

## Editorial

The prevalence of neurodegenerative diseases (ND) increases with age and clearly represent a major public health problem in aging populations. Strategies for the prevention of dementia are therefore needed. Furthermore the onset of ND is insidious and the neurodegenerative process may exist for many years before dementia.

ND can be influenced by many factors; among them several nutrients may play an important role. Higher intake of several nutrients (vitamins C, E, B12, folates, flavonoids, unsaturated fatty acids) have been associated with a lower risk for Alzheimer disease or slower cognitive decline. However results of different available studies are contradictory and may suggest the importance of combination of several anti-oxidants.

There is now converging evidence that composite dietary patterns as Mediterranean Diet or consumption of fruits or vegetables are related not only to lower risk for cardiovascular diseases but also to slower cognitive decline or reduction in risk for Alzheimer's disease, and attractive hypotheses are suggested.

Converging results of future prospective studies of long duration including patients at early stage and controlling for known confounding factors should lead to specific recommendations in the future.

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# Nutritional status determinants and cognition in the elderly

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Many studies carried out in recent years have ascertained that nutritional factors are linked with dementia, in particular with AD, both as risk or protective factors in the onset of the disease and as elements able to modify the course of the disease.

## Risk factors

Vitamin B12, vitamin B6 and folate play an important role in DNA synthesis and their deficiency may lead to increased levels of HCY that are correlated with an increased risk for AD. This may be due to HCY-induced apoptosis of hippocampal neurons consequent to DNA damage. However the use of supplements, with folic acid, vitamin B12 and B6, did not show positive results for the prevention of AD.

The link between obesity and AD may be separately considered in two different periods of life: midlife and old age. For obesity in the elderly, the data are not definitive and different studies reached different conclusions. The available data are more conclusive considering the relation between obesity in middle age and future risk of dementia. The link between obesity and dementia may be explained by different pathogenetic mechanisms. Cardiovascular disease and diabetes, frequently associated with or caused by obesity, may be a reason for an increased risk of dementia with adiposity. Moreover, an inflammatory status is frequently present in patients with increased adiposity and may have a direct effect on neuronal degradation (cerebral atrophy, white matter hyperintensity). Adipocytokines may first affect the integrity of the blood brain barrier where the receptors for them are located, suggesting an influence and a role in the central nervous system. Adipose tissue-related compounds (steroid hormones, insulin, interleukins, neurotrophins, growth factors, adipocytokines, fatty acids) then cross the blood-brain barrier leading to a dysregulation in hippocampus, hypothalamus and, ultimately, to dementia symptoms and AD

## Protective factors

Oxidative stress plays a role in neuronal loss associated with different neurological disorders (Parkinson's disease, AD, amyotrophic lateral sclerosis) and the neurotoxicity caused by amyloid- $\beta$ -peptide in AD is a result of its associated free radicals. Many studies demonstrate the neuroprotective actions of vitamin C and E (radical scavenging activity, suppression of COX-2 activity) and some epidemiological studies show that high dietary intake of these vitamins lowers the risk of AD. However, current

knowledge provides insufficient support for antioxidant supplementation as a means of delaying the aging process and for any major beneficial effect on cognitive functions

Different studies show a relationship between cognitive functions and the  $\omega$ -3-PUFA. In particular, elderly people who frequently eat fish are at lower risk of developing dementia, including AD. The role of  $\omega$ -3-PUFA as protective factors in the onset of AD may be explained by their ability to provide vascular protection, reduce inflammation in the brain and facilitate the regeneration of nerve cells. Once more, the results of supplementation with  $\omega$ -3-PUFA are not consistent and, at the moment, there is no good evidence to support the use of dietary or supplemental  $\omega$ -3-PUFA for the prevention of cognitive impairment or dementia.

## Mediterranean diet and dementia

Diet may play an important role in the prevention or delay of the onset of dementia. However, the results of epidemiological data are conflicting: many nutritional factors may be involved in the pathogenesis of dementia as protective factors but in all cases, supplementation with these factors don't give consistent results either for the prevention or the delay in onset of the disease. The effect is much stronger and consistent for foods rich in antioxidant or  $\omega$ -3-PUFA than for single vitamin supplements. This is probably due to the fact that foods contain compounds and phytochemicals whose intake enhances the action of the single nutrient factor with possible additive and interactive effects among nutritional components. Both prospective studies and reviews on this topic show that a healthy and socially integrated lifestyle involving regular exercise and a balanced and regular diet, rich in antioxidants (vitamin C, vitamin E, flavonoids) and unsaturated fatty acids, with at least five portions of fruits and vegetables per day and one portion of fish per week, as in Mediterranean diet, seems to be the key to the prevention of several age-related diseases including dementia.



