Chapter 15
Are Antioxidant Food and Nutrients Useful in Preventing Cognitive Decline?

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Abstract With the aging of the population, cognitive impairment is increasingly common, and dementia, the most common disorder that affects the brain of elderly adults, is increasing worldwide. At present, no cure is available against dementia and prevention strategies to delay cognitive decline are sought. Epidemiological studies have reported several risk factors and a consensus emerged that low educational level, vascular factors and dietary habits may be important factors. Among the latter, intake of dietary antioxidants could contribute to limit oxidative damage associated with brain aging and neurodegenerative disease. The aim of this chapter is to critically review evidence from observational and intervention studies regarding the link between intake of antioxidants and cognitive function in older adults.

15.1 Background

The free radical theory of aging states that organisms age because cells accumulate free radical damage over time [1]. Free radicals such as reactive oxygen species (ROS) are produced during normal metabolism: a certain amount of ROS production is, in fact, necessary for good health. For instance, it helps the body's immune system to kill microorganisms. ROS are mainly produced in mitochondria [2] and are oxidants, i.e., molecules or atoms which can oxidize a substrate and are reduced

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in this reaction. They are able to damage several key cellular components like membrane lipids, nucleic acids, carbohydrates and proteins, thereby severely disturbing major cellular and organic physiologic functions. This type of damage occurs when the host defenses against oxidants are quantitatively and/or qualitatively unable to counteract the production and effects of oxidants themselves. This state is called oxidative stress.

The antioxidant defense system provides protection against oxidative reactions. A network of endogenous antioxidant enzymes is available to scavenge ROS once they are generated. Superoxide dismutase, catalase, glutathione and glutathione-dependent enzymes as well as other sulfur- or selenium-containing proteins and low molecular weight compounds are synthesized by the organism for defense.

Natural dietary antioxidants are exogenous molecules and include vitamins A, C, and E, carotenoids, flavonoids and other polyphenols and selenium. Vitamin C is rapidly distributed to all tissues, whereas vitamin E is incorporated into lipoproteins in the liver, and is then secreted together with them into plasma [3]. Vitamin C can scavenge many reactive species and may stabilize catecholamine from forming ROS. Vitamin E is a family of several fat soluble compounds including tocopherols and tocotrienols. Vitamin E is a powerful antioxidant that inhibits lipid peroxidation [4]. Carotenoids can scavenge singlet oxygen and a range of other ROS in vitro, but there is still little evidence that they contribute significantly to the antioxidant defense system in the central nervous system [3]. Flavonoids belong to a group of natural substances with variable phenolic structures and are found in fruits, vegetables, grains, flowers, tea, and wine [5]. Selenium is a cofactor associated with the antioxidant enzyme activity of glutathione peroxidase. These dietary antioxidants are an essential component of the antioxidant defense network.

The brain is particularly sensitive to oxidative stress [6]. Weighing about 2 % of the body mass, the brain utilizes 20 % of the total oxygen consumption. It is enriched with readily peroxidizable polyunsaturated fatty acids. In addition, the brain is not particularly rich in antioxidant defenses: it has a very low level of catalase activity and only moderate amounts of the endogenous antioxidant enzymes, superoxide dismutase and glutathione peroxidase. Additionally, the brain has high levels of iron and vitamin C, which are the key catalysts for lipid peroxidation.

15.2 Data from Observational Epidemiological Studies

15.2.1 Association Between Biomarkers of Antioxidant Status and Cognition

The association between plasmatic concentration of antioxidants and cognitive performance was assessed in normal subjects. Goodwin et al. found a correlation between memory test scores and plasma levels of vitamin C in 260 healthy individuals aged 60 years and older [7]. In a population based sample of 885 individuals aged

74–79 years from the SENECA study, higher cognitive performance measured by the Mini Mental State Examination (MMSE) was positively correlated with higher plasmatic concentrations of lycopene, alpha-carotene, beta-carotene, total carotene, beta-cryptoxanthin, and alpha-tocopherol [8]. In 1,389 elderly volunteers from the EVA study, low levels of carotenoids were associated with poor cognitive performance in tests assessing visual attention (Odds ratio (OR) = 1.34, $p = 0.055$) or logical reasoning (OR = 1.38, $p = 0.04$) but low levels of other antioxidants were not related to poor cognitive functioning [9]. In the third National Health and Nutrition Examination Survey, Perkins et al. measured serum antioxidant concentrations and administered two tests of verbal memory to 4,809 multiethnic men and women sampled from the US general population [10]. They found that the risk of a low score on their two tests was significantly lower among subjects with the highest vitamin E concentrations than among those with the lowest concentrations (Relative risk (RR) = 0.48; 95 % Confidence Interval (CI) [0.34:0.98]) but that vitamin C had no effect.

