnaire to reflect the levels of LCω−3PUFA exposure is also supported in other studies [40, 41]. Fourth, similar to other observational studies, the possibility of residual confounding from dietary and non-dietary factors cannot be completely ruled out. But the consistent results from the main and sensitivity analyses provide reassurance about the validity of our findings.

CONCLUSIONS

Findings from this longitudinal study support that intakes of LCω−3PUFA and non-fried seafood are associated with better cognitive performance in psychomotor speed. This study adds additional scientific evidence supporting the recommendation of seafood consumption for preventing or slowing down the process of cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

95% CI	95% confidence interval
ANOVA	analysis of variance
BMI	body mass index
CARDIA	Coronary Artery Risk Development in Young Adults Study
DBP	diastolic blood pressure
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
DSST	Digit Symbol Substitution Test
EPA	eicosapentaenoic acid
HDL	high-density lipoprotein
Hg	mercury
IQR	inter-quartile range
LCω−3PUFA	long-chain omega-3 polyunsaturated fatty acids
LDL	low-density lipoprotein
NA	not applicable
RAVLT	Rey Auditory Verbal Learning Test
RCT	randomized clinical trials
Ref.	reference
SBP	systolic blood pressure
SD	standard deviation
Se	selenium

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Highlights

- Intake of long-chain omega-3 polyunsaturated fatty acids was significantly associated with better cognitive performance in psychomotor speed.
- Similar results were observed for intakes of EPA, DHA, and non-fried seafood.
- The observed associations were more pronounced in overweight and obese participants.
- Levels of mercury or selenium did not materially modified the observed associations.

Table 1.

Characteristics of the study population by quintiles (Q) of cumulative average daily intake of LCω−3PUFA: the CARDIA study (*n*=3,231), 1985–2010.[a,b]

	Quintiles of LCω−3PUFA intake					Total (*n*=3,231)	*P* value
	Q1 (*n*=630)	Q2 (*n*=650)	Q3 (*n*=663)	Q4 (*n*=637)	Q5 (*n*=651)		
LCω−3PUFA (g/day)	0.04±0.02	0.08±0.01	0.13±0.02	0.19±0.03	0.41±0.22	0.17±0.17	NA
DHA (g/day)	0.02±0.01	0.04 ±0.01	0.06±0.02	0.09±0.02	0.20±0.11	0.08±0.08	NA
EPA (g/day)	0.01±0.01	0.03±0.01	0.05±0.01	0.07 ±0.02	0.16±0.11	0.06±0.07	NA
Non-fried seafood (servings/day)	0.24±0.43	0.50±0.29	0.80±0.50	1.19±0.62	2.04±1.25	0.96±0.94	NA
Fried seafood (servings/day)	0.04±0.18	0.05±0.17	0.06±0.19	0.10±0.35	0.08±0.32	0.07 ±0.26	NA
Total energy (kcal/day)	2348.7±1074.6	2501.1±1126.7	2683.6±1237.2	2768.7±1098.8	3227.4±1280.8	2707.9±1204.4	<0.01
Age at exam Y25 (year)	49.6±3.8	50.0±3.6	50.1 ±3.7	50.6±3.5	50.5 ±3.6	50.1±3.6	<0.01
Female (%)	64.0	60.2	56.6	54.6	46.7	56.4	<0.01
Blacks (%)	38.9	42.2	47.4	44.3	52.4	45.1	<0.01
Education attained through exam Y25 (year)	14.8±2.7	15.1±2.7	15.1 ±2.7	15.4±2.5	15.3±2.6	15.1±2.7	<0.01
Smoking status (%)							0.02
Never smoker	63.7	63.6	62.6	61.5	57.8	61.8	
Former smoker	18.6	18.8	22.5	23.8	26.4	22.1	
Current smoker	17.7	17.6	14.9	14.7	15.8	16.1	
Alcohol consumption (ml/day)							<0.01
Median	3.7	4.1	4.8	7.5	7.8	5.5	
IQR	0.3–11.5	0.4–12.3	0.9–13.8	1.8–16.3	2.1–21.3	0.9–15.0	
Physical activity (exercise unit)							<0.01
Median	265.1	305.8	321.3	334.8	386.3	323.8	
IQR	161.1–414.2	191.9–458.5	198.8–476.9	213.1–481.1	254.0–573.9	200.4–479.1	
BMI(%)							0.12
<18.5 kg/m^2	0.5	1.1	0.9	0.5	0.3	0.7	
18.5–24.9 kg/m^2	40.2	43.1	36.1	44.0	39.9	40.6	
25.0–29.9 kg/m^2	33.7	28.8	39.4	35.6	36.6	34.8	
≥30.0 kg/m^2	25.7	27.1	23.7	20.0	23.2	23.9	
HDL-cholesterol (mg/dL)	53.1±12.5	53.0±13.0	53.2±11.9	53.9±12.7	54.6±13.6	53.6±12.8	0.08
LDL-cholesterol (mg/dL)	110.7±25.8	109.2±26.3	110.3±26.1	110.5±25.7	113.0±26.3	110.7±26.0	0.12
Triglycerides (mg/dL)	89.0±40.7	93.3±62.1	89.7±51.2	89.7 ±51.1	94.6±63.2	91.3±54.4	0.24
Glucose (mg/dL)	89.3±12.8	90.5±14.4	89.7±12.9	89.7±10.5	91.3±15.2	90.1±13.3	0.048
SBP (mmHg)	110.5±9.9	111.2±9.5	111.6±9.3	111.0±9.9	111.8±10.1	111.2±9.7	0.14
DBP (mmHg)	70.3±7.3	71.0±7.3	71.1 ±7.0	70.7 ±7.6	71.1 ±7.7	70.8±7.4	0.22
Toenail selenium at exam Y2 (ppm)	0.88±0.15	0.87 ±0.16	0.86±0.16	0.85 ±0.13	0.84±0.15	0.86±0.15	<0.01
Toenail mercury at exam Y2 (ppm)	0.22±0.25	0.26±0.26	0.30±0.32	0.37 ±0.41	0.43±0.50	0.32±0.37	<0.01