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# Fruit and vegetable consumption and age-related cognitive decline

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Based on evidence from numerous epidemiologic and animal studies, food components can modify the rate of cognitive decline that occurs with aging. Because foods are a complex mixture of nutritive and non-nutritive constituents, many professionals believe these relationships should be not be examined only at the level of nutrients, but as foods or food groups or as a function of food patterns. Thus far, clinical trials designed to test the efficacy of nutrient supplements on health outcomes have not produced expected or optimal outcomes. Perhaps, it is the complement of food constituents (some yet to be identified) as found in foods consumed together at the table that contribute to cognitive health, either positively or negatively.

Animal experiments, in particular those feeding whole food extracts such as blueberry, spinach extracts or apple juice concentrates to rats show that neuronal function can be preserved with aging<sup>(1, 2)</sup>. Rats fed vitamin E, strawberry and spinach extracts from adulthood to older age did not experience the losses in cognitive performance shown in rats fed standard chow. Blueberry supplemented diets increased neurogenesis in the dentate gyrus of the hippocampus of rats, a region critical for short-term memory.

Prospective cohort designs provide the best opportunity to examine the relationship between dietary behavior and changes in cognitive performance. Associations between cognitive change and fruit and vegetable intake have been studied in two large well-characterized cohorts. One includes a sample from the Nurses' Health Study (NHS); 13,038 stroke-free participants completed multiple food frequency questionnaires and were interviewed by telephone using six standardized cognitive tests twice over a 2 year period<sup>(3)</sup>. Such relationships were also explored in the Chicago Health and Aging Project or CHAP. Specifically, 3718 elderly residents over a median follow-up of 5.5 years<sup>(4)</sup> were interviewed in their homes using standardized cognitive tests at least twice on everyone approximately 3 years apart and for 1946 persons, three times over a median follow-

up of 6.3 years. The global cognitive score was based on four cognitive tests, all of which were also used in the NHS study.

In both the NHS and CHAP cohorts, dietary information was garnered from participants who completed similar semi-quantitative food frequency questionnaires that have been shown to provide valid and reproducible nutrient estimates<sup>(5,7)</sup>. In NHS, the questionnaire includes 15 fruits (juices too) and 30 vegetables (excluding French fries and potato chips). Total fruit consumption was based on 14 items listing 21 different fruits on the CHAP questionnaire, while 19 items representing 28 different vegetables, excluding potatoes are present. Food intakes in NHS analyses were based on averaged intakes across four to five questionnaires, from 1984 to the first cognitive test. For the CHAP analyses, the food group data were derived from a single questionnaire administered at baseline. Both included older persons. Whereas the NHS sample was exclusively female, the CHAP sample was slightly more than one third male (38%) and 62% black.

In both, the reported rate of change in cognitive scores was a decline of 0.04 standardized units/year! NHS women consumed a median of 3.1 servings of vegetables daily, and 2.4 servings of fruits. In CHAP, the averages were slightly lower: 2.3 servings per day of vegetables, and for fruit, 2.2. In both, however, a slower rate of cognitive decline was observed with higher vegetable intakes, and, in particular, higher intakes of green leafy vegetables (NHS, median, 0.8; CHAP, 0.36 daily servings). In NHS, the rate of decline among persons in the top fifth of vegetable intake was equivalent to being 1.5 years younger in age. In the CHAP cohort, the decline rate was seen in the top two-fifths of the sample (more than 2 vegetable servings per day) and was equivalent to 5 years of younger age. In NHS, higher intakes of legumes were also associated with reduced rates of decline; this association was not observed in CHAP. In both, fruit consumption was unrelated to cognitive changes.

It is always possible that the reported associations may be due to residual or unmeasured confounding. Yet, it is assuring that in two different population samples of older adults, the findings are remarkably consistent. Moreover, in the CHAP analyses, the inverse association between green leafy vegetable consumption and cognitive change was attenuated when models included vitamin E. These vegetables are often the richest in vitamin E content and also usually consumed with added fats (salad dressing, margarine, etc) that are also only vitamin E rich but enhance the absorption of vitamin E and other fat soluble nutrients. In CHAP, intakes of vitamin E and total vitamin C in food were related to slower cognitive decline over 3 years<sup>(6)</sup>. Other constituents of vegetables, in particular, green leafy vegetables, have been associated with rates of cognitive decline. These include folate, and the class of antioxidant -rich polyphenolics known as flavonoids. Cognitive performance was the secondary endpoint in the randomized clinical trial, FACIT. In that 3 year trial, daily supplements of 800 mcg folate (against placebo) improved memory and other cognitive domains that decline with age<sup>(9)</sup>. Two groups<sup>(10, 11)</sup> found that higher dietary flavonoid intake was related to a lower risk of AD in the Rotterdam cohort and the French cohort, PAQUID (Personnes Agées Quid), respectively. In a 10 year follow-up of PAQUID cohort<sup>(12)</sup>, cognitive evolution was again better with higher dietary flavonoid intake.