When analyzing a pathological state such as dementia, cross-sectional analyses, based mainly on case–control studies, have shown conflicting results. Rivière et al. reported that patients with Alzheimer's disease (AD) had lower plasma vitamin C concentrations (despite similar intakes) as compared to control subjects [11]. Indeed, in Alzheimer subjects, vitamin C plasma levels decreased in proportion to the severity of the cognitive impairment despite similar vitamin C intakes. In the group of hospitalized Alzheimer, patients had normal vitamin C intakes, but their plasma vitamin C was lower than that of controls. Institutionalized Alzheimer patients had normal vitamin C level and vitamin C intakes compared with community-dwelling subjects of similar degree of cognitive impairment. Interestingly, in these patients, vitamin E levels did not correlate with the degree of cognitive impairment.

Sinclair et al. reported that plasma concentrations of vitamin C and beta-carotene were not different in AD vs. controls. On the opposite, plasma vitamin E was lower in AD versus controls [12]. Plasma lipid peroxides and total antioxidant capacity were not different across groups.

However, Rinaldi et al. reported that the plasma concentrations of several antioxidant micronutrients, including vitamins A, C, E, and carotenoids, were lower in AD patients and in individuals affected by Mild cognitive impairment (MCI) as compared to control subjects, independently of the apolipoprotein E (ApoE) genotype [13].

Few studies have investigated the relationship between selenium (Se) status and cognitive function. In a population-based sample of 1,389 volunteers aged 59–71 years included in the EVA study, levels of selenium, carotenoids, and thiobarbituric reactive substances in plasma, and of vitamin E, glutathione peroxidase and Cu–Zn superoxide dismutase in red blood cells were measured [14]. Cognitive functioning was evaluated through several psychometric tests. Low levels of total carotenoids were associated with poor performance in two tests (visual attention and executive functioning). After controlling for demographic factors, alcohol and tobacco intake and history of cardiovascular diseases, low levels of selenium are no longer associated with poor performance in visual attention.

Cardoso et al. measured selenium levels in plasma, erythrocytes, and nail samples of 28 AD subjects and 29 healthy elderly controls. Se levels in plasma (50.99 μg/l) and erythrocytes (76.19 μg/l) were significantly higher in the control group than in AD subjects (32.59 and 43.74 μg/l in plasma and erythrocytes respectively) [15]. In nails, higher values in the control group were also observed when compared with the AD group (0.400 vs. 0.302 μg/l).

A cross-sectional study performed in a large population-based sample of elderly Chinese also used selenium levels measured in nail samples as a biomarker of selenium status [16]. Lower selenium levels were significantly associated with lower cognitive score ($p < 0.0087$ for all tests).

The main difficulty in interpreting cross-sectional study results lies in the fact that it is impossible to assess whether the lower plasma concentrations of antioxidant, micronutrients, including vitamins A, C, E, and carotenoids in AD vs. controls are due to their lower intake or to increased demand.

Several studies aimed at investigating the occurrence of dementia according to antioxidant biomarkers. In a nested case–control study, Helmer et al. matched 46 incident cases of dementia with 136 controls and measured plasmatic vitamin A and E levels as well as Malondialdehyde level (MDA, a lipoperoxidation product and therefore a marker of the oxidative stress level) [17]. The risk of dementia was significantly increased in the lowest vitamin E tertile (<21.0 mmol/l) (OR = 3.12, $p = 0.033$) compared to the highest one (>25.5 mmol/l). The risk of Alzheimer's disease was also increased, with borderline significance (OR = 3.06, $p = 0.053$). Similarly, there was a trend to an increased risk of dementia in the highest tertile of MDA (OR = 2.44, $p = 0.13$).

