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Polyunsaturated Fatty Acids and Reduced Odds of MCI: The Mayo Clinic Study of Aging

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Abstract

Mono- and polyunsaturated fatty acids (MUFA, PUFA) have been associated with a reduced risk of dementia. The association of these fatty acids with mild cognitive impairment (MCI) is not fully established. The objective of the study was to investigate the cross-sectional association of dietary fatty acids with MCI in a population-based sample. Participants aged ≥ 70 years on October 1, 2004, were evaluated using the Clinical Dementia Rating Scale (participant and informant), a neurological evaluation, and neuropsychological testing. A panel of nurses, physicians, and neuropsychologists reviewed the data for each participant in order to establish a diagnosis of MCI, normal cognition, or dementia by consensus. Participants also completed a 128-item food-frequency questionnaire.

Among 1,233 non-demented subjects, 163 (13.2%) had MCI. The odds ratio (OR) of MCI decreased with increasing PUFA and MUFA intake. Compared to the lowest tertile, the OR (95% confidence interval) for the upper tertiles were 0.44 (0.29–0.66; p for trend = 0.0004) for total PUFA; 0.44 (0.30–0.67; p for trend = 0.0004) for omega-6 fatty acids; 0.62 (0.42–0.91; p for trend = 0.012) for omega-3 fatty acids; and 0.56 (0.38–0.83; p for trend = 0.01) for (MUFA+PUFA):saturated fatty acid ratio after adjustment for age, sex, number of years of education, and caloric intake. In this study, higher intake of PUFA and MUFA was associated with a reduced likelihood of MCI among elderly persons in the population-based setting.

Keywords

Cross-sectional studies; dietary fats; polyunsaturated fatty acids; monounsaturated fatty acids; population-based; mild cognitive impairment

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INTRODUCTION

Dietary fat intake represents a potential modifiable risk factor for mild cognitive impairment (MCI). Several studies have reported associations of high intake of dietary saturated fat with Alzheimer's disease (AD), vascular dementia, and cognitive impairment [1–7]. In contrast, monounsaturated fatty acids (MUFA) and n-3 polyunsaturated fatty acids (PUFA) have been reported to have beneficial effects on cognitive function [4,8,9]. MUFAs are derived primarily from olive oil. PUFAs include omega-3 PUFAs and linolenic acids (primarily from fish and plant sources), and omega-6 PUFAs and linoleic acids are derived primarily from seed oils. A few other studies have not found an association of any dietary fats with incident dementia [10], or have reported that high intake of n-6 PUFA is associated with cognitive impairment assessed from the Mini-Mental State Exam (MMSE) [11,12].

The association of the components of dietary fat intake with MCI has not been fully established in a population-based setting. Our objective is to investigate these associations in a community-based sample of subjects in the Mayo Clinic Study of Aging who have been well-characterized for MCI using previously specified criteria for MCI at the time of the evaluation, and in whom dietary fat intake has been ascertained using a comprehensive food frequency questionnaire.

MATERIALS AND METHODS

Study participants

The details of the study design have been published previously [13]. Briefly, we identified all Olmsted County, MN, residents aged 70–89 years on October 1, 2004, using the medical records-linkage system of the Rochester Epidemiology Project [14]. From among 9,953 subjects enumerated, we identified 4,398 eligible subjects: 2,719 agreed to participate (61.8% response) by telephone ($n = 669$) or via a face-to-face evaluation ($n = 2,050$). Information from the medical records-linkage system showed that non-participants were more likely to be older, men, less educated, to have diabetes, and greater comorbidity [13]. Only subjects who participated in the face-to-face evaluation were considered for eligibility for the dietary assessments.

Of the 2,050 subjects that had an in-person evaluation at baseline, 67 had dementia at baseline and 14 did not complete the evaluation and therefore could not be assigned a diagnosis; these 81 subjects were not eligible for the food frequency questionnaire study. Of the remaining 1,969 non-demented subjects who completed the full evaluation at baseline, subjects who had died ($n = 22$), refused further participation since the baseline evaluation ($n = 22$), or were non-English speaking ($n = 1$) were considered ineligible. Thus, the food frequency questionnaires were mailed to 1,924 eligible subjects. A total of 1,567 (81.4%) subjects returned the food frequency questionnaire and 357 did not. We also excluded data for 334 subjects who had 1) missing responses on > 10 of the 128 'How often' questions on frequency of consumption of foods ($n = 268$); 2) persons who reported extreme caloric intake (low intake = < 800 [in men] or < 600 [in women] kcal/day; high intake = > 6,000 [in men] or > 5,000 [in women] kcal/day); and 3) persons who were demented at the time of the evaluation ($n = 10$; at baseline, 9 had MCI and 1 was cognitively normal; Fig.). Thus, of those who received the questionnaire, 691 subjects were not included in the present analyses.

Measurements

Assessment of cognitive status—Each study participant was evaluated by a nurse or study coordinator, and underwent a neurological evaluation by a physician and neuropsychological testing. A nurse or study coordinator administered the Clinical Dementia Rating (CDR) Scale [15] to the participant and an informant by interview. We performed

neuropsychological testing using nine tests to assess performance in four cognitive domains: memory, executive function, language, and visuospatial skills, as previously described [13]. The raw scores from the neuropsychological test battery were age-adjusted using normative data from the Mayo's Older American Normative Studies and scaled to a mean of 10 and standard deviation (SD) of 3 [16], and were also summed and scaled to obtain domain scores [13]. An expert panel of physicians, neuropsychologists, and nurses reviewed all the information collected for each participant to reach a consensus diagnosis of normal cognition, MCI, or dementia.

Definition of cases and controls—We defined MCI (cases) according to previously published criteria: cognitive concern by participant, physician, nurse, or informant (from CDR); impairment in one or more of the four cognitive domains from the cognitive testing battery; essentially normal functional activities (from CDR); and absence of dementia [17]. A diagnosis of dementia was made according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* criteria [18]. Subjects were characterized as cognitively normal according to published criteria [16]. Subjects with dementia were not included in this study.

Assessment of dietary lipid intake from a food frequency questionnaire—We mailed a self-administered food frequency questionnaire that was a modification of the Block 1995 Revision of the Health Habits and History Questionnaire [19] to the homes of participants, with a self-addressed, stamped envelope for its return. The questionnaire included 103 food items, 25 beverages, cooking doneness for 7 meats, and use of 15 types of supplements; it was focused on usual eating habits during the year prior to enrollment, including food eaten in a restaurant. It also included questions about 1) type of fat most often used in cooking; 2) type of fat added at the table to bread, potatoes, and vegetables; 3) types of margarine used; 4) other forms of fat intake; and 5) fat preferences for milk and meat products. Dietary sources of MUFAs include olive oil, canola oil, peanut oils, peanuts and almonds, dairy, and meat. Omega-3 PUFA is present primarily in fish and seafood but is also found in animal products such as meat, poultry, eggs, and dairy; sources of linolenic acid include some nuts and vegetable oils (flaxseed, canola oil, soybean oils, walnuts) as well as from green leafy vegetables. Omega-6 PUFA and linoleic acids are present in vegetable oils (safflower, canola, and sunflower oils), soybeans, butter, and cheese. For each food, participants 1) indicated their usual portion size consumed (small, medium, or large), with the medium size specified (e.g., medium serving = 1 banana, 1 cup); and 2) how often they had consumed each food (never or < 1/month, 1–3/month, 1/week, 2–4/week, 5–6/week, 1/day, 2–3/day, 4–5/day, 6+/day). We analyzed the data using the Food Processor SQL nutrition analysis software (version 10.0.0., ESHA Research, Salem, OR), under the direction of a registered dietician (HMO). Using this database, we multiplied daily food consumption by 30 and weekly food consumption by 4 to determine monthly intake, and calculated the total nutrient intake (grams) and total caloric intake (kilocalories/day).

