

DIETARY FATTY ACIDS, AGE-RELATED COGNITIVE DECLINE, AND MILD COGNITIVE IMPAIRMENT

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Abstract: Currently available epidemiological evidence suggested that an increase of saturated fatty acids (SFA) could have negative effects on cognitive functions, while increased polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA) may be protective against cognitive decline. In a Southern Italian elderly population from the Italian Longitudinal Study on Aging (ILSA), a clear reduction of risk of age-related cognitive decline (ARCD) has been found with elevated intake of PUFA and MUFA. Furthermore, in the ILSA, while dietary fatty acids intakes were not associated with incident mild cognitive impairment (MCI), high PUFA intake appeared to have borderline non-significant trend for a protective effect against the development of MCI. These epidemiological findings on predementia syndromes, i.e. MCI or ARCD, together with a recent randomised controlled trial on a possible effect on cognitive and depressive symptoms of ω -3 PUFA supplementation in patients with very mild AD, suggested a possible role of fatty acids intake in maintaining adequate cognitive functioning and possibly in preventing or delaying the onset of dementia.

Key words: MUFA, PUFA, fatty acids, predementia syndromes, dementia, Alzheimer's disease, vascular dementia, mild cognitive impairment, age-related cognitive decline.

Introduction

The transitional phase between mild nondisabling cognitive decline and disabling dementia is an ambiguous diagnostic period during which it is unclear whether mild cognitive deficits predict incipient dementia or not. The term "predementia syndrome" identified all conditions with age-related deficits in cognitive function reported in the literature, including a mild stage of cognitive impairment based on a normality model and pathological conditions considered predictive or early stages of dementia (1, 2). Such predementia syndromes have been defined for Alzheimer's disease (AD) and vascular dementia (VaD), but have not yet been operationalized for other specific forms of dementia. Therefore, the clinical label predementia syndromes included different conditions and among these predementia syndromes, mild cognitive impairment (MCI) is, at present, the most widely used term to indicate nondemented aged persons with a mild memory or cognitive impairment that cannot be accounted for any recognized medical or psychiatric condition (1-3). MCI was also identified as the predementia syndrome for AD (1, 2). Different diagnostic criteria have been proposed for other predementia syndromes, and the terms age-related cognitive decline (ARCD) (4) and aging-associated cognitive decline (AACD) (5) have been recently proposed to distinguish individuals with mild cognitive disorders associated with aging from non affected individuals.

The causes of cognitive decline and dementia are at present unknown. However, some studies have suggested that these conditions may be prevented (6, 7). The role of the diet in cognitive decline has not been extensively investigated, with a few data available on the role of macronutrient intake in the pathogenesis of predementia and dementia syndromes (6, 7). Since several dietary factors affect the risk of cardiovascular disease, it can be assumed that they also influence the risk of dementia. Some recent studies have suggested that dietary fatty acids may play a role in the development of cognitive decline associated with aging or dementia (9). This concept is further supported by recent evidence that certain diets have been associated with a lower incidence of AD. In fact, antioxidants, dietary fatty acids, and micronutrients appear to have a role, and evidence is at least suggestive that diets rich in fruits and vegetables and other dietary approaches may permit a beneficial effect on the risk of dementia (6, 7).

The aim of this article is to examine the possible role of dietary fatty acids in modulating the risk of age-related changes in cognitive function, and predementia syndromes, as well as the possible mechanisms behind the observed associations. Special attention was paid to the findings from the Italian Longitudinal Study on Aging (ILSA), a large, population-based, prospective study with a sample of 5,632 subjects 65-84 years old, independent or institutionalized, randomly selected from the electoral rolls of eight Italian municipalities after stratification for age and gender (10).

Dietary fatty acids and predementia syndromes: is it the case for a treatment?

Only a few epidemiological and clinical studies have addressed the link between unsaturated fatty acids (UFA) intake and cognitive function, most being cross-sectional (9). In the last years, the study approach was to associate single micro- or macronutrients to ARCD, MCI, AD, or VaD. In this picture, several hallmarks of the Mediterranean diet were linked to increased risk or with a protective effect against cognitive impairment (11). The typical dietary pattern of Mediterranean diet is characterized by high intakes of vegetables, fruits and nuts, legumes, cereals, fish, and monounsaturated fatty acids (MUFA); relatively low intakes of meat, and dairy products, and moderate consumption of alcohol. In fact, higher levels of consumption of olive oil are considered the hallmark of the traditional Mediterranean diet. In particular, MUFA, consequently to the high consumption of extra-virgin olive oil, represent the most important fat in Mediterranean diet. Cumulative evidence suggests that extra-virgin olive oil may have a role in the protection against cognitive decline, other than against coronary disease and several types of cancer because of its high levels MUFA and polyphenolic compounds. The cross-sectional association between dietary macronutrients and cognitive impairment was examined in 278 nondemented elderly subjects aged 65-84 years from the Italian Longitudinal Study on Aging (ILSA). After adjustment for educational level, the odds ratios (ORs) of cognitive decline (MMSE score < 24) decreased exponentially with the increase of MUFA energy intakes. Despite the lower education (≤ 3 years), MUFA energy intake over 2400 kJ/day was associated with a reduction in OR of cognitive impairment. The age as a confounder of the interaction term "education by MUFA" was associated with a further increase in OR of cognitive impairment. Furthermore, selective attention performances were independently associated with MUFA intake (10).

