Chapter 6
Rationale for a Combination of Selected Micronutrients to Improve Cognition and Prevent or Slow Down Age-Related Cognitive Impairment

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Abstract This chapter deals with the question as to whether micronutrients contribute to the maintenance of cognitive function during the aging process. The onset of mild cognitive impairment (MCI) and at least the development of dementia are insidious, and occur years before the loss of cognition becomes apparent. Besides a couple of factors, including genetics and lifestyle, nutrition is claimed as an important factor which interacts with basic pathologies of cognitive decline. In particular, micronutrients (vitamins, trace elements and minerals) can mitigate the risk of cognitive decline, especially in elderly people at risk of deficiencies. Based on epidemiological findings and existing scientific evidence, two major groups of micronutrients will be discussed: homocysteine-lowering vitamins and antioxidants. Cognitive decline, with its early clinical diagnosis mild cognitive impairment (MCI), becomes evident in the age group >60 years. The quality of diet determines survival and health status in free-living elderly people within a European population. High plasma levels of ß-carotene (as a marker for vegetable intake) and α-tocopherol (as a marker for edible plant oils) are especially associated with lower mortality in the elderly (Buijsse et al. 2005). Epidemiological studies demonstrate that with increasing age, the prevalence of nutritional deficiencies increases, in particular deficiencies of antioxidants (ß-carotene, vitamins C, E and selenium and zinc) and B-vitamins (folic acid, B_6, B_{12}). Deficiencies of micronutrients however, may contribute to, or even promote, cognitive impairment. Consequently it is suggested that a straightforward strategy to improve micronutrient status may improve cognition or delay the onset of MCI and Alzheimer dementia (AD).

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6.1 Micronutrient Intake in the Elderly

The inadequacy of micronutrient supply in the elderly is documented by an increasing number of studies. Recently, a meta-analysis summarized the data from 41 such studies. These show that, depending on the individual micronutrient, between 15 and 90% of elderly people were at risk of deficiency [1]. The risk was calculated for elderly people who were below the estimated average requirement (EAR). Consequently, according to the definition of the EAR, they are at risk of developing a deficiency with clinical consequences if they stay on the intake below EAR. In particular B-vitamin supply is inadequate—a problem which may be harmful for cognition and mood.

6.2 Antioxidants

6.2.1 Importance for Brain Function and Cognition

The brain is considered extremely sensitive to oxidative damage that may occur from reactive oxygen species produced primarily by mitochondria during respiration. The exact amount of ROS produced is around 2% of the total oxygen consumed during respiration, but it may vary depending on several parameters. Some critical components come together in the brain: it is enriched in easily peroxidizable unsaturated fatty acids (20:4 and 22:6), consumes 20% of the total oxygen consumption, and has low antioxidant levels, e.g. 10% of the catalase activity of the liver (Floyd and Carney 1992) and low levels of SOD and GSH (Yoon et al. 2000). Whereas the decrease of endogenous antioxidant enzymes with age cannot really be prevented, exogenous antioxidants may be delivered with the diet or as a supplement to accumulate in the brain. Ascorbic acid seems to be the major-water soluble antioxidant in human brain, at a 15-times higher concentration than in human plasma (Floyd 1999). There is some evidence that oxidative stress contributes to the onset and development of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Barenham 2004). Improving the cellular defense against ROS-induced oxidation of neuronal tissue might prevent cognitive impairment and neurodegeneration. In cases of AD, PD and ALS, reduced levels of catalase, super-oxide dismutase and oxidized and reduced glutathione have been documented (Andersen 2004). Deficiencies in antioxidant micronutrients may further contribute to the progression of neurodegenerative diseases and at least

cognitive decline with age. At least three prominent changes occur in the brain resulting in cognitive impairment:

- Accumulation of non-essential substances (lipofuscin prominently in cortical neurons), loss of myelin (e.g. in the limbic cortices), and a general shrinkage;
- Reduction in the branching of dendrites and reduction of neurotransmitter availability; and
- Reduction of cerebral blood flow and decline of cerebral blood volume, or at least ischemia.