Assessment of demographic variables and other covariates—We ascertained date of birth, number of years of education, marital status, and potential confounders including diabetes, hypertension, coronary heart disease, and stroke by interview and from medication bottles provided by subjects. We validated comorbidities using the medical records-linkage system [14] with the medical record as the gold standard when there was a discrepancy. We assessed a history of depressive symptoms from an informant using the Neuropsychiatric Inventory Questionnaire [20]. We assessed frequency of moderate physical exercise in the year prior to the evaluation as ≤ 1/month, 2–3/month, 1–2/week, 3–4/week, 5–6/week, and daily [21]. Each participant underwent a blood draw at baseline to assess Apolipoprotein (ApoE) ε4 allele status. The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved all study protocols.

Statistical analyses

To calculate the energy-adjusted values of dietary fats, we used the residual from a regression model with the log(energy) as the independent variable and the log(nutrient) as the dependent variable, plus the mean log(nutrient) value derived from the regression model [22]. This method yields a measure of nutrient intake that is not (or minimally) correlated with the total energy intake.

We included linoleic acid as a marker of omega-6 (n-6) PUFA because it is the most frequently consumed dietary n-6 PUFA in Western populations [23], and we also evaluated total omega-6 PUFA intake. Similarly, we assessed linolenic acid as a measure of plant-derived omega-3 (n-3) PUFA intake, and total omega-3 PUFA that includes linolenic acid, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). We computed odds ratios (OR) and 95% confidence intervals (95% CI) for the association between tertiles of fatty acids and MCI using multiple logistic regression models and tested for linear trends across tertiles. The tertiles were determined from sex-specific distributions for cases and controls combined. We performed the same analyses by MCI subtype (amnesic [a-MCI] and non-amnesic [na-MCI]). In the first model, we adjusted for age, sex, number of years of education, and total energy intake (as continuous variables). In the fully-adjusted model, we also included diabetes, stroke, ApoE ϵ 4 allele status (ApoE ϵ 4+ vs. ApoE ϵ 4-), coronary heart disease, body mass index, and depressive symptoms. Total energy intake was included as a covariate to avoid spurious associations [24]. We investigated potential effect modification by age, sex, number of years of education, and ApoE genotype by including a product term of these variables with dietary fats in the model. We used the information from the face-to-face evaluation that was closest to the date of completion of the food frequency questionnaire. We also assessed the effects of additional potential confounders: marital status, dyslipidemia, alcohol intake (moderate [$> 0 - < 30$ gm/day] vs. low or high [0 or ≥ 30 gm/day]), cigarette smoking (yes vs. no), and moderate exercise (yes vs. no), with each variable added separately to the base model and with all variables simultaneously included in the fully-adjusted models.

Potential non-participation

To adjust for potential non-participation bias, we used a propensity score approach [25,26]. We developed a logistic regression model that predicted the probability of participation. We included demographic (e.g., age, sex, number of years of education) and clinical (e.g., diabetes, stroke, depressive symptoms, MCI status), characteristics that could affect participation. We then used the reciprocal of the predicted probabilities as covariates in the multiple regression analyses. The results for the models without the adjustment for non-participation were essentially the same and are not presented, but are available online (Appendix 1 and Appendix 2).

Sensitivity analyses

To determine whether recall bias from subjects with memory problems could influence our findings, we performed separate analyses after excluding 1) subjects with a memory domain score at the 5th percentile or lower ($n = 110$); 2) subjects with more than 12 months between the diagnosis and completion of the food frequency questionnaire ($n = 19$); and 3) subjects who had a medical record notation of cognitive impairment prior to enrollment in the study based on a review of their medical record ($n = 17$).

Preliminary longitudinal analyses

In subjects who were cognitively normal at baseline, we used proportional hazards models to investigate the association of baseline levels of PUFA, MUFA, omega-3 and omega-6 fatty acids, linoleic and linolenic acids (key variables) with incident MCI or dementia during follow-

up; subjects were censored at the time of death or loss to follow-up. All analyses were performed using SAS® (SAS Institute, Cary, NC).

RESULTS

A total of 1,233 subjects were included in the present study. Subjects who were not included ($n = 691$) were older (median = 82.2 vs. 80.1 years; $p < 0.0001$); had a higher frequency of stroke (14.2% vs. 10.1%; $p = 0.007$), diabetes (16.1% vs. 12.1%; $p = 0.014$), depressive symptoms (16.3% vs. 12.3%; $p = 0.018$), and MCI (23.9% vs. 13.2%; $p < 0.0001$) compared to participants; a lower frequency was married (52.5% vs. 64.9%; $p < 0.0001$); and a lower frequency had > 12 years of education (49.2% vs. 56.0%; $p < 0.0001$) but they were similar in regard to history of hypertension, coronary heart disease, sex, and ApoE $\epsilon 4$ genotype. There were no differences between MCI cases who were excluded and MCI cases who were included in regard to age (median = 83.6 vs. 82.9 years; $p = 0.21$), percentage of men (51.5% vs. 59.5%; $p = 0.15$), and any ApoE $\epsilon 4$ allele (31.4% vs. 33.3%; $p = 0.72$) respectively.

Our present findings are based on the 1,233 subjects who provided useable data. Questionnaires for these subjects were completed at a median of 3.3 months (interquartile range = 1.5–6.1) from the most recent diagnostic assessment. The median memory domain score was 0.28 (interquartile range = -0.46 – 1.08). MCI cases were more likely to be older ($p < 0.0001$), male ($p = 0.04$), have fewer years of education ($p = 0.001$), have a higher frequency of prior stroke ($p < 0.0001$) and depressive symptoms ($p < 0.0001$), and an ApoE $\epsilon 4$ allele ($p = 0.008$) than controls (Table 1).

MCI cases had lower daily intake of several dietary fats compared to controls (Table 2). There were significant differences between cases and controls regarding intake of PUFA, omega-6 PUFA, omega-3 PUFA, fatty acids, linoleic acid, and linolenic acid. The (MUFA+PUFA):SFA ratio was also lower in MCI cases ($p = 0.049$), and trans-fatty acids intake was marginally higher in MCI cases.