Very recently, in the Doetinchem Cohort Study, after adjusting for age, gender, education, alcohol consumption, smoking, and energy intake, higher dietary cholesterol was associated with an increased risk of impaired memory function and cognitive flexibility cognitive function, whereas higher SFA intake was associated with an increased risk of impairment in memory function, psychomotor speed, and cognitive flexibility by 15% to 19%, although not significantly. Fatty fish and marine n-3 polyunsaturated fatty (PUFA) consumption were significantly associated with a decreased risk of global cognitive function impairment and psychomotor speed by 19% to 28%. These associations appeared to be independent of differences in cardiovascular risk factors (12).

To our knowledge, only a few epidemiological studies on the association between fatty acids and cognitive functioning were longitudinal (9, 13-15), indicating a crucial need for prospective studies that could confirm initial observations. In particular, one of these prospective studies, the Zutphen Study of 476 men aged 69-89 years, found that high linoleic acid

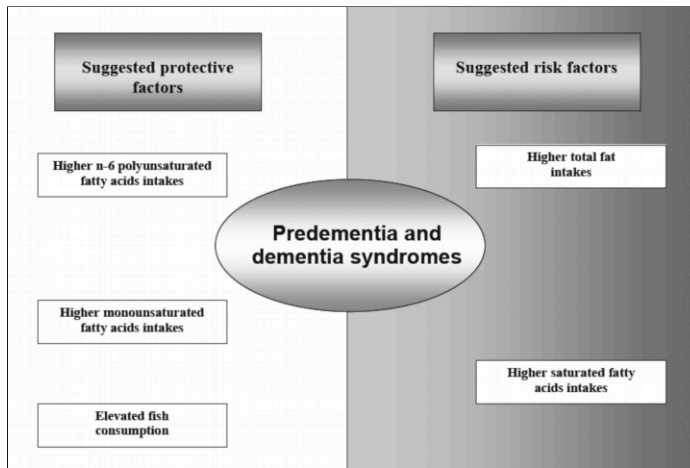
intake was positively associated with cognitive impairment in elderly subjects only in cross-sectional study after an adjustment for age, education, cigarette smoking, alcohol consumption, and energy intake. High fish consumption, an important source of long-chain n-3 PUFA, tended to be inversely associated with cognitive impairment and cognitive decline at 3-year follow-up, but not significantly (13). Finally, recent findings from the Chicago Health and Aging Project (CHAP) showed that in a large population-based sample of 2,560 persons, aged 65 years and older, a high intake of saturated and trans-unsaturated fat were associated with a greater cognitive decline over a 6-year follow-up. Intake of MUFA was inversely associated with cognitive change among persons with good cognitive function at baseline and among those with stable long-term consumption of margarine, a major food-source. Slower decline in cognitive function was associated with higher intake of PUFA, but the association appeared to be due largely to its high content of vitamin E, which shares vegetable oil as a primary food source and which is inversely related to cognitive decline. Finally, cognitive change was not associated with intakes of total fat, animal fat, vegetable fat, or cholesterol (14). Moreover, in a total of 732 men and women, 60 years or older, participating in the EPIC-Greece cohort (European Prospective Investigation into Cancer and Nutrition) and residing in the Attica region, six to 13 years later, seed oil consumption may adversely affect cognition, whereas adherence to the Mediterranean diet, as well as intake of olive oil, MUFA and SFA exhibited weakly positive but not significant associations (15).