Accumulation of lipofuscin mainly appears as a result of oxidative stress. The reduction of blood flow may also be a consequence of oxidative modification and, as discussed in the chapter on B-vitamins in this book, the consequence of high homocysteine. With respect to memory, the metabotropic receptors acting via G-proteins are of importance. After binding of a neurotransmitter to that receptor type, the production of a second messenger molecule is induced within the neuron. The induction of the second messenger, travelling in the neuron, results in different cellular reactions. Of greatest importance is the activation of kinases. These enzymes, which can remain active for up to a couple of hours, are involved in long-term changes of the neurons and at least gene expression. The latter may contribute to the formation of novel protein expression and, in some cases, formation of dendrites and new (more or less stable) networks, resulting in a memory. The appearance of a cognitive impairment might be based on a reduced production of neurotransmitters and subsequently reduced activation of kinases. Studies with aging rats revealed that a long-term diet rich in antioxidants can slow down the onset of neuronal degeneration and cognitive impairment (Floyd et al. 1998, 1999). Furthermore, it was shown that the age-related decline in the neuronal process controlled via metabotropic receptors is compensated by a diet rich in antioxidants. The compensation is a result of an improvement of the G-protein on- and off-action (Joseph et al. 1999). Indeed, the animals fed a high antioxidant diet had higher vitamin E levels in the hippocampus compared to the control animals. The hippocampus however, is involved in memory functioning. From the above-described aspects of oxidative stress and its impact on memory, it is suggested that deficiency of antioxidants may contribute to the development of cognitive impairment.

6.2.2 Antioxidant Deficiencies in the Elderly

Age is an important determinant of the serum values of antioxidants, predominantly vitamin E, vitamin C, and ß-carotene [2, 3]. The data from the European SU.VI. MAX trial clearly showed that plasma levels of retinol, tocopherol and ß-carotene decrease with age in 12,741 volunteers aged 35–60 years [3]. Female senior

citizens from Germany aged 60–70 years showed inadequate intake and a poor antioxidant status (selenium, vitamin E, vitamin C and ß-carotene) (Wolters et al. 2006). The Iowa Rural Health Study revealed that in 420 individuals aged 79 years or older, 60% had inadequate intake of vitamin E and 25% of vitamin C (Marshall et al. 2001). Interactions of micronutrients with drugs, more frequently consumed by the elderly, increases the problem of antioxidant deficiency [4]. The occurrence of a low antioxidant status is not restricted to a few countries or areas with low socio-economic status: it seems to be a general and unrecognized problem of the aging population. The consequences of a low antioxidant intake are frailty, degenerative diseases, walking disabilities, and higher mortality (Semba et al. 2006, 2007; Michelon 2006). A low intake of antioxidant contributes to a decline in cognition and promotes the development of dementia.

6.2.3 Human Studies

Based on recent published data, the intervention with antioxidants to decrease either the progression or the onset of cognitive impairment is controversial. However, subdividing the studies into short- and long-term interventions, it becomes clear that an interventional approach needs more than one year to be effective. The EVA study evaluated in 980 subjects aged 62–72 years the relationship between the enzymatic system—restricted to copper and zinc superoxide dismutase (Cu/Zn SOD) and the seleno-dependent glutathionperoxidase (GSH-Px)—and decline in cognitive function. Cognitive decline over a four-year period was associated with a lower activity of the GSH-Px and a higher Cu/Zn SOD. Table 6.1 summarizes trials with antioxidants. Five out of six studies which examined the effect of antioxidant supply via food documented statistically significant inverse associations (**). Four out of five observational studies found an inverse relationship between antioxidant intake from supplements (vitamin E, vitamin C) and the risk of AD (*) or cognitive decline (***).

Table 6.1 summarizes the data of prospective and intervention studies with antioxidants.

The above-cited studies clearly show that antioxidants play a preventive role against the development and progression of dementia. Intake of supplements containing antioxidants (vitamins A, C and E, Se and Zn) over a longer period (five years and more) in six studies with more than 800 participants (one with 162) showed prevention of dementia or a benefit to cognitive function. Three studies with a rather low number of participants (<250) were without effect. This shows that, dependent on the statistical power, the effect of antioxidants on cognitive decline becomes evident.