The OR of MCI decreased significantly with increasing intake of total PUFA and (MUFA+PUFA):SFA ratio (Table 3). A similar trend was observed for MUFA intake, MUFA:SFA ratio, and total fat, but these trends were not statistically significant. Table 4 demonstrates a dose-response association of the components of PUFA with MCI. Increasing intake of omega-6 fatty acid and linoleic acid (both n-6 PUFA), and of omega-3 fatty acid and linolenic acid (both n-3 PUFA), was associated with a reduced OR of MCI. There was no potential confounding by dyslipidemia, hypertension, marital status, current smoking status, moderate alcohol intake, or moderate exercise when these variables were included in the base models separately (data not presented). When they were simultaneously included in the fully-adjusted models, there was little change in the estimates. For example, the OR (95% CI) for the highest vs. lowest tertile (reference) were as follows: 0.42 (0.24–0.73) for PUFA; 0.52 (0.30–0.91) for (MUFA+PUFA):SFA ratio; 0.43 (0.25–0.75) for omega-6 fatty acid; 0.46 (0.27–0.79) for omega-3 fatty acid; 0.42 (0.24–0.74) for linoleic acid; and 0.35 (0.19–0.62) for linolenic acid.

There was no interaction of fatty acids with age, sex, or number of years of education. However, there was a significant interaction of MUFA with sex, and of cholesterol with ApoE $\epsilon 4$ allele. High intake of MUFA was associated with a reduced OR of MCI in men (OR = 0.71; 95% CI = 0.53–0.94; ordinal p value across tertiles = 0.018) but not in women (OR = 1.08; 95% CI = 0.77–1.51; ordinal p value across tertiles = 0.67; p for interaction = 0.04). High intake of cholesterol was associated with a reduced OR of MCI in persons who were ApoE $\epsilon 4+$ (OR = 0.62; 95% CI = 0.43–0.92; ordinal p value = 0.016) but not in persons who were ApoE $\epsilon 4-$ (OR = 1.06; 95% CI = 0.83–1.35; ordinal p value = 0.64; p for interaction = 0.03). We examined the associations further across specific ApoE $\epsilon 4$ genotypes and age group (Table 5). The OR

(95% CI) decreased with increasing numbers of $\epsilon 4$ alleles: ApoE $\epsilon 3\epsilon 3$ –1.05 (0.80, 1.36; $p = 0.73$); ApoE $\epsilon 3\epsilon 4$ –0.78 (0.51, 1.20; $p = 0.26$); and ApoE $\epsilon 4\epsilon 4$ –0.20 (0.03, 1.26; $p = 0.09$); however, the sample sizes were much reduced and none of the associations reached statistical significance. The same pattern was observed when stratified by age.

Table 6 presents the associations of PUFA, MUFA and their components with MCI subtypes. Intake in the upper tertile was significantly associated with a reduced OR of a-MCI for all the variables considered in this table. The OR of na-MCI was significantly reduced for intake in the upper tertile of omega-6 fatty acid and for linoleic acid; estimates for PUFA, (MUFA + PUFA):SFA ratio, omega-3 fatty acid, and linolenic acid were also reduced, but the CIs included 1.

Sensitivity analyses

After exclusion of subjects with a memory score in the 5th percentile or lower ($n = 110$), our results remained essentially the same as for the total sample. Compared to the lowest tertile, there was a dose-response association of MCI with daily intake of PUFA (middle-tertile OR = 0.60, 95% CI = 0.38–0.95; upper tertile–OR = 0.42, 95% CI = 0.25–0.68; p for trend = 0.002); omega-6 fatty acids (middle tertile–OR = 0.64, 95% CI = 0.41–1.01; upper tertile–OR = 0.43, 95% CI = 0.26–0.71; p for trend = 0.004); linoleic acid (middle tertile–OR = 0.64, 95% CI = 0.41–1.01; upper tertile–OR = 0.43, 95% CI = 0.26–0.70; p for trend = 0.004), and linolenic acid (middle tertile–OR = 0.98, 95% CI = 0.63–1.53; upper tertile–OR = 0.55, 95% CI = 0.33–0.91; p for trend = 0.038). The dose-response association persisted for omega-3 fatty acids (middle tertile–OR = 0.79, 95% CI = 0.50–1.26; upper tertile–OR = 0.76, 95% CI = 0.47–1.22; p for trend = 0.46), but the test for trend was no longer significant due to the reduced power. When we excluded subjects with more than 12 months lag between diagnosis and food frequency questionnaire ($n = 19$), and subjects who had a medical record notation of cognitive impairment prior to enrollment in the study ($n = 17$), the results were essentially unchanged, and the data are not presented.

Preliminary longitudinal analyses

Among subjects who were cognitively normal at baseline, 889 completed ≥ 1 longitudinal clinical evaluations after assessment of dietary intake, and there were 93 incident MCI events over a median follow-up of 2.7 years (interquartile range = 2.5, 3.7). Due to the relatively short follow-up time and number of incident events, we did not have adequate power to detect significant associations of dietary intakes with incident MCI. Nonetheless, the HR of MCI was reduced between 7% and 21% for persons with intake in the upper tertile at baseline: 0.79 (95% CI = 0.46–1.35) for PUFA; 0.90 (95% CI = 0.53–1.54) for omega-3 fatty acid, 0.92 (95% CI = 0.57–1.48) for (MUFA+PUFA):SFA ratio; and 0.93 (95% CI = 0.53–1.64) for omega-6 fatty acids compared to the lowest tertile, but the CIs included 1.

DISCUSSION

We observed significant dose-response associations between increasing dietary intake of polyunsaturated fatty acids, increasing (MUFA+PUFA):SFA ratio, and prevalent MCI. A similar but non-significant trend was observed for MUFA. In contrast, higher intake of trans-fatty acids was associated with an elevated OR of MCI. Although other studies have reported similar associations with dementia and cognitive impairment (using different diagnostic criteria), our findings provide support for a potential beneficial role of PUFA and MUFA in MCI. We observed similar associations with the MCI subtypes. Since MCI is an intermediate stage between normal cognitive aging and dementia, these findings may have potential implications for intervention if established in longitudinal studies assessing incident MCI.

Our study has several strengths. Given the population-based design, our findings are generalizable to the community. We used a previously validated questionnaire to assess dietary intakes [19]; this previously validated questionnaire had an 81% response rate of which 79% provided useable data. Our study endpoint, MCI, was rigorously assessed using a clinical protocol that involved three independent evaluators. In this epidemiological setting, the ascertainment of information on cognitive concern includes a subjective concern expressed by the study participant, a concern about the participant raised by a study partner, or concern about cognition raised by the examining clinician, thus enhancing the capture of all potential MCI cases. The ultimate diagnosis of MCI was made by consensus using previously specified criteria. However, the diagnosis of MCI was made at the time of the evaluation; this is in contrast to other studies that have either retrospectively applied MCI criteria to previously collected data or have assigned diagnoses based solely on neuropsychological test results.