In a dementia free sample of 232 subjects aged 80+ years and followed for 6 years, higher level of plasma vitamin E were associated with a reduced risk of developing AD (HR = 0.55, 95 % CI [0.32:0.94]) [18]. According to the several isoforms of vitamin E, the risk of developing AD was reduced only in association with high plasma levels of beta-tocopherol (HR = 0.62, 95 % CI [0.39:0.99]).

In the EVA cohort, a sample of 1,389 subjects followed for 9 years, cognitive decline was correlated with plasma selenium change [19]. Cognitive decline was associated with decrease of plasma selenium over time. Among subjects who had a decrease in their plasma selenium levels, the greater the decrease in plasma selenium, the higher the probability of cognitive decline. Among subjects who had an increase in their plasma selenium levels, cognitive decline was greater in subjects with the smallest selenium increase. However, there was no association between short-term (2-year) selenium change and cognitive changes.

15.2.2 Cross-sectional Association Between Dietary Antioxidants and Cognition

Dietary intake of antioxidants may better reflect the actual exposure since some vitamins are highly regulated in the body. In a sample of 5,182 subjects aged 55–95 years living in Rotterdam (Netherlands), Jama et al. showed that lower

dietary intake of beta-carotene was associated with a lower cognitive performance, but no association was found with dietary intake of vitamin C and vitamin E [20]. Cross-sectional studies have also shown an association between fruit and vegetable consumption and cognitive impairment. In a sample of 260 non institutionalized elderly aged 65–90 years, Ortega et al. showed that better cognitive functioning (characterized by good performance to the MMSE) was associated with higher intake of fruits [21]. Subjects with poorer performance tended to have poorer fruit intake (388 g/d (sd = 194 g/d) in men and 318 g/d (sd = 188 g/d) in women) than did those who performed better on the MMSE (398 g/d (sd = 214 g/d) in men and 331 g/d (sd = 225 g/d) in women). As expected, subject with better cognitive performance had higher intake of fiber and vitamin C. However, no association was found with beta-carotene or vitamin E.

Dietary intake of selenium was assessed in AD 28 subjects compared to 29 elderly controls, both aged between 60 and 89 years [15]. Se intake was evaluated by using a 3 day dietary food record and deficient Se intake was largely observed in the AD group.

The major problem in cross-sectional studies is that dietary intake and cognition are recorded at the same time. Therefore, people who have poorer cognitive functioning may have changed their dietary intake because of cognitive impairment. In such studies, it is not possible to assess whether dietary intake caused poor cognitive functioning or cognitive impairment caused bad dietary habits. Longitudinal studies are more powerful in this respect as dietary intake is recorded some time prior to the occurrence of a cognitive deficit.

15.2.3 Longitudinal Association Between Dietary Antioxidants and Cognition

In Zutphen (Netherlands), 342 men were followed for 3 years [22]. The decline of more than two points to the MMSE was not associated with dietary intake of vitamin C ($p < 0.9$), vitamin E ($p < 0.7$), beta-carotene ($p < 0.6$) or flavonoids ($p < 0.06$). However, the follow-up was probably too short to capture a big decline of cognitive performance.

In South–West of France, a sample of 1,642 subjects aged 65 years and older was followed for 10 years [23]. At the initial visit, individuals in the higher quartile of flavonoid intake had better MMSE score than those in the lower quartiles. In addition, after 10 years of follow-up, subjects of the highest quartile tended to have lower decline than the others. Moreover, a gradient in cognitive decline was observed according to flavonoid intake since MMSE decline increased as dietary flavonoid intake decreased.

Fruits and vegetables are major providers of combinations of antioxidant nutrients, including vitamin C, carotenoids and polyphenols, and to a lesser extent, vitamin E. In the US, 13,388 nurses were followed for 2 years and cognitive functioning was assessed using psychometric tests [24]. The authors showed that vegetable

intake was associated with the decline in cognitive functioning. In a dose-dependent manner, women who consumed more green leafy vegetables experienced a lower decline. Apparent benefits generally increased linearly with each level of intake. For cruciferous vegetables, significantly less memory decline was found in those at the highest quintile of intake. No linear dose–response relations were observed; instead a threshold effect at the fourth quartile was seen.