Table 6.1 Data of prospective and intervention studies with antioxidants

Micronutrients	Participants	Duration	Results	Authors
Serum selenium levels	1389 subjects, age 60–71 years (EVA study)	9 years Adjustment for time, sex, education, baseline Se level, cardiovascular risk factors	Decline in Se was associated with cognitive decline as measurement by 4 neuropsychological tests. Probability of cognitive decline increased with the decrease of plasma Se change over time	[6]
Serum β-carotene and ApoE genotype	455 elderly, age $\geq$ 65 years (MacArthur Studies of Successful Aging)	7 years Adjustment for age, sex, race, baseline SPMSQ score, education, income, smoking status, alcohol consumption, serum CRP and IL6 levels, total and HDL cholesterol level, BMI	The adjusted OR of high β-carotene level for cognitive decline was 0.1 I (95% CI 0 0.02, 0.57) in participants with at least one ApoE4 allele and 0.89 (95% CI 0 0.54, 1.47) among those who were ApoE4 negative	[7]
Supplemental use of antioxidant vitamins	894 subjects with no evidence of dementia (CSHA study), age $\geq$ 65 years	5 years Adjustment for age, sex, education, sitting diastolic blood pressure, baseline 3MS score, baseline institutional residence	Subjects reporting a combined use of vitamin E and C supplements and/or multivitamin consumption at baseline were significantly less likely to experience significant cognitive decline (adjusted OR 0 0.51; 95% CI 0 0.29, 0.90)	[8]
Food intakes of vitamin E, α-tocopherol equivalents, individual tocopherols	1041 persons clinically evaluated for analysis of AD and 3718 persons for analysis of cognitive change; age $\geq$ 65 years (CHAP study)	6 years Adjustment for age, sex, race, education, ApoE4 genotype, interaction between ApoE4 and race, time from the determination of disease-free status to the time of clinical evaluation of incident disease, frequency of participation in cognitive activities, intake of saturated fat, trans unsaturated, DHA	162 persons developed AD. Higher intakes of vitamin E (RR = 0.74 per 5 mg/d increase; 95% CI = 0.62, 0.88) and α-tocopherol equivalents (RR = 0.56 per 5 mg/day increase; 95% CI = 0.32, 0.98) were associated with a reduced incidence of AD. A slower rate of cognitive decline was associated with intake of vitamin E and α-/γ-tocopherols equivalents	[9]

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Table 6.1 (continued)

Micronutrients	Participants	Duration	Results	Authors
Supplemental use of antioxidant vitamins	3227 elderly county residents, age $\geq$65 years (Cache County Study)	3 years Adjustment for age, sex, education, dummy-coded terms for the presence of 1 and 2 ApoE4 alleles, interaction between age and the dummy-coded ApoE4 terms, an indicator term for general health status	104 persons developed AD. Use of vitamin E and C supplements in combination was associated with reduced AD incidence (adjusted HR = 0.36; 95% CI = 0.09, 0.99). No evidence of a protective effect with use of vitamin E or C supplements alone was found	[10]
Midlife dietary intake of antioxidants	2459 Japanese-American men, age 71–93 years (Honolulu-Asia Aging Study)	3 years Adjustment for age, education, physical activity, cardiovascular risk factors, supplemental vitamin intakes, total energy intake, ApoE4 genotype	235 persons developed dementia (102 AD cases, 44 VaD cases, 38 AD cases with contributing cerebrovascular diseases). Intakes of β-carotene, flavonoids, vitamin E, vitamin C were not associated with the risk of dementia or its subtypes	[11]
Intake of antioxidant vitamins	980 elderly subjects initially free of dementia, age $\geq$65 years (WHICAP study)	4 year-adjustment for age, education, sex, ApoE4 status, ethnicity, smoking	242 subjects developed AD in 4023 person-years of follow-up (6 per 100 person-years). Intake of carotenes and vitamin C or vitamin E in supplemental dietary (non-supplemental) form or in both forms was not related to a decreased risk of AD	[12]
Use of supplemental antioxidants	2082 elderly subjects initially free of dementia, age $\geq$65 years (epidemiologic studies of the elderly)	7 years Adjustment for age, sex, race, education, residence, income, BMI,	34.5% experienced cognitive decline during follow-up. Current antioxidant users had a 29% lower	[13]

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Table 6.1 (continued)

Micronutrients	Participants	Duration	Results	Authors
(vitamins A, C, E plus Se or Zn)		smoking history, alcohol consumption, health status index	risk of experience cognitive decline (adjusted RR = 0.71; 95% CI = 0.49, 1.01)	
Use of supplements containing vitamins C and E	14,968 women, age 70–79 years (Nurses' Health Study)	15 years Adjustment for age at interview, education, history of diabetes, hypertension and heart disease; multivitamin use, anti-depressant use, HRT, BMI, aspirin use, smoking, mental-health index, energy-fatigue index	33% of women currently used both specific vitamin E and C supplements. Long-term current of vitamin E with vitamin C supplements had better global scores than non-users. There was a trend for increasingly higher mean scores with increasing duration of use. These associations were strongest among women with low dietary intakes of α-tocopherol	[14]
Intake of antioxidant nutrients, vitamin E, vitamin C, β-carotene	815 residents free of AD at baseline, age $\geq$65 years (CHAP study)	3.9 years Adjustment for age, education, sex, race, ApoE4 genotype, length of follow-up	Increasing vitamin E intake from food was associated with decreased risk of developing AD: RR from lowest to highest quintile of intake were 1.00, 0.71 (95% CI = 0.24, 2.07), 0.62 (95% CI = 0.26, 1.45), 0.71 (95% CI = 0.27, 1.88) and 0.30 (95% CI = 0.10, 0.92) (p for trend = 0.5). The protective effect of vitamin E was observed only among persons who were ApoE4 negative. Adjustment for other baseline	[15]

