Macronutrients, aluminium from drinking water and foods, and other metals in cognitive decline and dementia

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Abstract. A possible role of the macronutrients and the basic elements of carbohydrates (glucose administration or depletion), proteins (amino acids such as tryptophan and tyrosine), and fat (unsaturated fatty acids) was recently proposed for age-related changes of cognitive function, and the cognitive decline of degenerative (AD) or vascular origin. The availability and utilization of glucose has 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. Furthermore, many lines of evidence have focused on the importance of oxidative stress mechanisms and free radical damage in AD pathogenesis. In addition, epidemiological studies have recently reported an association between alcohol and the incidence of AD and predementia syndromes. Foods with large amounts of aluminium-containing additives or aluminium from drinking water may affect the risk of developing AD, aluminium more likely acting as a cofactor somewhere in the cascade of events leading to the demented brain. A role for other metals in dementia have been speculated, given the encouraging results reported from studies on peripheral zinc concentrations, zinc supplementation, serum copper, either bound with ceruloplasmin or not, and iron metabolism in AD. Nonetheless, more data are needed to support a possible role of these metals in dementing diseases. Healthy diets, antioxidant supplements, and the prevention of nutritional deficiencies or exposure to foods and water with high content of metals could be considered the first line of defence against the development and progression of cognitive decline.

Keywords: Carbohydrates, proteins, diet, aluminium, copper, iron, dementia, Alzheimer’s disease, vascular dementia

1. Introduction

In occidental countries, the most common forms of dementia are Alzheimer’s disease (AD) and vascular dementia (VaD), with respective frequencies of 70% and 15% of all dementias [296]. Therefore, AD is the most common dementia and primary neurodegenerative disorder in the elderly, that gradually leads to a complete psychological and physical dependency and finally to death within one to two decades. It involves aberrant protein processing and is characterized by the presence of both intraneuronal protein clusters composed of paired helical filaments of hyperphosphorylated tau protein [neurofibrillary tangles (NFTs)], and extracellular protein aggregates [senile plaques (SPs)]. The SPs are the result of misprocessing of the amyloid-\(\beta\) protein precursor (A\(\beta\)PP) by \(\beta\)- and \(\gamma\)-secretases to form toxic amyloid-\(\beta\) (A\(\beta\)) peptide that aggregates and initiates a pathogenic self-perpetuating cascade ultimately leading to neuronal loss and dementia. According to the “amyloid cascade hypothesis” [112], the development of SPs is thought to precede and precip-
itate the formation of NFTs as a result of the cellular changes invoked. A recent longitudinal clinicopathologic cohort study, using summary measures of amyloid load and NFTs, showed no correlation between amyloid load and clinical AD and global cognitive function, suggesting that the effect of amyloid deposition on clinical disease is mediated by NFTs [22].

In the present review, we will use the term “pre dementia syndrome” to identify all conditions with age-related deficits in cognitive function reported in the literature, including a mild stage of cognitive impairment based on a normality model and pathological conditions considered predictive or early stages of dementia [220]. Such predementia syndromes have been defined for AD and VaD, but have not yet been operationalized for other specific forms of dementia. Mild cognitive impairment (MCI) is, at present, the most widely used term to indicate nondemented aged persons with a mild memory or cognitive impairment that cannot be accounted for any recognized medical or psychiatric condition [52,226]. Different diagnostic criteria have been proposed, and the terms age-related cognitive decline (ARCD) [3] and aging-associated cognitive decline (AACD) [157] have been recently proposed to distinguish individuals with mild cognitive disorders associated with aging from non affected individuals. At present, it difficult to establish whether these entities are an expression of a normal aging process, or are clinically distinguishable from dementing syndromes, or, eventually, are a continuum with dementia. In fact, while MCI is assumed to be pathology-based and therefore amenable to interventions, ARCD and AACD are generally considered nonprogressive, a phenomenon of normal aging. Furthermore, MCI may be a prodromal phase of dementia, with estimates of 12% of MCI patients developing dementia in 1 year [219,226], and 20% over 3 years [227]. Recently, in the Italian Longitudinal Study on Aging (ILSA), a population-based study with a sample of 5,632 65–84 year old subjects, we found a progression rate to dementia of MCI of 3.8/100 person-years [268].

The transitional phase between mild nondisabling cognitive decline and disabling dementia is an ambiguous diagnostic period during which it is unclear whether mild cognitive deficits predict incipient dementia, or not [113]. Adding further to this uncertainty are neuropathology-based studies identifying unexpectedly high burdens of vascular [207] and AD [98] types of pathology in clinically nondemented individuals. In fact, recent studies showed that many people with neuropathological changes of degenerative or vascular origin did not have cognitive impairment [197], also suggesting that MCI could not have a neuropathological basis. In fact, in a sample of nondemented elderly individuals, pathologically confirmed preclinical AD was not associated with cognitive impairment or decline, even on neuropsychological measures shown to be sensitive to very mild AD [98,196]. These individuals truly are preclinical in that there is no detectable cognitive deficits despite the presence of neuropathological AD, and detectable cognitive decline already may represent “clinical” AD. In fact, a substantial body of evidence supports the suggestion that MCI largely represents very mild AD [207].

The clinical presentation of VaD varies greatly depending on the causes and location of cerebral damage [246]. Large-vessel disease leads commonly to multiple cortical infarcts and a multifocal cortical dementia syndrome, whereas small-vessel disease, usually resulting from hypertension and diabetes, causes periventricular white matter ischemia and lacunar strokes characterized clinically by subcortical dementia with frontal lobe deficits, executive dysfunction, slow information processing, impaired memory, inattention, depressive mood changes, slowing of motor function, Parkinsonian features, small-step gait, urinary disturbances and pseudobulbar palsy [245]. Very recently, the term Vascular Cognitive Disorder (VCD), has been proposed by Sachdev [253] and it would become the global diagnostic category for cognitive impairment of vascular origin [247]. VCD would include the group of syndromes and diseases characterized by cognitive impairment resulting from a cerebrovascular etiology. The main categories of VCD are Vascular Cognitive Impairment (VCI) [i.e., vascular cognitive impairment no dementia (vascular CIND), and vascular MCI], VaD, and mixed AD plus cerebrovascular disease (CVD) [247,253]. Dementia is defined as executive control deficit producing loss of function for instrumental activities of daily living, while mixed AD plus CVD is defined as pre-existing AD worsened by stroke (equivalent to prestroke dementia). Finally, VCI is a term referred to all forms of mild to severe cognitive impairment associated with CVD, including vascular CIND and vascular MCI, e.g. predementia syndromes with a presumed primary vascular basis. VCI is considered a premonitory phase of VaD, although VCI not always proceeds to VaD [247,253]. The characteristic neuropsychological profile of VCI is believed to include frequently early impairment of attention and executive control function, with slowing of motor performance and information processing, while episodic memory is relatively spared compared to that in AD [62].
It is still not known what causes AD, and specific risk factors for the disease are difficult to isolate. However, since rare mutations that occur in three genes: APP, presenilin1 (PSEN1), and presenilin2 (PSEN2) [106, 241,261] cause familial autosomal-dominant AD with early-onset (less than 5% of all AD cases) and all result in increased production of Aβ, it is clear that this pathway is important. Furthermore, since the remaining 95% of AD cases, predominantly of sporadic and late-onset nature, are neuropathologically indistinguishable from familial forms, it is possible that the disease results from a combination of hereditary and environmental factors that somehow involve the APP pathway. Yet attempts to identify environmental and genetic risk factors associated with AD have not been conclusive. The risk factors identified so far are intriguing but not completely illuminating.

The apolipoprotein E (APOE) ε4 allele is a major risk factor for sporadic AD. Numerous genes related to vascular disease have been shown to increase susceptibility for sporadic AD [217]. Among these genetic risk factors, APOE which is located on chromosome 19 and occurs in three common alleles, ε2, ε3, and ε4, is the best-documented one. The importance of APOE in the central nervous system (CNS) became evident with the association of the ε4 allele of APOE with familial and sporadic late-onset AD [256]. Nonetheless, APOE is neither necessary nor sufficient to cause AD and this is the main reason why APOE is classified as a risk factor for a AD and not a causative one. Furthermore, APOE genotyping predictive value is poor and it is not very sensitive and specific, and this is the main case used to argue against proposals for the inclusion of APOE genotyping in clinical diagnoses of AD. Thus APOE testing can be performed only in patients suspected of having AD, but not in healthy people or relatives of AD patients as screening or predictive test [2]. For a person with symptoms of dementia, APOE testing may offer additional support that any dementia may be due to AD, and thus potentially increase confidence to the clinical diagnosis [177]. In AD Centers, clinical diagnosis is already deemed to be correct over 90% of the time without any APOE testing. When APOE genotyping is performed in combination with the clinical criteria for the disease, the specificity of the diagnosis is increased by an estimated additional 4%.

Finally, there is no doubt that depression can be associated with cognitive impairment [136], but there are various hypotheses that might explain this relationship. In fact, there is sufficient evidence to support the possibility that depression is a risk factor for dementia and cognitive decline [137]. Further work is needed to confirm if depression may be a prodrome of dementia [235], or could play a causal role in dementia, as a source of hippocampal damage through a glucocorticoid cascade [255].