Our findings are consistent with previous studies. High MUFA and PUFA intake were significantly associated with better cognition in the Italian Longitudinal Study of Aging [27]. In longitudinal studies, high PUFA intake was associated with a reduced risk of cognitive impairment in two Italian cohorts [3,28]; olive oil and MUFA had beneficial effects on MMSE scores [12], and linoleic acid was associated with a reduced risk of dementia [7]. In the Chicago Health and Aging Project, high MUFA and PUFA:SFA ratios were associated with less cognitive decline [2,4], total MUFA intake was associated with a reduced risk of AD [29], and high intake of trans-fatty acids was associated with greater cognitive decline [2]. Beneficial effects of PUFA and PUFA:SFA ratios were reported in the Cardiovascular Risk Factors, Aging, and Dementia Study after 21 years of follow-up [30], and in elderly French women [31]. In the Nurses Health Study, higher intake of trans-fatty acids and a lower PUFA:SFA ratio were associated with worse cognitive decline in women with type 2 diabetes mellitus [32]. In clinical trials, mild AD subjects treated with omega-3 fatty acids had a slower decline in MMSE scores [33], and short-term supplementation (90 days) with arachidonic acid and DHA was associated with improvement in memory and attention in MCI patients [34].

In other studies, high PUFA intake was adversely associated with MMSE scores [12], linoleic acid was associated with prevalent and incident cognitive impairment, and n-3 PUFA was not associated with cognitive impairment [11]. Others have found no association of low MUFA intake and cognitive function [10,35].

The implications of the interactions of MUFA with sex, and cholesterol with ApoE $\epsilon 4$ allele in the present study are not clear. However, the latter is consistent with the suggestion that high serum levels of cholesterol may have beneficial effects in the elderly [36], in contrast to the adverse effects of high levels in mid-life [37,38]. Other studies have observed no beneficial association [39,40] or an adverse effect [41]. Yet, this finding may be of interest since ApoE is the principal cholesterol carrier protein in the brain [42]. Alternately, it is highly probable that the significant interaction observed when grouped as $\epsilon 4$ carrier versus non-carrier was due to a spurious association caused by the small number of $\epsilon 2\epsilon 4$ MCI cases and, in particular, to the five $\epsilon 4\epsilon 4$ MCI cases who survived to a late age. In the analyses stratified by all six ApoE genotypes, we observed no significant associations even among the $\epsilon 3\epsilon 4$ genotype, the $\epsilon 4$ carrier group with the largest number of MCI cases. Further longitudinal studies will help determine whether the beneficial association of high cholesterol intake in ApoE $\epsilon 4$ carriers is real, due to bias, or simply a spurious association as is possible in our study.

The beneficial effects of PUFA and MUFA on cognitive function may occur through several mechanisms. PUFA may reduce the risk of thrombosis, cardiovascular risk [43], and stroke [44], and may also inhibit inflammation [45]. They may improve the lipid profile of the brain [46], maintain the structural integrity of neuronal membranes [47], exert antioxidant effects [48], or decrease β -amyloid levels [49]. Alternately, others suggest that n-6 PUFA constitutes

a high component of low-density lipoprotein, and consequently may increase the susceptibility of low-density lipoproteins to oxidation [50]. This would, in turn, promote atherosclerosis, thrombosis, strokes, infarctions, and white matter changes that may lead to cognitive impairment [11].

Despite the small number of subjects with na-MCI, the magnitude of the associations for na-MCI was similar to a-MCI, albeit with fewer significant associations. This would suggest that the potential beneficial effects of PUFA and MUFA are on both neurodegenerative and vascular mechanisms, or through an alternate mechanism.

The inconsistencies across studies could be due to several reasons. Methods used to assess cognitive function differ; some investigators use a single test such as the MMSE, whereas others use a neuropsychometric testing battery with or without a clinical assessment. Differences in nutritional databases, volunteer versus random sample, cross-sectional or longitudinal design, duration of longitudinal studies, and cultural differences in diet across populations may also be important. For example, in contrast to a Mediterranean setting, use of olive oil (MUFA) and fish intake in a Midwestern community may be well below the threshold at which significant beneficial effects can be detected in the research setting. Daily MUFA intake in the present study was about half that reported in an Italian community, whereas PUFA intake was higher [27].

Potential limitations include recall bias in reporting of dietary nutrients. In particular, it is possible that cases would report dietary intakes in a biased manner that would affect the validity of the study findings. However, the MCI cases were relatively mild (the median CDR sum of boxes was only 1.0, and the median memory domain score was -1.1). Cases were not informed that they received an MCI diagnosis at the evaluation, and the results were essentially the same after exclusion of subjects with a medical record notation of cognitive impairment prior to enrollment. Furthermore, the results remained essentially the same after exclusion of subjects in the lowest 5% of memory domain or subjects with more than 1 year between evaluation and completion of the food frequency questionnaire. However, these efforts to assess bias do not provide information on the direction or magnitude of any potential bias. A possible mechanism to validate dietary intakes and to determine the magnitude of bias would have been to ascertain dietary intakes in cases and controls by interview of the participant informants (i.e., proxy interview) using a matched case-control design. Nevertheless, this method would also yield valid data only where the proxy had detailed knowledge about the dietary habits of the participant over the period of time evaluated in the dietary questionnaire.

Another potential limitation that cannot be evaluated is that of reverse causality. The consistency of the findings across several longitudinal studies, including population-based studies, suggests that the associations between MUFA and PUFA and cognition may not be due entirely to reverse causality [2–4,7,21,28]. Nonetheless, given that some studies have not confirmed the relationships, further evaluation of the associations in large population-based studies are needed to clarify this issue. Despite the potential for non-participation bias, the differential participation by MCI cases did not influence our results; the results with and without adjustment for propensity to participate were essentially unchanged. Due to multiple testing, a Bonferroni correction would require a *p* value of 0.0036 for statistical significance; yet, even at this conservative *p* value, the associations of PUFA with MCI remain statistically significant. Finally, the study was conducted among a predominantly Caucasian population; thus, the findings are generalizable to similar settings.

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Fig.

Flow-chart of subjects included in the analyses. Subjects who were not eligible to receive the food frequency questionnaire included 45 subjects who died ($n = 22$) after the baseline assessment, refused further participation ($n = 22$), or were non-English speaking ($n = 1$) and could not complete the questionnaire. Subjects who were excluded had missing responses on more than 10 of the 128 'How often' questions on frequency of consumption of foods ($n = 268$), reported extreme caloric intake (low intake = < 800 [in men] or < 600 [in women] kcal/day; high intake = $> 6,000$ [in men] or $> 5,000$ [in women] kcal/day) or were demented at the time of the evaluation ($n = 10$).

