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Mediterranean diet and cognitive decline

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Abstract

Objective: To investigate the possible role of diet in age-related cognitive decline (ARCD) and cognitive impairment of both degenerative (Alzheimer's disease, AD) and vascular (vascular dementia, VaD) origin.

Design: Literature review.

Results: In an elderly population of southern Italy with a typical Mediterranean diet, high energy intake of monounsaturated fatty acids (MUFA) appeared to be associated with a high level of protection against ARCD. In addition, dietary fat and energy in the elderly seem to be risk factors, while fish consumption and cereals are found to reduce the prevalence of AD in European and North American countries. Finally, the relative risk of dementia (AD and VaD) was lower in the subjects of a French cohort who drank three or four glasses of red wine each day compared with total abstainers.

Conclusion: Essential components of the Mediterranean diet – MUFA, cereals and wine – seem to be protective against cognitive decline. As such, dietary antioxidants and supplements, specific macronutrients of the Mediterranean diet, oestrogens and anti-inflammatory drugs may act synergistically with other protective factors, opening up new therapeutic interventions for cognitive decline.

Keywords
Age-related cognitive decline
Alzheimer's disease
Vascular dementia
Mediterranean diet

Cognitive impairment is a major component of dementia syndromes and influences the individual's ability to function independently. Due to ageing of the population, the prevalence of cognitive impairment is expected to increase. Different diagnostic criteria have been proposed to distinguish individuals with mild cognitive disorders associated with ageing from non-affected individuals, and one of the best established of these classifications is age-associated memory impairment (AAMI)[1]. AAMI, however, is generally non-progressive and is thus more likely to be a phenomenon of normal ageing[2,3]. The terms 'age-related cognitive decline' (ARCD) and 'ageing-associated cognitive decline' have recently been proposed[4,5] to indicate an objective decline in cognitive functioning associated with the ageing process but within normal limits given the person's age. Whether ARCD is the expression of a normal ageing process, or represents a distinct clinical entity or, eventually, a continuum with dementia, is still difficult to establish[2,6]. In fact, recent results from longitudinal studies suggest that the subgroup at high risk for developing dementia may be identified by using a more detailed procedure for the assessment of cognitive decline than those listed in the AAMI criteria. In effect, a high incidence (45%) of dementia was found in individuals aged >75 years who were diagnosed as having 'minimal dementia' by the CAMDEX interview[7]. Furthermore, 44% of patients aged between 73 and 85 years, identified as having 'mild cognitive impairment' according to Clinical Dementia Rating scale, developed dementia within 3 years[8].

The causes of ARCD are unknown, but some studies have suggested that it may be prevented[9]. Cardiovascular and other chronic diseases[10,11], hypertension[12], diabetes mellitus[13], depression[14] and low levels of physical activity have been identified as risk factors for ARCD[15]. On the contrary, high socio-economic status, a flexible personality in middle age and the maintenance of vision and hearing have been identified as protective factors against ARCD[16]. The role of diet in ARCD has not been extensively investigated. Deficiencies of micronutrients (vitamins B_1, B_2, B_6, B_{12} and C and folate) have been described quite frequently in elderly people and found to be significantly associated with cognitive impairment[17,18]. On the other hand, very few data are available on the role of macronutrient intake in ARCD[19].

In the 1950s and 60s, Keys' studies found the typical dietary pattern of the Greek island of Crete to be associated with especially good health, and this pattern has come to be viewed as the model Mediterranean diet. This model has been extended to include diets consumed in olive-producing Mediterranean regions, because olive oil was a principal source of fat in the Cretan diet. Therefore, the trivial term 'Mediterranean diet' is used to refer to dietary patterns similar to those of Crete in the

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early 1960s and other regions in the Mediterranean where olive oil is a major fat source[20].

Mediterranean diet and age-related cognitive decline

In a recent study, we investigated the relationships between dietary macronutrient intakes and age-related changes in cognitive functions in southern Italy, a region with the typical Mediterranean dietary pattern[21–23]. The subjects of this study were part of a larger study, the Italian Longitudinal Study on Aging, promoted by the Italian National Research Council-Targeted Project on Aging, with a sample of 5632 subjects aged 65–84 years, free-living or institutionalised[22].

In this study, a standardised test battery assessing global cognitive functions (Mini Mental State Examination, MMSE), selective attention (Digit Cancellation Test, DCT) and episodic memory (Babcock Story Recall Test), and a semi-quantitative food-frequency questionnaire evaluating macronutrient energy intakes, was performed on 278 non-demented elderly subjects from the randomised cohort of Casamassima, Bari ($n = 704$).

