

DIETARY FATTY ACIDS AND PREVENTION OF MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

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Abstract: Several studies suggested that an increase of saturated fatty acids (SFA) could have negative effects on cognitive functions. Furthermore, a clear reduction of risk of cognitive decline has been found in a population sample with a high intake of polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA). These findings were confirmed by studies in which high intakes of n-6 PUFA, n-3 PUFA, MUFA, and weekly fish consumption, providing large amount of n-3 PUFA, appear to be protective against the risk of Alzheimer's disease. In our elderly population from Southern Italy, elevated unsaturated fatty acids intake (MUFA and PUFA), high levels of antioxidant compounds, and very low SFA intake could act synergistically in improving cognitive performance, and high PUFA intake appeared to have borderline non-significant trend for a protective effect against the development of mild cognitive impairment. 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.

Key words: MUFA, PUFA, fatty acids, dementia, Alzheimer's disease, vascular dementia, mild cognitive impairment, cognitive decline.

INTRODUCTION

Alzheimer's Disease (AD) is the most common form of dementia in the Western world, comprising from 50-80% of cases of late-onset cognitive impairment. As cognitive impairment advances, patients become progressively impaired in both cognitive and functional capacities, and the burden on caregivers increases. Due to aging of the population, the prevalence of cognitive impairment and dementia are expected to increase.

The causes of cognitive decline and dementia are at present unknown. However, some studies have suggested that these conditions may be prevented [1-3]. Previous works have linked cognitive decline to cardiovascular disease, diabetes mellitus, hypertension, and high and low blood pressure. Various genetic and non genetic factors known to increase the risk of vascular disease, including apolipoprotein E (APOE) and angiotensin I converting enzyme 1 (ACE1) genotypes, total cholesterol, lipoprotein(a) [Lp(a)], diabetes mellitus, atrial fibrillation, hypertension, serum APOE levels, and C-reactive protein levels an inflammation, have been evaluated as risk factors for AD and vascular dementia (VaD), and cognitive decline.

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 dementia and age-related cognitive decline (ARCD). 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. 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 .

DIETARY FATTY ACIDS, AGE-RELATED COGNITIVE DECLINE, AND MCI

Only a few epidemiological and clinical studies have addressed the link between UFA intake and cognitive function, most being cross-sectional. In the last years, the study approach was to associate single micro- or macronutrients to ARCD, mild cognitive impairment (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. The

DIETARY FATTY ACIDS & PREVENTION OF MILD COGNITIVE IMPAIRMENT

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 evaluated by DCT were independently associated with MUFA intake [2].

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 [1].

To our knowledge, only a few epidemiological studies on the association between fatty acids and cognitive functioning were longitudinal [1], 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 [1]. 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 [1].

Therefore, on the basis of the previous significant suggestions [2], 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 [3].

Furthermore, in these studies, cognitive functioning was assessed by simple neuropsychological tests in nondemented people while, at present, there was any study with a focus on predementia syndromes, identifying with this term all conditions with age-related deficits in cognitive function and operational clinical criteria, including a mild stage of cognitive impairment based more on a normality model (ARCD or age-associated cognitive decline) and concepts considered as a pathological condition and therefore a risk state for dementia (MCI). 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 [4].

DIETARY FATTY ACIDS & PREVENTION OF MILD COGNITIVE IMPAIRMENT

DIETARY FATTY ACIDS AND DEMENTIA

The first paper establishing a strong dietary link to AD was published in 1997 [1]. In this cross-sectional ecological study, the primary finding is that fat and total caloric supply have the highest correlations with AD prevalence rates. In addition, a combination of fat and fish consumption is found to reduce the prevalence of AD in the European and North American countries, i.e. one calorie of fish was found to counter the effects of approximately 4.3 calories of fat. These ecological evidences are in agreement with various recent epidemiologic studies [1]. In fact, the finding that total dietary fat is a possible risk factor for the development of AD, has been reported in the Rotterdam Study with 5,386 participants <55 years of age, although not at a statistically significant level. In the same study, fish consumption was confirmed to reduce AD risk and linoleic acid was inversely correlated with AD. This study suggested that an elevated intake of lipids and saturated fat increased the risk for dementia with a cerebrovascular component [1].

The cohort of the Rotterdam Study was re-examined in a 6.0-year follow-up, and a high intake of total fat, saturated fat, trans fat, and cholesterol and low intake of MUFA, PUFA, n-6 PUFA, and n-3 PUFA were not associated with an increased risk of dementia or its subtypes [1]. The discrepancy with the results of the first study were explained by the authors by the shorter follow-up (2.1 years) and a consequent smaller number of incident cases of dementia.