The boundaries of the age-related decline of cognition are at present largely unknown, and the factors influencing predementia syndromes and dementia, and particularly the role of environmental factors and dietary habits have been poorly investigated. In fact, the relationships of macro- and micronutrients with predementia syndromes, VaD, and AD are unclear. Given that at present there are no effective treatments for this kind of diseases, prevention could be crucial. Low serum levels of micronutrients (B1, B2, B6, B12, C vitamins, and folate) have been quite frequently described in older people and significantly associated with cognitive impairment in epidemiological studies [224,225]. More recently, ascorbic acid seemed to be protective against cognitive decline in a cohort study in which vitamin C intake was measured at baseline, and cognitive function was assessed 4 years later [216]. Moreover, other evidence supports cognitive effects of caloric intake or serum levels of folate, vitamins A, E, C, B12, and B6 [151,239,284]. In conclusion, cognitive disorders may derive from severe vitamin deficiencies and with some improvement in cognitive performance after vitamin supplementation in these vitamin-deficient patients [171]. Furthermore, higher intake of antioxidants could have a protective effect on cognitive function, but one important question is whether this effect could be obtained by increasing the dietary amounts of fresh fruits and vegetables. Animal studies suggested that diets high in antioxidant-rich foods, such as spinach, strawberries, and blueberries, rich in anthocyanins and other flavonoids, may be beneficial in slowing age-related cognitive decline [138]. Finally, high plasma homocysteine levels can be largely attributed to inadequate B vitamin status, and are associated with stroke and thrombosis [199]. Silent brain infarcts and white matter lesions are both associated with an increased risk of stroke and dementia, and epidemiological studies found associations between hyperhomocysteaemia and both histologically confirmed AD and disease progression [199,218]. The recent findings of the Rotterdam Scan Study, a population-based study of 1,077 people aged 60 to 90 years who had cerebral magnetic resonance imaging, suggest that total homocysteine levels are associated with silent brain infarcts and white matter lesions independent of each other and of other cardiovascular risk factors [288]. Furthermore,
in another study on a sample of 1,092 subjects without dementia from the Framingham Study was examined the relation of the plasma total homocysteine level measured at baseline and eight years earlier to the risk of newly diagnosed dementia on follow-up. It was found that with a plasma homocysteine level greater than 14 micromol/L, the risk of AD nearly doubled. Therefore, an increased plasma homocysteine level seems to be a strong, independent risk factor for the development of dementia and AD, suggesting that the elevated homocysteine levels precede the onset of dementia, not resulting from dementia-related nutritional and vitamin deficiencies [260]. Finally, recent evidence suggested that subjects with lowest serum folate had significantly higher risk for MCI and dementia, while hyperhomocysteinemia was significantly associated with dementia and AD, suggesting that relative folate deficiency may precede AD and VaD onset [232]. The underlying mechanism is unknown but recent data suggest that impaired one-carbon metabolism resulting from folic acid deficiency and high homocysteine levels promotes accumulation of DNA damage and sensitizes neurons to Aβ toxicity [149].

There is currently a rapidly growing interest in the potential of specific foods to influence various aspects of the mental and physical performance. The main components of the diet that can readily be manipulated are the macronutrients: carbohydrate (CHO), protein, fat, and alcohol. Concerning the role of dietary macronutrient intake in cognitive decline, very few data are available and therefore research examining the role of specific macronutrients on cognitive function in adults is inconclusive [49,166,267]. The aim of this review article was firstly to examine the possible role of the macronutrients and the basic elements of CHO (glucose administration or depletion) and proteins (amino acids such as tryptophan and tyrosine), except for fat (see the review of Solfrizzi et al. for dietary fatty acids) [257] in age-related changes of cognitive function, and the cognitive decline of degenerative (AD) or vascular origin (VaD). In fact, there is a recent increase in the level of interest in the possible role of dietary fatty acids in cognitive decline. At present, several studies suggested that an increase of saturated fatty acids (SFA) could have negative effects on cognitive functions [107, 297]. Furthermore, a clear reduction of risk of cognitive decline has been found in a population sample with a high intake of polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA) [140,141,266,269–271]. This effect could be related to the role of dietary fatty acids in maintaining the structural integrity of neuronal membranes, determining the fluidity of synaptosomal membranes and thereby regulate neuronal transmission [135].

Secondly, we aimed to review the current knowledge about the possible role of aluminium from drinks and foods and other metals (zinc, copper, and iron) in dementing disorders.

2. Carbohydrates, proteins, and other macronutrients in cognitive decline

Current evidence suggests that poor glucose regulation is associated with poor cognitive performance [145,278] and that the consumption of dietary CHO can improve memory in certain situations [148, 183]. The availability and utilization of glucose which is the primary substrate of neuronal metabolism has 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 [293].

Blood glucose is normally 4 to 5.5 mmol/L [64] and is controlled by a series of hormonal mechanisms; if it falls below 2.2 mmol/L, hypoglycaemia occurs [4] that is a common side effect of insulin treatment in subjects with type 1 (insulin-dependent) diabetes mellitus (IDDM). After induced hypoglycaemia in normal subjects and in patients with IDDM, effects on mental performance (i.e., visual and auditory information processing) have been demonstrated [178]. Decreased cognitive capacity on standard tests of performance and lowered intelligence quotient have been proposed to be enduring effects in follow-up studies of IDDM patients [47]. These effects are suggested to result from repeated episodes of hypoglycaemia [150]. Nonetheless, Austin and Deary [12], in a reanalysis of the long-term data of the Diabetes Control and Complications Trial (DCCT), found no association between repeated episodes of hypoglycaemia and cognitive decrement or baseline cognitive performance.

Non-insulin dependent diabetes mellitus (NIDDM) or type 2 diabetes has a later onset, is often associated with obesity, and has effects on cognitive function [278]. Verbal memory and concept formation were the most commonly affected cognitive functions in NIDDM [59,278]. In adults with NIDDM, poorer glycemic control is associated with lower performance on tests of declarative memory. Acute ingestion of high
glycemic index CHO foods further contributes to the underlying memory impairment [108].

In IDDM, complex tasks that require speed and sustained attention are more reliable disrupted by hypoglycaemia [53]. Cerebral blood-flow alterations have been observed during hypoglycaemia in IDDM [168], in particular an increase in frontal lobes. Frontal-lobe and psychomotor function are less consistently affected in studies of NIDDM [287]. The reason for the difference in the cognitive functions impaired during hypoglycaemia in NIDDM and IDDM is, at present, unclear. It is possible that delivery of glucose to the cortex may be prioritised in some manner so that supply to the frontal lobes is protected [53]. An alternative possibility is that, because age at onset and length of time of undetected diabetes differ greatly between these two types of diabetes, the incidence of repeated and untreated episodes of hypoglycaemia and potential cerebral disruption of glucose availability also differ [59]. In summary, lack of glucose availability produces definite impairment of cognitive performance in diabetics of both types and in normal subjects [53]. Therefore, enhancing glucose availability through the ingestion of CHO should ameliorate impairment and indeed enhance performance.

In fact, Kaplan et al. [145] firstly showed that cognitive performance is associated with glucose regulation in the elderly before the diagnosis of impaired glucose tolerance and that, in addition to glucose, common CHO-containing foods can improve cognition. Importantly, the CHO-enhancing effects were independent of their effects on plasma glucose. High glucose response curve, poor β cell function, good 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 g CHO as glucose, potatoes, or barley improved verbal declarative memory in individuals with poor baseline memory or poor β cell function and also improved performance on a visuo-motor task in those with poor β cell function. Thus, individuals with relatively poor glucose regulation perform worse on cognitive tests than do those with better regulation and are most sensitive to the cognitive-enhancing effects of carbohydrates. Several investigators have shown that a glucose drink improves memory in rodents and humans [148]. The results of the study by Kaplan et al. [145] reported that glucose may not be special in this respect because consumption of the same amount of CHO as a high-glucose food (potato) or a low-glucose food (barley) produced similar cognitive-enhancing effects. In fact, a stronger relation between baseline performance and memory improvement was observed for barley than for glucose or potato, suggesting that low-glucose foods may actually have greater benefits. Several studies, including that by Kaplan et al. [145], showed that individuals with poor glucose regulation may be more sensitive to the cognitive-enhancing effects of glucose than those with better regulation [183]. Consistent with these data, the results from Kaplan et al. [145] also suggest that glucose and other CHOs have a stronger effect on functions mediated by the medial temporal lobe, such as long-term verbal declarative memory [175,176,223], rather than those mediated by other brain regions, such as short-term or working memory [40,175,176], procedural memory [40,82,176], or response inhibition [23,40]. The CHO effects were stronger for the long-term than for the short-term memory tests which are mediated by the prefrontal lobe [99], and minimal effects were seen on the attention task (mediated by a neural network including the parietal and frontal lobes). Nevertheless, other brain regions may also be influenced, albeit to a lesser extent [1].

