

Mediterranean diet and cognitive decline: what role for omega-3 polyunsaturated fatty acids?

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Abstract: The Mediterranean diet is characterized by a high consumption of fruits, vegetables, legumes, cereals, and olive oil as the main source of added fat, a moderate consumption of fish and wine, and a low consumption of meat and dairy products as a source of saturated fat. Several epidemiological studies have shown that higher adherence to a Mediterranean diet was associated with slower cognitive decline in older persons. This protective effect might be mediated by omega-3 poly-unsaturated fatty acids (n-3 PUFA). We investigated this hypothesis in 1050 participants in the 3City study from Bordeaux. After multivariable adjustment including apolipoprotein E (ApoE) genotype, plasma docosahexaenoic acid and total n-3 PUFA were positively associated with a score of adherence to a Mediterranean diet. Plasma eicosapentaenoic acid was positively associated with adherence only in ApoE4 non-carriers. These data suggest that the protective effect of the Mediterranean diet on cognitive functions might be partly mediated by higher plasma n-3 PUFA.

Key words: diet, cognition, aging, fatty acids, omega-3, mediterranean diet

Cognitive decline is a major threat to the quality of life of older persons. In the absence of efficient medical treatment, several potential paths for prevention are currently investigated, among which diet raises increasing interest. Higher adherence to a Mediterranean-type diet is associated with lower risks of cardiovascular mortality (Sofi *et al.*, 2008), coronary heart disease (Buckland *et al.*, 2009), and overweight (Beunza *et al.*, 2010) which are well-known risk factors of cognitive decline and dementia (Fotuhi *et al.*, 2009). Accordingly, several observational studies have also evidenced a link between adherence to a Mediterranean diet and better cognitive performances (Feart *et al.*, 2010). The aim of this paper is to summarize these findings and to examine whether these protective effects might be mediated by polyunsaturated fatty acids of the omega-3 series (n-3 PUFA).

This paper will successively address the following points:

- What are the general features of the so-called Mediterranean diet?
- What are the links between the Mediterranean diet and cognition, based on epidemiological evidence coming in particular from the French Three-City (3C) study?
- And finally, which components of the Mediterranean diet could contribute to improve cognition in older persons, focusing on fatty acids.

Characteristics of the Mediterranean diet

By definition, the Mediterranean diet is the traditional dietary pattern of the populations bordering the Mediterranean Sea. This may translate into various traditional dishes, for instance fish and vegetables in southern France, pasta in Italy, couscous or tajine in the Maghreb, bread and tomato in Spain, without forgetting the famous Greek salad.

Despite their apparent diversity, these traditional dishes have some common features which led to the conceptualization of a so-called « Mediterranean diet » characterized by a high consumption of fruits, vegetables and cereals as the basis of daily dietary intake, regular consumption of fish and seafood, and a relatively low consumption of meat and dairy products as a source of saturated fat (Trichopoulou *et al.*, 2003). Meals are accompanied by a moderate consumption of wine in some countries, but not all especially in the Maghreb. Last but not least, olive oil is the main traditional source of added fat.

Trichopoulou *et al.* (Trichopoulou *et al.*, 2003) proposed a nine-point score to assess adherence to the Mediterranean diet. Each individual is given one point on this score if his or her consumption is above the sex specific median of the sample for components which are supposed to be beneficial to health, including fruits, vegetables, legumes, cereals, fish and the ratio of monounsaturated

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(MUFA) to saturated fat (SFA). Conversely, one point is given for consumption below the sex-specific median for meat and dairy products which are supposed to be detrimental, in particular because of their high content in saturated fat. For alcohol, a moderate consumption is generally defined according to the recommendations of the World Health Organization. Thus, the total score ranges from 0 to 9 and increases with increasing adherence to a Mediterranean diet. A meta-analysis (Sofi *et al.*, 2008), recently updated (Sofi *et al.*, 2010), showed that a 2-point increase on the score of adherence to the Mediterranean diet was associated with a 9% decreased risk of all-cause mortality.