Table 1

Demographic and clinical characteristics of study participants by MCI status, Mayo Clinic Study of Aging, 2004–2006*

Variable	All <i>n</i> = 1,233	MCI <i>n</i> = 163	No MCI <i>n</i> = 1,070	<i>p</i>
Age, years				
Median (Q1, Q3)	80.1 (75.7, 84.4)	82.9 (78.3, 86.4)	79.6 (75.5, 84.1)	< 0.0001
Gender				
Male, <i>n</i> (%)	641 (52.0)	97 (59.5)	544 (50.8)	0.04
Female, <i>n</i> (%)	592 (48.0)	66 (40.5)	526 (49.2)	
Education, years				
Median (Q1, Q3)	13 (12, 16)	12 (12, 15)	13 (12, 16)	0.001
Marital Status				
Married, <i>n</i> (%)	800 (64.9)	104 (63.8)	696 (65.0)	0.76
Not married, <i>n</i> (%)	433 (35.1)	59 (36.2)	374 (35.0)	
Body mass index [†]				
< 25	389 (32.5)	53 (35.1)	336 (32.2)	0.31
25–29	484 (40.5)	65 (43.0)	419 (40.1)	
≥ 30	323 (27.0)	33 (21.9)	290 (27.8)	
Diabetes				
Yes, <i>n</i> (%)	149 (12.1)	22 (13.5)	127 (11.9)	0.55
No, <i>n</i> (%)	1,084 (87.9)	141 (86.5)	943 (88.1)	
Hypertension				
Yes, <i>n</i> (%)	876 (71.0)	122 (74.8)	754 (70.5)	0.25
No, <i>n</i> (%)	357 (29.0)	41 (25.2)	316 (29.5)	
Coronary heart disease				
Yes, <i>n</i> (%)	333 (27.0)	51 (31.3)	282 (26.4)	0.19
No, <i>n</i> (%)	900 (73.0)	112 (68.7)	788 (73.6)	
Stroke				
Yes, <i>n</i> (%)	124 (10.1)	35 (21.5)	89 (8.3)	< 0.0001
No, <i>n</i> (%)	1,109 (89.9)	128 (78.5)	981 (91.7)	
Dyslipidemia				
Yes	597 (48.4)	82 (50.3)	515 (48.1)	0.60
No	636 (51.6)	81 (49.7)	555 (51.9)	
Depressive symptoms [‡]				
Yes, <i>n</i> (%)	148 (12.3)	41 (25.8)	107 (10.3)	< 0.0001
No, <i>n</i> (%)	1,053 (87.7)	118 (74.2)	935 (89.7)	
ApoE ε4 [§]				
ε3ε4/ε4ε4, <i>n</i> (%)	264 (22.7)	47 (31.1)	217 (21.5)	0.008
ε2ε2/ε2ε3/ε3ε3, <i>n</i> (%)	897 (77.3)	104 (68.9)	793 (78.5)	
ε2ε2	1 (0.1)	0 (0.0)	1 (0.1)	0.11
ε2ε3	150 (12.6)	22 (14.1)	128 (12.3)	
ε2ε4	32 (2.7)	5 (3.2)	27 (2.6)	

Variable	All <i>n</i> = 1,233	MCI <i>n</i> = 163	No MCI <i>n</i> = 1,070	<i>p</i>
ε3ε3	746 (62.5)	82 (52.6)	664 (64.0)	
ε3ε4	235 (19.7)	41 (26.3)	194 (18.7)	
ε4ε4	29 (2.4)	6 (3.8)	23 (2.2)	
Moderate exercise				0.014
Yes	421 (38.8)	39 (29.1)	382 (40.2)	
No	663 (61.2)	95 (70.9)	568 (59.8)	
Current cigarette smoking				0.94
Yes	39 (3.2)	5 (3.1)	34 (3.2)	
No	1,194 (96.8)	158 (96.9)	1,036 (96.8)	
Alcohol intake, gm/day				0.05
Moderate (> 0 or < 30)	801 (65.0)	95 (58.3)	706 (66.0)	
Low or high (0 or ≥ 30)	432 (35.0)	68 (41.7)	364 (34.0)	
Domain z scores, median (Q1, Q3)				
Memory domain score ^{//}	0.28 (−0.46, 1.08)	−1.12 (−1.77, −0.72)	0.48 (−0.19, 1.17)	< 0.0001
Executive function domain score [¶]	0.30 (−0.35, 0.86)	−1.01 (−1.79, −0.17)	0.42 (−0.13, 0.93)	< 0.0001
Visuospatial domain score ^{**}	0.28 (−0.47, 0.85)	−0.73 (−1.39, −0.03)	0.38 (−0.31, 0.94)	< 0.0001
Language domain score ^{††}	0.24 (−0.39, 0.78)	−0.75 (−1.58, minus;0.24)	0.32 (minus;0.20, 0.91)	< 0.0001
Clinical Dementia Rating scale ^{‡‡}	0.00 (0.00, 0.00)	1.00 (0.50, 1.50)	0.00 (0.00, 0.00)	< 0.0001

* MCI = mild cognitive impairment; Q1 = first quartile; Q3 = third quartile.

[†] 37 missing in total cohort: 25 missing in No MCI, 12 missing in MCI.

[‡] 32 missing in total cohort: 28 missing in No MCI, 4 missing in MCI.

[§] 40 missing in total cohort: 33 missing in No MCI, 7 missing in MCI.

^{//} 52 missing in total cohort: 39 missing in No MCI, 13 missing in MCI.

[¶] 108 missing in total cohort: 81 missing in No MCI, 27 missing in MCI.

^{**} 100 missing in total cohort: 78 missing in No MCI, 22 missing in MCI.

^{††} 86 missing in total cohort: 67 missing in No MCI, 19 missing in MCI.

^{‡‡} 6 missing in total cohort: 6 missing in No MCI.

Table 2

Dietary fatty acids of participants (median [interquartile range]) at baseline by MCI status*

Variable	All <i>n</i> = 1,233	MCI cases <i>n</i> = 163	Controls <i>n</i> = 1,070	<i>p</i>
PUFA, g/day	10.23 (8.47–12.26)	9.64 (8.14–11.41)	10.39 (8.55–12.41)	0.009
Omega-6 fatty acids, g/day	8.84 (7.27–10.74)	8.29 (7.02–10.10)	8.97 (7.34–10.87)	0.005
Omega-3 fatty acids, g/day	0.94 (0.79–1.13)	0.89 (0.76–1.08)	0.94 (0.80–1.14)	0.018
Linoleic acid, g/day	8.66 (7.12–10.59)	8.03 (6.90–9.90)	8.79 (7.21–10.70)	0.006
Linolenic acid, g/day	0.84 (0.72–1.00)	0.81 (0.68–0.94)	0.85 (0.72–1.00)	0.014
(MUFA+PUFA):SFA ratio	1.56 (1.32–1.80)	1.51 (1.28–1.70)	1.57 (1.33–1.81)	0.049
Trans-fatty acids, g/day	0.74 (0.48–1.13)	0.82 (0.59–1.10)	0.73 (0.46–1.14)	0.065
MUFA:SFA ratio	1.04 (0.91–1.17)	1.01 (0.89–1.14)	1.04 (0.91–1.17)	0.23
MUFA, g/day	20.73 (17.33–24.78)	21.07 (16.91–24.17)	20.69 (17.36–24.91)	0.78
Cholesterol, g/day	257.79 (186.34–388.93)	254.06 (178.16–373.71)	258.43 (188.21–389.46)	0.43
SFA, g/day	20.20 (16.59–24.39)	20.29 (16.81–24.61)	20.20 (16.56–24.35)	0.58
Total fat, g/day	61.72 (52.71–71.96)	62.12 (51.61–72.41)	61.62 (53.02–71.96)	0.69
Fish intake, g/day	15.03 (6.75–26.02)	12.46 (6.33–23.83)	15.33 (6.96–26.21)	0.15
Total calories, kcal/day	1.81 (1.37–2.37)	2.06 (1.51–2.68)	1.79 (1.35–2.33)	0.001

* MCI = mild cognitive impairment; MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids.