Kaplan et al. [145], in a clinical trial involving 22 individuals aged 61–79 years, observed that intakes of protein, CHO, or fat enhanced memory independently of elevations in blood glucose. While, as seen above, the benefits of glucose were supported by several studies in humans and animals [148,183], the finding that protein and fat enhanced memory was novel. Several studies showed that consuming a mixed macronutrient breakfast can improve cognition compared with not eating breakfast, but some CHO was always included in the meal, with the assumption that blood glucose must increase for an improvement to be observed [21,143]. CHO provides the most rapidly available source of glucose, the brain’s only metabolic fuel, that is required for the synthesis of neurotransmitters such as serotonin, noradrenaline, and acetylcholine.

The mechanisms through glucose intake may improve memory in the healthy elderly are, at present, unclear. One common hypothesis is that glucose ingestion may improve memory by increasing plasma glucose concentration, leading to alteration in glucose uptake and utilization by the brain and ultimately to an increase in glucose-mediated synthesis of acetylcholine in the hippocampus region [237]. Evidence in rodents supports this acetylcholine hypothesis [184,233]. Others suggested that the insulin response to an increase in glucose may be responsible for the effects on memo-
ry [41,42]. The findings from Kaplan et al. [146] showing that the ingestion of energy can improve memory independently of elevations in blood glucose do not rule out the acetylcholine or insulin hypotheses but suggest that macronutrients may affect cognition by more than one mechanism. In fact, the increase in memory soon after the ingestion of energy from any macronutrient may be explained by an evolutionary perspective [146].

A mechanism that would allow an animal to remember the details of a successful hunt for food would clearly be beneficial for survival [67]. Any potential mechanism must be consistent with the finding that glucose, protein, and fat enhanced memory 15 minutes after ingestion. Within this time period, which precedes fat absorption, activation of the gut-brain axis probably plays an important role [53]. Several gut peptides, including cholecystokinin [67] and gastrin–releasing peptide, pancreatic, and amylin [195], influence memory in rodents, probably via stimulation of ascending fibers of the vagus nerve [67]. Thus, memory may have been enhanced by all 3 macronutrients via gut-mediated responses, explaining the nonnutrient-specific improvements observed.

Furthermore, Kaplan et al. [146] found that, in contrast with glucose and fat, protein was the only macronutrient to influence the rate of forgetting on the paragraph recall test (a cognitive test assessing verbal episodic memory) at 15 minutes: the rate of forgetting is associated with both the medial temporal and diencephalic regions [147]. In fact, after protein ingestion, subjects surprisingly remembered more information during delayed recall than during immediate recall. This finding suggests that some aspect of memory, not shown by the immediate and delayed recall scores, may be enhanced by protein. The immediate, delayed, and forgetting scores measure aspects of encoding, storage, and retrieval processes to different extents.

In recent years, other studies indicated an association between single dietary macronutrient intakes and cognitive functions (Table 1). In one study, the association between functional variables and alcohol intake was probably related to a better health status in moderate alcohol consumers [230]. In another longitudinal study on older community residents, a significant association between protein intakes and cognitive performances was found [151]. This finding relies on the assumption that foods with different proportion of protein and CHO influence cognitive performance by changes in brain serotoninergic function. The theoretical background linking CHO and serotonin implies that the dietary effects are mediated by changes in the ratio of plasma tryptophan to large neutral amino acid (TRP/LNAA) [53]. The mechanisms by which a high-CHO meal increases brain tryptophan and enhances serotoninergic neurotransmission have been well documented [72,73]. Nonetheless, 4% protein added to a high-CHO meal can abolish the tryptophan effect [280].

Another issue is the extent to which the TRP/LNAA must increase brain serotonin. Some authors maintained that a 50% elevation of TRP/LNAA must occur in humans to produce a meaningful rise in brain serotonin [7]. However, 20% to 40% increases in the TRP/LNAA have been demonstrated to produce neuroendocrine alterations indicative of altered brain serotonin [5,139].

Furthermore, non-institutionalized older subjects with lower intake of MUFA, SFA, and cholesterol, and higher intakes of total food, fresh fruit, carbohydrate, thiamine, folate, vitamin C, and minerals (iron and zinc) had the best performance in cognitive tests [211]. Therefore the observed association between protein intake and cognitive performance [151] could be due to protein intake, and also to zinc, meat being one of the most important sources of zinc. Moreover, socio-economic and educational factors, determining the choice of nutrients in different populations and countries, might influence the strength of association of various nutrients and cognitive functions.

It has been shown that caffeine may improve cognitive performance [84]. Higher levels of coffee consumption were associated with improved cognitive performance in older British people in a preliminary study [132]. Older people appeared to be more susceptible to the performance-improving effects of caffeine than were younger people. Similar but weaker associations were found for tea consumption. These associations have not yet been studied in clinical trials.

Several studies have assessed alcohol consumption and cognitive function among older adults [6,35,36,56,60,61,89,118,142,153,155,156], but with inconsistent results. However, many of these studies were limited by cross-sectional design, restriction by age or sex, or incomplete ascertainment [209]. Launer et al. [153] showed in the Zutphen Elderly Study that men with cardiovascular disease or diabetes and low-to-moderate alcohol intake had a significantly lower risk of poor cognitive function compared to abstainers. In the Framingham Heart Study the association between alcohol consumption and cognitive performance was analyzed separately for men and women, since the researchers expected a different alcohol-cognition relationship for male and female drinkers [60]. Test
Table 1
Principal studies on the relationships among dietary macronutrients (except for fatty acids) or dietary habits and cognitive functions, dementia, vascular dementia (VaD), Alzheimer’s disease (AD), and mild cognitive impairment (MCI)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting and study design</th>
<th>Subjects</th>
<th>Methods</th>
<th>Results and conclusions</th>
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<tr>
<td>Pradignac et al., 1995 [227]</td>
<td>Cross-sectional, population-based</td>
<td>441 subjects aged &gt; 65 years</td>
<td>Mini-Mental State Examination (MMSE), Geronte scale for the assessment of daily living activities, evaluation of dietary intake.</td>
<td>In men, alcohol intake was associated with improved functional and cognitive parameters, while polyunsaturated (PUFA) intake only with functional status. In women, lipid intakes were related to better cognitive performance. Overweight in both sexes was associated with an improvement in functional status.</td>
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<tr>
<td>Launer et al., 1996 [152]</td>
<td>Cross-sectional and longitudinal, population-based (3 years)</td>
<td>489 men aged 69–89 years</td>
<td>MMSE, evaluation of alcohol intake and smoking habits</td>
<td>After adjustment for age, education, and smoking status, men with CVD/diabetes and low-to-moderate alcohol intake had a significantly lower risk for poor cognitive function than abstainers. Alcohol intake was not associated with cognitive decline.</td>
</tr>
<tr>
<td>La Rue et al., 1997 [150]</td>
<td>Longitudinal, population-based (6 years)</td>
<td>137 subjects aged 66-90 years</td>
<td>Cognitive tests (Wechsler Memory Scale, Rey-Osterrieth Complex Figure Test, Shipley-Hartford Abstraction Test), evaluation of dietary intake, biochemical assays</td>
<td>Concurrent correlations between dietary protein intake and memory test scores. Significant relation between past nutritional status assessed via biochemical markers (vitamins A, E, B6, and B12) and cognitive performance.</td>
</tr>
<tr>
<td>Ortega et al., 1997 [210]</td>
<td>Cross-sectional</td>
<td>260 subjects aged 65–90 years</td>
<td>MMSE, Pfeiffer’s Mental State Questionnaire, evaluation of dietary intake, biochemical assays</td>
<td>A diet poor in fatty acids, saturated fatty acids, and cholesterol, but rich in carbohydrates, fibers, vitamins (folic acid, vitamin C and E, and β-carotene, and minerals (zinc and iron) seems to improve cognitive skills.</td>
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<tr>
<td>Orgogozo et al. 1997 [209]</td>
<td>Longitudinal, population-based (3 years)</td>
<td>3777 subjects aged 65 and over</td>
<td>Diagnosis of dementia and AD; evaluation of alcohol intake</td>
<td>In the 318 moderate drinkers, as compared to the 971 non-drinkers, and after adjusting for possible confounders, the odds ratios were respectively 0.19 for incident dementia and 0.28 for AD. Among the 922 mild drinkers respect to the abstainers the relative risk for AD was reduced significantly.</td>
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<tr>
<td>Elias et al. 1999 [60]</td>
<td>Cross-sectional and longitudinal, population-based (24 years)</td>
<td>1786 subjects aged 55–88 years</td>
<td>Eight cognitive tests of verbal memory, learning, visual organization and memory, attention, abstract reasoning, and concept formation; evaluation of weekly alcohol intake</td>
<td>Women who drank moderately (2–4 drinks/day) showed superior performance in many cognitive domains relative to abstainers. For men, superior performance was found within the range of 4–8 drinks/day, although fewer significant relations were observed. These results were confirmed by prospective analyses of 24-year drinking history.</td>
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<tr>
<td>Ross et al., 1999 [246]</td>
<td>Cross-sectional, population-based</td>
<td>Cohort of 3734 Japanese American men aged 71 to 93</td>
<td>Diagnosis of dementia, VaD, and stroke without dementia, evaluation of vascular risk factors, dietary habits, and questionnaire on supplementary vitamin E and C use and alcohol intake.</td>
<td>The antioxidant vitamin E and unknown factors related to a Western diet, high in animal fat and protein and low in complex carbohydrates, as opposed to an Oriental diet may be protective against developing VaD.</td>
</tr>
<tr>
<td>Kaplan et al., 2001 [145]</td>
<td>Cross-sectional study</td>
<td>11 men and 11 women aged 61–79 years</td>
<td>Cognitive tests were administered 15 and 60 min after ingestion of a 300-mL</td>
<td>Energy intake from protein, carbohydrate, or fat can enhance memory independently of elevations in blood glucose.</td>
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Table 1, continued