Finally, the findings of the re-examined cohort of the Rotterdam Study are at odds with several recent studies [1]. In fact, a 4-year cohort study in New York, the Washington Heights-Inwood Columbia Aging Project, found that dietary fat was an important risk factor for AD for those with the APOE e4 allele, but not for those without that allele. They also confirmed previous ecological findings on the possible role of cereals as a risk reduction factor [1]. Furthermore, findings coming from the PAQUID study, showed that participants who ate fish or seafood at least once a week had a significantly lower risk of dementia in the 7 subsequent years [1]. Finally, very recently, two studies from the cohort of the CHAP, increased the evidence of a strict linkage between dementia and fatty acid intake [1]. In fact, in this cohort of 815 subjects, aged 65 years and older, after a mean follow-up of 3.9 years, 131 persons developed AD. A high intake of saturated fat and trans-unsaturated fat may be associated with a higher risk of AD; while a high intake of n-6 PUFA and MUFA may be protective against AD. Furthermore, in the same cohort, a higher intake of n-3 PUFA and weekly fish consumption may reduce the risk of incident AD. In fact, in this study people who ate fish once or more weekly had a relative risk for AD of 0.4:

the absolute risk reduction was about 9.5 percent [1]. These results confirmed our findings on a possible protective role of MUFA and PUFA intakes against ARCD and MCI [2-4].

Comparing the approach of the re-analysis of the Rotterdam Study, with those of the Washington Heights-Inwood Columbia Aging Project, the PAQUID study, and the CHAP, we could draw possible explanations of these conflicting findings [1]. In particular, some methodological issues, i.e. the normalization of fat to energy, omitted patients with early onset of dementia (those who did not respond to the invitation to participate), a population with low fish consumption, and, finally, no genetic analysis (presence of APOE $\epsilon 4$ allele), may help to explain why the findings from the Rotterdam study are at odds with the other studies considered.

Very recently, in a community-based study involving 2,258 nondemented individuals in New York, adherence to a traditional Mediterranean diet was associated with significantly reduction in risk for AD [5]. However, in this study, the median daily intake of MUFA to SFA ratio for individual food categories by Mediterranean diet score tertiles was <1 and in overall about 2.5 times lower than the same value calculated from other studies on Mediterranean diet [5]. In this report was used a scale indicating the degree of adherence to the traditional Mediterranean diet originally constructed by Trichopoulou and colleagues and revised to include fish intake [5]. A value of 0 or 1 was assigned to each of nine indicated components with the use of the sex-specific median as the cut-off. The total Mediterranean-diet score (MeDi) ranged from 0 (minimal adherence to the traditional Mediterranean diet) to 9 (maximal adherence). The wide diffusion of this methodological approach exploring possible associations between dietary habit, in particular Mediterranean diet, and several outcomes in more and more epidemiological areas (cancer, cardiovascular disease, or dementia) has undeniable advantages but some concern it should be admit. In fact, several devices related to the use of dietary composite score should be considered, in evaluating the effects of nutrient intakes in different groups (low and high consumption) in unbiased manner [5]. In particular, a variation in group heterogeneity, which could be caused by selection of cut-offs, can change in predictable ways the reliability and validity of the scale indicating the degree of adherence to a particular dietary pattern. The effects of change in observed-score variance on reliability can be estimated, if it is assumed that error variance remains constant after selection [5]. On the basis of these considerations, it is not difficult to guess that a "whole-diet approach" such as MeDi could not be readily transferred to other populations, included study population traditionally eating according to Mediterranean dietary pattern. The above-reported findings strongly suggested that further observational studies on cognitive decline need to be implemented on the

DIETARY FATTY ACIDS & PREVENTION OF MILD COGNITIVE IMPAIRMENT

adherence to a specific dietary pattern rather than association studies with single nutrients. If successfully replicated, randomized clinical trials should ideally follow to specifically address the question of whether a dietary pattern may have a role in the prevention of cognitive impairment.

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% [2]. 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 [1]. 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 [1]. 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 [1]. Moreover, fatty acid composition of neuronal membranes in advancing age demonstrated an increase in MUFA content and a decrease in PUFA content [1]. In fact, rats administered diets high in SFA or PUFA were impaired on various tests of learning and memory [1]. In rats, dietary oleic acid deficiency leads to a reduction of the oleic acid concentration in many tissues, including the sciatic nerve, but not in the brain [1]. In many organs, endogenous synthesis therefore does not compensate for the absence of oleic acid in food [1]. This fatty acid is therefore not synthesized

in sufficient quantities, at least in rats and especially during pregnancy-lactation, implying a need for dietary intake. It must be remembered that organization of the neurons is almost complete several weeks before birth, and that these neurons remain for the subject's life time. Consequently, any disturbance of these neurons, an alteration of their connections, and impaired turnover of their constituents at any stage of life, will tend to accelerate aging [1].