Table 3

Association of tertiles of PUFA, MUFA, and SFA with MCI*

Variable	Controls <i>n</i> = 1,070 <i>n</i> (%)	MCI cases <i>n</i> = 163 <i>n</i> (%)	MCI					
			OR (95% CI) [†]	<i>p</i>	<i>p</i> for trend	OR (95% CI) [‡]	<i>p</i>	<i>p</i> for trend
PUFA, g/day								
< 9.06	342 (32.0)	69 (42.3)	1.00 (reference)	---	---	1.00 (reference)	---	---
9.06–11.49	358 (33.5)	54 (33.1)	0.68 (0.47–0.98)	0.040		0.69 (0.46–1.03)	0.07	
> 11.49	370 (34.6)	40 (24.5)	0.44 (0.29–0.66)	< 0.0001	0.0004	0.37 (0.23–0.58)	< 0.0001	0.0001
(MUFA+PUFA):SFA ratio								
< 1.42	346 (32.3)	65 (39.9)	1.00 (reference)	---	---	1.00 (reference)	---	---
1.42–1.71	353 (33.0)	59 (36.2)	0.91 (0.64–1.31)	0.63		0.98 (0.66–1.45)	0.90	
> 1.71	371 (34.7)	39 (23.9)	0.56 (0.38–0.83)	0.004	0.010	0.52 (0.33–0.81)	0.004	0.007
MUFA, g/day								
< 18.52	356 (33.3)	55 (33.7)	1.00 (reference)	---	---	1.00 (reference)	---	---
18.52–23.29	358 (33.5)	54 (33.1)	0.78 (0.53–1.17)	0.23		0.70 (0.45–1.09)	0.11	
> 23.29	356 (33.3)	54 (33.1)	0.70 (0.45–1.09)	0.12	0.27	0.56 (0.34–0.91)	0.021	0.06
MUFA:SFA ratio								
< 0.96	353 (33.0)	58 (35.6)	1.00 (reference)	---	---	1.00 (reference)	---	---
0.96–1.12	358 (33.5)	54 (33.1)	0.91 (0.63–1.32)	0.62		0.94 (0.63–1.42)	0.78	
> 1.12	359 (33.6)	51 (31.3)	0.82 (0.56–1.20)	0.31	0.60	0.79 (0.52–1.20)	0.27	0.52
Trans-fatty acids, g/day								
< 0.56	372 (34.8)	39 (23.9)	1.00 (reference)	---	---	1.00 (reference)	---	---
0.56–0.98	343 (32.1)	69 (42.3)	1.71 (1.15–2.54)	0.008		1.63 (1.05–2.52)	0.028	
> 0.98	355 (33.2)	55 (33.7)	1.25 (0.83–1.89)	0.29	0.024	1.27 (0.81–1.99)	0.29	0.09
Total fat, g/day								
< 55.53	352 (32.9)	59 (36.2)	1.00 (reference)	---	---	1.00 (reference)	---	---
55.53–68.17	363 (33.9)	49 (30.1)	0.72 (0.48–1.07)	0.10		0.73 (0.47–1.14)	0.16	
> 68.17	355 (33.2)	55 (33.7)	0.67 (0.43–1.05)	0.08	0.15	0.59 (0.36–0.97)	0.037	0.11
Cholesterol, g/day								
< 210.22	349 (32.6)	62 (38.0)	1.00 (reference)	---	---	1.00 (reference)	---	---
210.22–324.58	364 (34.0)	48 (29.4)	0.68 (0.46–1.00)	0.049		0.75 (0.49–1.15)	0.18	
> 324.58	357 (33.4)	53 (32.5)	0.75 (0.51–1.10)	0.14	0.12	0.83 (0.54–1.28)	0.40	0.40

Variable	Controls <i>n</i> = 1,070 <i>n</i> (%)	MCI cases <i>n</i> = 163 <i>n</i> (%)	MCI			
			OR (95% CI) [†]	<i>p</i>	<i>p</i> for trend	<i>p</i> for trend
SFA, g/day						
< 17.91	363 (33.9)	48 (29.4)	1.00 (reference)	---		---
17.91–23.05	360 (33.6)	52 (31.9)	1.03 (0.69–1.54)	0.87		0.97
> 23.05	347 (32.4)	63 (38.7)	1.20 (0.79–1.83)	0.39	0.65	0.81
						0.95

* 95% CI = 95% confidence interval; MCI = mild cognitive impairment; MUFA = monounsaturated fatty acids; OR = odds ratio; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids.

[†] Adjusted for age, sex, years of education, and total caloric intake.

[‡] Additional adjustment for body mass index, ApoE ε4 allele, stroke, coronary heart disease, diabetes, and depression.

Table 4

Association of tertiles of omega-6, omega-3, linoleic acid, and linolenic acid with MCI*

Variable	Non-MCI n = 1,070 n (%)	MCI n = 163 n (%)	MCI					
			OR (95% CI) [†]	p	p for trend	OR (95% CI) [‡]	p	p for trend
Omega-6 fatty acids, g/day								
< 7.80	342 (32.0)	69 (42.3)	1.00 (reference)	---	---	1.00 (reference)	---	---
7.80–10.09	359 (33.6)	53 (32.5)	0.66 (0.45–0.95)	0.027		0.67 (0.44–1.01)	0.053	
> 10.09	369 (34.5)	41 (25.2)	0.44 (0.30–0.67)	< 0.0001	0.0004	0.38 (0.24–0.59)	< 0.0001	0.0001
Omega-3 fatty acids, g/day								
< 0.84	343 (32.1)	68 (41.7)	1.00 (reference)	---	---	1.00 (reference)	---	---
0.84–1.05	364 (34.0)	48 (29.4)	0.60 (0.41–0.88)	0.008		0.57 (0.37–0.86)	0.008	
> 1.05	363 (33.9)	47 (28.8)	0.62 (0.42–0.91)	0.015	0.012	0.53 (0.34–0.81)	0.004	0.005
Linoleic acid, g/day								
< 7.65	342 (32.0)	69 (42.3)	1.00 (reference)	---	---	1.00 (reference)	---	---
7.65–9.94	357 (33.4)	55 (33.7)	0.68 (0.47–0.99)	0.045		0.69 (0.46–1.04)	0.08	
> 9.94	371 (34.7)	39 (23.9)	0.42 (0.28–0.63)	< 0.0001	0.0002	0.37 (0.23–0.58)	< 0.0001	< 0.0001
Linolenic acid, g/day								
< 0.76	346 (32.3)	65 (39.9)	1.00 (reference)	---	---	1.00 (reference)	---	---
0.76–0.93	357 (33.4)	55 (33.7)	0.77 (0.53–1.11)	0.17		0.77 (0.51–1.15)	0.19	
> 0.93	367 (34.3)	43 (26.4)	0.56 (0.38–0.84)	0.005	0.019	0.47 (0.30–0.75)	0.001	0.005
Fish intake, g/day								
< 8.74	353 (33.0)	58 (35.6)	1.00 (reference)	---	---	1.00 (reference)	---	---
8.74–21.20	354 (33.1)	58 (35.6)	1.10 (0.76–1.60)	0.60		0.97 (0.64–1.47)	0.88	
> 21.20	363 (33.9)	47 (28.8)	1.07 (0.72–1.58)	0.75	0.87	1.04 (0.68–1.59)	0.85	0.95
Omega-6:Omega-3 ratio								
< 8.68	357 (33.4)	54 (33.1)	1.00 (reference)	---	---	1.00 (reference)	---	---
8.68–10.49	358 (33.5)	54 (33.1)	0.89 (0.61–1.31)	0.55		0.93 (0.62–1.41)	0.74	
> 10.49	355 (33.2)	55 (33.7)	0.85 (0.58–1.25)	0.42	0.70	0.72 (0.47–1.10)	0.13	0.28

* 95% CI = 95% confidence interval; MCI = mild cognitive impairment; OR = odds ratio.