(continued)

Table 6.1 (continued)

Micronutrients	Participants	Duration	Results	Authors
			dietary factors reduces the protective association. Intake of vitamin C, β-carotene, vitamin E from supplements was not significantly associated with risk of AD	
Randomized clinical trial	6377 women 65 years or older participated in an sub-study of cognitive function of the Women's Health Study (WHS). WHS is a randomized, double-blind, placebo-controlled trial of vitamin E supplementation (600 IU on alternate days)	Supplementation period: 1992 and 1995. The sub-study was initiated 5.6 years after randomization and was conducted for 4 years	There were no differences in global score between the vitamin E and placebo groups 5.6 years and 9.6 years after randomization. Mean cognitive change over time was also similar in the vitamin E group compared with the placebo group for the global score. The RR of substantial decline in the global score in the vitamin E group compared with placebo was 0.92 (95% CI = 0.77, 1.10)	[16]
Randomized clinical trial	769 subjects with a MCI were randomly assigned to receive daily either vitamin E (2000 IU) or donepezil (10 mg) or placebo	3 years	212 subjects developed AD. There were no significant differences in the probability of progression to AD in the vitamin E compared to domepezil or placebo groups during the 3 years of treatment. No significant differences emerged among ApoE4 carriers between the vitamin E and placebo groups	[17]

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Table 6.1 (continued)

Micronutrients	Participants	Duration	Results	Authors
Randomized clinical trial	341 patients with AD of moderate severity were randomly assigned to receive either the selective monoamine oxidase inhibitor selegiline (10 mg/day), or α-tocopherol (vitamin E, 2000 IU/day) or both selegiline and α-tocopherol or placebo	2 years	As compared with the placebo group (440 days), there were significant delays in the time to primary outcome for the patients treated with selegiline (median time, 655 days; $p = 0.012$), α-tocopherol (670 days, $p = 0.001$) or combination therapy (585 days, $p = 0.049$) after adjustment an baseline MMSE score	[18]
Randomized clinical trial	220 healthy free living women aged 60–91. 111 in the suppl. group 150 mg ascorbic acid, 50 mg Mg, 36 mg a-tocopherol, 9 mg ß-carotene, 60 µg Selenium and further water sol. vitamins	6 months	No effect on cognitive performance. The 6-month period, however, seems too short (claimed by the authors)	Wolters et al. (2005)
Randomized clinical trial	910 men > 65 years divided in two groups: supplemented with multivitamin. (50–210% of RDA) (456) and placebo (454)	12 months	Evidence for a beneficial effect in two subgroups: benefit on verbal fluency tests in supplemented participants >75 and in those with increased risk of nutritional deficiencies	McNeill et al. (2007)

The clinical trials showed controversial results. In the Kang trial, there was an 8% reduction in the decline of the global score. The Peterson trial seems to be without effects of antioxidants on cognitive decline or AD development. However, nearly one third of all patients developed AD within three years. Based on a couple of epidemiological and observational studies, the development of AD in patients with MCI is around 5% per year and not more than 10%, as is the case in that study. This difference might be due to an increased number of early AD patients in the MCI group at the beginning of the trial. Antioxidants however, have nil or only a very moderate impact in cases of existing AD.

6.3 Homocysteine-Lowering Vitamins

6.3.1 Importance of B-Vitamins for Cognition

B-vitamins (B_6, B_{12}, folic acid) are involved in the methylation of homocysteine (Hcy). Low intake, higher demand or polymorphism of enzymes (MTHFR; GCPII) results in hyperhomocysteinemia. Hcy is a non-protein-forming sulfhydryl-containing amino acid. Because Hcy is highly cytotoxic, the i.c. concentration is kept low by catabolism and by a cellular export mechanism into plasma. Consequently, a high plasma concentration documents a high cellular Hcy formation. A couple of diseases are discussed as related to high homocysteine levels, such as arteriosclerosis, myocardial infarction, stroke, and peripheral vascular disease, as well as Parkinson's disease and Alzheimer- and vascular-dementia (***). Epidemiological studies show an increase of Hcy with increasing age and a negative correlation with cognitive function. Differing pathomechanisms are discussed as responsible for the effect of Hcy on brain structure and function, such as direct toxicity on dopaminergic neurons (Imamura et al. 2007), or on the vascular endothelium (**). High Hcy or low folate or B_{12} show an influence on cellular redox status, including up-regulation of redox-sensitive transcription factors (NFkB, AP-1), thus promoting calcium influx, amyloid and tau protein accumulation, apoptosis and neuronal death (***). Under conditions of hyperhomocysteinemia, neural cells are exposed to the neurotoxic activity of Hcy. The consequences are a disturbed metabolism of excitatory neurotransmitters (e.g. glutamate), which causes excitotoxic effects associated with increased ROS formation and at least oxidative damage of neuronal tissues (**). This excitotoxic effect of Hcy is assumed to be realized via NMDA receptors (Sachdev 2005). Indeed, Streck and coworker (2003) demonstrated significant increased lipid peroxidation in rat hippocampus following Hcy treatment. The involvement of oxidative stress in the pathogenesis of dementia has been frequently shown in in vitro and in vivo experiments (**). Oxidative stress activates gene expression of

