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Review

Nutritional factors, cognitive decline, and dementia

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Abstract

Nutritional factors and nutritional deficiencies have been repeatedly associated with cognitive impairment. Most of the evidence is based on cross-sectional studies, which cannot prove whether a nutritional deficit is the cause or the consequence of an impaired cognitive status. In fact, cognitive impairment, in turn, can determine changes in dietary habits and consequent nutritional deficiencies. We reviewed clinical and epidemiological studies from January 1983 to June 2004. Several cross-sectional and fewer prospective studies reported an association between dietary or supplemental intake of antioxidants and protection from cognitive decline and dementia. There are negative reports as well and some methodological biases might have affected the consistencies across studies. Deficiencies of several B vitamins have been associated with cognitive dysfunction in many observational studies. More recently, deficiencies of folate (B_9) and cobalamine (B_{12}) have been studied in relation to hyperhomocysteinemia as potential determinants of cognitive impairment, dementia, and Alzheimer's disease (AD). A small number of studies assessed the association between intake of macronutrients and cognitive function or dementia. Among the others, the intake of fatty acids and cholesterol has received particular attention. Although the results are not always consistent, most studies have reported a protective role of dietary intakes of poly- and mono-unsaturated fatty acids against cognitive decline and AD. We point out that well designed intervention studies are warranted in order to establish specific levels of micro- and macronutrient deficiencies and to set general recommendations for the population.

Keywords: Malnutrition; Dementia; Cognitive functions; Micronutrients; Macronutrients

Contents

1. Introduction

Malnutrition, indicating a poor nutritional status, recognizes a broad spectrum of possible causes. Deficiencies in dietary intake, digestion and absorption, metabolism, excretion, as well as alterations in the metabolic requirements of dietary energy, protein and other macronutrients related to specific conditions can determine malnutrition [119]. Nevertheless, a state of malnutrition only gains clinical interest when it is the result of prolonged exposure to a relatively insufficient intake or absorption of micronutrients or macronutrients.

In fact, since aging is associated with a reduction in the intake of both macro-and micronutrients [80,107,116] and with alter-

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ations in the absorption and metabolic requirements of vitamins [14,50], elderly individuals constitute the largest population at risk for nutritional deficiencies [134]. In a multicenter European study (SENECA) recruiting 1389, 70–79-year-old individuals, over the course of a 4-year follow-up, it was documented that there was not only a decrease in nutrient intake, but that there was also an increase in the percentiles of the population at risk for malnutrition (i.e., with intakes below the recommended dietary allowances). Deficiencies in the intake of Vitamins B, A, and calcium were the most frequently observed [3].

Cognitive impairment and dementia are common disorders among elderly persons influencing the individual's ability to function independently. Due to the aging of the population, the prevalence of cognitive impairment and dementia are increasing [29].

Mild cognitive impairment (MCI) is a widely used term to indicate a syndrome characterized by a mild memory or cognitive impairment that cannot be accounted for by any recognized medical or psychiatric condition [131]. Different operational definitions of MCI have been presented and discussed by a number of research and clinical groups [42,109,131]. The general criteria for MCI require a subjective complaint of memory loss, an objective impairment of memory function for age and education (1 or two standard deviations below the mean score of the examined sample) assessed by formal neuropsychological testing, no evidence of dementia, intact activities of daily living and other cognitive domains remaining generally preserved [131].

Estimates of the prevalence of MCI range from 3% for subjects age 60 and older [153] to 15% for subjects age 75 and older [45]. In a recent longitudinal study with a 3.5-year follow-up, involving a total of 2963 individuals aged 65–84 years, free-living or institutionalized, we found a 3.3% prevalence rate for MCI, an incidence rate of 21.5/1000 person-years, and a progression rate to dementia of 3.8/100 person-years [174].

In contrast to MCI, a diagnosis of dementia is made when cognitive impairment is greater than that found in normal aging and it affects two or more cognitive domains and the person's ability to function (American Psychiatric Association [1]). In fact, an essential condition to establish the diagnosis of dementia is that the cognitive failure must be severe enough to impair the usual social and occupational daily activities. The most common forms of dementia are Alzheimer's disease (AD) and vascular dementia (VaD), with respective frequencies of 70 and 15% of all forms of dementia [195]. AD can only be diagnosed with certainty at autopsy, but a clinical diagnosis can be formulated according to the criteria established in 1984 by the National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [97]. AD is characterized by a slowly progressive dementia along with neurohistological lesions, including senile plaques and neurofibrillary tangles, in excess of the expected amount, according to the age. This neurodegenerative disease commonly leads to complete psychological and physical dependency and death within one to two decades. Although the degenerative process starts several years before the first symptoms appear [17,181], and many promising approaches have been undertaken, including neuroimaging [56,68,96,146–148,169], there are no sensitive and specific tests for this pre-clinical stage [118], and a clinical diagnosis cannot be established before the onset of dementia or, perhaps, mild cognitive impairment [130,131].

VaD is an even less clearly defined disease. In fact, various criteria for VaD have been proposed in the last decades [1,25,158], but the diagnosis of certainty, based on post-mortem findings, does not usually confirm the clinical suspicion [47]. The clinical presentation of VaD varies greatly depending on the causes and location of cerebral damage [156]. Large-vessel disease leads commonly to multiple cortical infarcts and a multifocal cortical dementia syndrome, whereas small-vessel disease causes periventricular white matter ischemia and lacunar strokes characterized clinically by subcortical dementia with frontal lobe deficits, impaired memory, mood changes, slowing of motor function, urinary disturbances and pseudobulbar palsy [157].

Malnutrition has been repeatedly associated with cognitive impairment. Associations between the intake of nutrients and cognitive function have been documented (reviewed in [150,159,173]), but the large majority of these studies reported on cross-sectional associations, which cannot prove whether a nutritional deficit is the cause or the consequence of an impaired cognitive status. In fact, cognitive impairment, in turn, can determine changes in dietary habits and consequent nutritional deficiencies [22,46,58,76,162]. At the extreme end of cognitive dysfunction, in advanced states of dementia, agnosia (i.e., difficulties in interpreting sensory data), apraxia (i.e., incapacity in executing coordinated movements such as opening the mouth for eating), and sensory deficits [32] may compromise eating behavior as well [84].

It is also known that cognitive function depends on many factors other than nutritional status, such as education, intelligence quotient (IQ), age, and genetic factors [37,180,182]. All these factors need to be accounted for when attempting to resolve the effect of nutritional deficiencies on cognitive performance. Moreover, a specific nutrient deficiency is rarely the only result of poor dietary habits; more often, it is the epiphenomenon of a state of malnutrition, which is the result of multiple deficiencies, where causes of cognitive dysfunction are entangled with its confounders.

On the other hand, the administration of nutrients by supplements does not necessarily have the same impact on the risk of dementia as the dietary intake of the same nutrients. The quality and proportions of the nutrients naturally present in a food produce effects on absorption and metabolism and ultimately on their bioavailability that are substantially different from the effects that we might expect from the administration of a single nutrient in pharmacological doses [18].

Furthermore, data collected in observational epidemiological settings from supplement users are likely affected by selection biases because persons that use supplements are often engaged in healthier life-styles than the general population, whether because of cultural awareness [69] or because of underlying health problems [8]. Finally, the reliability of the dietary data collected with food frequency questionnaires, besides being affected by the number of items and validation in a specific study population, is a function of the cognitive and especially mem-

ory status of the participants. Although adjustment for memory scores or cognitive status can be applied, this bias would affect the prospective results, particularly when the measurements of cognitive and dietary variables are not simultaneous [43].

With all these caveats, here we provide a review of the most convincing evidence for the relationships among various nutritional deficiencies, cognitive decline, and dementia. We reviewed clinical and epidemiological studies from the international literature through keyword (malnutrition; dementia; cognitive functions; micronutrients; macronutrients; antioxidants; b vitamins) and author searches in Medline from January 1983 to June 2004.

