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Adipose tissue fatty acid composition and cognitive impairment

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ABSTRACT

Objective: The aim of this study was to examine the association among adipose tissue eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), and the ratios of EPA to AA and DHA to AA with impaired cognitive function.
Methods: This cross-sectional analysis comprised 481 men participating in the Cohort of Swedish Men-Clinical and for whom adipose tissue fatty acid composition and results from a telephone-based cognitive test were available. Impaired cognitive function was defined using a predefined cutoff on the cognitive test. Binomial log-linear regression models were used to estimate prevalence ratios. In secondary analyses, Cox proportional hazards models were used to estimate relative risk for incident dementia ascertained by linkage with population-based registers.
Results: We observed a graded reduction in the prevalence of impaired cognitive function across tertiles of adipose tissue EPA/AA- ratio ($P_{trend} = 0.01$); compared with the lowest tertile, the multivariable-adjusted prevalence ratios were, respectively, 0.89 (95% confidence interval [CI], 0.67–1.17) and 0.64 (95% CI, 0.45–0.91) for the second and third tertiles. EPA, DHA, and the DHA/AA ratio showed similar patterns of association; however, the CIs included the null. AA alone was not associated with impaired cognitive function. Although with lower precision, estimates obtained from the prospective analysis were broadly consistent with the main analysis.
Conclusions: Findings from this study suggest that a high ratio of EPA to AA in adipose tissue may be associated with better cognitive function. A similar association was observed with EPA, DHA, and the ratio of DHA to AA, but the results did not exclude a null association.

Introduction

The marine long-chain ω-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been hypothesized to protect against cognitive decline through their potential antiinflammatory properties [1]. Mechanistic evidence indicates that inflammation may be implicated in the development of age-related cognitive decline [2]. In previous observational studies, data on ω-3 PUFAs or fish (the main source of EPA and DHA) were either obtained from self-reported questionnaires [3–7] or measurement of biomarkers [8–13]. Self-reported information is subject to measurement error, especially in individuals with poor cognitive function, which may lead to attenuated or even spurious associations. Moreover, previous studies using biomarkers of ω-3 PUFA intake have measured these fatty acids in either plasma or erythrocytes, which reflect dietary intake over approximately the past weeks and months, respectively [14]. Because fish is generally consumed infrequently, a biomarker that reflects intake over weeks or months may not adequately capture long-term exposure, especially if seasonal variations exist. Adipose tissue fatty acid composition may be a more reliable biomarker of exposure to EPA and DHA as it reflects intake over a longer time period (≤2 y) [14]. However, no study has investigated the association between ω-3 PUFAs in

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adipose tissue and cognitive function. Furthermore, data on the potentially proinflammatory ω-6 PUFA arachidonic acid (AA), in adipose tissue in relation to cognitive function are lacking.

In the present study, we used previously collected data on adipose tissue PUFA composition as a biomarker of long-term exposure to EPA and DHA and related this to cognitive function as assessed by a telephone-based cognitive test. Additionally, we investigated the association of adipose tissue arachidonic (AA), as well as the ratios of EPA to AA and DHA to AA with cognitive function. The EPA/AA ratio is of interest as both of these PUFAs may act as substrates in the production of eicosanoids, which are important in the regulation of inflammation [1]. Eicosanoids derived from EPA are considered to be less inflammatory than AA [1], and thus a higher EPA/AA ratio may be associated with lower inflammation. The DHA/AA ratio was investigated in previous studies [10,11,15,16], which have reported on the association of this ratio with cognitive function. We additionally performed secondary (prospective) analyses with incident dementia (including mild cognitive impairment) as the outcome.

Material and methods

Participants

In the present study, we used previously collected data from the Cohort of Swedish Men-Clinical (COSM-C), which is a subcohort of COSM [17]. COSM was initiated in 1997, when all male residents in Västmanland and Örebro counties born between 1918 and 1952 were invited to complete a diet and lifestyle questionnaire. The subcohort, COSM-C, was initiated in 2010 when members of COSM residing in Västmanland County were invited to participate in a telephone-based cognitive test and a health examination. Participants were selected from COSM based on year of birth, starting with the oldest individuals. Fatty acid composition of adipose tissue was determined in the first 496 men who completed the health examination (80–92 y of age). Among these, 11 men were excluded because they did not complete the cognitive test due to impaired audition. Four men were excluded based on missing values for potential confounders; smoking status (n = 3) or education (n = 1). Thus, the analytical sample consisted of 481 men. The study was approved by the regional ethical review board, and all participants provided written informed consent.

In the secondary (prospective) analyses, incident cases of dementia (including mild cognitive impairment) were identified through linkages with the Swedish National Patient Register and The Swedish Cause of Death Register. As registry data is known to have a low sensitivity for identifying dementia cases, we used a broad outcome definition considering any occurrence of dementia-related International Classification of Diseases (ICD) codes in either registries to identify cases (details and ICD codes used in these analyses are available in the supplementary appendix).