In Manhattan, 980 subjects were followed for 4 years and 242 incident cases of dementia were diagnosed [25]. Luchsinger et al. found no association between developing dementia and dietary intake of beta-carotene, vitamin C, or vitamin E. In Rotterdam, 5,395 subjects were followed for 6 years and 197 incident cases of dementia were identified. A lower risk of dementia was observed with higher intake of vitamin C (HR = 0.82, $p < 0.05$) and vitamin E (Hazard Ratio (HR) = 0.82, $p < 0.04$), but no association was found with beta-carotene (HR = 0.87) or flavonoids (HR = 0.99). When the analyses were stratified for smoking habits, the risk of AD associated with higher intake of vitamin C and vitamin E was lower in current smokers than in former or nonsmokers (HR = 0.65 vs. 0.91 and 0.83 respectively). High intake of flavonoids and beta-carotene was also associated with reduced risk of AD in current smokers (HR = 0.54 and HR = 0.49 respectively).

In Chicago, 815 elderly aged 65 years and older were followed for 4 years. Although 131 incident cases were identified [26], total vitamin E intake (from foods and supplements) did not predict the incidence of the disorder. Vitamin E intake from foods had a statistically significant dose–response protective effect in the age-adjusted model ($p = 0.04$). The risk for persons in the top fifth of intake was lower by 67 % compared with that of persons in the lowest fifth of intake. Among persons who were ApoE ε4 negative, vitamin E from foods showed a strong linear protective association with AD. Vitamin C intake from foods appeared to have an inverse relationship with AD but was statistically significant in the fourth quintile only, and no dose–response relationship was seen. Therefore, intake of vitamin E from food was inversely associated with incident AD. There was no association with the use of vitamin E as a supplement. Vitamin C and beta-carotene also had no statistically significant association with AD. The linear protective association of vitamin E was found only among persons who were ApoE ε4 negative.

Occurrence of dementia has also been associated with fruit and vegetable intake. In King County (US), 1,589 Japanese American were followed for 6 years [27]. During this period, 81 new cases of dementia were diagnosed. Compared to subjects with a low fruit and vegetable juice intake (less than one per week), subjects with high intake (three or more juices per week) had a lower risk of developing dementia (HR = 0.24, 95 % CI [0.09:0.61]). Subjects with moderate intake (1 or 2 times per week) had a nonsignificant reduced risk (HR = 0.84, 95 % CI [0.31:2.29]). The inverse association between fruit and vegetable juices and AD appeared in all strata of education, smoking status, tea drinking, regular physical activity, ApoE genotype, and total fat intake. However, the association tended to be stronger among those who were former or current smokers, drank tea less often, were positive for the ApoE ε4 allele, and were less physically active.

In the Three City study, 8,085 elderly were followed for 4 years, and 281 incident cases of dementia were diagnosed [28]. A lower risk of developing dementia was observed (HR = 0.72, $p < 0.02$) in subjects with frequent (every day) fruit and vegetable intake. The strength of the association remained almost unchanged after controlling for ApoE genotype, body mass index and diabetes.

15.3 Results from Clinical Trials

Few clinical trials have studied the effect of antioxidant components on cognition [29]. We shall first review the evolution of cognition in random clinical trials designed initially for investigating the effect of vitamin supplementation on prevention of major health conditions. A cognitive sub-study was performed in the Women's Health study. This study was a randomized double-blind placebo-controlled supplementation with vitamin E (600 IU) and low dose aspirin (100 mg) for the prevention of cardiovascular disease and cancer [30]. A total of 39,876 women were enrolled in 1992–1995. In 1998, 5.6 years after randomization, 6,377 women performed cognitive tests and were followed on average 4 years with a contact every 2 years. Whatever the type of measure considered (mean performance, mean cognitive change over time, risk of substantial decline), there were no difference in global performance between vitamin E and placebo groups. However, the vitamin E group experienced less adverse cognitive change compared with the placebo group among women with dietary intake below the median of 6.1 mg/day. In contrast, among women with high intakes of dietary vitamin E, the two groups were similar in their change.

In the Physicians' Health Study II (an extension of the Physicians' Health Study (PHS) which began in 1982 when 22,071 physicians were randomized in a trial for prevention of cardiovascular disease and cancer), 4,052 subjects from PHS agreed in 1997 to participate to PHS II and 4,052 new physicians were included from 1998 to 2001 [31]. Half were included in the treatment group (50 mg beta-carotene, alternate days) and the others in the placebo group. Mean duration of treatment ranged from 2 months to 20 years. Cognitive functioning was evaluated using psychometric tests administered on telephone at baseline in 1998 and at follow-up in 2002. In newly recruited participants, there was no evidence of cognitive benefits with short-term beta-carotene supplementation. In participants with long-term treatment, those assigned to beta carotene performed significantly better on the global score compared with the placebo group (mean difference in z scores, 0.047 standard units; $p = 0.03$). Although beta-carotene supplementation was associated with higher mortality [32], long term beta-carotene supplementation may provide cognitive benefits.