2. Antioxidants

Brain tissue is particularly vulnerable to free-radical damage because of its low level of endogenous antioxidants [149]. Neuropathological studies documented typical lesions from exposure to free radicals in the brain of patients with AD [6,24,136,187]. Lipid peroxidation seems to be especially susceptible to oxidative stress [70,133,170]. Increasing evidence also implicates neuronal membrane associated oxidative stress (for example, consequent to deposition of amyloid β-peptide (Aβ)) and alteration of membrane lipid metabolism (and consequent accumulation of ceramides and cholesterol) as pathogenetic factors of synaptic dysfunction and neuronal degeneration [28,105]. However, carbohydrates, proteins, and nucleic acid metabolism, as well as mitochondrial function, also as a possible source of increased deposition of iron [55], are affected [10,86,179]. Many different micronutrients exert antioxidant effects and may act synergistically as free-radical scavengers [2,30,76].

Several epidemiological studies have indicated a relationship between blood concentrations of antioxidant micronutrients and cognitive impairment (Table 1). It must be noted, however, that some results are confounded by the fact that blood samples were not always drawn in fasting conditions (Table 1). Goodwin et al. [48] found a correlation between memory test scores and plasma levels of Vitamin C (and other vitamins) in 60 years and older healthy individuals. This paper introduced the concept of "subclinical" malnutrition as possible cause or effect of the decline of cognitive function in elderly individuals [48]. After this classical work, few studies investigated the relationship between cognitive function and blood concentrations of antioxidants (Table 1). The SENECA study reported a positive, although weak, correlation between plasma concentrations of lycopene, α-carotene, β-carotene, total carotenes, β-cryptoxanthin, α-tocopherol (as well as folate and cobalamin) and Mini Mental State Examination (MMSE) scores [53]. In the elderly populations studied by Ortega et al. dietary intake of Vitamin C, β-carotene, and other micronutrients [123] as well as Vitamin E [124] were associated with a better cognitive function. The Austrian Stroke Prevention Study reported a lower plasma concentration of α-tocopherol in individuals with a poor cognitive function as compared to control subjects [162]. In the multiethnic elderly sample of the Third National Health and Nutrition Examination Survey, low serum levels of Vitamin E, but not of other antioxidants, were associated with poor memory performance [128]. In this study, blood concentrations were not measured after a standard period of fast, hence these results must be considered with caution.

In turn, prospective studies investigated the effect of the intake of antioxidant vitamins on the risk of developing cognitive impairment reporting controversial results (Table 1). Perrig et al. [129] showed that higher plasma ascorbic acid and β-carotene concentrations were associated with better memory performance in older people, both cross-sectionally and longitudinally (over a 22-year period [129]). Vitamin E (from food and supplements) and Vitamin C (from supplements) protected against cognitive decline, respectively, in a 3.2 [114] and a 4-year [125] follow-up studies. On the contrary, after a 3-year follow-up, Kalmijn et al. did not find an association between intakes of antioxidant vitamins and cognitive decline [64].

The studies on dementia reported even more controversial results. In fact, there are conflicting cross-sectional data about the relationship between antioxidant vitamin intake and the risk of AD [152,154,170] (Table 2). In one of these studies, patients with AD not only had lower plasma Vitamin C concentrations (despite similar intakes) as compared to control subjects, but also their plasma concentrations of Vitamin C were correlated with cognitive function. Interestingly, in these patients, Vitamin E levels did not correlate with the degree of cognitive impairment [154]. Another cross-sectional study 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 MCI as compared to control subjects, independently of the apolipoprotein E (APOE) genotype [152].

Prospective studies (Fig. 1) also showed an association between supplementation with Vitamins C and E and a lower risk of AD [110], or between the intake of flavonoids and a lower risk of dementia [27]. At variance, in the Honolulu-Asia Aging Study, supplementation with Vitamins C and E was associated with a reduced prevalence of VaD but not AD, and was positively correlated with cognitive function in non-demented people [90]. In the same study, when incident cases of dementia were considered as the outcome variable, supplemental intake of Vitamin C or Vitamin E or both did not show any protective effect [74]. One of the limitations of this study was that no measures of cognitive function were collected at baseline, when the vitamin consumption was determined. If cognitive decline has already begun, it might have caused the subjects to stop taking vitamins. Furthermore, this study is ethnically biased, given that Japanese-American men have higher incidence rates of stroke and VaD [62,194].

Recently, a new cross-sectional and prospective population-based study found an association between supplemental use of antioxidant Vitamins (C and E) and a reduced prevalence and incidence of AD in elderly individuals; however, the use of supplements containing Vitamin C or Vitamin E alone did not show any association with AD either cross-sectionally or prospectively [197].

Other studies provided only partial evidence of a relationship between the intake of antioxidants and the risk of dementia. In the Rotterdam Study, for example, a lower intake of β-carotene, but not of Vitamins C and E, was associated with impaired

Table 1
Principal cross-sectional and prospective case-control and population-based studies on the relationship between intake of antioxidants and cognitive impairment

Study	Design	Subjects	Methods		Relevant results
			Nutritional status and nutritional intervention	Cognitive status and dementia	
Cross-sectional studies					
Goodwin [48]	Cross-sectional	$N = 260$ age ≥ 60 years	Nutrient intake: 3-day food records (FR); blood concentrations under fasting conditions	Cognitive status: Halstead-Reitan Categories Test (HRCT) and the Wechsler Memory Test (WMT)	Plasma concentrations of Vitamin C was correlated with cognitive performance [see also Table 2]
Jama [58]	Cross-sectional, population-based	$N = 5182$ age = 55–95 years	Nutrient intake:semi-quantitative food frequency questionnaire (FFQ)	Cognitive status: Mini-Mental State Examination (MMSE)	Low dietary intake of β-carotene was associated with impaired cognitive function. No association was observed between cognitive function and intake of Vitamins C or E
Haller [53]	Cross-sectional, population-based	$N = 885$ age = 74–79 years	Blood concentrations under fasting conditions	Cognitive status: MMSE and Geriatric Depression Scale (GDS)	Plasma concentrations of lycopene, carotenes, β-cryptoxanthin, α-tocopherol (as well as folate, and cobalamin) were associated with cognitive performance
Ortega [123]	Cross-sectional	$N = 260$ age = 65–90 years	Nutrient intake: 7-day weighed FR	Cognitive status: MMSE and Pfeiffer's Mental Status Questionnaire (PMSQ)	Dietary intakes of Vitamins C, E, folates, β-carotene, and minerals (zinc and iron) were associated with better cognitive function
Mendelsohn [100]	Cross-sectional, population-based	$N = 1059$ age = 74.5 years (mean)	Nutrient intake: self-report to measure current use of nutritional supplements	Cognitive status: Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological tests	No differences in cognitive performance were observed between antioxidant supplement users and nonusers
Schmidt [162]	Cross-sectional	$N = 1769$ age = 50–75 years	Blood concentrations under fasting conditions	Cognitive status: Mattis Dementia Rating Scale (MDRS)	Plasma concentrations of Vitamin E were associated with cognitive function.
Perkins [128]	Cross-sectional	$N = 4809$ age ≥ 60 years	Blood concentrations after a variable period of fasting	Cognitive status: delayed recall test	Serum concentrations of Vitamin E were associated with memory performance
Ortega [124]	Cross-sectional	$N = 120$ age = 65–91 years	Nutrient intake: 5-day weighed FR; blood concentrations under fasting conditions	Cognitive status: PMSQ	Dietary intakes and serum concentrations of Vitamin E were associated with better cognitive function
Prospective studies					
Kalmijn [64]	Prospective (follow-up = 3 years), population-based	$N = 476$ age = 69–89 years	Nutrient intake: cross-check dietary history	Cognitive status: MMSE	Intakes of β-carotene, Vitamins C, E, and flavonoids were not associated with cognitive impairment
Perrig [129]	Cross-sectional and longitudinal (22 years), population-based	$N = 442$ age ≥ 65 years	Blood concentrations under fasting conditions	Cognitive status: Priming, working-memory, free recall, recognition and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (semantic memory)	Plasma concentrations of Vitamin C or β-carotene correlated with memory performance
Paleologos [125]	Cohort (follow-up = 4 years)	$N = [42]7$ age = 69–91 years	Nutrient intake: semi-quantitative FFQ (no information on the number of items)	Cognitive status: MMSE	Vitamin C supplements protected against cognitive decline
Morris [114]	Prospective (follow-up = 3.2 years), population-based	$N = 2889$ age = 65–102 years	Nutrient intake: semi quantitative FFQ (139 items)	Cognitive status: East Boston Memory Test (EBMT); MMSE; and the Symbol Digit Modalities Test (SDMT)	Intakes of Vitamin E (from food and supplements) were associated with reduced rate of cognitive decline

CERAD, battery of 15 tests assessing performance in several cognitive domains (global mental functioning, naming, immediate and delayed learning, verbal fluency, etc.); EBMT, immediate and delayed recall; HRCT, nonverbal test of abstract thinking and problem solving; MDRS, global cognitive function; MMSE, global cognitive function; PMSQ, global cognitive function; SDMT, perceptual speed; WAIS, cognitive performance, intelligence quotient (IQ); WMT, immediate recall.