Adherence to a Mediterranean diet and cognitive decline

Few epidemiological studies have examined the link between adherence to a Mediterranean diet and risk of cognitive decline or dementia. The first study was the Washington Heights-Inwood Columbia Aging Project (WHICAP), a cohort study which included at baseline 2258 elderly community-dwellers in New-York, a city which provides international food but not specifically renowned for its Mediterranean traditions. There were 262 incident cases of AD over 10 years of follow-up. When the participants were classified according to tertiles of the Mediterranean diet score, there was a significant trend for a longer survival without developing AD with higher adherence to the Mediterranean diet (Scarmeas *et al.*, 2006). This association was independent of physical activity level (Scarmeas *et al.*, 2009) and vascular risk factors (Scarmeas *et al.*, 2006). A similar protective association was also observed against incidence of mild cognitive impairment in the same study (Scarmeas *et al.*, 2009).

The second study that examined the relationship between the Mediterranean diet and cognitive decline in older persons was the French 3C study which took place much closer to the Mediterranean basin. The general aim of the 3C study was to analyze the role of vascular risk factors in dementia (Three-City Study Group, 2003). A cohort of 9294 community dwellers aged 65 and over was constituted at baseline in 1999

in three French cities: Bordeaux, Dijon and Montpellier. The participants were examined again every two years on average for 10 years since. Cognitive decline was assessed by neuropsychological tests at each examination, including in particular the Mini-Mental Status Examination (MMSE), a global test of cognitive performance. There was an active search for incident cases of dementia, in particular AD, which were validated by an independent committee of neurologists. In Bordeaux, we added a detailed dietary survey. Adherence to the Mediterranean diet (scored as 0 to 9) was computed from a food frequency questionnaire and 24-hour recall. For alcohol, we defined as moderate a consumption of 7 to 14 glasses per week for men, and 1 to 4 for women, which corresponded approximately to the second quartile of the distribution in our sample. We used the same categories of Mediterranean diet score as previously described in other studies: low (score 0-3), middle (score 4-5) and high adherence (score 6-9). We also performed measurements of plasma lipids and fatty acids at baseline.

The statistical analyses were conducted in a sample of 1410 non demented 3C participants in the dietary survey at the first follow-up in Bordeaux (Feart *et al.*, 2009). As expected, the mean number of weekly servings of dairy products and meat decreased with increasing adherence to the Mediterranean diet. Conversely, the number of servings of vegetables, fruits, legumes, cereal and fish increased. Regarding especially fish, the mean number of weekly servings increased from 2 in low adherents to almost 4 in high adherents. The proportion of moderate alcohol drinkers and the MUFA to SFA ratio also increased with increasing adherence. There was a significant inverse association between higher adherence to the Mediterranean diet score and decline on the MMSE over 5 years. Mean annual decline on the MMSE was significantly slower in those who were in the highest tertile of adherence to the Mediterranean diet (score between 6 and 9) compared to those in the lower categories.

These studies were included in a recent meta-analysis which estimated that the overall risk of neurodegenerative disease was decreased by 13% for a 2-point increase of adherence score to the Mediterranean diet (Sofi *et al.*, 2010).

One study (Gao *et al.*, 2007) included in this meta-analysis did not concern Alzheimer's disease or other dementias but Parkinson's disease, and notably, the effect was in the same direction.

A recently published study (Tangney *et al.*, 2011) was not included in the previous meta-analysis. These data come from another US study, the Chicago Health and Aging Project, which included 3,790 older persons followed for 12 years. The authors used a modified version of the Mediterranean diet score ranging from 12 to 45. Here again, individuals in the upper tertile of adherence had significantly slower rates of global cognitive decline.

Which components of the Mediterranean could explain its protective effects against brain aging?

The clinical expression of late-onset AD and other dementias can be viewed as the result of an interaction between genetic predisposition and environmental factors (Fotuhi *et al.*, 2009). In early-onset familial form of AD, mutations in APP, PS1 or PS2 genes lead to the classical amyloid cascade in which accumulation of the beta-amyloid protein is accompanied by increased inflammation and oxidative damage. In late-onset dementia, cognitive impairment results from genetic predisposing factors (the $\epsilon 4$ allele of the Apolipoprotein E gene (ApoE4) and recently discovered genes such CLU, CR1 or PICALM (Lambert *et al.*, 2009)) but also from many acquired chronic conditions on which nutrition may act such as hypertension, obesity, chronic inflammation, stroke, or diabetes. The impact of these factors is exacerbated by inflammation and oxidative stress associated with beta-amyloid deposition.