a couple of components related to apoptosis and at least neuronal degeneration, such as caspase 3- and 6-dependent activation of apoptotic pathways (Anantharam et al. 2007). Oxidative stress induces apoptotic cell death in dopaminergic-derived N27 cell line and, to a lesser extent, in GABAergic striatum derived and hippocampal cell lines (Anantharam et al. 2007). Cell death was mediated via caspase 3-dependent pathways. The active proteases caspase 3/6 cleave tau proteins at specific sites, generating toxic tau fragments or enhancing the aggregation properties of these microtubule-associated proteins (Park and Ferreira 2005). Caspase 6, a potent cleaving protease of the tau protein (Guo et al. 2004), has been detected in neurofibrillary tangles of humans with MCI, and it is concluded that the activity of caspase 6 precedes the clinical and pathological diagnosis of AD (Albrecht et al. 2007). The interactions of hyperhomocysteinemia, oxidative stress and caspase activation may explain the beneficial effect of lowering Hcy and antioxidative treatment on cognitive impairment (McCaddon 2015; de Lau et al. [5]).

6.3.2 *Deficiencies of B-Vitamins in the Elderly*

Elderly people with low circulating folate or vitamin B_{12} have higher fasting total homocysteine concentrations. Supplementation with B-vitamins results in normalization of elevated Hcy plasma levels. Data from NHANES III, including 3563 male and 4523 female participants, clearly showed that high homocysteine concentrations were significantly associated with low serum vitamin (folate, B_{12}) concentrations (Selhub 2011). With increasing age, Hcy increases in plasma, mainly due to a low folate intake. Sixty-six percent of the participants (747) aged 67–96 years had a folate intake below the recommended 400 µg, and 16.7% were below 200 µg. Data from the German nutrition survey show that 60% of the population (aged 18–79 years) has an intake of folate below 75% of the recommendation. Low folate and B_{12} intake is a general problem in the elderly and critically contributes to cognitive decline and arteriosclerosis.

6.3.3 *Human Studies*

Studies estimating intake of foods rich in B-vitamins revealed a clear-cut inverse relationship between the highest intake of fruit and vegetables and fish consumption and cognitive decline in the elderly (Table 6.2).

Table 6.2 Nutrition and prevention of cognitive decline: data from prospective studies on food groups and dietary patterns

Micronutrients	Participants	Duration	Results	Authors
Dietary consumption of fruit, vegetables and fish	3632 elderly (Cache County study on memory, health and aging)	7 years Adjustment for age, gender, education	Participants in the highest quintile of "fruit and vegetables" intake had average score 0.94 points higher than those in the lowest quintile ($p = 0.01$). Participants consuming >1 serving of fish per week had averages 3MS scores 0.81 points that those not consuming fish ($p = 0.008$). Participants with high intakes of both "fruit and vegetables" and fish had averages 3MS scores 1.50 higher than those of the low intakes especially among ApoE4 non-carriers	[19]
Dietary consumption of fruit, vegetables and fish	8085 initially non-demented subjects, age ≥ 65 years (3C study)	4 years Adjustment for age, sex, race, education, center, income, marital status	Similar patterns were found with the risk of AD. 282 subjects developed dementia (including 183 AD). Daily consumption of fruits and vegetables were associated with a reduced risk of all causes dementia (RR = 0.70, 95% CI: 0.52, 0.94; $p = 0.02$). Fish consumption (at least once per week) was associated with a reduced risk of dementia only in ApoE4 non carriers (RR = 0.60, 95% CI: 0.41, 0.89; $p = 0.01$)	[20]
Fruit and vegetable consumption	3718 participants, age ≥ 65 years (CHAP study)	6 years Adjustment for age, sex, race, education	Compared with the rate of cognitive decline among persons in the lowest quintile of vegetable intake, the rate for persons in the fourth quintile was slower by 0.019 SU/year ($p = 0.01$) and by 0.018 SU/year ($p = 0.02$) in the fifth quintile ($p = 0.02$). Fruit consumption was not associated with cognitive change	[21]