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<td>Maia and de Mendonca, 2002 [169]</td>
<td>Case-control</td>
<td>54 patients with probable AD and 54 controls cognitively normal, matched for age and sex</td>
<td>Diagnosis of AD; evaluation of average daily caffeine intake during the 20 years that preceded diagnosis of AD, or during the corresponding 20 years of their lifetimes for controls</td>
<td>Caffeine exposure during this period was found to be significantly inversely associated with AD, independently of other possible confounding variables</td>
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<td>Ruitenberg et al., 2002 [248]</td>
<td>Longitudinal, population-based study (6 years)</td>
<td>5,395 subjects aged 55 and older</td>
<td>Diagnosis of AD, VaD, or other dementia; evaluation of alcohol intake</td>
<td>Light-to-moderate drinking (one to three drinks per day) was significantly associated with a lower risk of any dementia and VaD. No evidence that the relation between alcohol and dementia varied by type of alcoholic beverage was found</td>
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<td>Mukamal et al., 2003 [201]</td>
<td>Nested case-control of a longitudinal, population-based study</td>
<td>373 cases with incident dementia and 373 controls</td>
<td>Diagnosis of incident dementia (AD and VaD), average alcohol consumption, and magnetic resonance imaging findings</td>
<td>Compared with abstention, consumption of 1 to 6 drinks weekly is associated with a lower risk of incident dementia among older adults. A trend toward greater odds of dementia associated with heavier alcohol consumption was most apparent among men and participants with an APOE ε4 allele, with similar relationships of alcohol use with AD and VaD</td>
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<td>Luchsinger et al., 2004 [166]</td>
<td>Longitudinal, population-based study (4 years)</td>
<td>908 subjects aged 65 years and older</td>
<td>Diagnosis of incident dementia (AD and dementia associated with stroke) and alcohol intake</td>
<td>After adjusting for age, sex, APOE ε4 status, education, and other alcoholic beverages, only intake of up to three daily servings of wine was associated with a lower risk of AD. Stratified analyses by the APOE-epsilon 4 allele revealed that the association between wine consumption and lower risk of AD was confined to subjects without the APOE ε4 allele</td>
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<td>Anttila et al., 2004 [6]</td>
<td>Longitudinal, population-based study (23 years)</td>
<td>1464 men and women aged 65–79 years</td>
<td>Diagnosis of incident dementia and MCI, and subjects classified as those who never drank alcohol, those who drank “infrequently” (less than once a month), and those who drank “frequently” (several times a month)</td>
<td>Alcohol drinking in middle age showed a U shaped relation with risk of MCI in old age. Only the carriers of APOE ε4 had an increased risk of dementia with increasing alcohol consumption</td>
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Performance of moderate male drinkers (>2 and <4 drinks/day) were significantly better than abstainers on logical memory delayed-recall, whereas heavy (>4 and <8 drinks/day) drinkers performed better on logical memory delayed-recall, attention and concentration (AC) composite score, and total composite score. Female drinkers showed superior performance compared to abstainers on more cognitive tests than male drinkers. Light female drinkers (1–2 drinks/day) performed better on logical memory delayed-recall, on the learning and memory (LM) composite and the total composite, whereas moderate female drinkers scored significantly better than abstainers on delayed memory, word fluency, similarities and the AC, LM, and total composite.
3. Dietary patterns and single macronutrients in dementia

Evidence of overlap between degenerative and vascular disorders is emerging from pathologic and epidemiological studies. Apart from the association between AD and vascular risk factors [221], such as arterial hypertension [262], diabetes mellitus [213], atrial fibrillation [212], and generalized atherosclerosis [120], dietary patterns and preferences for different foods appear to be similar in patients with VaD and AD. In fact, in a study where these two groups of patients were compared with elderly normal controls, it was found that AD patients had a greater preference than normal controls for sugar and sweet foods, but did not significantly differ in preference for foods high in complex carbohydrates and protein [204]. A similar pattern of food preference was present in VaD patients. The craving for sweet food could be a form of disinhibited behaviour associated with dementia, or might have a more specific biological substrate, that is an increased demand of brain serotonin in demented patients. Complex CHO's should increase availability of tryptophan and facilitate serotonin synthesis, whereas high protein foods might inhibit these processes [298]. Furthermore, there is increasing evidence that a disturbed glucose metabolism, oxidative stress and formation of advanced glycation endproducts and their interaction in a vicious cycle are important for the onset and progression of AD. In fact, a recent hypothesis suggests that sporadic late-onset AD is caused by non-insulin dependent diabetes mellitus which is confined to the brain [124,125]. This hypothesis is based on recent findings clearly demonstrating a perturbation of the neuronal insulin/insulin receptor signal transduction pathway in AD patients which is considered to be the pathobiochemical basis for the drastic reduction in glucose/energy metabolism in AD brain [65]. The desensitization of the neuronal insulin receptor along with a reduction in brain insulin concentration is assumed to induce a cascade-like process of disturbances including cellular glucose, acetylcholine, cholesterol, and ATP which are associated with abnormalities in membrane pathology and the formation of both amyloidogenic derivatives and hyperphosphorylated tau protein [203]. Furthermore, a Japanese study compared dietary habits in patients with AD and those with VaD showing similar results from the viewpoint of nutrition, except for the higher consumption of animal fats for AD patients, probably reflecting Westernization of dietary habits in recent years [214].

Some have claimed there is a J or U shaped relation between alcohol drinking and cognitive impairment [89,141,156]; that is, light to moderate alcohol drinking might have a protective effect compared with total abstention and heavy drinking. Moreover, a recent study showed that midlife alcohol drinking was related to the risk of MCI in old age in a U shaped manner, with both non-drinkers and frequent drinkers having a higher risk than infrequent drinkers [6]. It is possible that moderate lifestyles in general, which obviously vary according to different cultural environments, protect from cognitive deterioration. Thus, it may not be the direct effect of alcohol or specific substances in alcoholic drinks that provide the protection, but moderate alcohol drinking may be an indicator of a complex set of favourable social and lifestyle factors.

Like caffeine, alcohol produces clear effects on cognitive function and can be used as a standard for the comparisons of nutritional or food manipulation. In general, alcohol impairs performance on psychomotor tracking, driving tasks, perception, sustained attention, and information processing [58,68,114]. Food intake may mitigate the detrimental effects of alcohol on performance. Millar et al. [186] found that eating lunch (435 kcal, mixture of CHO, protein, and fat) reduced the performance impairment due to consumption of ethanol, but no effect of lunch was found on a dual-tracking and reaction-time task. Lloyd and Rogers [158] compared the effects of three drinks containing 0 g (no alcohol), 8 g (low alcohol), and 24 g (high alcohol) of alcohol consumed as a part of a small lunchtime meal on a battery of cognitive tasks. The low-alcohol drink significantly increased the hit rate on a difficult rapid information-processing vigilance task compared to the no-alcohol drink. In contrast, the high-alcohol drink tended to impair performance on this task. There were no reliable effects of alcohol on performance on less-demanding tasks. However, Finnigan et al. [70] did not find that the impairment of performance after drinking alcohol (60 mg/100 mL) was reduced by consumption of either a high-CHO or a high-protein meal (85% and 94% energy, respectively). There was no effect of meal type on performance in the placebo condition. CHO meals reduced blood alcohol levels, whereas high-protein meals did not. In conclusions, the effects of food on cognitive performance and blood alcohol level depend on the amount of alcohol consumed and the macronutrient composition of the meal.
One of the most interesting findings from a recent study on VaD risk factors conducted on the cohort of the Honolulu Heart program (HHP) – Honolulu-Asia Aging Study (HAAS) was the protective effect of a Western diet against the development of VaD [249]. A traditional 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 low in animal fat and protein (Table 1). This is an interesting approach in which dietary patterns and not only single micro- or macronutrients are considered in explaining the possible role of diet in cognitive decline. The mechanism by which an oriental diet leads to VaD remains speculative. The higher risk of stroke could probably be referred to the lower intake of animal fat and protein. As these findings do not allow analysis of separate nutrients, a hypothesis could be that more fat intake may stabilize the integrity of smaller intracranial arterioles, while the quantity and quality of dietary protein may affect small vessel pathology.

In 1049 men aged 70–91 years from five cohorts of the Seven Countries Study, a healthy diet indicator was calculated (HDI) [127] based on the WHO guidelines for the prevention of chronic diseases. There was a tendency towards a lower prevalence of cognitive impairment associated with increased HDI in four out of five cohorts (not in East Finland), suggesting that a healthy diet might be associated with a better cognitive function in elderly men [128].