Thus, accumulation of amyloid plaques and neurofibrillary tangles, the neuropathological hallmark of AD, results from non-modifiable risk factors such as aging and genetics, but also from an imbalance between deleterious and protective factors among which nutrition may play a major role. Indeed, metabolic disorders such as diabetes and metabolic syndrome, but also probably subtle deficiencies in some specific nutrients may precipitate the

disease process. On the other hand, protective nutritional factors include n-3 PUFA but also antioxidants and B vitamins.

The Mediterranean diet is a good source of foods and nutrients that could interact to protect the aging brain (Frisardi *et al.*, 2010). First, high adherence to a Mediterranean diet may be associated with lower total energy intake, lower energy density and lower glycemic index, hence a lower risk of obesity, metabolic syndrome and diabetes. The Mediterranean diet could therefore contribute to lower insulin resistance, which might be associated with a higher risk of dementia. Dietary anti-oxidants such as vitamin E are found in olive oil and seeds, carotenoids in colored fruits and vegetables, while polyphenols are found in fruits and vegetables but also in virgin oil and wine. Adherence to a Mediterranean diet is associated with lower plasma concentrations of lipid peroxidation products (Gaskins *et al.*, 2010). A high consumption of fruits and vegetables is also associated with a reduced risk of hypertension and stroke (Dauchet *et al.*, 2005), as evidenced by the Dietary Approach to Stop Hypertension diet (Smith *et al.*, 2010). Long-chain n-3 PUFA found in fish contribute to decrease inflammation and improve cardiovascular status. Finally, B vitamins, including B6, B12 and folate, are found in cereals and green leafy vegetables. Thus, the Mediterranean diet would be a kind of optimal “brain food”, combining micro- and macronutrients in adequate amounts, working in synergy to slow down age-related cognitive decline (figure 1). In particular, the protective effect of the Mediterranean diet could be explained by a better n-3 PUFA status whose protective effect against brain aging by various mechanisms has been extensively studied (Cunnane *et al.*, 2009).

To test this hypothesis, we examined the association between the score of adherence to a Mediterranean diet and plasma fatty acids in a subsample of 1050 participants in the 3C study from Bordeaux who had determination of the proportion of each plasma fatty acid (Feart *et al.*, 2011). Their mean age was 75.9 y. Cross-sectional analyses of the association between plasma fatty acids and the score of adherence to a Mediterranean diet were performed

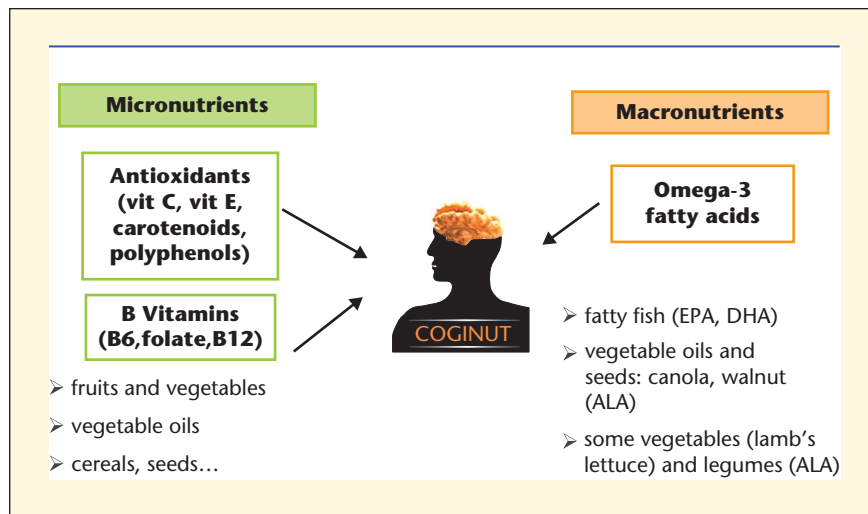


Figure 1. Components of the Mediterranean diet that could explain its protective effect against brain aging. ALA: Alpha-linolenic acid; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid.