Table 2
Principal prospective case-control and population-based studies on the relationship between intake of antioxidants and dementia (Alzheimer's disease, AD and vascular dementia, VaD)

Study	Design	Subjects	Methods		Results
			Nutritional status and nutritional intervention	Cognitive status and dementia	
Cross-sectional studies					
Riviere [154]	Case-control	$N = 72$ (53 cases, 19 controls) age not reported	Nutrient intake: dietary history. Nutritional status: Mini Nuitritional Assessment (MNA), and plasma concentration of albumin. Blood concentrations (no information on fasting conditions)	Cognitive status: MMSE. Diagnosis of probable Alzheimer disease (AD): National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria	Plasma concentrations of Vitamin C (but not of Vitamin E) were lower in AD vs. controls (despite similar dietary intakes) and were inversely associated with cognitive impairment
Sinclair [170]	Case-control	$N = 83$ (25 AD, 17 VaD, and 41 controls) age = 74.3 (mean for AD), 75.5 (mean for VaD), 73.4 (mean for controls)	Nutrient intake: qualitative dietary assessment to exclude vitamin supplementation. Blood concentrations 2-h after a meal	Cognitive status: MMSE. Diagnosis of probable AD: NINCDS-ADRDA criteria. Diagnosis of probable VaD: National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et I'Enseignement en Neurosciences (NINDS-AIREN) criteria	Plasma concentrations of Vitamin C were lower in VaD (but not in AD) vs. controls. Plasma Vitamin E was lower in AD (but not in VaD) vs. controls. β-carotene was higher in VaD vs. controls (not different from controls in AD). Plasma lipid peroxides and total antioxidant capacity were not different across groups
Rinaldi [152]	Case-control	$N = 144$ (25 MCI, 63 AD, and 56 controls) age = 76 (mean for MCI), 77 (mean for AD), 76 (mean for controls)	Blood concentrations (no information on fasting conditions)	Cognitive status: MMSE and other cognitive tests. Diagnosis of probable AD: NINCDS-ADRDA criteria	Plasma levels of Vitamins C, E, A, and carotenes, as well as levels of antioxidant enzymes, were similarly lower in MCI and AD patients as compared to controls
Prospective studies					
Morris [110]	Prospective (follow-up = 4.3 years)	$N = 633$ age $\geq$ 65 years	Nutrient intake: direct inspection of vitamin supplement consumption	Diagnosis of probable AD: clinical assessment	Supplementations with Vitamin C or Vitamin E were associated with absence of AD
Commenges [7]	Prospective (follow-up = 5 years), population-based	$N = 1367$ age $\geq$ 65 years	Nutrient intake: a detailed questionnaire (no information on the number of items) and a coarse questionnaire (20 categories of foods) were used in 2 different population samples	Diagnosis of probable AD: DSM-III-R criteria and clinical assessment	Intakes of flavonoids protected against dementia
Masaki [90]	Prospective (follow-up = 3–5 years), population-based	$N = 3385$ Japanese-American men age = 71–93 years	Nutrient intake: questionnaire to assess the consumption of Vitamin E and C supplements	Cognitive status: Cognitive Abilities Screening Instrument (CASI). Diagnosis of dementia: DSM-III-R criteria Diagnosis of probable AD: NINCDS-ADRDA criteria. Diagnosis of probable VaD: California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) criteria	Supplementations with Vitamin C and E were associated with reduced prevalence of vascular dementia. Use of either Vitamin C or E supplements was associated with better cognitive function among non-demented subjects
Engelhart [35]	Prospective (follow-up = 6 years), population-based	$N = 5395$ age = 55–95 years	Nutrient intake: semi-quantitative FFQ (100 items)	Diagnosis of probable AD: DSM-III-R and NINCDS-ADRDA criteria	High dietary intakes of Vitamin C and Vitamin E were associated with lower risk of AD. Among current smokers, this relationship was most pronounced and also was present for intake of β-carotene. The associations did not vary by education or apolipoprotein E (APOE) genotype
Morris [112]	Prospective (follow-up = 3.9 years), population-based	$N = 815$ age $\geq$ 65 years	Nutrient intake: semi quantitative FFQ (139 items)	Diagnosis of probable AD NINCDS-ADRDA criteria	Dietary intakes of Vitamin E protected against AD, only among individuals without the APOE ε4 allele
Luchsinger [82]	Prospective (follow-up = 4 years), population-based	$N = 980$ age $\geq$ 65 years	Nutrient intake: semi-quantitative FFQ (61 items)	Diagnosis of dementia: DSM-IV criteria. Diagnosis of probable AD: NINCDS-ADRDA criteria	Intakes (from food or supplements) of Vitamin E, or carotenoids were not associated with risk of AD
Zandi [197]	Cross-sectional and prospective (follow-up = 3 years)	$N = 4740$ age $\geq$ 65 years	Nutrient intake: interview to assess consumption of Vitamins E and/or C (vitamin users were defined as subjects taking more than 400 IU of Vitamin E or more than 500 mg of Vitamin C)	Diagnosis of probable AD: NINCDS-ADRDA criteria	Use of both Vitamins E and C supplements was associated with reduced prevalence and incidence of AD

CASI, global cognitive function; MNA, comprehensive evaluation of the nutritional status, including anthropometric measures, a dietary questionnaire, and a global assessment.