An interesting line of research has pointed out that the basic components of dietary proteins, in terms of the aminoacidic composition, may play a role in the risk of developing AD [105]. In fact, plasma levels of several amino acids have been studied in few studies related to dementia. Significantly lower levels of tryptophan and methionine have been observed in AD patients as compared to control subjects [71]. Furthermore, increased plasma tyrosine/LNAA ratio and plasma taurine/methionine+serine ratio have been observed in AD patients as compared to control subjects [71]. The first ratio is of special interest, because it indicates the quantity of tryptophan and tyrosine available in the central nervous system for serotonin and noradrenaline/dopamine synthesis, respectively [73]. Intriguingly, acute tryptophan depletion has been associated with impaired cognitive function, including proof-reading, focused attention, decision making, learning and long-term memory consolidation [237]. Furthermore, Rogers et al. [244] observed similarities between the cognitive deficits induced in healthy individuals after tryptophan depletion and the cognitive deficits associated with chronic use of amphetamine. The second ratio (taurine/methionine+serine) is a reflection of the status of the amino acids involved in transmethylation [71]. However, the pathophysiological importance of these relative aminoacidic deficits to the development of AD remains to be determined.

Recent findings showing that older African-Americans [116] and Japanese living in the United States [295] have much higher prevalence of AD (6.24% and 4.1%, respectively) than those still living in their ethnic homelands (<2%) suggested that the prevalence of AD is more strongly influenced by diet and nutrition, environment, and/or lifestyle, than by genetics. However, the simple comparison of prevalence data might be misleading, since there are large differences in selective survival and other cultural effects. A more valuable comparison would be that of the overall dementia rate among different countries, culturally adjusted. In a cross-sectional study on AD, regression analyses were performed in the 65+ age population of 11 countries obtained from 18 community-wide studies versus components of the national diets [100]. The primary finding was that fat and total caloric supply have the highest correlations with AD prevalence rates. In addition, fish consumption was found to reduce the prevalence of AD in the European and North American countries.

These ecological evidences are in agreement with other epidemiologic studies on dementia and ARCD [13,101,102,152,165,266,269–271] (Fig. 1). In fact, the finding that total dietary fat is a high risk factor for the development of AD has been reported in the Rotterdam Study, although not at a statistically-significant level. In the same study fish consumption was confirmed to reduce AD risk and linoleic acid was inversely correlated with AD [141]. Moreover, very recently, two studies from the cohort of the Chicago Health and Aging Project, increased the evidence of a strict linkage between dementia and fatty acid intake [200,201]. In fact, in this cohort of 815 subjects, aged 65 years and older, after a mean follow-up of 3.9 years, 131 persons developed AD. A high intake of saturated fat and transunsaturated fat may be associated with a higher risk of AD; while a high intake of n-6 PUFA and MUFA may be protective against AD [200]. Furthermore, in the same cohort, a higher intake of n-3 PUFA and weekly fish consumption may reduce the risk of incident AD. In fact, in this study people who eat fish once or more weekly had a relative risk for AD of 0.4: the absolute risk reduction was about 9.5 percent [201]. These re-
sults confirmed our findings on a possible protective role of MUFA and PUFA intakes against ARCD [266, 270]. In particular, very recently, our group demonstrated that high MUFA and PUFA energy intakes and total energy intake were significantly associated with a better cognitive performance in a 8.5-year follow-up of the ILSA [270]. Finally, recent findings from the ILSA demonstrated that while dietary fatty acids intakes were not associated with incident MCI, high PUFA intake appeared to have borderline non-significant trend for a protective effect against the development of MCI [271].

A significant inverse correlation was found between the fraction of calories derived from cereals and AD prevalence [101]. Cereals are the primary sources of copper, manganese, and selenium in most diets and the major source of zinc in many vegetarian diets [93]. While whole grains have antioxidant vitamins and minerals, it is not clear whether the cereals generally consumed are whole grains. Therefore, this relationship could be due to the fact that countries with low fat supply have high cereals supply, rather than to a direct therapeutic effect of the cereals. Moreover, phytate, which is present in staple foods like cereals, corn and rice, has a strong negative effect on zinc absorption from composite meals [94,161].

There are now treatments able to ameliorate cognitive symptoms in AD [55]. Nonetheless, at present, there is no intervention that could slow down, or ideally reverse, the progression of AD pathogenic changes. The promising preliminary results of propentofylline [187], a xanthine developed for this purpose, were not confirmed in a subsequent large clinical trial, the Propentofylline Plus Study [51]. The relatively short-term use of a neuroprotective substance would hardly markedly modify the progression of a neurodegenerative disorder as AD [92]. Interestingly, caffeine, another xanthine, is the most widely consumed behaviourally active substance in the Western countries [84]. Neuroprotective effects for chronic administration of caffeine were shown in experimental models of hypoxia and ischaemia [170]. If caffeine intake could protect against neurodegeneration in AD, then higher levels of caffeine consumption in normal subjects as compared with AD patients should be detectable in the presumably long period when insidious pathogenic changes of AD are taking place. A recent study with a retrospective design showed an inverse association between caffeine intake and AD [170]. By authors, this inverse association was explained by a long-lasting unknown genetic or
environmental factors that might favour the inclination for caffeine consumption, and also protect from AD. Caffeine intake was found to be also associated with a lower incidence of another neurodegenerative disorder, Parkinson’s disease, in a large longitudinal study [250].

Epidemiological studies have recently reported an association between wine consumption and the incidence of AD [134]. Particularly, red wine, another component of Mediterranean diet, was investigated in the PAQUID study, in which the relative risk for dementia and AD among 318 subjects who drank three or four glasses of wine each day in comparison with 971 total abstainers were 0.21 and 0.25, respectively. Among the 922 older subjects who drank no more than one or two glasses of wine each day respect to the abstainers the relative risk for AD was reduced significantly (0.55) [210]. A possible mechanism for the protective effect of wine is provided by the antioxidant properties of polyphenoles which are most prominent in red wine. These effects are independent of alcohol and can also occur in alcohol-free red wine [259]. More recently, the relation between alcohol consumption and risk of dementia (AD, VaD, or other dementia) was examined in the Rotterdam Study. The findings of this study, with an average follow-up of 6 years, suggested that light-to-moderate alcohol consumption is associated with a reduced risk of dementia in individuals aged 55 years or older; this effect seems to be unchanged by the source of alcohol [251] (Table 1). In the Rotterdam study, the protective effect of alcohol drinking was found mainly for VaD, and the authors suggested that moderate alcohol intake might protect against dementia via a reduction in vascular risk factors [251]. In a nested case-control study on 373 cases with incident dementia and 373 controls who were among 5,888 adults aged 65 years and older, and participated in the Cardiovascular Health Study (CHS), the adjusted odds ratio for dementia among whose weekly alcohol consumption was less than 1 drink were 0.65, compared with abstention; 1 to 6 drinks, 0.46; 7 to 13 drinks, 0.69; and 14 or more drinks [202]. In the Copenhagen City Heart Study, the risk of developing dementia was significantly lower among occasional wine drinkers, in weekly drinkers and, but not significantly, in daily drinkers. An increased risk for beer and for spirits was found in occasional, weekly, and daily drinkers [282].

A trend toward greater odds for dementia associated with heavier alcohol consumption was most apparent among men and participants bearing an APOE ε4 allele, with similar relationships of alcohol use with AD and VaD [202]. The findings from the CHS were consistent with the PAQUID Study [210] and the Rotterdam Study [251], but suggested a higher risk of dementia with consumption greater than 2 drinks per day. The results of the CHS were also consistent with those of the Epidemiology of Vascular Aging Study which found that alcohol intake was associated with a lower risk of cognitive deterioration among subjects without an APOE ε4 allele, but a higher risk in APOE ε4 carriers [57]. Surprisingly, the Rotterdam Study found that the lower risk of dementia associated with alcohol use was more consistent among individuals with an APOE ε4 allele [251], but no significant interaction was detected. Finally, in the Washington Heights Inwood-Columbia Aging Project, with 908 subjects aged 65 years and older, consumption of up to three servings of wine daily is associated with a lower risk of AD in elderly individuals without the APOE ε4 allele [167].

As seen above for cognitive decline, some have claimed there is a J or U shaped relation also between alcohol drinking and dementia [129,159,210,251], while a recent study showed no U shaped relation for dementia, but the APOE genotype seemed to modify the relation, with risk of old age dementia increasing with increasing midlife alcohol consumption only among carriers of the APOE ε4 allele [6]. Therefore, genetic susceptibility seems to modify the effect of alcohol on risk of dementia. The observation that APOE ε4 allele may modify the effect of alcohol is in agreement with the concept that cognitive status is the consequence of both genetic and environmental factors. One possible explanation could be that people with the ε4 allele have less effective neural repair mechanisms [169], and thus they would be more susceptible to the deleterious effects of alcohol.

Alcohol use might be inversely associated with dementia through protective changes in cerebral vasculature. In fact, a light-to-moderate alcohol use is associated with a lower prevalence of MRI-defined white matter lesions and sub-clinical infarcts [202], but MRI findings, HDL cholesterol levels, and fibrinogen levels only modestly mediated the association of alcohol use and dementia in the CHS [202]. Finally, light-to-moderate alcohol intake is associated with a lower prevalence of vascular brain findings and, in apoE4 carriers, with hippocampal and amygdale atrophy on MRI [50]. Experimental studies found than ethanol initially increases hippocampal acetylcholine release, which could conceivably improve memory performance [65].