Abbreviations: BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; IQR, inter-quartile range; LCω−3PUFA, long chain ω−3 polyunsaturated fatty acids; LDL, low-density lipoprotein; ml, milliliters; NA, not applicable; SBP, systolic blood pressure; Y, year.

[a] All variables are cumulative averages of all available observations of the variable in question, except where noted. Results are presented by means ± standard deviations, medians (inter-quartile ranges) or proportions.

[b] *P* values are for any differences across quintiles of LCω−3PUFA intake (Analysis of variance, Kruskal-Wallis test, or chi-squared test, as appropriate).

Table 2.

Multivariable-adjusted mean differences (95% CI) in cognitive test scores according to quintiles (Q) of cumulative average daily intakes of LCω3PUFA, DHA, EPA, and non-fried seafood: the CARDIA study (*n*=3,231), 1985–2010.[a–d]

	RAVLT words Mean=8.7 (SD=2.6)		DSST symbols Mean=70.4 (SD=16.0)		Stroop test points Mean=22.7(SD=10.6)	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
LCω−3PUFA (g/day)						
Ql (≤0.06)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)
Q2 (0.07–0.10)	0.15 (−0.10,0.40)	0.12 (−0.13,0.36)	0.21 (−1.35,1.78)	−0.12 (−1.60, 1.36)	−0.92 (−2.00,0.16)	−0.77 (−1.84,0.30)
Q3 (0.11–0.15)	0.09 (−0.16,0.34)	0.02 (−0.23,0.27)	1.06 (−0.51,2.62)	0.28 (−1.21, 1.77)	0.04 (−1.04,1.12)	0.46 (−0.61,1.53)
Q4 (0.16–0.25)	0.09 (−0.17,0.35)	−0.03 (−0.28, 0.22)	1.35 (−0.24,2.94)	0.02 (−1.50, 1.54)	−1.10 (−2.20,−0.003)	−0.39 (−1.49,0.70)
Q5 (>0.25)	0.17 (−0.09,0.43)	0.08 (−0.17,0.34)	2.79 (1.19,4.40)	1.74 (0.19,3.29)	−1.42 (−2.53,−0.31)	−0.76 (−1.88,0.36)
P for trend	0.38	0.84	<0.01	0.048	0.013	0.21
DHA (g/day)						
Ql (≤0.03)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)
Q2 (0.04–0.05)	0.26 (0.005,0.51)	0.26 (0.02,0.50)	−0.54 (−2.10,1.02)	−0.55 (−2.02,0.93)	−0.39 (−1.47,0.70)	−0.29 (−1.35,0.78)
Q3 (0.06–0.07)	0.13 (−0.12,0.38)	0.07 (−0.18,0.31)	1.26 (−0.30,2.81)	0.59 (−0.89,2.06)	−0.25 (−1.33,0.82)	0.10 (−0.97,1.17)
Q4 (0.08–0.12)	0.18 (−0.08,0.43)	0.04 (−0.21,0.29)	1.55 (−0.02,3.13)	0.21 (−1.29,1.71)	−1.00 (−2.09,0.09)	−0.26 (−1.35,0.82)
Q5 (>0.12)	0.24 (−0.01,0.50)	0.15 (−0.11,0.40)	2.80 (1.21,4.38)	1.75 (0.22,3.28)	−1.50 (−2.60,−0.40)	−0.82 (−1.93,0.28)
P for trend	0.09	0.41	<0.01	0.051	<0.01	0.16
EPA (g/day)						
Ql (≤0.02)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)