There is also evidence associating a dietary deficiency of n-3 PUFA with changes in cortical dopaminergic function [1]. The n-3 PUFA from fish may be inversely associated with dementia because it lowers the risk of thrombosis, stroke, cardiovascular disease, 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 [1]. Furthermore, the n-3 PUFA may be important as lipids in the brain, particularly for the possible influence of docosahexaenoic acid on the physical properties of the brain that are essential for its function [1]. Furthermore, fish oil was a better source than α -linolenic acid for the incorporation of n-3 PUFA into rat brain phospholipid subclasses [1]. On the contrary, high linoleic acid intake (n-6 PUFA) may increase the susceptibility of LDL cholesterol to oxidation, which makes it more atherogenic [1], even if the association between linoleic acid and atherosclerosis is controversial [1]. Therefore the ratio of dietary n-3/n-6 PUFA intake may influence the potential role of PUFA on cognitive decline and dementia, the optimal ratio of n-6:n-3 should be <5:1 [1].

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 n-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 [1]. High serum total cholesterol during middle age or early old age seems to confer an increased risk of AD in old age [6]. Epidemiological studies showed that the onset of AD occurs earlier in APOE ϵ 4-carriers with high serum total cholesterol [6]. On the contrary, a cross sectional study reported an association between AD and lower total cholesterol [6] which has been supported by work by our group [6]. Furthermore, in a population-based 70-year-old birth cohort followed for 18 years found that increasing total cholesterol levels at ages 70, 75, and 79 were associated with a reduced risk of dementia between ages 79 and 88 [6]. In conclusion, we suggested that the lack of consensus regarding the association between total cholesterol and AD may be also explained by the hypothesis that only mid-life elevation in TC may be a risk factor for AD [6]. Therefore, it is possible that high TC plays a role in protecting against dementia and MCI. Finally, in our recent study we analyzed the relationship

DIETARY FATTY ACIDS & PREVENTION OF MILD COGNITIVE IMPAIRMENT

between sporadic AD and Lp(a), a LDL-like particle with apolipoprotein[a], that is believed to have atherogenic and thrombotic properties and has been associated with cerebrovascular disease as well as VaD [6]. We found that Lp(a) serum levels were significantly associated, according to a nonlinear relationship, with an increased risk for AD, independently of APOE genotypes, and dependent on age [6]. A high saturated fat intake increases low density lipoprotein (LDL) cholesterol showing that AD patients have higher LDL cholesterol and lower high-density lipoproteins cholesterol than nondemented controls [6]. Moreover, Lp(a) is a LDL-like particle, and a recent study found increased levels of serum LDL cholesterol in AD patients correlate with brain β -amyloid ($A\beta$) N-42 levels, suggesting that LDL cholesterol may influence the expression of AD-related pathology [6].

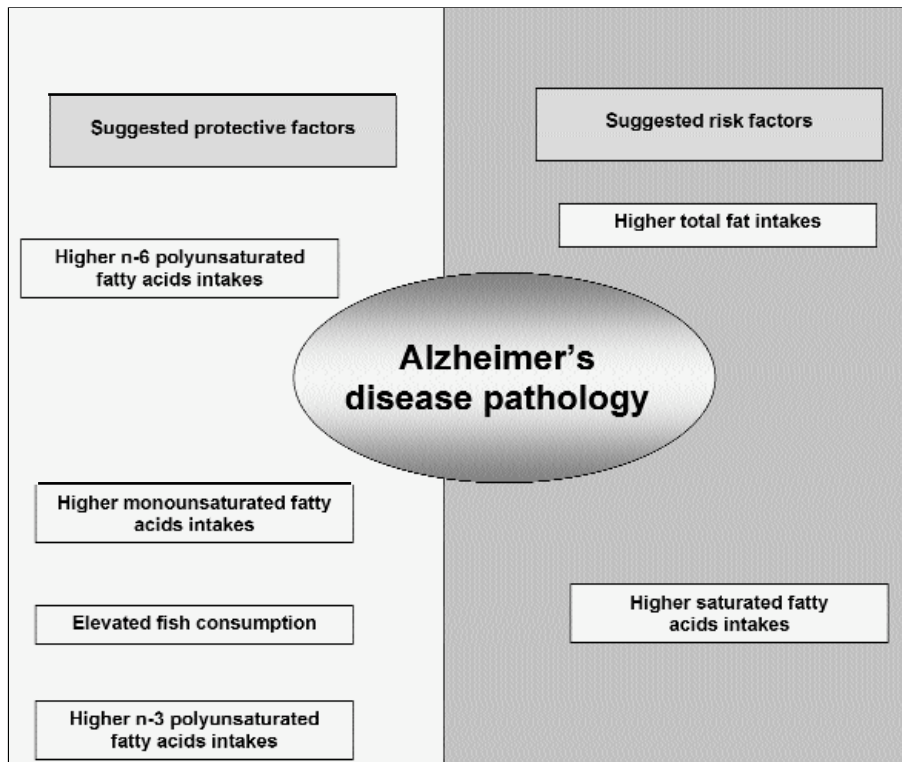
CONCLUSIONS

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. These findings were confirmed by studies in which high intakes of n-6 PUFA, n-3 PUFA, and MUFA appear to be protective against the risk of AD. Furthermore, weekly fish consumption, providing n-3 PUFA, may reduce the risk of incident AD. 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 $A\beta$, 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, these

recommendations have not yet been tested with a double-blind, clinical trial. 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.

Figure 1



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