The Mediterranean diet could be therefore an interesting model to further study the association between dietary patterns and cognitive functioning, given the
suggested role of many components of this diet (MUFA, cereals, and red wine) in contrasting cognitive impairment [101,133,251,266,269–271]. The typical dietary pattern of Mediterranean diet is characterized by high intakes of vegetables, fruits and nuts, legumes, cereals, fish, and MUFA; relatively low intakes of meat, and dairy products, and moderate consumption of alcohol. In fact, higher levels of consumption of olive oil are considered the hallmark of the traditional Mediterranean diet. In particular, MUFA, consequently to the high consumption of extra-virgin olive oil, represent the most important fat in Mediterranean diet. Cumulative evidence suggests that extra-virgin olive oil may have a role in the protection against cognitive decline [266, 270,271], other than against coronary disease and several types of cancer because of its high levels MUFA and polyphenolic compounds.

Very recently, Scarmeas and colleagues reported the results of a community-based study involving 2,258 nondemented individuals in New York, in which adherence to a traditional Mediterranean diet was associated with significantly reduction in risk for AD [258]. However, in the study of Scarmeas and colleagues, the median daily intake of MUFA to SFA ratio for individual food categories by Mediterranean diet score tertiles was <1 and in overall about 2.5 times lower than the same value calculated from other studies on Mediterranean diet [272]. Scarmeas and colleagues, used in this report a scale indicating the degree of adherence to the traditional Mediterranean diet originally constructed by Trichopoulou and colleagues [283] and revised to include fish intake [126]. A value of 0 or 1 was assigned to each of nine indicated components with the use of the sex-specific median as the cut-off. The total Mediterranean-diet score ranged from 0 (minimal adherence to the traditional Mediterranean diet) to 9 (maximal adherence).

The wide diffusion of this methodological approach exploring possible associations between dietetic habit, in particular Mediterranean diet, and several outcomes in more and more epidemiological areas (cancer, cardiovascular disease, or dementia) has undeniable advantages but some concern it should be admit. The advantages in using composite score (MeDi) for adherence to a particular dietary pattern were largely described [126, 283]. On the other hand, several devices related to the use of dietary composite score should be considered, in evaluating the effects of nutrient intakes in different groups (low and high consumption) in unbiased manner [273]. In particular, a variation in group heterogeneity, which could be caused by selection of cut-offs, can change in predictable ways the reliability and validity of the scale indicating the degree of adherence to a particular dietary pattern. The effects of change in observed-score variance on reliability can be estimated, if it is assumed that error variance remains constant after selection. On the basis of these considerations, it is not difficult to guess that a “whole-diet approach” such as MeDi could not be readily transferred to other populations, included study population traditionally eating according to Mediterranean dietary pattern. Finally, the parameters which are used for composite score deriving from different unit of measurements (grams for food and nutrients and measurement of ratio for the ratio of MUFA to SFA) should be transformed in normative scores to allow they may be comparable across the individual component of interest of the MeDi [273].

These findings strongly suggested that further observational studies on cognitive impairment need to be implemented on the adherence to a specific dietary pattern rather that association studies with single nutrients. If successfully replicated, randomized clinical trials should ideally follow to specifically address the question of whether a dietary pattern may have a role in the prevention of cognitive impairment. A recent study by Small and colleagues, in people with mild age-related memory complaints, demonstrated the positive effects of a 14-day healthy longevity lifestyle program on word fluency, and activity in the left dorsolateral prefrontal cortex at [fluorine-18]fluorodeoxyglucose (FDG) positron emission tomography (PET) scans in comparison of the control. Cardiovascular conditioning and brief relaxation exercises designed to lower stress are recommended each day. Suggested shopping lists and menus guide subjects to follow a healthy diet plan, including five daily meals emphasizing antioxidant fruits and vegetables, n-3 PUFA, and low glycemic index carbohydrates [263]. The conceptual basis for the healthy diet plan suggested in the study of Small and colleagues was that diets high in n-3 PUFA from olive oil or fish, as well as those rich in antioxidant fruits and vegetables, are associated with less ARCD. It is also possible that moderate lifestyles in general, which obviously vary according to different cultural environments, protect from cognitive deterioration. Thus, it may not be the direct effect of diet or specific nutrients that provide the protection, but healthy diets very similar to the Mediterranean diet pattern may be an indicator of a complex set of favourable social and lifestyle factors [222]. Future longitudinal studies will determine the long-term effects of such interventions, whether they eventually lower the risk for developing cognitive impairment, and the weight of a specific di-
etary pattern in these combined healthy lifestyle programs.

Many lines of evidence have focused on the importance of oxidative stress mechanisms and free radical damage in AD pathogenesis [103]. The complex nature and genesis of oxidative damage in AD can be partly answered by mitochondrial and redox-active metal abnormalities. Evidence indicates that in the initial phase of AD development, A\(\beta\) deposition and hyperphosphorylation of tau, hallmarks of the disease, are consequences of oxidative stress [290]. Many free radical scavengers are present in food, particularly in fresh fruit and vegetable (eg, as carotenoids and flavonoids) [291]. Regular consumption of antioxidants in the diet may have a beneficial effect in humans [30]. Vegetarian diet contains more antioxidant vitamins (vitamin C, vitamin E, and \(\beta\)-carotene) and copper than that of omnivores. Intake of zinc is generally comparable to that by omnivores. However, the bioavailability of zinc in vegetarian diets is generally lower than that of omnivores [234]. Furthermore, data on the relationship between vegetable and fresh fruit consumption and risk of degenerative disease demonstrated that other nutrients in addition to the well-known antioxidants may play important roles in the central nervous system [172]. Moreover, fresh fruits and vegetables could also have protective effects against stroke [96] and subsequently against VaD. In fact, in a recent study, the risk of poststroke dementia is high (28.5% in a 3-year follow-up, with most of patients during the first 6 months after stroke), with about one-third of patients meeting the criteria for AD and two-thirds meeting the criteria for VaD [117].

The AD brain is under intense oxidative stress, and A\(\beta\) leads to neuronal lipid peroxidation, protein oxidation and DNA oxidation by mechanisms that are inhibited by free-radical antioxidants, particularly vitamin E, and involve the single methionine residue of this peptide [31–33]. Further, synaptosomes from allele-specific APOE knock-in mice have tiered vulnerability to A\(\beta\)(1-42)-induced oxidative stress, with APOE4 more vulnerable to A\(\beta\)(1-42) than are those from APOE2 or APOE3 mice. Taken together, the findings from \textit{in-vitro} studies of lipid peroxidation induced by A\(\beta\)(1-42) and postmortem studies of lipid peroxidation (and its sequela) in AD brain may help explain the APOE allele-related risk for AD, some of the functional and structural alterations in AD brain, and strongly support a causative role of A\(\beta\)(1-42)-induced oxidative stress in AD neurodegeneration [32].

Some recent epidemiological studies supported the protective role of antioxidants against AD. In fact, in a sub-sample of 1416 subjects from the PAQUID cohort, those who ate fish or seafood at least once a week had a significant reduced risk of incident dementia adjusted for age and sex. Moreover, a nested case-control study was performed among 182 subjects. Adjusted for confounders, the risk of dementia was significantly increased for the lowest vitamin E concentration compared to the highest one, confirming a possible protective role of a diet rich in polyunsaturated fats and antioxidant components [152]. Moreover, in another nested case-control study within the PAQUID cohort among 626 subjects, after adjusting for confounders, the risk of dementia was significantly increased in the lowest vitamin E tertile compared to the highest one, while risks for dementia and AD associated with vitamin A were nonsignificant. Similarly, there was a trend to an increased risk of dementia in the highest tertile of malondialdehyde plasma concentrations, a final lipid peroxidation product, suggesting that subjects with low plasma vitamin E concentrations are at a higher risk of developing a dementia in subsequent years [115]. In a recent study, final lipid peroxidation products were significantly higher in mild and moderate AD with respect to controls, but not in severe AD patients, with a significant inverse correlation between disease severity and lipid peroxidation [90]. Thus, oxidative stress, expressed as \textit{ex vivo} susceptibility to plasma lipid peroxidation, appears to be an early phenomenon, probably related to AD pathogenetic mechanisms. In the same study, treatment of a subgroup of mild and moderate AD patients with vitamin C and E for three months decreased plasma lipoperoxidation susceptibility by 60% [90]. Promising antioxidant strategies, with the focus on fighting oxidative stress, appear to be the most encouraging therapeutics in reducing the clinical manifestation and evolution of AD [193]. The possibility of the therapeutic use of antioxidants and free radical scavengers (eg, vitamin E, Gingko Biloba extract EGb 761, melatonin, flavonoids, and carotenoids) to reduce the risk or slow the progression of the disease has been suggested [254].