An ancillary study of the SU.VI.MAX trial was designed to assess the long term effects of antioxidant nutrient supplementation on the cognitive performance of the participants, 6 years after the end of the trial [33]. The SU.VI.MAX study is a double-blind, placebo-controlled, randomized trial that enrolled 5,583 subjects aged 45–60 years. From 1994 to 2003, participants received daily vitamin C (120 mg),

beta-carotene (6 mg), vitamin E (45 IU), selenium (100 μg), and zinc (20 mg) in combination or a placebo. In 2007–2009, the cognitive performance of 4,447 participants was assessed with 4 neuropsychological tests. Subjects receiving active antioxidant supplementation showed better episodic memory scores. Verbal memory scores were better only in supplemented subjects who were nonsmokers or who had low serum vitamin C concentrations at baseline. Although this study showed that supplemented subjects have better performance on specific cognitive domains, the study did not assessed cognition at baseline and initial comparability of the groups was not assured.

Other trials have investigated the effect of vitamin supplement in a secondary prevention perspective. Petersen et al. treated 769 subjects with MCI which is considered to be a prodromal state of AD [34]. Three arms of the study were constituted: Donepezil, vitamin E (2,000 IU), or placebo and the main outcome was to delay the conversion to dementia. After 3 years of follow-up, no difference was observed between treatments and placebo. However, in a more recent follow-up publication, the same authors reported that brain imaging showed that changes in the volumes of some areas of the brain (hippocampus, enthorinal cortex) were lower in the group that received vitamin E rather than placebo [35].

Finally, trials were also designed to evaluate the effect of supplements in diseased subjects. Sano et al. conducted a double-blind placebo controlled trial in patients with AD [36]. A total of 341 AD patients were divided into four arms: Vitamin E (2,000 IU a day), Selegiline (a selective monoamine oxidase inhibitor), both, and no treatment. The primary outcome was the time to the occurrence of any of the following: death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia. After a follow-up of 2 years, high doses of vitamin E resulted in a longer time to institutionalization and a delayed time to deterioration of activities of daily living although cognitive function did not appear to be improved.

More recently, Lloret et al. treated 57 AD patients with 800 IU of vitamin E and assessed responsiveness to the antioxidant treatment [37]. The authors checked the blood oxidative status of the patients using the blood total glutathione levels and oxidized glutathione (GSSG). They found that not all patients respond equally to antioxidant treatment and identified "responders" (vitamin E treatment resulted in a reduction of the GSSG levels) and "nonresponders." In responders to vitamin E, cognitive performance measured by the MMSE was maintained, whereas in nonresponders, cognition decreased sharply, to levels even lower than those of patients taking placebo. Although the number of subjects is low, this result highlights that giving vitamin E to AD patients may be harmful, especially if the oxidative stress status of the patients is not carefully monitored.

This aspect of differential response to supplementation is probably a key factor that is underestimated. Indeed, another clinical trial showed cognitive difference according to the response to a formulation of six vitamins and nutraceuticals (30 IU of vitamin E, 6 μg of vitamin B12, 400 μg of folic acid, 400 mg of *S*-adenosyl methionine, 600 mg of *N*-acetyl cysteine, 500 mg of Acetyl L-carnitine) [38]. Adults (age 18–86 years) of both genders without dementia received the treatment or a placebo.

After 3 months of follow-up, participants who received the treatment had improved to the Trail making test that evaluated executive function ($p<0.03$), while those receiving placebo did not improve. However, unlike younger participants, participants ≥74 years of age receiving treatment did not on an average demonstrate improvement versus placebo. The percentage of responders (i.e., subjects that showed an improvement to the test after 3 months of treatment) tended to decrease with age. Nonresponders within all age groups up to 74 years of age displayed similar performance but lower than responders, while those ≥74 years of age displayed substantially poorer scores at 3 months than did all other age groups. Therefore, elder non responders showed poorer performance than younger non responders. This age-related decline may be due to decreased absorption of nutrients, and/or decreased basal vitamin levels due to suboptimal nutrition. This result may explain why clinical trials performed on elderly individuals did not show a beneficial effect of antioxidant vitamins since it may be too late and/or the supplement may not be adapted to the physiology of the older adult.