(continued)

Table 6.2 (continued)

Micronutrients	Participants	Duration	Results	Authors
Fruit and vegetable juice consumption	1836 Japanese Americans free of dementia, age $\geq$65 years (Kame project)	9 years Adjustment for age, dietary intake of vitamin C, vitamin E and β-carotene	The HR for AD was 0.24 (95% CI = 0.09, 0.61) for subjects who drank juices at least 3 times per week versus those who drank juices less often than once per week (p for trend <0.1). This inverse association was more pronounced among ApoE4 carriers. No association were found for dietary intake of vitamins E, C or β-carotene or tea consumption	[22]
Mediterranean diet	2258 community-based non-demented individuals (WHICAP study); mean age, 77.2 ± 6.6 years	4 ± 3 years (range: 0.2–13.9) Adjustment for cohort, age, sex, ethnicity, education, ApoE genotype, caloric intake, smoking, comorbidity index, BMI	262 persons developed incident AD. High adherence to the MeDi* was Associated with lower risk for AD (HR: 0.91; 95% CI: 0.83, 0.98; p = 0.0015). Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had an HR of 0.85 (95% CI: 0.63, 1.16) and those of the highest tertile had an HR of 0.60 (95% CI: 0.42, 0.87) (p for trend = 0.007) *Mediterranean diet	[23]

Table 6.3 Trials with B-vitamins and cognitive impairment

Micronutrients	Participants	Duration	Results	Authors
Intake of folate and vitamins B_6 and B_{12}	965 persons 65 years or older without dementia at baseline (WHICAP-study)	6.1 ± 3.3 years, Adjustment for age, sex, education, ethic group, Apoe4, vitamins B_6 and B_{12} levels, cardiovascular risk factors	192 m persons developed incident AD. The highest quartile of total folate intake was related to lower risk of AD (HR = 0.5, 95% Cl = 0.3, 0.9; p = .02 for trend)	Luchsinger et al. (2007)
Dietary intakes of folate, B_{12}, B_6	1041 residents initially free of AD; ≥ 65 years (CHAP study)	3.9 years, Adjustment for age, sex, race, education, cognitive activities, ApoE4, dietary intake of vitamin E, total niacin	162 persons developed incident AD. No association between quintiles of folate intake or of vitamin B_{12} intake was found with the risk of developing AD. Intake of vitamin B_6 was not associated with incident AD after control for dietary intakes of vitamin E and total niacin	[24]
tHcy and related vitamin plasma concentrations	499 high-functioning community-dwelling persons; age 70–79 years (MacArthur studies of successful aging)	7 years, Adjustment for age, sex, education, baseline cognitive function, baseline physical function, smoking, homocysteine and vitamin levels	Subjects in the lowest quartile of folate had a 1.6-fold increased risk of 7-year cognitive decline (95% CI: 1.01, 2.31; $p = 0.04$)	[25]

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Table 6.3 (continued)

Micronutrients	Participants	Duration	Results	Authors
Dietary intakes of folate and vitamin B_{12}	3718 residents initially free of AD, $\geq$65 years (CHAP study)	6 years, Adjustment for age, sex, education, race, vitamin E, vitamin C	The rate of cognition decline among persons in the top fifth of total folate intake (median, 742 µg/day) was more than twice that of those of the lowest fifth of intake (median, 186 µg/day). Similar patterns were found, with high folate intake from food and with folate vitamin supplementation of more than 400 µg/day. High total B_{12} intake was associated with slower cognitive decline only among the oldest participants	[26]
Total intake (diet plus supplements) of antioxidant vitamins (E, C, carotenoids) and B vitamins (folate, B_{12}. B_6)	579 non demented elderly volunteers, age 49–93 years (Baltimore longitudinal study of aging)	9.3 years, Adjustment for age, gender, education, caloric intake	57 persons developed incident AD. Higher intake of folate (RR = 0.1; 95% CI: 0.22, 0.76), vitamin E (RR = 0.56; 95% CI: 0.30, 1.06) and vitamin B_6 (RR = 0.41; 95% CI: 0.20, 0.84) were associated individually with decreased risk of AD. When the 3 vitamins were analyzed together, only total intake of folate at or above the DRI (RR = 0.45; 95% CI: 0.21, 0.97) was associated with a significantly decreased risk of AD. No association was found with total intake of vitamin B_{12}, vitamin C or carotenoids	[27]

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Table 6.3 (continued)