4. Metals, aluminium from drinking water and foods, and dementia

Different studies suggested possible effects of metals in affecting cognitive function, because of their involvement in metabolic process and redox reaction of the central nervous system [30]. Particular attention has been focused on aluminium (Al) since excessive
Al concentration has been shown both in bulk brain samples and in NFTs and SPs [19, 24, 63, 110, 179, 181, 257], despite this toxic element having a low permeability of the blood-brain barrier [24]. Moreover, a possible interference of Al with aging and dementia has been suggested by animal experimental studies where neuropathological and clinical modifications associated with administration and a long-term exposure of Al that resembled those diagnosed in AD were observed in the animals [66, 188, 189]. In addition, the association between Al and AD has been also supported by one clinical study that reported a decrease in the rate of disease progression in AD patients treated with desferrioxamine, a trivalent ion chelator [43, 180].

So far, the most of epidemiological studies on Al and AD have focused on exposure through drinking water [76, 77, 208]. In fact, dissolved Al is present naturally as a result of leaching from minerals in the soil and bedrock in the catchment of the water source. Moreover, Al is widely used in water treatment as a coagulant, to reduce the number of small particles and improve the colour of the water. However, there is controversy about the possible link between Al and AD. The first studies conducted in Norway population indicated a dose-response relationship between Al in drinking water and mortality of dementia [74, 289]. Later, several other epidemiological studies have been performed in different populations and reported inconsistent results. In fact, some reports confirmed the hypothesis that a high concentration of Al in drinking water may be a risk factor for dementia and cognitive impairment [54, 78–80, 83, 173, 174, 185, 206, 248], while others failed to reproduce these findings [28, 34, 81, 279, 294], or reported an association between cognitive impairment and Al depending on water pH and the silica concentration [130, 131]. In one study carried out speciation of Al, only exposure to organic monomeric Al estimated at the onset of the disease was associated with AD, after adjustment for education level, presence of family cases, and APOE ε4 allele, suggesting the importance of analysis of Al speciation and consideration of genetic characteristics in the assessment of the association between Al and AD [91].

The positive relationship between Al in drinking water and AD, which has been shown in the majority of the epidemiological studies, cannot be totally dismissed, although the relative risks for AD from exposure to Al were generally low. Nonetheless, all the individual epidemiological studies of Al in drinking water are more or less open to critique, particularly considering the difficulty in producing high-quality data for exposure and especially for the disease [162]. A fundamental difficulty in the interpretation of the epidemiological studies indicating increased risk for AD with increased Al concentrations in drinking water is that even at high concentrations (0.1–0.4 mg/l) drinking water accounts for less than 5% of total daily Al intake. Moreover, in contrast with the findings of these epidemiological studies is that many studies examining antacid exposure and AD have been largely negative, being the typical daily dose of antacids 1 g of Al or more, that is thousands of times more than the amounts taken in through drinking water [160]. Finally, a very recent report investigated at baseline the potential association between the composition of drinking water and the level of cognitive function in women taking part in the Epidemiology of Osteoporosis (EPIDOS) Study, determining during follow-up the effects of the composition of drinking water on the risk of AD. This study found that a low silica concentration was associated with low cognitive performance at baseline, and a multivariate analysis including potential confounding factors showed that women with AD appeared to have been exposed to lower amounts of silica at baseline, suggesting a protective role against AD of silica in drinking water [95].

There are only a few studies devoted to investigating the relationship between Al in food and AD. One pilot study [243] that focused on foodstuffs high in Al due to aluminium-containing food additives [109] showed a crude odds ratio (OR) of 2.0 for daily intake of any such high-Al foodstuffs and OR of 8.6 adjusted for kilocalories, body mass index, education, and intake of vitamins A, C, and E. Although suggestive, the results of this study clearly need to be reproduced in larger studies before too much confidence can be placed in them. It has been suggested that, even with a normal dietary intake, AD patients have increased absorption of Al, supporting the hypothesis that a long-term diet high in acid-forming foods such as proteins leads to increased Al absorption even after the diet has changed [240]. Tea consumption has also been investigated, since tea infusions contain rather large amounts of Al, typically 2–6 mg/l [61]. Three of these studies showed slightly, but non significantly elevated ORs. In addition, patients with an increased serum Al have been found to experience a variety of memory disturbances [123], due to a marked deficiency of zinc and/or manganese, and high aluminium concentration has been shown to be strictly correlated with AD [264]. The combined weight of evidence seems to suggest that, if Al does play an active role in AD, it more likely acts as a co-
factor somewhere in the cascade of events leading to the demented brain. Since the exact mechanism of Al toxicity is not known and a direct causal role has not been determined, it is likely to suppose that the buildup of Al in the brain of AD patients is the result of damage to nerve cells, rather than the cause of this damage. Finally, epidemiological studies of matched cohorts of elderly people are needed to resolve the current controversy on the role of Al in the pathogenesis of AD with particular attention to known or suspected confounding factors, such as APOE allele status and family history of the disease.

A role for other metals in dementia have been speculated, as recent studies showed that Aβ houses atoms of zinc, copper and iron deep within its folds, and in turn the ionic concentrations of zinc, copper or iron may influence the structure and aggregated state of Aβ peptide [69,163]. There is also evidence indicating that zinc, copper, and iron are significantly elevated in the AD brain [10], and drugs with metal chelating properties could produce a significant reversal of Aβ plaque deposition in vitro and in vivo [37].

Dual effects of zinc on Aβ toxicity in vitro have been suggested. In fact, some studies reported that higher zinc concentration enhances Aβ toxicity [164, 192]. While other reports showed that low zinc concentrations directly or indirectly protects against Aβ toxicity [44,86,164,299], likely by inhibiting neurotoxicity through displacing copper and iron enriched in Aβ plaques and suppressing cell-free H₂O₂ production [34], or probably through enhancement of Na⁺/K⁺-ATPase activity that prevents the disruption of calcium homeostasis and cell death associated with Aβ toxicity [164]. In animal models, synaptic zinc contributes predominantly to amyloid deposition [154]. Moreover, it is known that an adequate zinc is necessary to maintain the integrity of all biological membranes [231], and it was found, when experimenting with rats fed with sub-optimal zinc, that aluminium concentrations increased three-fold in the frontolateral cortex and eight-fold in the hippocampus [292]. Therefore, it has been suggested that suboptimal zinc nutrition may lead to leaky blood-brain barrier and thereby increase transfer of aluminium and other toxins to the brain, likely causing AD [27]. The onset of senile dementia has also been associated with zinc deficiency, due to a possible genetically based progressive inability of neurons to incorporate zinc ions into the DNA-handling system [29]. On the other hand, zinc is fairly redox inert and should be considered as indirect antioxidant. Therefore studies suggested that when taken daily for 1 year zinc delay the cognitive decline observed in AD subjects [229,286]. Although encouraging, it is also possible that the improvement in cognition observed in these studies may be due to other factors rather than the only zinc supplementation. Finally, there is a possible link between diet and brain zinc metabolism in AD. In fact, zinc transporter (ZnT) 3 has been identified as a putative transporter of zinc into synaptic vesicles of neurons and is found in brain areas such as hippocampus and cortex. A very recent study evaluated the influence of dietary omega-3 PUFA on the expression of the ZnT3 gene in the brains of adult male Sprague-Dawley rats, suggesting that over-expression of ZnT3 due to a perinatal omega-3 PUFA deficiency caused abnormal zinc metabolism in the brain [133]. Therefore, this suggested influence of dietary omega-3 PUFA on brain zinc metabolism could explain the observation made in population studies that the consumption of fish is associated with a reduced risk of dementia and AD [13,269].

Inconsistent results have been reported from studies on peripheral zinc concentrations in AD patients compared to non-demented controls. In fact, some studies found increased serum zinc levels in AD subjects [104,252], while others did not observed any difference [16,285]. Similarly, reports on zinc cerebrospinal fluid concentrations produced highly variable results [16,46,252], while others did not observed any difference [16,190]. These inconsistencies may be related to different methodologies used, technical difficulties and small sample size. Finally, more information is needed to clarify the hypothetical role of dietary zinc in AD.

Unlike zinc, copper, and to a lesser extent iron, appear to be the most serious metal toxicities in AD. Copper enhances β-sheet formation of Aβ fibrils under slightly acidic conditions, and this enhancement is potentiated by APOE ε4 [191]. Given the elevated concentration of copper in SPs, copper interactions with Aβ could be responsible for causing the covalent di-tyrosine cross-linking of Aβ in these structures [11]. Furthermore, copper binds more strongly to Aβ/42 than to Aβ/40 and is a greater catalyst of free radical formation than are the other metals [144]. It has been also demonstrated that copper depletion significantly reduced APP protein levels and down-regulated APP gene expression, suggesting that copper can regulate APP expression and further supporting a role for APP to function in copper homeostasis [20]. In vivo studies defined an inverse relationship between copper levels in the CNS and amyloid burden, indicating that increasing the amounts of copper in mouse models of amyloidogenesis, either by genetic manipulation or by
dietary intervention, seems to reduce Aβ concentrations and develop of pathogenic Aβ plaques [18,228]. These findings were supported by studies in cultured cells which revealed that copper inhibits Aβ production and stimulates the non-amyloidogenic pathway of AβPP secretion [25].