In view of these results, one may wonder if antioxidants reduce oxidative stress in the brain and have any influence on the pathological pathway of AD. Galasko et al. enrolled 78 AD patients and looked for change in potential CSF biomarkers (Aβ42, tau, and phospho-tau) and oxidative stress (F2-isoprostane) as well as cognition (Mini-Mental State Examination) and daily function (ADCS Activities of Daily Living Scale) at the end of a 16-week treatment period [39]. One-third of the participants were randomized into a placebo group. The others received either a daily supplement of 800 IU vitamin E, 500 mg vitamin C, and 900 mg α-lipoic acid (E/C/ALA group) or 400 mg coenzyme Q (CoQ group). None of the AD biomarkers changed whatever the treatment, leading to the conclusion that supplements did not alter the pathological pathway. CSF levels of F2-isoprostane fell about 19 % in the E/C/ALA group, suggesting that this antioxidant combination lowered oxidative stress in the brain. In contrast, CoQ did not change CSF F2-isoprostane levels. From the cognitive point of view, the E/C/ALA group seemed to decline faster with a 2.8 point change on MMSE scores from baseline, compared to 0.9–1.0 point change in the placebo and CoQ groups.

15.4 Discussion

Clinical trials have found that antioxidant supplementation does not delay or avoid cognitive decline. It however reduces oxidative stress as measured by GSSG or F2 isoprostanes. The increased decline in cognitive performance observed in some trials suggests that higher dose of vitamin E may be harmful in subjects that are non-responders. Even observational studies have produced inconsistent results with anti-oxidant micronutrients. In contrast, fruit and vegetable intake has tended to be more consistently associated with a lower risk of developing dementia, although the number of available studies is small. This indicates that specific antioxidant nutrients such as vitamin E are not sufficient to protect against cognitive deficit.

This is also consistent with studies that have shown that people consuming a Mediterranean diet have a lower risk of developing cognitive impairment. The traditional Mediterranean diet is characterized by high consumption of plant foods (vegetables, fruits, legumes, and cereals), high intake of olive oil as the principal source of monounsaturated fat but low intake of saturated fat, moderate intake of fish, low to moderate intake of dairy products, low consumption of meat and poultry, and wine consumed in low to moderate amounts, normally with meals. In a cohort study of a large community-based population without dementia in New York, higher Mediterranean diet adherence was associated with a reduced risk for mild cognitive impairment and AD [40]. A cohort study in France also showed less cognitive decline in subjects who adhered to a Mediterranean diet [41]. The biological basis for the apparent health benefits of a Mediterranean diet involves a decrease in oxidative stress, inflammation, and vascular disease, which also participate in the pathophysiology of neurodegenerative diseases. The Mediterranean diet pattern probably does not fully explain the better health of persons who adhere to it, but it may contribute directly. A Mediterranean diet also may indirectly constitute an indicator of a complex set of favorable social and lifestyle factors that contribute to better health.

Do these observations mean that the oxidative-stress hypothesis of AD is not valid anymore? First, considering the complexity of the redox system in vivo, we may probably need better antioxidant drugs and, in certain cases, a combinatory approach would be preferable to a single antioxidant. Second, before starting any antioxidant therapy trial, it will be extremely important to have clear information on the endogenous antioxidant levels of the participating subjects. This aspect is important for patient selection in order to identify potential responders versus nonresponders to a drug with antioxidant properties.

In conclusion, fruits and vegetables are associated with a better cognitive evolution. It has not been possible to demonstrate that specific antioxidant nutrients such as vitamin E were at the origin of the protection. Fruit and vegetable intake is more complex than the addition of specific nutrients. Dietary behavior may also be involved, and Mediterranean diet is an illustration of a combination of several foods that may be beneficial. In a preventive point of view, rather than recommending antioxidant nutrients intake in the form of vitamins, it would be wiser to promote fruits and vegetables consumption that may bring benefit not only on cognitive aging but also on other pathologies like cardiovascular disease and cancer.

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