[†] Adjusted for age, sex, years of education, and total caloric intake.

[‡] Additional adjustment for body mass index, ApoE ε4 allele, stroke, coronary heart disease, diabetes, and depression.

Table 5

Association of cholesterol intake with MCI across ApoE genotypes

Variable	All			Aged 70–79 years			Aged 80–89 years		
	MCI n	OR (95% CI)	p	MCI n	OR (95% CI)	p	MCI n	OR (95% CI)	p
No ε4	104	1.06(0.83–1.35)	0.64	35	0.77 (0.51–1.16)	0.21	69	1.24 (0.93–1.67)	0.15
ε2ε4 or ε3ε4 or ε4ε4	52	0.62 (0.43–0.92)	0.016	15	0.55 (0.27–1.10)	0.09	37	0.71 (0.45–1.13)	0.15
ε2ε2	0	--		0	--		0	--	
ε2ε3	22	1.15 (0.62–2.14)	0.66	9	0.63 (0.20–1.96)	0.42	13	1.62 (0.75–3.53)	0.22
ε2ε4	5	--	1.0	1	--	1.0	4	--	1.00
ε3ε3	82	1.05 (0.80–1.36)	0.73	26	0.81 (0.51–1.29)	0.38	56	1.19 (0.87–1.65)	0.28
ε3ε4	41	0.78 (0.51–1.20)	0.26	13	0.52 (0.24–1.12)	0.095	28	1.01 (0.60–1.72)	0.96
ε4ε4	6	0.20 (0.03–1.26)	0.086	1	--	1.00	5	0.08 (0.00–1.36)	0.080

* 95% CI = 95% confidence interval; MCI = mild cognitive impairment.

Table 6

Association of tertiles of PUFA, MUFA, omega-6, omega-3, linoleic acid, and linolenic acid with MCI subtypes*

Variable	Amnesic MCI (n = 113)			Non-amnesic MCI (n = 41)		
	n (%)	OR (95% CI) [†]	p	n (%)	OR (95% CI) [†]	p
PUFA, g/day						
< 9.06	45 (10.9)	1.00 (reference)		21 (5.1)	1.00 (reference)	
9.06–11.49	44 (10.7)	0.90 (0.59–1.37)	0.63	8 (1.9)	0.35 (0.17–0.75)	0.007
> 11.49	24 (5.9)	0.42 (0.25–0.68)	0.0005	12 (2.9)	0.53 (0.27–1.06)	0.07
(MUFA+PUFA):SFA ratio						
< 1.42	48 (11.7)	1.00 (reference)		14 (3.4)	1.00 (reference)	
1.42–1.71	40 (9.7)	0.80 (0.53–1.21)	0.30	17 (4.1)	1.38 (0.72–2.65)	0.33
> 1.71	25 (6.1)	0.49 (0.31–0.78)	0.003	10 (2.4)	0.78 (0.37–1.64)	0.51
Omega-6 fatty acids, g/day						
< 7.80	46 (11.2)	1.00 (reference)		20 (4.9)	1.00 (reference)	
7.80–10.09	41 (10.0)	0.80 (0.53–1.23)	0.31	10 (2.4)	0.47 (0.23–0.94)	0.033
> 10.09	26 (6.3)	0.46 (0.28–0.73)	0.001	11 (2.7)	0.47 (0.23–0.96)	0.037
Omega-3 fatty acids, g/day						
< 0.84	52 (12.7)	1.00 (reference)		12 (2.9)	1.00 (reference)	
0.84–1.05	29 (7.0)	0.42 (0.27–0.67)	0.0002	18 (4.4)	1.79 (0.90–3.56)	0.10
> 1.05	32 (7.8)	0.49 (0.32–0.77)	0.002	11 (2.7)	1.14 (0.53–2.45)	0.73
Linoleic acid, g/day						
< 7.65	46 (11.2)	1.00 (reference)		20 (4.9)	1.00 (reference)	
7.65–9.94	42 (10.2)	0.83 (0.55–1.27)	0.39	11 (2.7)	0.50 (0.25–0.99)	0.047
> 9.94	25 (6.1)	0.44 (0.27–0.71)	0.0008	10 (2.4)	0.42 (0.20–0.87)	0.019
Linolenic acid, g/day						
< 0.76	48 (11.7)	1.00 (reference)		13 (3.2)	1.00 (reference)	
0.76–0.93	35 (8.5)	0.60 (0.39–0.93)	0.022	19 (4.6)	1.67 (0.87–3.21)	0.12
> 0.93	30 (7.3)	0.50 (0.32–0.80)	0.003	9 (2.2)	0.74 (0.33–1.65)	0.46

* 95% CI = 95% confidence interval; MCI = mild cognitive impairment; OR = odds ratio.

[†] Adjusted for age, sex, years of education, and total caloric intake. Additional adjustment for body mass index, ApoE ε4 allele, stroke, coronary heart disease, diabetes, and depression did not change the estimates (data not presented).