Assessment of cognition

The telephone-based cognitive test was a translated and modified version of the telephone assessment for dementia (TELE) [18,19]. The modified version of TELE used in the present study was validated in a Finnish population [20]. This validation study showed a strong correlation between scores on TELE and the Mini-Mental State Evaluation test (MMSE) (Pearson's r = 0.87), Clinical Dementia Rating Sum of Boxes (Pearson's r = –0.71) and a good ability to discriminate between healthy and demented individuals (area under receiver operating curve = 0.96) [20]. The TELE consists of questions designed to assess orientation, long- and short-term memory, abstraction, and calculation and has a maximum score of 20 points. In the present study, we defined impaired cognitive function as scores <17 on the TELE. This corresponded to a sensitivity of 90% and a specificity of 89% against a clinical diagnosis of dementia in the validation study [20].

Fatty acid analysis

Adipose tissue samples were taken from the upper buttocks with a fine needle attached to a vacuum container, according to a previously described procedure [21]. The samples were protected from light and stored at –80°C for a maximum of 18 mo until analyzed. Fatty acids were extracted and transmethylated according to a previously described procedure [22].

The fatty acid methyl esters were separated by gas-liquid chromatography on a 30-m glass capillary column coated with Thermo TR-FAME (Thermo Electron Corporation, Waltham, MA USA), with helium gas as a carrier. A system consisting of Agilent Technologies GLC (model 6890 N), autosampler (model 7683) and Agilent ChemStation was used. The temperature was programmed to 150°C to 260°C. Fatty acids were identified by comparing each peak's retention time with fatty acid methyl ester standard Nu Check Prep (Elysian, MN, USA).

Other covariates

Using standardized procedures, weight, height, blood pressure (supine position after 5 min of rest), fasting glucose, sagittal abdominal diameter, and waist and hip circumferences were measured at the health examination. Information on habitual physical activity and smoking status was collected with a self-administered questionnaire in conjuncture with the health examination. The questionnaire pertained to time spent in specific activities (six predefined categories of walking/bicycling, household chores, exercise, sitting, reading, or watching TV). The phone interview included a nonvalidated instrument relating to depressive symptoms; participants were asked if they had experienced periods of ≥2 wk with five depression-related symptoms during the preceding year (feeling down/depressed, having reduced appetite/losing ≥5 kg weight, having trouble sleeping, having low energy, and having trouble concentrating). We defined more than two of these symptoms to indicate possible depression in sensitivity analyses. Participants were also asked to specify any dietary supplement usage. Participants who reported current use of any supplement containing EPA or DHA were considered ω-3 supplement users.

Statistical analysis

Characteristics of the participants are presented as medians along with interquartile ranges according to scoring below or above the cutoff on the TELE-test. In the main cross-sectional analysis, prevalence ratios (PR) with 95% confidence intervals (CIs) were calculated for impaired cognitive function across tertiles (tertiles rather than quartiles or quintiles were used due to the relatively small sample size and to increase power) of DHA, EPA, AA, EPA/AA, and DHA/AA ratio. PRs and CIs were estimated using binomial log-linear regression models as implemented in the STATA command "binreg" [23]. Trend analyses across tertiles were performed by assigning the median value for each tertile and entering the variable as a continuous variable.

In these analyses, we used two models: Model 1 was adjusted only for age (continuous), and model 2 was further adjusted for education (1–9, 10–12, or ≥13 y), smoking status (current, former, or never), and body mass index (BMI; continuous). Choice of adjustment was guided by hypothesized risk factors for dementia. Results after additional adjustment for number of depressive symptoms, height, fasting glucose, systolic and diastolic blood pressure, physical activity (time spent walking/bicycling and exercising), time spent sitting, and replacing BMI with other measures of adiposity (sagittal abdominal diameter, waist, and waist-to-hip ratio) were consistent with the results obtained from model 2, and are thus not reported.

We also performed a series of sensitivity analyses. First, we excluded participants who reported to have experienced unintentional weight loss during the year before the telephone interview. This was done because EPA, DHA, and AA appear to be selectively mobilized from adipose tissue during fasting [24]. Assuming that this also occurs during long-term weight loss, a depletion of these PUFAs in adipose tissue is plausible and this might have affected our estimates as weight loss often occurs in the early stages of dementia [25]. Second, we excluded participants who reported use of ω-3 supplements. This analysis was performed as we hypothesized that using ω-3 supplements may be a marker of good cognitive functioning (i.e., indicating awareness of potential health benefits of these PUFAs). Third, we excluded participants who reported more than two depressive symptoms, as depression may result in temporarily impaired cognition [26]. Finally, we excluded participants in the highest category of attained education (≥13 y) because of the strong correlation between education and cognitive function in this study population and between education and dementia in previous studies [27]. In a second set of sensitivity analyses we explored the effect of lowering the cutoff used to define impaired cognitive function to <16 and <15 points. As the number of cases was lower in these sensitivity analyses and the adjustment for BMI and smoking status had minor effect on our estimates, we only adjusted for age and education in these analyses, to retain a reasonable event-to-predictor ratio.

In the secondary (prospective) analyses, we used Cox proportional hazards regression models with age as the underlying time scale to estimate hazard ratios and 95% CIs across tertiles of each exposure. In this analysis, we only adjusted for age (as the time scale) and education because of the limited number of incident cases. All statistical tests are two-sided. Analyses were performed using Stata (version 14.1).

Results

In the present study of 481 men with a mean age of 84 y (range 80–92), 157 (33%) scored below the cutoff on the cognitive test