Q2 (0.03–0.04)	0.04 (−0.21,0.29)	−0.06 (−0.30, 0.19)	1.23 (−0.33,2.78)	0.43 (−1.05, 1.91)	−1.49 (−2.56,−0.41)	−1.12 (−2.19,−0.06)
Q3 (0.05–0.06)	0.16 (−0.10,0.41)	0.09 (−0.16,0.33)	0.99 (−0.59,2.57)	0.18 (−1.32, 1.68)	−0.72 (−1.81,0.37)	−0.29 (−1.37,0.79)
Q4 (0.07–0.09)	0.07 (−0.19,0.32)	−0.07 (−0.32, 0.18)	2.12 (0.53,3.71)	0.69 (−0.83,2.22)	−1.58 (−2.69,−0.48)	−0.84 (−1.94,0.26)
Q5 (>0.09)	0.07 (−0.19,0.33)	−0.01 (−0.27,0.24)	2.51 (0.90,4.11)	1.50 (−0.06,3.05)	−1.63 (−2.74,−0.52)	−0.99 (−2.11,0.13)
P for trend	0.35	0.68	<0.01	0.02	0.015	0.15
Non-fried seafood (servings/day)						
Ql (≤0.29)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)	0 (Ref.)
Q2 (0.30–0.55)	0.34 (0.09,0.59)	0.21 (−0.03,0.46)	1.68 (0.12,3.24)	0.65 (−0.83,2.13)	−1.44 (−2.52,−0.36)	−0.96 (−2.02,0.11)
Q3 (0.56–0.88)	0.21 (−0.04,0.47)	0.09 (−0.16,0.33)	−0.04 (−1.61,1.52)	−1.45 (−2.94,0.04)	−0.38 (−1.47,0.70)	0.24 (−0.83,1.32)
Q4 (0.89–1.43)	0.28(0.03,0.54)	0.13 (−0.12,0.38)	1.28 (−0.30,2.85)	−0.25 (−1.75,1.26)	−1.36 (−2.45,−0.27)	−0.56 (−1.65,0.52)
Q5 (>1.43)	0.11 (−0.14,0.37)	−0.01 (−0.27,0.24)	2.87 (1.29,4.45)	1.48 (−0.05, 3.01)	−1.72 (−2.81,−0.62)	−0.97 (−2.08,0.14)
P for trend	0.58	0.96	<0.01	0.04	<0.01	0.13

Abbreviations: BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; DHA, docosahexaenoic acid; DSST, Digit Symbol Substitution Test; EPA, eicosapentaenoic acid; LCω−3PUFA, long chain ω−3 polyunsaturated fatty acids; RAVLT, The Rey Auditory Verbal Learning Test; Ref., reference; SD, standard deviation.

[a]All models were constructed using general linear model analysis. *P* for trend was examined by using the continuous variable of exposure with values over 99th percentile excluded.

[b]Model 1 was adjusted for age, sex (female or male), race (white or black), and study center.

[c] Model 2 was additionally adjusted for educational attainment through exam year 25 (<12.0, 12.0–15.9, or ≥16.0 years), cumulative average BMI (<18.5, 18.5–24.9, 25.0–29.9, or ≥30.0 kg/m^2), smoking status at exam year 25 (never, former, or current smokers), cumulative average alcohol consumption (0, 0.1–11.9, 12.0–23.9 or ≥24 ml/day), cumulative average physical activity (quintiles), and cumulative average glucose level (continuous).

[d] Fried seafood intake (yes or no) was adjusted for in both model 1 and 2 when studying non-fried seafood consumption.

Table 3.