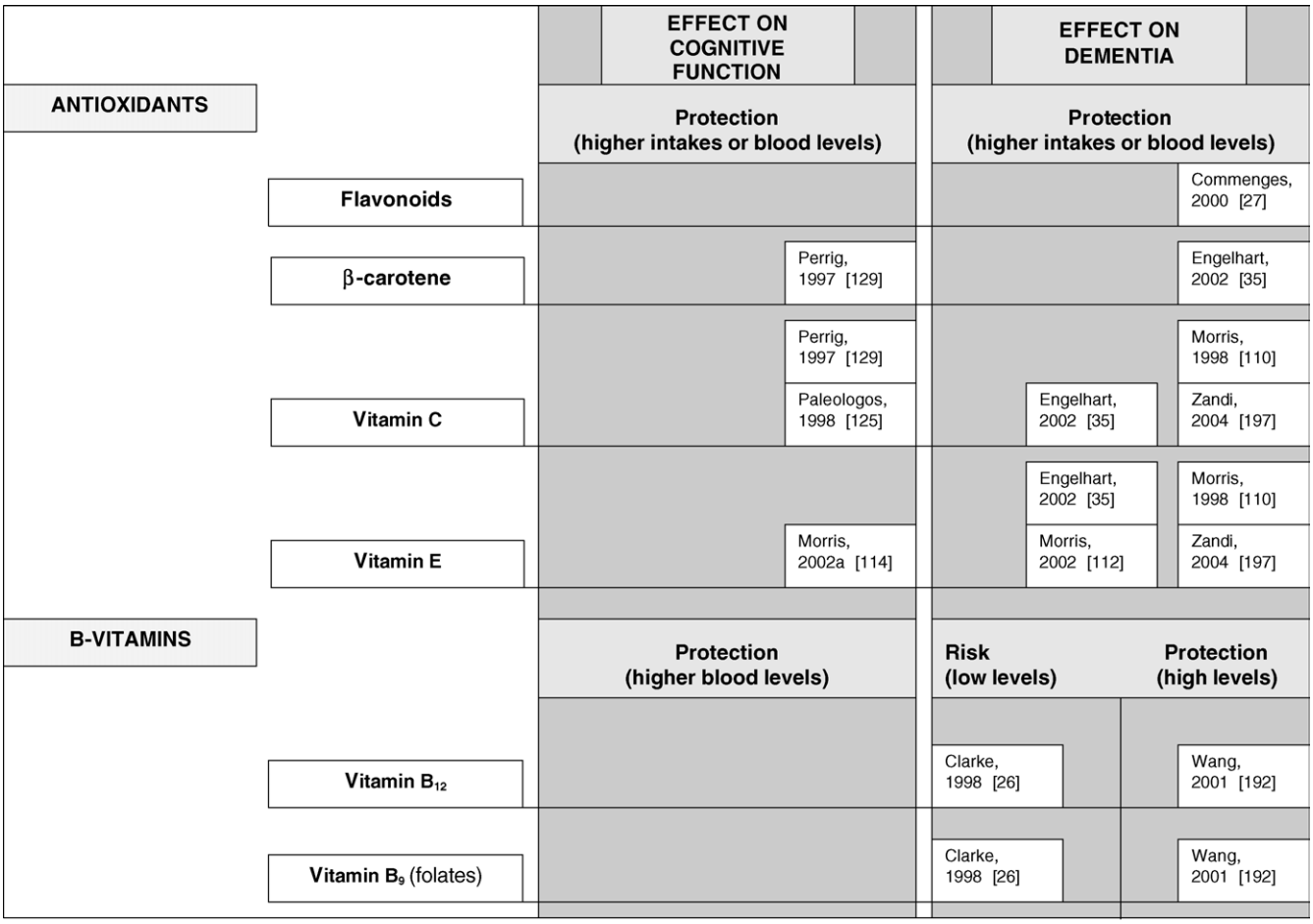

Fig. 1. Synopsis of the evidence from prospective population-based studies on the possible effects of antioxidants and B vitamins on cognitive function and dementia in the elderly.

cognitive function [58]. However, in the same study, higher dietary intakes of Vitamin C and E were associated with a lower risk of AD, independently of the APOE genotype [35]. The Chicago Health and Aging Project (CHAP) reported an association between a higher dietary intake of Vitamin E and a lower risk of AD, but no association with total (dietary and supplemental) Vitamin E or Vitamin C intake. Furthermore, the association with Vitamin E intake was limited to individuals not carrying the APOE $\varepsilon 4$ allele [112]. Therefore, these two studies found an inverse relationship between Vitamin E intake from food, but not from supplements, and risk of AD. It must be noted, however, that the absence of a protective effect from consumption of supplements containing Vitamin E is based on a limited number of subjects and no data on duration and frequency of use of supplements were available [112].

There are negative reports as well. In a cohort of 69–89-year-old men of the Zutphen Elderly Study, intakes of β-carotene, Vitamins C and E, and flavonoids were not associated with cognitive impairment or decline [64]. Furthermore, in the Monongahela Valley Independent Elders Survey, a population-based cross-sectional study conducted on 1059 rural, non-institutionalized elderly residents, after adjustment for age, education, and sex, there were no significant differences in cognitive test performance between antioxidant supplement users and nonusers [100]. Similarly, in 980 elderly individuals of the Washington Heights-Inwood Columbia Aging Project (WHICAP) intakes of carotenes and Vitamins C or E were not associated with a decreased risk of AD over the course of 4 years [82]. It must be noted that in this study vitamin intakes were assessed by using a 61-item food frequency questionnaire (FFQ), which may be less accurate in assessing nutrient intakes than a more articulated FFQ, such as the one used in the CHAP (131 items). This, in turn, may explain, at least in part, the inconsistency between the outcomes of these studies.

Anyway, the most convincing evidence that the intake of antioxidant molecules has an impact on cognitive function is provided by intervention studies. In fact, it has been documented that rats given dietary supplements of fruit and vegetable extracts for 8 months, beginning at 6 months of age, slowed age-related declines in neuronal and cognitive functions [61]. More importantly, these rats were able to reverse age-related deficits in several neuronal and behavioral parameters when the administration was started at 19 months of age [60]. Furthermore, recent studies have suggested that garlic extract (rich in flavonoids such as diallyl sulfide and allyl methyl trisulfide) can prevent brain atrophy [108], as well as learning and memory impairments [122] in the senescence-accelerated mouse. In humans, a 1-year randomized, double-blind, placebo controlled interven-

tion study reported that supplementation with antioxidants and B vitamins enhanced cognitive function (except for long-term memory recall) in elderly individuals. However, no significant correlations were observed between circulating concentrations of single micronutrients and cognitive performance [23].

In fact, among the antioxidants it has been difficult to determine which are the most effective, because indices of activity are not measurable in a standardized and reliable fashion [20]. It is also possible that it is the interaction of antioxidants, especially flavonoids with other chemicals present in fruits and vegetables that is the actual determining factor of these beneficial effects. Finally, the sites and mode of action of vitamins and phytonutrients in the brain can be molecule-specific. Much research work is needed in this field. In the brain of Fischer rats it has been documented that the frontal cortex and thalamus have the highest concentration of Vitamin E [188], while Martin et al. measured a larger increase of Vitamin E in the cortex and hippocampus than in the striatum and cerebellum of 6-month-old male Fischer rats exposed for 8 months to a Vitamin E enriched diet as compared to controls [88]. Furthermore, diets enriched with Vitamin E or with extracts of strawberry or spinach (rich in flavonoids and Vitamin C) were associated with enhanced dopamine release from striatal slices as compared to control diets [88].

The link between oxidative stress, especially its long-term effects, and cognitive impairment may be a direct result of selective neuronal damage as well as the indirect result of atherogenic factors. In fact, antioxidants such as β-carotene [58], Vitamin C [46], and Vitamin E [161] have been shown to be protective factors against both atherosclerosis and dementia.

In addition to a pure antioxidant activity, some vitamins and phytonutrients have other protective effects for the molecular integrity of tissues. It is known, for example, that flavonoids can increase membrane fluidity [52,139,178], antagonize arachidonic acid transport [71], suppress the 5-lipoxygenase pathway [106], and subsequently reduce inflammatory responses. Recent evidence also indicates that Vitamin E may have structure-specific roles, by modulating signal transduction pathways [4,87,101], and participating in the synthesis pathways of neurotransmitters.

3. B vitamins

Deficiencies of several B vitamins, including thiamine (B_1), riboflavin (B_2), niacin (B_3), pyridoxine (B_6), folate (B_9), and cobaiamin (B_{12}), have been associated with cognitive function in many observational studies [29,150] (Table 3). In some cases, pathophysiological models have been formulated, including the association of B vitamin deficiencies with metabolic disturbances in the structural constituents of cerebral tissue, such as phospholipids and myelin, as well as in signaling molecules, such as neurotransmitters [140]. In particular, thiamine deficiency has been associated with lactic acid accumulation, reduction in oxygen uptake, decrease in transketolase activity, and an impairment in cholinergic activity, leading to the loss of memory and other cognitive functions [102]. Based on this, high doses of thiamine have been considered as an alternative treatment to cholinesterase inhibitors in the treatment of AD [99], although a study showed that supplementation with thiamine enhanced mood and shortened reaction times, but did not improve memory performance [9]. In other cases, suggestive biological findings were provided showing an inverse relationship between serum folate concentrations and neocortical atrophy as observed in individuals affected by AD participating in the Nun Study [172].