Micronutrients	Participants	Duration	Results	Authors
Serum concentration of homocysteine, vitamin B_{12}, or folic acid	599 subjects; 85 years of age (Leiden 85-Plus study)	4 years, Adjustment for sex and education level	There were no significant associations of serum concentrations of Hcy, vitamin N_{12} or folic acid with rate of cognitive decline (battery of cognitive tests: MMSE, Stroop test, a letter digit coding test, a word recall test)	[28]
Plasma tHcy, folate, vitamin B_{12}, vitamin B_6 and dietary B vitamin intakes	321 aging men, age 50–85 years (veterans affairs normative aging study)	3 years, Adjustment for baseline cognitive measures, age, education, smoking, alcohol intake, BMI, diabetes, systolic blood pressure, time of second measure relative to folic acid fortification, time interval between the 2 cognitive measures, serum creatinine (for plasma) or total energy intake (for diet)	Decline in constructional praxis (special copying) was significantly associated with plasma tHcy, folate, vitamin B_6, vitamin B_{12} and with the dietary intake of each vitamin. Dietary folate was also protective against a decline in verbal fluency. A high homocysteine concentration was associated with a decline in recall memory	[29]

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Table 6.3 (continued)

Micronutrients	Participants	Duration	Results	Authors
High plasma tHcy concentration	816 subjects initially free of dementia, mean age 74 years (Conseltic Study of Brain Aging)	4 years, Adjustment for age, sex, education, ApoE genotype, vascular risk factors, serum concentrations of folate and vitamin B_{12}	112 persons developed dementia (including 70 cases of AD). In the subjects with hyperhomocysteinemia (Hcy >15 µmol/l); HR was 2.08 (95% CI: 1.31, 3.30; $p = 0.002$) for dementia and 2.11 (95% CI: 1.19, 3.76; p = 0.011) for AD. Low folate concentrations ($\leq$11.8 nmol/l) were independently associated with an increased risk of both dementia (1.87; 95% CI: 1.21, 2.89; $p = 0.005$) and AD (1.98; 95% CI: 1.15, 3.40; $p = 0.014$). No significant relation was found with vitamin B_{12}	[30]
High Hcy levels	909 elderly subjects, age 77.2 $\pm$ 6.3 years (WHICAP study)	1.5 years, Adjustment for age, sex, education, ApoE4	109 persons developed AD (Incidence: 3206 person-years): Adjusted HR of AD for the highest quartile of Hcy was 1.4 (95% CI: 0.8, 2.4; p for trend = 0.31). High Hcy levels were not related to a decline in memory scores over time. Age was a significant confounder in all the analyses	[31]
Serum tHcy concentration	144 subjects, age 30–80 years	6 years, Adjustment for age, sex, education	No correlation was observed between serum Hcy, vitamin B_{12} and folic acid concentrations, and performance at any of the time-points	[32]

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Table 6.3 (continued)

Micronutrients	Participants	Duration	Results	Authors
Plasma tHcy level	1092 subjects without dementia; mean age: 76 years (Framingham study)	8 years, Adjustment for age, sex, education, ApoE genotype, plasma vitamin levels, vascular risk factors	111 persons developed dementia (including 83 cases of AD). The RR of dementia was 1.4 (95% CI: 1.1, 1.9) for each increase of 1 SD in the log-transformed Hcy value at baseline or 8 years earlier. The RR of AD was 1.8 (95% CI: 1.3, 2.5) per increase of 1 SD at baseline and 1.6 (95% CI: 1.2, 2.1) per increase of 1 SDD eight years before baseline. The risk of AD nearly doubled with plasma tHcy level greater than 14 μmol/l	[33]
Serum level of vitamin B_{12} and folate	370 non-demented persons, age ≥ 75 years (Kungsholmen Projet)	3 years, Adjustment for age, sex, education	Persons with low levels of B_{12} (≤ 150 pmol/l) or folate (≤ 10 nmol/l) had twice the risk of developing AD (RR = 2.1, 95% CI: 1.2, 3.5) compared with people with normal levels of these vitamins. Similar relative risk was found for subjects with both vitamins at low levels and for low levels of B_{12} or folate respectively defined as ≤ 250 pmol/l or ≤ 12 nmol/l	[34]

Despite the fact that pure nutrition studies have certain limitations, the data show that a diet rich in phytochemicals and water-soluble vitamins may protect against accelerated cognitive decline. Furthermore, fish intake was inversely correlated with cognitive decline. This preventive effect might be attributed to either n-3 fatty acids and/or vitamin D—essential nutrients that are both present mainly in fish. The data from the nutrition studies show that a mixed diet, rich in antioxidants (fruits, vegetables), which also contains edible oil (vitamin E), meat as a source for selenium and optimum bioavailable folate, and at least B_{12} (Mediterranean diet) does indeed prevent the progression of MCI.

To further elucidate whether single micronutrients are responsible for the preventive effect, studies are carried out which measure either biomarkers of intake of selected micronutrients or else plasma levels of these micronutrients.