Therefore, on the basis of the previous significant suggestions (9), we tested further the hypothesis that high MUFA and PUFA intakes may protect against the development of cognitive impairment over time in a median follow-up of 8.5 years of the ILSA. The major finding of this study was that high MUFA, PUFA, and total energy intake were significantly associated with a better cognitive performance in time. Total energy intake should be considered an important confounder of diet-ARCD relationships and, as we proposed in our methodological approach, suggesting that association between macronutrient intake and cognitive decline should be adjusted by total energy intake. No other individual dietary components of our study population was significantly associated with cognitive impairment in time. The association between high MUFA, PUFA intakes and cognitive performance remained robust even after adjustment for potential confounding variables such as age, sex, educational level, Charlson comorbidity index, body mass index, and total energy intakes (16). Finally, recent findings from the ILSA demonstrated that while dietary fatty acids intakes were not associated with incident MCI, high PUFA intake appeared to have borderline non-significant trend for a protective effect against the development of MCI (17). In the Figure, we summarized the evidence on the possible effects of dietary fatty acids on predementia and dementia syndromes.

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Figure 1

Synopsis of the evidence on the possible effects of dietary fatty acids on predementia and dementia syndromes



Very recently, Freund-Levi and colleagues examined the effects of dietary ω -3 PUFA supplementation randomizing 204 patients with moderate AD to receive docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (for a total dose of 1,720 mg DHA/600 mg EPA) or placebo for 6 months (OmegAD Study). After the treatment period, all the subjects received open label ω -3 PUFA for another 6 months. The supplementation did not delay the rate of cognitive decline but, in the group of 32 patients with the most mild AD (MMSE >27, Clinical Dementia Rating Score 0.5-1), ω -3 PUFA supplementation slowed the decline in MMSE scores (18). In addition, the subjects in the placebo group of these very mild AD patients also showed a statistically significant slowing of decline when they were switched to treatment between 6 and 12 months, suggesting that ω -3 PUFA might be of benefit to slow the progression of the disease in MCI or very mild AD (18). Furthermore, in the OmegAD Study, supplementation with ω -3 PUFA in patients with mild to moderate AD did not result in marked effects on neuropsychiatric symptoms except for possible positive effects on depressive symptoms in non-apolipoprotein E (APOE) ϵ 4 carriers and agitation symptoms in APOE ϵ 4 carriers (19).

Some experimental evidence suggested that essential ω -3 PUFA protect against neuronal deficits, decrease β -amyloid (A β) levels, and decrease the number of activated microglia in the brain using transgenic mouse models of AD (20, 21). At present, the effect of arachidonic acid and DHA (240 mg/day) after a 90-day supplementation upon MCI, organic brain lesions or AD, showed a significant improvement of the immediate memory and attention score for MCI patients, and a significant improvement of immediate and delayed memories for patients with organic brain damages (22). The AD group showed no improvement after the supplementation of arachidonic acid and DHA, and the placebo group showed no significant improvement of cognitive functions by the supplementation of 240 mg/day of olive oil (high MUFA content) (22). The lack of

cognitive effects of the olive oil supplementation may be probably explain from the very small amount of olive oil administered in comparison with our ILSA sample in which the mean consumption of olive oil was particularly high: 46 g/day (12.6 to 113.1 g/day) (11). A recent study in people with mild age-related memory complaints, demonstrated the positive effects of a 14-day healthy longevity lifestyle program on word fluency, and activity in the left dorsolateral prefrontal cortex at [fluorine-18] fluorodeoxyglucose (FDG) positron emission tomography (PET) scans in comparison of the control. Cardiovascular conditioning and brief relaxation exercises designed to lower stress are recommended each day. Suggested shopping lists and menus guide subjects to follow a healthy diet plan, including five daily meals emphasizing antioxidant fruits and vegetables, ω -3 PUFA, and low glycemic index carbohydrates (23). The conceptual basis for the healthy diet plan suggested in this study was that diets high in ω -3 PUFA from olive oil or fish, as well as those rich in antioxidant fruits and vegetables, are associated with less ARCD (24). On the basis of these evidences, we strongly suggest also for predementia syndromes, a high-risk condition for progression to dementia of vascular and degenerative origin, intervention trials using measures of dietary supplementation similar to the OmegAD Study to determine if such supplements will slow cognitive decline (25).

Fatty acids and cognitive decline: possible mechanisms

The mechanisms by which high UFA intake could be protective against cognitive decline and dementia in healthy older people are, at present, unknown. In the older subjects of the ILSA, which fulfilled a Mediterranean dietary pattern, total fat is 29% of energy, with a high consumption of olive oil (46 g/d), a MUFA energy intake of 17.6% of total energy, 85% of which derived from olive oil, and a SFA intake of only 6% (10). In our population, the prolonged protection of MUFA intake against age-related changes in cognitive functions, may be linked to the relevant quota of antioxidant compounds in olive oil, including low molecular weight phenols (26). In fact, animal studies suggested that diets high in antioxidant-rich foods, such as spinach, strawberries, and blueberries, rich in anthocyanins and other flavonoids may be beneficial in slowing age-related cognitive decline (27). The possible role of antioxidant compounds from olive oil do not diminish or otherwise alter the argument concerning the fatty acids, because this is only a possible explanation of the role of MUFA on age-related cognitive changes in our population, in which MUFA intake derived for a large part from olive oil.