More recently, the association between the deficiency of B vitamins, particularly folate and cobalamin, and cognitive impairment has been investigated in relation to hyperhomocysteinemia. Homocysteine is an aminoacid entirely derived from the body's intermediary metabolism [39,132], which can be converted to either methionine or cysteine. Both folate and cobalamin participate in the methylation of homocysteine to methionine and in the remethylation and synthesis of *S*-adenosylmethionine [16,127]. The other metabolic pathway, which converts homocysteine to cysteine requires the active form (pyridoxal phosphate) of Vitamin B_6 [132] (Fig. 2).

The most common cause of hyperhomocysteinemia is considered to be a deficiency of folate or cobalamin [163]. In fact, although the catabolic rate of homocysteine results from the interaction between genetic make-up and B vitamin status, it is generally accepted that elevated plasma homocysteine concentrations are a sensitive marker for folate and cobalamin tissue deficiency [16,38,59,79,92,120,121,127]. It has been shown that plasma homocysteine is a better correlate of cognitive function than the serum folate or cobalamin concentrations themselves [79], thus indicating a model for the relationship

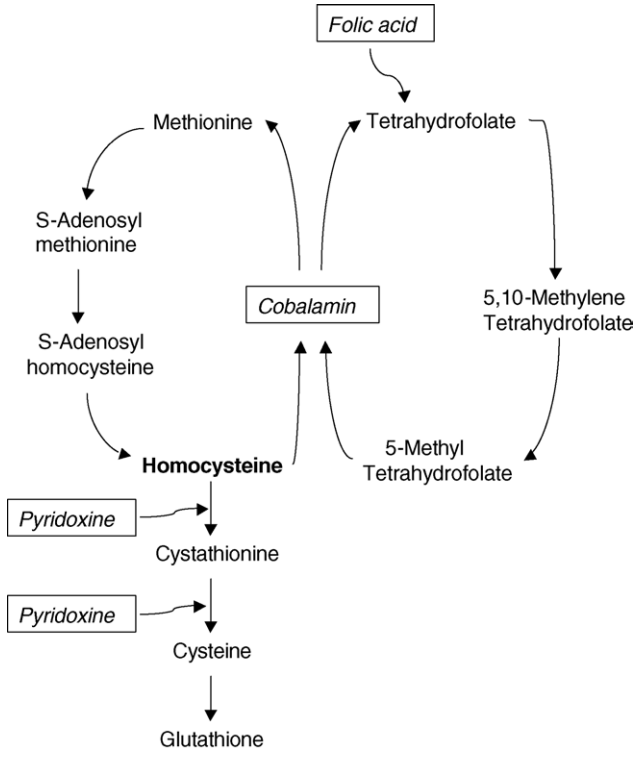

Fig. 2. Homocysteine metabolism. Homocysteine is catabolized through two pathways: (1) the conversion to methionine, catalyzed by the methionine synthase, which requires cobalamin, by accepting a methyl group from 5-methyl tetrahydrofolate; (2) the conversion to cystathionine, catalyzed by the cystathionine b-synthase, which requires pyridoxine.

Table 3
Principal cross-sectional and prospective case-control and population-based studies on the relationship between Vitamin B status and cognitive functions in older people

Reference	Design	Subjects	Methods		Results
			Nutritional status and nutritional intervention	Cognitive status and dementia	
Cross-sectional studies					
Goodwin [48]	Cross-sectional	$N = 260$ age ≥ 60 years	Nutrient intake: 3-day FR; blood concentrations under fasting conditions	Cognitive status: HRCT and WMT	Plasma concentrations of Vitamin B_{12} was positively associated with cognitive performance; plasma concentration of riboflavin and folic acid were positively associated with abstraction test scores
Tucker [183]	Cross-sectional	$N = 28$ age ≥ 60 years	Nutrient intake: dietary history, and 7-day FR; blood concentrations (no information about fasting conditions)	Brain activity: electroencephalography (EEG) performed while cognitive function (neuropsychological tests) and blood concentrations were measured	Circulating levels of thiamine and riboflavin were associated with cognitive performance and with increments in alpha-wave activity at the EEG
Riggs [151]	Cross-sectional, population-based	$N = 70$ age = 54–81 years	Blood concentrations (no information on fasting conditions)	Cognitive status: battery of cognitive tests	High circulating levels of homocysteine and low circulating levels of folates and Vitamin B_{12} were associated with low cognitive performance; circulating levels of pyridoxine were positively associated with memory performance
Ortega [123]	Cross-sectional	$N = 260$ age = 65–90 years	Nutrient intake: 7-day weighed FR	Cognitive status: Mini-Mental State Examination (MMSE) and Pfeiffer's Mental Status Questionnaire (PMSQ)	Dietary intakes of Vitamins C, E, folates, β-carotene, and minerals (zinc and iron) were associated with better cognitive function
Morris [115]	Cross-sectional, population-based	$N = 1200$ age ≥ 60 years	Blood concentrations after a variable period of fasting	Cognitive status: MMSE; short recall and paragraph delayed-recall test	Serum homocysteine concentrations above the 80th percentile of the population distribution were associated with poorer memory performance
Ventura [189]	Cross-sectional	$N = 600$ age = 65–102	Blood concentrations under fasting conditions	Diagnosis of dementia (International Classification of Diseases-9^{th} revision-Clinical Modification, ICD-9-CM)	Hyperhomocysteinemia was more prevalent in demented than in normal subjects
Duthie [34]	Cross-sectional, population-based	$N = 331$ age = 63–79 years	Blood concentrations under fasting conditions	Cognitive status: MMSE, the National Adult Reading Test (NART), Raven's Progressive Matrices (RPM), the Auditory Verbal Learning Test (AVLT), and the digit symbol substitution (DST) and block design (BDT) tests from the WAIS-R	Circulating B vitamins and homocysteine were associated (positively and negatively, respectively) with cognitive performance
Prins [137]	Cross-sectional Population-based	$N = 1077$ age = 60–90 years	Blood concentrations under non-fasting conditions	Cognitive status: MMSE, the Geriatric Mental Schedule (GMS), abbreviated Stroop Test (ST), Letter-Digit Substitution Task (LDST), a verbal fluency test, a Paper-and-Pencil Memory Scanning Task (PPMST), and a 15-word verbal learning test to assess immediate and delayed recall	Hyperhomocysteinemia was associated with decreased cognitive performance, particularly psychomotor speed, in non-demented elderly individuals.
Miller [104]	Cross-sectional	$N = 1789$ age ≥ 65 years	Blood concentrations under fasting conditions	Cognitive status: modified MMSE, tests of delayed recall, object naming, picture association, verbal conceptual thinking, verbal attention span, and pattern recognition	Plasma homocysteine concentrations, independently of folate and Vitamin B_{12}, were associated with worse cognitive performance
Ravaglia [143]	Cross-sectional, population-based	$N = 650$ age ≥ 65 years	Blood concentrations under fasting conditions	Cognitive status: MMSE	Circulating levels of homocysteine were inversely associated with cognitive function, independent of B vitamins
Prospective studies					
Kalmijn [65]	Prospective (follow-up = 2.7 years)	$N = 702$ age = 55 years	Blood concentrations under non-fasting conditions	Cognitive status: MMSE	Circulating homocysteine levels were not associated with prospective cognitive impairment or cognitive decline
McCaddon [93]	Prospective (follow-up = 5 years)	$N = 32$ age ≥ 80 years	Blood concentrations under fasting conditions	Cognitive status: MMSE and the cognitive component of the Alzheimer's Disease Assessment Scale (ADAS-Cog)	Circulating homocysteine predicted cognitive performance at follow-up and rate of cognitive decline, independently of demographics, smoking, hypertension, and B vitamin status
Dufouil [33]	Prospective (follow-up = 4 years), population-based	$N = 1241$ age = 61–73 years	Blood concentrations under fasting conditions	Cognitive status: MMSE; Trail Making Test part B (TMT-B) and the Digit Symbol Substitution Test (DST) of the WAIS-R; Finger Tapping Test (FTT)	Circulating levels of homocysteine were inversely associated with cognitive performance

ADAS-Cog, several cognitive domains; AVLT, verbal learning and memory; BDT and DST, speed of information processing and visuo-spatial organization, respectively; FTT, psychomotor speed; GMS, mental state in the elderly; LDST, speed of information processing; NART, preservation of verbal abilities; PPMST, attention; RPM, non-verbal intelligence; ST, selective attention; TMT-B, attentive capabilities.

between subclinical vitamin deficiency and cognitive function [79,159].