Associations [adjusted mean differences (95% CI)] between cumulative average daily intake of LCω−3PUFA and DSST score by pre-specified factors, the CARDIA study (*n*=3,231), 1985–2010.[a]

	Levels of LCω−3PUFA [mean (SD)]	Tertiles of LCω−3PUFA intake			*P* for trend
		T1 (≤0.09 g/day	T2 (0.09–0.18 g/day)	T3 (≥0.18 g/day)	
All participants	0.17 (0.17)	0 (Ref.)	0.37 (−0.78, 1.52)	1.12 (−0.08, 2.32)	0.048
Age at exam Y25					
<Median 51 years	0.16 (0.16)	0 (Ref.)	0.13 (−1.40, 1.66)	1.32 (−0.30, 2.94)	0.11
≥Median 51 years	0.18 (0.17)	0 (Ref.)	0.51 (−1.25,2.27)	0.19 (−1.61, 2.00)	0.59
P for interaction	−-		0.68		
Sex					
Female	0.15 (0.14)	0 (Ref.)	0.35 (−1.17, 1.86)	0.66 (−0.97, 2.29)	0.26
Male	0.19 (0.19)	0 (Ref.)	0.34 (−1.43, 2.11)	1.57 (−0.22, 3.36)	0.12
P for interaction	--		0.65		
Race					
Blacks	0.19 (0.19)	0 (Ref.)	1.24 (−0.53, 3.00)	2.57(0.77,4.37)	0.03
Whites	0.16 (0.14)	0 (Ref.)	−0.20 (−1.72, 1.32)	−0.19 (−1.81, 1.42)	0.66
P for interaction	--		0.50		
BMI					
<25 kg/m^2	0.17 (0.18)	0 (Ref.)	1.38 (−0.41, 3.16)	0.73 (−1.11, 2.57)	0.97
≥25 kg/m^2	0.17 (0.16)	0 (Ref.)	−0.27 (−1.78, 1.24)	1.50 (−0.08, 3.09)	<0.01
P for interaction	--		<0.01		
Smoking status					
Never	0.16 (0.15)	0 (Ref.)	−0.11 (−1.53,1.32)	0.68 (−0.83, 2.19)	0.17
Former	0.19 (0.19)	0 (Ref.)	0.39 (−2.12, 2.90)	1.45 (−1.10, 4.01)	0.15
Current	0.17 (0.17)	0 (Ref.)	2.84 (−0.36, 6.03)	2.32 (−1.00, 5.65)	0.63
P for interaction	--		0.82		
Toenail selenium levels					
<Median 0.85 ppm	0.18 (0.16)	0 (Ref.)	−0.39 (−2.18, 1.41)	0.25 (−1.59, 2.09)	0.43
≥Median 0.85 ppm	0.16 (0.17)	0 (Ref.)	1.18 (−0.47, 2.83)	2.06(0.30,3.82)	0.04
P for interaction	--		0.25		
Toenail mercury levels					
<Median 0.22 ppm	0.14 (0.14)	0 (Ref.)	0.27 (−1.40, 1.94)	1.45 (−0.46, 3.35)	0.12
≥Median 0.22 ppm	0.20 (0.19)	0 (Ref.)	0.79 (−1.00, 2.58)	0.88 (−0.90, 2.67)	0.21
P for interaction	--		0.54		
Joint classification of selenium-mercury levels					
Low Se / high Hg	0.21 (0.18)	0 (Ref.)	−0.12 (−2.76, 2.52)	−0.30 (−2.90, 2.30)	0.76
Low Se / high Hg	0.19 (0.20)	0 (Ref.)	1.46 (−1.03, 3.95)	2.01 (−0.52, 4.53)	0.16
Low Se / low Hg	0.15 (0.15)	0 (Ref.)	−0.72 (−3.26, 1.81)	0.75 (−2.04, 3.54)	0.42
High Se / low Hg	0.13 (0.13)	0 (Ref.)	1.13 (−1.15, 3.41)	1.91 (−0.76, 4.58)	0.19
P for interaction	--		0.60		

Abbreviations: BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; DSST, Digit Symbol Substitution Test; Hg, mercury; LCω−3PUFA, long chain ω−3 polyunsaturated fatty acids; Ref., reference; SD, standard deviation; Se, selenium; Y, year.

[a] All models were constructed using general linear model analysis with adjustment for covariates in model 2, Table 2, except the potential modifier. *P* for trend and *P* for interaction were examined by using the continuous variable of LCω−3PUFA intake with values over 99th percentile excluded.