Further research is needed to confirm the vegetable-cognitive association. We suggest refinements in present dietary instruments used in epidemiologic studies ---first, queries regarding the mode of culinary preparation used for vegetables and to a lesser extent, fruits might be included. Many polyphenols exist primarily in the outer section or skins of fruits and vegetables. Thus, boiling or peeling can remove much of the polyphenolic content. Second, meal based questionnaires may be used. These changes could provide more sensitive and discriminatory tools to evaluate the contributions fruits and vegetables play in cognitive aging.

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# Mediterranean diet and risk of Alzheimer's disease

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Diet may play an important role in the causation and prevention of Alzheimer's Disease (AD) but epidemiological data on diet and AD have been conflicting<sup>[1]</sup>. Higher intake of vitamins C, E, flavonoids, unsaturated fatty acids, fish, higher levels of B12 and folate, modest to moderate ETOH and lower total fats have been related to a lower risk of AD or slower cognitive decline<sup>[1]</sup>. At the same time, other studies have found no association between risk for AD or cognitive decline and either antioxidants, such as vitamins C, E and carotenes or fat or levels of B12<sup>[1]</sup>.

Part of the explanation for the inconsistent findings could be the examination of each individual food or nutrient separately from the other elements of the diet. The alternative approach would be to investigate the effect of the whole diet or composite dietary patterns because individuals do not consume foods or nutrients in isolation but rather as components of their daily diet. Defining diet by composite dietary patterns has the ability to capture its multidimensionality because patterns can integrate complex or subtle interactive effects of many dietary constituents. For example, it has been shown that high fish consumption may have a beneficial effect on blood pressure, cholesterol and tendency to form clots only if it is part of a low fat diet. As a different example, the habit of adding a lot of olive oil in salads may be beneficial partially via increasing the total vegetable intake. Such composite dietary pattern analysis has recently received growing attention in relation to many non-neurological diseases (i.e. cirrhosis or various cancers). One such pattern is the Mediterranean diet (MeDi), which has received increased attention in recent years because of converging evidence relating it to lower risk for cardiovascular disease, several forms of cancer and overall mortality<sup>[2]</sup>. Despite the advantages of the composite dietary pattern approach, previous research in the neurological literature in general, but also in AD in particular, has focused only on individual dietary components.

The MeDi is characterized by high intake of vegetables, legumes, fruits and cereals; high intake of unsaturated fatty acids (mostly in the form of olive oil in salad dressing and cooking) but low intake of saturated lipids; a moderately high intake of fish; a low-to-moderate intake of dairy products (mostly in the form of cheese or yogurt); a low intake of meat and poultry; and a regular but moderate amount of ethanol, primarily in the form of wine and generally during meals. Therefore, the MeDi seems to include many of the components reported as potentially beneficial for AD and cognitive performance in some of the previous literature.

We sought to investigate the association between MeDi

and risk for AD<sup>[3]</sup>. A total of 2,258 community-based non-demented elderly individuals in New York were prospectively evaluated every 1.5 years. There were 262 subjects that developed AD cases during the course of 4 (0.2– 13.9) years of follow-up. We found that higher adherence to the MeDi was associated with lower risk of AD: Each additional unit of the MeDi score was associated with ~10% less risk of developing AD. Compared to subjects in the lowest MeDi adherence tertile, subjects in the middle MeDi adherence tertile had ~20% less risk of developing AD, while those at the highest tertile had ~40% less risk of developing AD, with a significant trend for a dose-response effect. Adjusting for a series of potential factors that could confound this association did not change the results. In analyses investigating the contribution of individual dietary components, mild to moderate alcohol consumption and higher vegetable consumption were the elements mostly driving the MeDi effect. However, additional analyses suggested that the overall composite dietary pattern of the MeDi may capture more than its individual parts.

In another study we wanted to investigate possible biological mechanisms via which the MeDi may protect from AD<sup>[4]</sup>. Given that in previous literature higher adherence to the MeDi has been associated with lower cardiovascular disease, which in turn may be related to AD, we hypothesized that the relation between MeDi and AD could be mediated by cardiovascular mechanisms (i.e. stroke, diabetes, hypertension, heart disease, lipid levels). However, we found that the MeDi's effect in cardiovascular diseases was not the reason for its protective action for AD. A possible explanation for this finding are the limitations in measuring cardiovascular disease with enough precision and accuracy.

## Conclusions

Research on dietary effects in AD have so far focused on individual foods and nutrients and results have been conflicting. Higher adherence to the composite dietary pattern of MeDi is associated with a reduced risk for developing AD. Mild / moderate alcohol and vegetable consumption seem to be the elements mostly responsible for this effect but the association seems to be driven mostly by the whole MeDi pattern, rather than its individual dietary components. The association between MeDi and AD is not fully mediated by cardiovascular diseases. This could be the result of additional biological mechanisms being implicated: the MeDi may be resulting not only in more favorable cardiovascular disease profile but also in reduction of oxidative stress and in less inflammation, all mechanisms potentially important for AD pathogenesis.

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