by multi-linear regression. After adjustment for age, sex, energy intake, physical activity, smoking, body mass index, plasma triacylglycerol and ApoE4 genotype, plasma docosahexaenoic acid (DHA) and total n-3 PUFA were positively associated with the adherence score (table 1). Regarding eicosapentaenoic acid (EPA), there was an interaction with the ApoE polymorphism thus analyses were stratified according to the possession of the ApoE4 allele. There was a significant positive association between higher adherence to a Mediterranean diet and EPA only in ApoE4 non-carriers ($\beta = 0.029$, $p = 0.02$) whereas no significant association was observed in ApoE4 carriers ($\beta = -0.032$, $p = 0.22$). Interestingly, a similar interaction was already observed in several studies (Barberger Gateau *et al.*, in press), including ours (Barberger-Gateau *et al.*, 2007), between n-3 PUFA status or fish consumption and ApoE4 on the risk for dementia. There was also an inverse association between adherence to a Mediterranean diet and all n-6 to n-3 fatty acid ratios in plasma. Indeed, the total n-6-to-n-3 PUFA, arachidonic acid (AA)-to-EPA, AA-to-DHA and AA-to-(EPA+DHA) ratios were significantly inversely associated with adherence to a Mediterranean diet (table 1). However, there was no association with n-6 PUFA indicating that the negative association of the Mediterranean diet score with the ratios was explained by a better n-3 status and

not by a lower intake of n-6 PUFA in higher adherents. The association with the MUFA-to-SFA ratio in plasma was not significant, contrarily to what was observed with the dietary ratio. This finding is not unexpected since plasma MUFA is not a good biomarker of MUFA intake. In particular, plasma oleic acid is partly obtained by biosynthesis from SFA. Similarly, there was no significant association between plasma alpha-linolenic acid (ALA) and adherence to a Mediterranean diet despite the high amount of ALA in this dietary pattern. Indeed, ALA is readily beta-oxidized after ingestion and its plasma concentration is not a good biomarker of dietary intake.

In conclusion, observational studies show that higher adherence to a Mediterranean diet is associated with slower cognitive decline in older persons, an effect partly mediated by n-3 PUFA but also probably by a joint protective effect of dietary antioxidants, polyphenols, B vitamins, and maybe other compounds. However, we cannot exclude that these protective effects would be explained, at least in part, by residual confounding due to a general healthier lifestyle of older persons adhering to a Mediterranean type diet. So, the Mediterranean diet should be considered as a component of a healthy lifestyle that may slow down age-related cognitive decline and dementia, in addition to many other health benefits. Intervention studies are needed to

Table 1. Association between the score of adherence to a Mediterranean-type diet and proportions of plasma fatty acids. The Bordeaux sample of the Three-City study, N=1050.

Plasma fatty acids ^a	β coefficient ^b	P value
Fatty acids		
Total n-3 PUFA	0.068	.006
22:5 n-3	0.004	.16
22:6 n-3 (DHA)	0.051	.0006
Ratios		
Total MUFA/SFA	-0.003	.24
Total n-6/n-3 PUFA	-0.140	.002
AA/EPA	-0.215	.013
AA/DHA	-0.075	.0001
AA/(EPA+DHA)	-0.050	.0005

AA: Arachidonic acid; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; MUFA: Mono-unsaturated fatty acids; PUFA: Polyunsaturated fatty acids; SFA: Saturated fatty acids

^a Proportions or ratios of total fatty acids as dependent variables, in separate models

^b Estimated by multivariate linear regressions adjusted for age, sex, energy intake, physical activity, smoking, body mass index, plasma triacylglycerol and ApoE4 genotype, for a 1-point increase of the Mediterranean diet score.

assess the impact of shifting to a Mediterranean diet on trajectories of cognitive decline in older persons.

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