Homocysteine is a well-established risk factor for vascular disease [145,184], but several epidemiological studies have also suggested that it may play a role in the cognitive performance [137] and pathophysiology of dementia in older people [7,26,120,190], possibly as the metabolic link between microvascular disease and old-age dementia [115,127]. It has also been proposed that hyperhomocysteinemia is one of the effects of the oxidation of Vitamin B_{12}, as a result of oxidative stress [95]. Experimental studies in cell cultures have shown that homocysteine is neurotoxic, possibly by activating *N*-methyl-D-aspartate (NMDA) receptors [78] or DNA damage and consequent apoptosis [72]. Furthermore, studies in mouse models of AD suggest that a diet deficient in folic acid as well as age-related accumulation of Aβ impair the ability of hippocampal neurons to repair DNA damage increasing the cell death rate [73] (for a review [91,167]).

Epidemiological evidence of an involvement of homocysteine in cognitive decline was initially provided by cross-sectional population-based studies of community-dwelling older adults, reporting an inverse association between total plasma homocysteine levels and cognitive function (Table 3) [7,77,151]. Case-control studies also reported higher plasma homocysteine levels in persons with AD [26,92,98] (Table 4). Other studies were published either providing [19,33,34,75,93,104,115,142,192], or denying [65,143,144] further support to this association (Tables 3 and 4).

Interestingly, in AD patients circulating homocysteine has been associated with atrophy of the medial temporal lobe and its rate of atrophy over time [26]. Furthermore, in 1077 non-demented subjects 60–90 years old, participating in the Rotterdam Scan Study, circulating homocysteine was associated with cortical and hippocampal atrophy [31], although the association with cognitive performance was independent of these structural brain changes [137]. Also, cerebral white matter changes (leukoaraiosis) in AD patients have been associated with circulating homocysteine levels [54]. Taken together these studies support the hypothesis of a direct pathogenetic role of homocysteine in AD that, anyway, is still controversial [15,103].

Recently a prospective study in the elderly, population-based cohort of the Framingham Study reported an association between the plasma levels of homocysteine and an increased risk of developing dementia over the next 8 years of follow-up [166]. In this study, a 5-μmol increment in the plasma homocysteine concentration increased the risk of AD by 40 percent. This relationship was independent of other risk factors of dementia, including age, APOE genotype, and B vitamin blood levels. Another evidence of a relationship between circulating B vitamins or homocysteine concentrations and cognitive performance was reported in a Scottish cohort study [34] and in a Swedish population-based prospective study [192].

It has been proven that folate supplementation reduces plasma homocysteine levels: this was observed by Jacques et al. in the Framingham Offspring Study cohort, after the folate fortification of grain products in the United States started in January 1998 [57], and by Naurath et al. in elderly people, after supplementation with pyridoxine, folate, and cobalamin [117]. Nevertheless, the relationship between dietary folic acid intakes and plasma homocysteine concentrations seems to be characterized by a threshold effect [164]: above a certain dosage of folate supplementation there is no additional effect on lowering circulating homocysteine. It is not clear where this threshold stands: a metanalysis of 12 randomized controlled trials assessed that the minimum dosage of folate capable of determining a maximum reduction (about 25%) of circulating homocysteine was 0.5 mg/day. More recent randomized trials determined this threshold at 0.8 mg/day [191] or 0.4 mg/day [186]: the differences are possibly explained by population selection biases [186]. Furthermore, supplementation with folic acid and Vitamin B_{12} showed that the latter may be the main determinant of plasma homocysteine concentration [138].

Whether dietary supplements of folic acid can improve the cognitive function of people at risk of cognitive decline associated with aging or dementia is subject of investigation. A recent review of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group found no evidence of benefit from folic acid with or without Vitamin B_{12} in comparison with placebo on any measures of cognition and mood for healthy or cognitively impaired or demented people [83].

4. Macronutrients

Although the intake of macronutrients is easier to quantify and has a more visible impact on the nutritional status of an individual, few studies have evaluated the relationship between macronutrients and cognitive function (Table 5). The availability and utilization of glucose, which is the primary substrate of neuronal metabolism, have been implicated in cognitive function not only as a result of nutritional and systemic metabolic conditions, but also, although speculatively, as a crucial phase of the mechanism of action of molecules used as cognitive-enhancers [126,193]. In fact, Kaplan et al. [67] firstly showed that cognitive performance is associated with glucose homeostasis in the elderly before the onset of an impaired glucose tolerance and also that common carbohydrate-containing foods can improve cognition. Importantly, the cognitive-enhancing effects of these foods were independent of their glycemic index (i.e., the increase in plasma glucose after food consumption). High glycemic response, poor β-cell function, normal insulin sensitivity, and low body mass index were associated with poor baseline short- and long-term verbal declarative memory and visuo-motor performance in cognitively intact elderly subjects with normal fasting plasma glucose. The consumption of 50 grams of carbohydrates as a glucose drink, mashed potatoes, or barley improved verbal declarative memory in individuals with poor baseline memory or poor β-cell function and improved performance on a visuo-motor task in those with poor β-cell function as well. Furthermore, Kaplan et al. [67], in a clinical trial involving 22 individuals age 61–79, observed that intakes of protein, carbohydrate, or fat enhanced memory independently of elevations in plasma glucose.

Finally, different aspects of glucose metabolism were implicated in the pathogenesis of AD, including impaired enzy-

Table 4
Principal cross-sectional and prospective case-control and population-based studies on the relationship between Vitamin B status and dementia (Alzheimer's disease, AD and vascular dementia, VaD)

Reference	Design	Subjects	Methods		Results
			Nutritional status and nutritional intervention	Cognitive status and dementia	
Cross-sectional studies					
McCaddon [92]	Prospective Case-control	$N = 60$ age ≥ 65 years	Blood concentrations under fasting conditions	Cognitive status: MMSE and the Cambridge Mental Disorders of the Elderly Examination (CAMDEX). Diagnosis of probable AD: DSM-III-R criteria	AD patients had a higher circulating homocysteine concentration compared with controls. No differences were observed in circulating cobalamin and folate, or in nutritional status as assessed by the circulating retinol binding protein
McIlroy [98]	Case-control	$N = 232$ age = 77.2, 77.3, 74.3 years (means in AD, VaD, and controls, respectively)	Min Nutritional Assessment (MNA); blood concentrations under fasting conditions	Diagnosis of probable AD: DMS-IV and NINCDS-DRDA criteria. Diagnosis of probable VaD: NINDS-AIREN criteria	Circulating homocysteine was higher and circulating folate and pyridoxal phosphate was lower in AD and VaD as compared to controls
Miller [103]	Case-control	$N = 80$ age ≥ 80 years	Blood concentrations (no information available about fasting conditions); diagnosis of vascular disease by reviewing both medical history and brain imaging (CT or MRI) data	Diagnosis of AD: NINCDS-ADRDA criteria	High circulating homocysteine was associated with vascular disease, not AD. Low circulating pyridoxal-5-phosphate was prevalent in AD patients
Selley [165]	Case-control	$N = 52$ age = 65–93 years	Blood and cerebrospinal fluid (CSF) concentrations (no information on fasting conditions)	Diagnosis of probable AD: DSM-IV and NINCDS-ADRDA criteria	Blood and CSF concentrations of homocysteine and (E)-4-hydroxy-2-nonenal (HNE, a neurotoxic product of lipid peroxidation) were higher in AD than in controls. Positive correlation was observed between plasma concentration of homocysteine and CSF concentration of homocysteine and HNE
McCaddon [94]	Case-control	$N = 107$ age = 79 years (median)	Blood concentrations under non-fasting conditions	Cognitive status: MMSE and ADAS-Cog. Diagnosis of probable AD: DSM-IV criteria.	Circulating homocysteine was higher and folate was lower in AD compared to controls
Prospective studies					
Clarke [26]	Prospective (follow-up = 3 years)	$N = 273$ age ≥ 55 years	Blood concentrations under non-fasting conditions	Cognitive status: MMSE and CAMDEX. Thickness of the medial temporal lobe: CT-scans. Diagnosis of probable AD: NINCDS-ADRDA criteria; in a sub-sample: histological confirmation of AD: Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria	High circulating levels of homocysteine, as well as low levels of folate and Vitamin B_{12} were associated with AD; after a 3-year follow-up, baseline homocysteine levels were predictive of "radiological" progression of the AD
Wang [192]	Prospective (follow-up = 3 years), population-based	$N = 370$ age ≥ 75 years	Blood concentrations (no information on fasting conditions)	Diagnosis of dementia and probable AD: DSM-III-R criteria. Diagnosis of probable VaD: DSM-III-R criteria and Hachinski scale	Circulating levels of both folate and Vitamin B_{12} were protective towards AD
Seshadri [166]	Prospective (follow-up = 8 years), population-based	$N =$ [42]92 age = 68–97 years	Blood concentrations (under non-fasting conditions)	Diagnosis of dementia: DSM-IV criteria. Diagnosis of probable AD: NINCDS-ADRDA criteria	Plasma homocysteine levels are a strong, independent risk factor for the development of dementia