Appendix 1

Association of tertiles of PUFA, MUFA, and SFA with MCI*

Variable	Controls <i>n</i> = 1,070	MCI cases <i>n</i> = 163	MCI					
	<i>n</i> (%)	<i>n</i> (%)	OR (95% CI) [†]	<i>p</i>	<i>p</i> for trend	OR (95% CI) [‡]	<i>p</i>	<i>p</i> for trend
PUFA, g/day								
< 9.06	342 (32.0)	69 (42.3)	1.00 (reference)	---	---	1.00 (reference)	---	---
9.06–11.49	358 (33.5)	54 (33.1)	0.68 (0.45–1.02)	0.060		0.70 (0.45–1.09)	0.11	
> 11.49	370 (34.6)	40 (24.5)	0.43 (0.28–0.68)	0.0003	0.001	0.37 (0.22–0.61)	0.0001	0.0005
(MUFA+PUFA):SFA ratio								
< 1.42	346 (32.3)	65 (39.9)	1.00 (reference)	---	---	1.00 (reference)	---	---
1.42–1.71	353 (33.0)	59 (36.2)	0.93 (0.63–1.38)	0.71		1.01 (0.65–1.56)	0.97	
> 1.71	371 (34.7)	39 (23.9)	0.56 (0.37–0.87)	0.010	0.025	0.55 (0.34–0.89)	0.015	0.023
MUFA, g/day								
< 18.52	356 (33.3)	55 (33.7)	1.00 (reference)	---	---	1.00 (reference)	---	---
18.52–23.29	358 (33.5)	54 (33.1)	0.79 (0.51–1.22)	0.28		0.71 (0.43–1.15)	0.17	
> 23.29	356 (33.3)	54 (33.1)	0.68 (0.42–1.12)	0.13	0.30	0.54 (0.31–0.93)	0.027	0.09
MUFA:SFA ratio								
< 0.96	353 (33.0)	58 (35.6)	1.00 (reference)	---	---	1.00 (reference)	---	---
0.96–1.12	358 (33.5)	54 (33.1)	0.92 (0.61–1.39)	0.70		0.99 (0.63–1.55)	0.95	
> 1.12	359 (33.6)	51 (31.3)	0.83 (0.55–1.26)	0.39	0.69	0.83 (0.52–1.32)	0.43	0.68
Trans-fatty acids, g/day								
< 0.56	372 (34.8)	39 (23.9)	1.00 (reference)	---	---	1.00 (reference)	---	---
0.56–0.98	343 (32.1)	69 (42.3)	1.69 (1.10–2.61)	0.017		1.62 (1.01–2.61)	0.046	
> 0.98	355 (33.2)	55 (33.7)	1.16 (0.74–1.83)	0.518	0.035	1.22 (0.74–1.99)	0.44	0.12
Total fat, g/day								
< 55.53	352 (32.9)	59 (36.2)	1.00 (reference)	---	---	1.00 (reference)		
55.53–68.17	363 (33.9)	49 (30.1)	0.71 (0.46–1.10)	0.13		0.73 (0.45–1.19)	0.21	
> 68.17	355 (33.2)	55 (33.7)	0.65 (0.40–1.06)	0.09	0.18	0.57 (0.33–0.98)	0.043	0.13
Cholesterol, g/day								
< 210.22	349 (32.6)	62 (38.0)	1.00 (reference)	---	---	1.00 (reference)	---	---
210.22–324.58	364 (34.0)	48 (29.4)	0.69 (0.45–1.05)	0.08		0.76 (0.48–1.21)	0.25	
> 324.58	357 (33.4)	53 (32.5)	0.72 (0.47–1.11)	0.13	0.16	0.77 (0.48–1.23)	0.28	0.43

Variable	Controls <i>n</i> = 1,070 <i>n</i> (%)	MCI cases <i>n</i> = 163 <i>n</i> (%)	MCI			
			OR (95% CI) [†]	<i>p</i>	<i>p</i> for trend	<i>p</i> for trend
SFA, g/day						
< 17.91	363 (33.9)	48 (29.4)	1.00 (reference)	---	1.00 (reference)	---
17.91–23.05	360 (33.6)	52 (31.9)	1.00 (0.64–1.54)	0.98	0.95 (0.59–1.55)	0.85
> 23.05	347 (32.4)	63 (38.7)	1.16 (0.73–1.85)	0.52	1.01 (0.60–1.72)	0.96

* 95% CI = 95% confidence interval; MCI = mild cognitive impairment; MUFA = monounsaturated fatty acids; OR = odds ratio; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids.

[†] Adjusted for age, sex, number of years of education, and total caloric intake.

[‡] Additional adjustment for body mass index, ApoE ε4 allele, stroke, coronary heart disease, diabetes, and depressive symptoms.

Appendix 2

Association of tertiles of omega-6, omega-3, linoleic acid, and linolenic acid with MCI*

Variable	Non-MCI <i>n</i> (%)	MCI <i>n</i> (%)	MCI					
			OR (95% CI) [†]	<i>p</i>	<i>p</i> for trend	OR (95% CI) [‡]	<i>p</i>	<i>p</i> for trend
Omega-6 fatty acids, g/day								
< 7.80	342 (32.0)	69 (42.3)	1.00 (reference)	---	---	1.00 (reference)	---	---
7.80–10.09	359 (33.6)	53 (32.5)	0.66 (0.44–0.99)	0.047	---	0.68 (0.43–1.06)	0.09	---
> 10.09	369 (34.5)	41 (25.2)	0.44 (0.28–0.69)	0.0003	0.002	0.38 (0.23–0.62)	0.0001	0.0007
Omega-3 fatty acids, g/day								
< 0.84	343 (32.1)	68 (41.7)	1.00 (reference)	---	---	1.00 (reference)	---	---
0.84–1.05	364 (34.0)	48 (29.4)	0.61 (0.40–0.93)	0.020	---	0.56 (0.36–0.89)	0.014	---
> 1.05	363 (33.9)	47 (28.8)	0.61 (0.40–0.94)	0.025	0.028	0.50 (0.31–0.81)	0.005	0.008
Linoleic acid, g/day								
< 7.65	342 (32.0)	69 (42.3)	1.00 (reference)	---	---	1.00 (reference)	---	---
7.65–9.94	357 (33.4)	55 (33.7)	0.69 (0.46–1.04)	0.08	---	0.71 (0.45–1.10)	0.13	---
> 9.94	371 (34.7)	39 (23.9)	0.41 (0.26–0.65)	0.0001	0.0006	0.37 (0.22–0.61)	<0.0001	0.0005
Linolenic acid, g/day								
< 0.76	346 (32.3)	65 (39.9)	1.00 (reference)	---	---	1.00 (reference)	---	---
0.76–0.93	357 (33.4)	55 (33.7)	0.78 (0.52–1.17)	0.23	---	0.75 (0.48–1.17)	0.21	---
> 0.93	367 (34.3)	43 (26.4)	0.57 (0.37–0.88)	0.012	0.043	0.47 (0.29–0.77)	0.003	0.011
Fish intake, g/day								
< 8.74	353 (33.0)	58 (35.6)	1.00 (reference)	---	---	1.00 (reference)	---	---
8.74–21.20	354 (33.1)	58 (35.6)	1.14 (0.76–1.71)	0.54	---	0.96 (0.61–1.50)	0.84	---
> 21.20	363 (33.9)	47 (28.8)	1.03 (0.67–1.58)	0.91	0.81	0.97 (0.60–1.55)	0.88	0.98
Omega-6:Omega-3 ratio								
< 8.68	357 (33.4)	54 (33.1)	1.00 (reference)	---	---	1.00 (reference)	---	---
8.68–10.49	358 (33.5)	54 (33.1)	0.93 (0.61–1.40)	0.71	---	0.97 (0.62–1.53)	0.90	---
> 10.49	355 (33.2)	55 (33.7)	0.84 (0.55–1.28)	0.42	0.72	0.74 (0.46–1.18)	0.21	0.39

* 95% CI = 95% confidence interval; MCI = mild cognitive impairment; OR = odds ratio.

[†] Adjusted for age, sex, number of years of education, and total caloric intake.

[‡] Additional adjustment for body mass index, ApoE ε4 allele, stroke, coronary heart disease, diabetes, and depressive symptoms.