Results showed an inverse relationship between energy intake from monounsaturated fatty acids (MUFA) and cognitive decline (MMSE < 24). The effect of education on the odds of having an MMSE score < 24 decreased exponentially with the increase of MUFA intake (> 2400 kJ day^{-1}: odds ratio, 0.69). Moreover, a significant inverse association was observed between MUFA intakes and DCT score (odds ratio, 0.99). No association was found between nutritional variables and episodic memory (Table 1). These findings appear to be consistent with other studies, and indicate an association between dietary intakes and cognitive functions. In a recent longitudinal study of a well-nourished and cognitively unimpaired sample of elderly community residents, a significant association between protein intakes and cognitive performances was found[24]. In another study, a significant association between functional variables (i.e. activities of daily living) and alcohol intake was found, probably in relation to a better health status of moderate alcohol consumers[25]. Finally, non-institutionalised elderly subjects with the best performance in cognitive tests had lower intakes of MUFA, saturated fatty acids (SFA) and cholesterol, and higher intakes of total food, fruit, carbohydrate, thiamin, folate and vitamin C[26]. These apparently conflicting results could be due in part to some methodological differences in food-frequency questionnaires and selection of participants, which was not performed randomly, but within three elderly persons' clubs.

Table 1 Change in the odds ratio (OR) and 95% confidence interval (CI) for cognitive decline, as assessed by Mini Mental State Examination (MMSE) score < 24, with energy intake from monounsaturated fatty acids (MUFA), controlling for education and age. Italian Longitudinal Study on Aging–Casamassima, first prevalence survey, 1992–1993 (modified from Solfrizzi *et al.*[22])

MUFA intake (kJ day^{-1})	Adjusted for education		Adjusted for education and age	
	OR	95% CI	OR	95% CI
≤800	33.0	8.2–133	37.5	9–156
801–1200	14.9	6.2–35.8	16.9	6.7–42.7
1201–1600	6.7	3.7–12	7.6	3.9–14.6
1601–2000	3.0	1.3–6.7	3.4	1.4–8
2001–2400	1.3	0.4–4.9	1.5	0.4–5.8
2401–2800	0.6	0.1–4.5	0.7	0.1–4.5

Due to the dietary pattern of our population, the typical Mediterranean diet and the rural setting of the study (Casamassima), the mean consumption of olive oil was particularly high: 46 g day^{-1} (range 12.6–113.1 g day^{-1}). MUFA as percentage of total energy intake was 17.6%, of which 85% was derived from olive oil. It cannot be excluded that the positive effect of dietary habits on cognitive functioning among healthy elderly subjects could be due in part to the antioxidant compounds of olive oil, i.e. tocopherols and polyphenols. In fact, some pathological conditions, which can be triggered to some extent by an uncontrolled production of free radicals, could probably be prevented or retarded with high intakes of dietary antioxidants (i.e. vitamins A, E and C and carotenes) that might yield beneficial effects on frontal/subcortical brain systems, with cognitive functions that might be enhanced (increased performance on effortful memory tasks)[27–29]. However, the antioxidant activity of dietary macronutrients has not been found to exert a protective effect on age-related changes in cognitive function in every circumstance. In fact, in a Japanese population study[16], high dietary intake of antioxidant compounds was significantly associated with Alzheimer's disease (AD) and ARCD.

High MUFA intake *per se* appears to be associated with the preservation of cognitive functions in healthy elderly people. This effect could be related to the role of fatty acids in maintaining the structural integrity of neuronal membranes. In fact, the factors that modify neuronal membrane fluidity are dietary fatty acids, in particular polyunsaturated fatty acids (PUFA). PUFA may determine the fluidity of synaptosomal membranes and thereby regulate neuronal transmission[30]. A recent study examined the influence of the $n-6/n-3$ fatty acids ratio on oxidative enzymes[31]. Furthermore, essential fatty acids can modify the function of the neurotransmitters' receptors such as cholinergic receptors, nicotinic receptors, adrenergic receptors, dopaminergic receptors, muscarinic receptors and *N*-methyl-D-aspartate receptors. Finally, free fatty acids, lipid metabolites and phospholipids modify the function of membrane proteins, including ion channels. In fact, a few studies have examined the effects of essential fatty acids on membrane function as they can affect the calcium, chloride and potassium ion channels[32]. A recent study on the fatty acid composition of neuronal membranes demonstrated an increase in MUFA content

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and a decrease in PUFA content with advancing age[33]. It seems that, in the ageing process, there is an increasing demand of unsaturated fatty acids. In fact, in lymphocytic and macrophage-like cells, an increase of Δ^9 desaturase activity, which converts stearic acid to oleic acid and increases the degree of differentiation of cells, has been observed[34]. These findings are consistent with another recent study in which high PUFA intake was positively associated with cognitive impairment, while high fish consumption tended to be inversely associated with cognitive impairment[35].