CAMDEX, comprehensive assessment of present cognitive status, past history and family history.

Table 5
Principal cross-sectional and prospective population-based studies on the relationships between dietary macronutrients and cognitive functions in older people

Reference	Design	Subjects	Methods		Results
			Nutritional status and nutritional intervention	Cognitive status and dementia	
Cross-sectional studies					
Pradignac [135]	Cross-sectional, population-based	$N = 441$ age ≥ 65 years	Nutrient intake: 3-day FR	Cognitive status: MMSE. Functional status: Geronte scale	In men, alcohol intake was associated with improved functional and cognitive parameters, while polyunsaturated fatty acid intake only with functional status. In women, lipid intake was correlated with a better cognitive performance. Overweight in both sexes was associated with an improvement in functional status
Ortega [123]	Cross-sectional, population-based	$N = 260$ age = 65–90 years	Nutrient intake: 7-day weighed FR	Cognitive status: MMSE and Pfeiffer's Mental Status Questionnaire (PMSQ)	Low intake of in fatty acids, and cholesterol, but rich in carbohydrates, fibers, and vitamins were associated with better cognitive function
Solfrizzi [176]	Cross-sectional, population-based	$N = 278$ age = 65–94 years	Nutrient intake: semi-quantitative FFQ (77 items)	Cognitive status: MMSE, Digit Cancellation Test (DCT), Babcock Recall Story Test (BRST)	Monounsaturated fatty acid intake was inversely correlated with cognitive decline.
Kalmijn [66]	Cross-sectional, population-based	$N = 1613$ age = 45–70 years	Nutrient intake: semi-quantitative FFQ (178 items)	Cognitive status: Visual Verbal Learning Test (VVLT), Concept Shifting Task (CST), Letter Digit Substitution Test (LDST), abbreviated Stroop Color Word Test (SCWT) and Category Fluency Test (CFT)	Marine n-3 PUFA consumption was associated with a decreased, whereas saturated fatty acid and cholesterol intakes were associated with an increased risk of impaired cognitive function
Prospective studies					
Kalmijn [64]	Prospective (follow-up = 3 years), population-based	$N = 476$ age = 69–89 years	Nutrient intake: cross-check dietary history	Cognitive status: MMSE	High linoleic acid intake was associated with cognitive impairment, whereas high fish consumption was protective [see also Table 1]

BSRT, episodic memory; CFT, semantic memory; CST, executive functions; DCT, selective attention; SCWT, selective attention; VVLT, visuo-verbal memory.

Table 6
Principal prospective population-based studies on the relationships between dietary macronutrients and dementia (Alzheimer's disease, AD and vascular dementia, VaD) (no cross-sectional studies explored this association)

Reference	Design	Subjects	Methods		Results
			Nutritional status and nutritional intervention	Cognitive status and dementia	
Barbeger-Gateau [5]	Prospective (follow-up = 7 years), population-based	$N = 1674$ age ≥ 68 years	Nutrient intake: FFQ (no information on the number of items)	Cognitive status: MMSE. Diagnosis of dementia and probable AD: DSM-III-R criteria	Fish or seafood consumption was associated with a lower risk of dementia
Engelhart [35]	Prospective (follow-up = 6 years), population-based	$N = 5395$ age ≥ 55 years	Nutrient intake: semi-quantitative FFQ (100 items)	Cognitive status: MMSE, GMS, CAMDEX. Diagnosis of dementia: DSM-III-R criteria. Diagnosis of probable AD: NINCDS-ADRDA criteria	High intakes of total fat, saturated fatty acids, *trans*-fatty acids, and cholesterol or low intakes of unsaturated fatty acids were not associated with an increased risk of dementia
Luchsinger [81]	Prospective (follow-up = 4 years), population-based	$N = 980$ age = 75 years (mean)	Nutrient intake: semi-quantitative FFQ (61 Items)	Diagnosis of dementia: DSM-IV criteria. Diagnosis of probable AD: NINCDS-ADRDA criteria	Higher energy and fat intakes were associated with higher risk of AD in individuals carrying the APOE ε4 allele
Morris [111]	Prospective (follow-up = 3.9 years), population-based	$N = 815$ age ≥ 65 years	Nutrient intake: semi-quantitative FFQ (154 items)	Diagnosis of probable AD: NINCDS-ADRDA criteria	Dietary intakes of saturated fat and *trans*-unsaturated were predictive of AD, while dietary intakes of n-6 PUFA and MUFA were protective against AD
Morris [113]	Prospective (follow-up = 3.9 years), population-based	$N = 815$ age ≥ 65 years	Nutrient intake: semi-quantitative FFQ (154 items)	Diagnosis of probable AD: NINCDS-ADRDA criteria	Dietary intake of n-3 PUFA protected against AD