The protective effect of dietary UFA could be related to the role of fatty acids in maintaining the structural integrity of neuronal membranes, determining the fluidity of synaptosomal membranes and thereby regulating neuronal transmission. Furthermore, essential fatty acids can modify the activity of certain membrane-bound enzymes (phospholipase A2, protein kinase C, and acetyltransferase), and the function of the

neurotransmitters' receptors. Finally, free fatty acids, lipid metabolites, and phospholipids, modify the function of membrane proteins including ion channels (28). Moreover, fatty acid composition of neuronal membranes in advancing age demonstrated an increase in MUFA content and a decrease in PUFA content (29). There is also evidence associating a dietary deficiency of n-3 PUFA with changes in cortical dopaminergic function (30). The ω -3 PUFA from fish may be inversely associated with dementia because it lowers the risk of thrombosis (31), stroke (32), cardiovascular disease (33), and cardiac arrhythmia, reducing the risk of thromboembolism in the brain and consequently of lacunar and large infarcts that can lead to VaD and AD. Furthermore, the ω -3 PUFA may be important as lipids in the brain, particularly for the possible influence of DHA on the physical properties of the brain that are essential for its function (34). Furthermore, fish oil was a better source than α -linolenic acid for the incorporation of ω -3 PUFA into rat brain phospholipid subclasses (1). On the contrary, high linoleic acid intake (ω -6 PUFA) may increase the susceptibility of LDL cholesterol to oxidation, which makes it more atherogenic (35), even if the association between linoleic acid and atherosclerosis is controversial (36). Therefore the ratio of dietary ω -3/ ω -6 PUFA intake may influence the potential role of PUFA on cognitive decline and dementia, the optimal ratio of ω -6: ω -3 should be <5:1 (37). Finally, a high dietary intake of SFA and cholesterol increases the risk for cardiovascular disease, and therefore for cognitive decline, VaD and AD (6). On the contrary, treatment for four weeks with a Mediterranean-inspired diet rich in ω -3 PUFA decreased blood lipids in healthy individuals with a low-risk profile for cardiovascular disease, with a beneficial effect also on vascular function and oxidative stress (38).

Conclusions

At present, several studies suggested that an increase of SFA could have negative effects on cognitive functions. Furthermore, a clear reduction of risk for cognitive decline has been found in a population sample with a high intake of PUFA and MUFA. Recent findings demonstrated that while dietary fatty acids intakes were not associated with incident MCI, high PUFA intake appeared to have borderline non-significant trend for a protective effect against the development of MCI. High MUFA intake may be a marker for other dietary factors responsible for the protection against cognitive disorders (i.e. the great amount of tocopherol and polyphenols, the antioxidant compounds of olive oil and the low intake of SFA). In our elderly population from Southern Italy, elevated UFA intake (MUFA and PUFA), high levels of antioxidant compounds and very low SFA intake, could act synergistically in improving cognitive performance. Several hypotheses could explain the association between fatty acids and cognitive functioning, including mechanisms through the co-presence of antioxidant compounds in food groups rich in fatty acids, via atherosclerosis and thrombosis, inflammation, accumulation of

$\text{A}\beta$, or via an effect in maintaining the structural integrity of neuronal membranes, determining the fluidity of synaptosomal membranes that thereby regulate neuronal transmission.

Nonetheless, at present, no definitive dietary recommendations on fish and UFA consumption or lower intake of saturated fat in relation to the risk for dementia and cognitive decline are possible. In fact, in a recent randomised controlled trial, ω -3 PUFA supplementation did not influence cognitive functioning during a follow-up of six months except in a small group of patients with very mild AD and for possible positive effects on depressive symptoms in non-APOE ϵ 4 carriers. These data together with epidemiological evidence support the idea that ω -3 PUFA may have a role in the primary and maybe secondary prevention of the disease but not when the disease process has already taken over (39). However, high levels of consumption of fats from fish, vegetable oils, and vegetables should be encouraged because this dietary advice is in accordance with recommendations for lowering the risk of cardiovascular disease, obesity, diabetes and hypertension. In conclusion, epidemiological studies on the association between diet and cognitive decline suggested a possible role of fatty acids intake in maintaining adequate cognitive functioning and possibly in preventing or delaying the onset of dementia, both of degenerative or vascular origin. Appropriate dietary measures or supplementation with specific macronutrients might open new ways for the prevention and management of cognitive decline and dementia.

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