Role of dietary macronutrients in vascular dementia

In contrast to ARCD, a diagnosis of dementia is made when cognitive impairment is greater than that found in normal ageing, affects two or more cognitive domains, and affects the person's ability to function[4,36]. Several studies have extensively investigated the causes of dementia, both primary degenerative dementia (AD) and vascular dementia (VaD). Vascular factors, particularly stroke and hypertension, probably play a role in about half of all cases of dementia (including VaD and mixed dementias, i.e. degenerative forms with vascular components). In fact, vascular-related dementias may be the most common type of dementia in the very old[37,38]. Risk factors for vascular cognitive decline, stroke and coronary artery disease are most likely the same[38,40]. Vascular risk factors include atherosclerosis, hypertension, obesity, transient ischaemic attacks, carotid stenosis, diabetes mellitus, alcohol abuse, antiphospholipid antibody syndrome, hyperviscosity, elevated fibrinogen and cigarette smoking. Frequently, several risk factors coexist in the same individual and interact with one another. The protective effect of some dietary micronutrients with antioxidant properties seems to be better defined in VaD than in AD[41,42]. Low dietary salt intake improves hypertension. In addition, dietary restriction of cholesterol, fats and calories is important for dyslipoproteinaemia, obesity and diabetes mellitus. A prospective 12-year follow-up study of 859 healthy subjects aged 50–79 years provided some preliminary evidence that dietary potassium may be vasoprotective; there was a 40% reduction in stroke mortality with a 10 mmol day^{-1} increase in dietary potassium intake[43].

One of the most interesting findings of a recent study on VaD risk factors conducted on the cohort of the Honolulu Heart Program, within the Honolulu–Asia Aging Study, was the protective effect of a Western diet preference against the development of VaD[44]. A traditional Western diet is high in animal fat and protein and low in complex carbohydrates compared with the traditional Japanese diet, which is high in complex carbohydrates and low in animal fat and protein. Several lines of evidence suggest the Oriental diet may predispose to stroke. The mechanism by which an Oriental diet leads to VaD remains speculative. The higher risk of stroke could probably be ascribed to the lower intake of animal fat and protein. However, these findings do not allow analysis of separate nutrients. Recent studies have hypothesised that greater fat intake may stabilise the integrity of smaller intracranial arterioles[45], while the quantity and quality of dietary protein may affect small vessel pathology[46].

Alzheimer's disease and diet

Recent findings showing that elderly African Americans[47] and Japanese living in the USA[48,49] have a much higher prevalence of AD (6.24% and 4.1%, respectively) than those still living in their ethnic homelands (< 2%) suggest that the prevalence of AD is more strongly influenced by diet and nutrition, environment and/or lifestyle than by genetics. Recent papers linking clinical expression of AD to oxidative stress[50,51] and cerebral infarct indicate that the clinical expression of AD is facilitated by cerebral infarction or stroke, and suggest that diet is a key factor in the development of AD[52,53]. In a recent study, regression analyses were performed on the prevalence of AD in the population aged 65 + of 11 countries obtained from 18 community-wide studies versus components of the national diets[54]. The primary findings are that the contributions of fat and total calories have the highest correlations with AD prevalence rates. In addition, fish consumption is found to reduce the prevalence of AD in European and North American countries. Recent findings that several dietary components and supplements have been found effective in delaying the onset of AD, including antioxidants, fish and non-steroidal anti-inflammatory drugs, are consistent with these data. This preliminary evidence is in agreement with the findings of recent epidemiological studies[55]. In fact, the finding that total dietary fat is a high risk factor for the development of AD has been reported in the Rotterdam Study, 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[56]. A significant inverse correlation was found between the fraction of calories derived from cereals and AD prevalence[55]. While whole grains have antioxidant vitamins and minerals, it is not clear whether the cereals generally consumed are whole grains. The inverse correlation is likely to arise from the fact that countries with low fat supply have high cereals supply, rather than any direct therapeutic effect of the cereals. This point should be investigated in greater depth. Finally, red wine – another component of the Mediterranean diet – was investigated in the PAQUID study. Here, the relative risk of dementia was 0.21 and of AD 0.25 among the 318 subjects of this cohort who drank three or four glasses of wine each day, compared with a relative risk of 1 in the 971 total abstainers. Among the 922 older subjects who drank no

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more than one or two glasses of wine each day, the relative risk for AD was significantly reduced (0.55)[57].

Summary

In conclusion, the Mediterranean diet pattern based on complex carbohydrates, fibre and non-animal fat appears to protect against ARCD and cognitive decline of vascular or degenerative origin. However, a clear reduction of ARCD risk has been found only in population samples with high intakes of MUFA from olive oil ($>2400\,kJ\,day^{-1}$, corresponding to $>100\,g$ of olive oil per day). Whether this protective effect of olive oil is attributable exclusively to the high MUFA intake or to the concomitant presence of antioxidant compounds (tocopherol and polyphenols) remains to be elucidated.

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