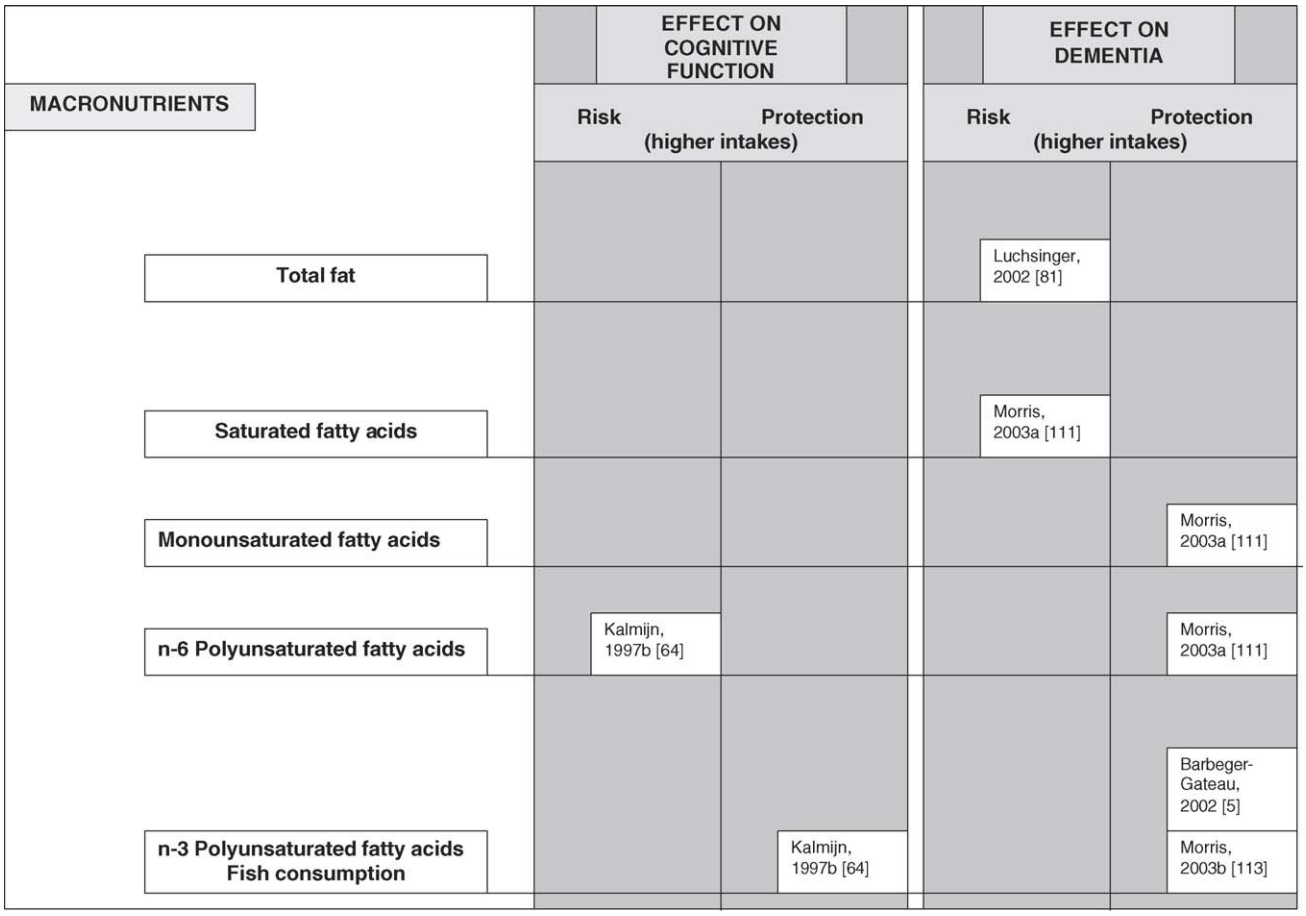

Fig. 3. Synopsis of the evidence from prospective population-based studies on the possible effects of macronutrients on cognitive function and dementia in the elderly.

matic activity in glucose catabolic pathways [21,168], impaired glucose transport [63,85,185], and impaired insulin activity [41,89,196].

It has also been reported that, in women, a chronic exposure to an excess of energy intake and the resulting obesity protect them from cognitive decline [135]. This epidemiological observation has been explained as a result of a greater availability of estrogens in obese women, given that the adipose tissue is the major endogenous source of estrogens in post-menopausal women [12]. A randomized, placebo-controlled trial has established that the administration of estrogens is associated with an improvement in cognitive function [11], possibly dependent on the intrinsic antioxidant activity of the hormone [13,76].

On the other hand, consistent with the evidence in animals (reviewed in [91]), high energy intakes in middle age and the resulting increase in body weight, have been associated with a loss of cognitive function in old age [44,49]. Actually, energy intake seems to be a stronger predictor of AD than body weight or body mass index (BMI). In fact, a prospective study of the association between dietary intakes and risk of AD in New York City pointed out that a low-calorie diet was protective against AD and that body weight or BMI were secondary correlates of the risk of AD [81]. In the Rotterdam Study, after a 6-year follow-up, a high intake of total fat, saturated fatty acids, *trans*-fatty acids, cholesterol and a low intake of unsaturated fatty acids were not associated with an increased risk of dementia or its subtypes [36]. These results are at odds with several other studies [5,64,66,82,111,113,176] (Table 6, Fig. 3).

In particular, in a cohort of 69–89-year-old men of the Zutphen Elderly Study, high linoleic acid intake was associated with cognitive impairment. The intake of n-3 polyunsaturated fatty acids (PUFA) was not associated with cognitive impairment, but high fish consumption tended to be inversely associated with cognitive impairment and cognitive decline [64]. In a prospective study of younger people (45–70-year-old) marine n-3 PUFA consumption was associated with a decreased risk, whereas saturated fatty acid and cholesterol intakes were associated with an increased risk of impaired cognitive function [66].

In the Italian Longitudinal Study of Aging our group reported that the intake of monounsaturated fatty acids (MUFA, mostly provided by consumption of olive oil) in an elderly population of Southern Italy was associated with a reduced risk of global cognitive decline and of selective attention performances [176]. Furthermore, we found an important interaction between intake of MUFA and the level of education: the relative risk of developing a cognitive impairment in people with a low educational level decreased exponentially with the increase in MUFA intake [175,176].

Intriguing results were found in the cohort of the Honolulu-Asia Aging Study, with the western diet showing protection

against the development of VaD in comparison with a traditional Japanese diet [160]. A typical Western diet is high in animal fat and protein and low in complex carbohydrates, compared to the traditional Japanese diet, which is high in complex carbohydrates and marine n-3 PUFA, and low in meat.

Therefore, although traditional vascular risk factors such as a high intake of calories, saturated fatty acids, or cholesterol have been involved in the development of AD-like neuropathology in animals [177] and are increasingly considered in association to both VaD and AD [51], the epidemiological evidence is still controversial, possibly because of confounding variables.

An interesting line of research has also pointed out that the quality of dietary proteins, in terms of the aminoacidic composition, may play a role in the risk of developing AD. In fact, reduced plasma concentrations of the aminoacids tryptophan and methionine have been reported in AD patients as compared to control subjects [39] and, interestingly, an increased ratio between the plasma concentrations of tyrosine and of large neutral aminoacids has been observed in AD patients as compared to control subjects [39]. Furthermore, Ravaglia et al. reported an increased ratio between fasting plasma phenylalanine and large neutral aminoacids (LNAA) in individuals with MCI or dementia [141], and Fekkes et al. reported an increased ratio between the fasting plasma concentrations of tyrosine and LNAA in AD patients [39]. These ratios are of special interest because they regulate the competitive transport of phenylalanine and tyrosine across the blood-brain barrier and the consequent availability of substrates for the norepinephrine/dopamine synthesis [40].

Intriguingly, acute tryptophan depletion has been associated with impaired cognitive function, including proofreading, focused attention, decision making, learning and long-term memory consolidation [150]. Furthermore, Rogers et al. observed similarities between the cognitive deficits induced in healthy individuals by tryptophan depletion and the cognitive deficits associated with chronic use of amphetamine [155]. In addition, a positron emission tomography study reported a decrease of neural activity in the anterior cingulate and orbitofrontal cortex in response to acute tryptophan depletion in recovered depressive patients [171].

Finally, other alterations of the normal aminoacidic ratios have been observed in AD patients, including an increased ratio between the plasma concentration of taurine and the plasma concentration of methionine and serine (the so-called TSM-ratio) [39], which reflects the availability of metabolites for transmethylation processes [40]. However, the pathophysiological importance of these relative aminoacidic deficits to the development of AD remains to be determined.

5. Conclusions

Nutrition plays an important role in cognitive function, but a thorough exploration of the nutrition-related risk factors of cognitive impairment is still lacking. It is plausible that severe or even moderate malnutrition increases the risk of dementia and AD in susceptible people. Nevertheless, an optimal intake of nutrients is not sufficient to protect susceptible individuals from developing the disease.

A large body of evidence indicates that sub-clinical deficiencies in essential micro-nutrients, such as antioxidants (Vitamins C, E, carotenes, etc.) and B vitamins are risk factors for cognitive impairment and dementia, but it is still uncertain whether a critical threshold in the degree of deficiency and in the duration of exposure can be reliably determined and translated into general recommendations for the population. Organizational challenges, including sample size and duration of the follow-up, hamper the accomplishment of this important goal in public health.

Randomized, double-blind, placebo-controlled trials are needed to assess the potential impact of micro-and macro-nutrient supplementation and/or dietary manipulations on the risk of developing cognitive impairment or dementia. On the other hand, results from intervention trials need to be considered in light of population-based longitudinal studies, because short-term exposure to a dietary or supplemental intake of nutrients is likely to have a different impact from long standing dietary habits on the risk of developing cognitive impairment.

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