Table 6.3 summarizes trials with either dietary or supplemental intake of B-vitamins and cognitive impairment.

High dietary intake of folate and other B-vitamins was associated with a lower rate of cognition decline and at least incidence of AD in nine out of 12 studies. No study showed any negative effect. Plasma levels of homocysteine are correlated with an increased risk of AD or increased cognitive decline in four out of five studies. One study with 1033 participants documented an inverse relationship between plasma folate and cognition and performance independent of Hcy concentration (de Lau et al.) [5]. Taken together, a sufficient intake of Hcy-lowering vitamins results in a decreased decline of cognitive function and a decreased risk of AD.

To further elucidate the role of Hcy-lowering vitamins, clinical intervention studies were carried out (Table 6.4).

Intervention studies reveal conflicting results. This may in part be due to differences in treatment time, dosage and at least study population. Nevertheless, the WHICAP study shows that persons with MCI indeed may benefit from a long-term treatment with Hcy-lowering vitamins. Based on the pathomechanisms discussed above, it seems important to treat patients with MCI with a combination of Hcy-lowering vitamins and antioxidants. Studies combining these micronutrients are at present not available. However, prospective studies estimating the effect of nutrition containing Hcy-lowering and anti-oxidative vitamins do exist (Table 6.4).

6.4 Summary: Key Messages

- Micronutrients support the maintenance of cognitive function during aging.
- Besides genetics and lifestyle, nutrition is claimed as an important factor which interacts with basic pathologies of cognitive decline.
- Vitamins, trace elements and minerals can mitigate the risk of cognitive decline, especially in elderly people at risk of deficiencies.

Table 6.4 Nutrition and prevention of cognitive decline: data from prospective studies and randomized clinical trials on homocysteine-related B vitamins

Micronutrients	Participants	Duration	Results	Authors
Plasma folate	1033 non-demented participants aged 60–90y. Cognition test, psychomotor test and memory. Rotterdam scan study		Higher plasma folate concentrations are associated with better global cognitive function and better performance on tests of psychomotor speed, regardless of homocysteine concentration	[5]
Intake of folate and vitamins B_6 and B_{12}	965 persons 65 years or older without dementia at baseline (WHICAP study)	6.1 ± 3.3 years, Adjustment for age, sex, education, ethic group, Apoe4, vitamins B_6 and B_{12} levels, cardiovascular risk factors	192 m persons developed incident AD. The highest quartile of total folate intake was related to lower risk of AD (HR = 0.5, 95% Cl = 0.3, 0.9; p = 0.02 for trend)	[35]
Intervention	276 healthy participants, ≥65 years with plasma homocysteine concentrations of at least 13 μmol/l, randomly assigned to receive a daily supplement containing folate (1000 μg), vitamin B_{12} (500 μg) and vitamin B_6 (10 mg)	2 years treatment	Plasma homocysteine concentration was 4.36 μmol/l lower in the vitamin group than in the placebo group during follow-up. There were no significant difference between the vitamin and placebo groups in cognition test scores	[36]

(continued)

Table 6.4 (continued)

Micronutrients	Participants	Duration	Results	Authors
Intervention	149 people at high risk of dementia were randomized to receive either low dose aspirin (81 mg) or placebo; and folic acid (2 mg) plus vitamin B_{12} (1 mg) or placebo; and vitamin E (500 mg) plus (C (200 mg) or placebo	12-week treatment	B vitamins lowered plasma Hcy concentration by 30%. No effect of treatment on cognitive function was detected	Vital trial collaborative group 2003 [37]
Intervention	211 healthy younger, middle-aged, and older women, who took either 750 µg folate, 15 µg vitamin B_{12}, 75 mg vitamin B_6 or placebo daily	1-month treatment	Supplementation had a significant positive effect on some measures of memory performance only and no effect on mood. Dietary intake status was associated with speed of processing, recall and recognition, and verbal ability	[38]
Intervention	30 patients with abnormal cognitive decline and folate level below 3 ng/ml randomly assigned to receive folic acid and supplementation	2-month treatment	Patients treated showed a significant improvement of both memory and attention efficiency when compared with placebo group. The intensity of memory improvement was positively correlated with initial severity of folate deficiency. The severity of initial cognitive decline was unrelated to the degree of folate deficiency	[39]

Epidemiological studies demonstrate that with increasing age, the prevalence of nutritional deficiencies increases, in particular deficiencies of antioxidants and B-vitamins.

- Micronutrient deficiencies may contribute to, or even promote, cognitive impairment.
- A strategy to improve micronutrient status may help improve cognition or delay the onset of MCI and at least Alzheimer dementia (AD).

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