A perturbation of copper homeostasis specific to AD patients, consisting of elevation of serum copper levels, has also been suggested by some studies [26,104,264,265,275–277]. Particularly, the results of a very recent study showed that the portion of serum copper unexplained by ceruloplasmin can discriminate subjects with AD from both normal controls and subjects with VaD better than copper explained by ceruloplasmin [277]. The authors proposed that the excess of serum copper in AD could be explained by an efflux from cortical cells, and that the increase of the copper fraction explained by ceruloplasmin, a marker of inflammation, may be related to general inflammatory mechanisms [277] which likely contribute to disease pathogenesis. Nonetheless, other studies did not find differences in serum copper levels between AD and controls [104,215]. Although copper homeostasis seems to be altered in AD, current data do not indicate that serum copper, either bound with ceruloplasmin or not, may be a marker for AD.

Support to the role for copper in AD came from a rabbit study. The authors found that cholesterol-fed rabbits were more likely to develop Aβ plaques in their brains if they were given tap water or distilled water spiked with copper supplements to drink, rather than purified distilled water. The copper-dosed rabbits also suffered dramatically poorer memories in complex tests [274]. They supposed that copper combined with cholesterol may prevent the brain from the clearance of Aβ protein. Epidemiological studies in humans might be noteworthy and revealed whether there is a correlation between copper in the water and AD. All together these results still leave open the debate on the role of copper in the pathogenic process of the disease, and suggest further investigation with consideration of diet, life style, and genetic background.

Like copper, iron has been hypothesized to contribute to the pathogenesis of AD, via the similar mechanisms seen for copper. Specifically, iron may participate to oxidative stress, and thus take part to the cascade of events that progressively increase oxidative damage in AD patients. It has been reported that RNA-bound iron plays a central role for RNA oxidation in vulnerable neurons in AD brain [121]. In vivo quantification of brain iron indicated increase in basal ganglia ferritin iron levels in AD patients [14], and in the younger-onset group of AD compared to its respective control group, but not in the older-onset patients [15], supporting the hypothesis that iron metabolism is disrupted in the ganglia of AD, and that elevated ferritin iron and its toxicity is a risk factor for age at onset of AD.

Further, as copper, iron has also been found to promote lipid peroxidation and cause damage to membrane proteins [281], and act as a transcriptional regulator of the AβPP [242]. Alterations of iron homeostasis have been associated with changes in the synthesis of heme, a form of iron critical to cell functioning. It has been reported that heme deficiency in human brain cells causes modifications in mitochondrial complex IV, AβPP, nitric oxide synthase, zinc and iron homeostasis, causing cells to degenerate and produce abnormal proteins; the damage observed in the cells deprived of heme parallels that seen in cells with AD [8]. One mechanism for the harm may be oxidative stress, or the mitochondrial decay that may play a crucial role in maintaining supply of heme. Deficiency in specific nutrients of the diet as iron or vitamin B6, and exposure to aluminium or other toxic metals, which are quite common for aging people may influence heme synthesis in brain cells [8]. In this view, vitamins B5, B6 and biotin could be of the most benefit. In a more recent paper, Atamna et al. compared heme levels in the autopsied brains of people with AD to those without the disease and found that heme-b in AD brains was increased to about three times its level in the normal brains [9]. They suggested that Aβ binds heme and reduces heme bioavailability, thus inducing functional heme deficiency. However, more data are needed that would likely to support these findings looking deeper into a possible role of iron in brain disease.

Finally, in different studies mercury was elevated in AD patients in most brain regions studied, but the high variability of mercury levels in both AD and control subjects prevented the AD-control difference from reaching significance [39,88], not supporting the hypothesis that mercury plays a significant role in the AD pathogenesis. On the other hand, blood levels of mercury, but not CSF levels [16], were increased in AD patients as compared to control subjects [16,119], with one notable exception [87], suggesting that yet unidentified environmental sources or release from brain tissue with the advance in neuronal death could be related to this increase. Dental amalgam releases low levels of mercury vapor and is a potential source of mercury for a large segment of the adult population, but, at present, but it was found no significant association of AD with...
the number, surface area or history of having dental amalgam restorations, suggesting that mercury in dental amalgam restorations does not appear to be a neurotoxic factor in the pathogenesis of AD. Finally, some investigators have suggested that apolipoprotein E ε4 allele has a reduced ability to bind metals like mercury and therefore explain the higher risk for AD [97,205].

In conclusion, evidence shows that metal ions such as Al, zinc, copper and iron play a role in the precipitation and cytotoxicity of Aβ [45,122] (Fig. 1). Despite recent advances in AD research, there is a lack of therapeutic agents to hinder the apparent aggregation and toxicity of Aβ. Recent studies show that drugs with metal chelating properties could produce a significant reversal of Aβ plaque deposition in vitro and in vivo. Therefore, although alterations in transition metal homeostasis, redox activity, and localization are well documented, it must be determined how alterations of specific copper- and iron-containing metalloenzymes are also involved in AD. The clarification of these phenomena can open a new window for understanding the mechanisms underlying neurodegeneration and, consequently, for the development of new therapeutic strategies such as gene therapy and new pharmaceutical formulations with antioxidant and chelating properties [194]. In fact, an early study indicated that sustained intramuscular administration of a potent iron chelator-desferrioxamine slowed the clinical progression of AD [43]. Moreover, a mild cognitive improvement has been reported for a small-scale open study of 30 AD patients following a 3 week treatment regime with another metal-complexing agent-clioquinol [236].

Further, a recent pilot phase II trial of clioquinol with double-blind placebo control has shown that the clioquinol treatment arrested cognitive decline and lowered plasma Aβ1-42 levels in AD subjects [238]. A major problem associated with widespread clinical use of metal-complexing agents is their poor target specificity and consequential clinical safety. In fact, the long-term use of these agents is likely to perturb the homeostasis of many biometals and normal physiological functions of essential metal-requiring biomolecules, thus, a new class of metal-complexing agents that specifically target amyloid is required. In particular, preliminary findings on a novel bifunctional molecule-XH1 indicated this agent as a candidate metal chelator targeting Alzheimer’s amyloidogenesis and warrant further investigations [48]. Moreover, curcumin, a polyphenolic diketone from turmeric with anti-oxidant and anti-inflammatory effects, it was tested in animal models of AD, reducing levels of amyloid and oxidized proteins and preventing cognitive deficits. An alternative mechanism of these effects is metal chelation, which may reduce amyloid aggregation or oxidative neurotoxicity. Since curcumin more readily binds the redox-active metals iron and copper than redox-inactive zinc, curcumin might exert a net protective effect against Aβ toxicity [17].

5. Conclusions

Although the intake of macronutrients is easier to quantify, few studies have evaluated the relationship among macronutrients or the basic elements of CHO (glucose administration or depletion) and protein (amino acids such as tryptophan and tyrosine) and cognitive function. The availability and utilization of glucose which is the primary substrate of neuronal metabolism has 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. The quality of dietary proteins, in terms of the aminocacidic 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. In addition, dietary fat and energy in older people seem to be risk factors, while fish consumption and cereals are found to reduce the prevalence of AD in the European and North American countries. Furthermore, there is increasing evidence that a disturbed glucose metabolism, oxidative stress and formation of advanced glycation endproducts and their interaction in a vicious cycle are also important for the onset and progression of AD. It is also known that, in women, a chronic exposure to an excess of energy intake and the resulting obesity protect them from AD. This epidemiological observation has been explained based on a greater availability of estrogens in obese women, given that adipose tissue is the major endogenous source of estrogen in menopausal women. Furthermore, epidemiological studies have recently reported an association between wine consumption and the incidence of AD. A possible explanation for the protective effect of wine is provided by the antioxidant properties of polyphenols which are most prominent in red wine. Moreover, foods with large amounts of aluminium-containing additives or aluminium from drinking water may affect the risk of developing AD. The positive relationship between Al in drinking wa-
ter and AD has been shown in the majority of the epidemiological studies, although the relative risks for AD from exposure to Al were generally low and all the epidemiological studies of Al in drinking water have some limitations. There are only a few studies on the relationship between Al in food and AD, and the combined body of evidence seems to suggest that Al may play an active role in AD but probably as a cofactor. A role for other metals in dementia, e.g. zinc, copper, and iron, have been speculated. Inconsistent results have been reported from studies on peripheral zinc concentrations in AD patients, with the onset of dementia associated with zinc deficiency, and with some studies suggesting that zinc supplementation may delay the cognitive decline observed in AD patients. Although copper homeostasis seems to be altered in AD, current data do not indicate that serum copper, either bound with ceruloplasmin or not, may be a marker for AD. In vivo quantification of brain iron suggested that iron metabolism is disrupted in the ganglia of AD, and that elevated ferritin iron and its toxicity is a risk factor for age at onset of AD. However, more data are needed to support a possible role of iron in dementia diseases. Dietary antioxidants and supplements and specific macronutrients of the diet may act synergistically with other protective factors opening new possibilities of intervention for dementia and cognitive decline (Fig. 1). A style of diet based of complex CHO, fibers, cereals, red wine, fresh fruit and vegetables, and nonanimal fat appears to protect against predementia syndromes, and cognitive decline of vascular or degenerative origin. At present, in patients with dementia, healthy diets, antioxidant supplements, and the prevention of nutritional deficiencies or exposure to foods and water with high content of Al or other metals, could be considered the first line of defense against the development and progression of cognitive decline.

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Conflict of interests

None declared.

References


[60] T.P. Flaten, An Investigation of the Chemical Composition of Norwegian Drinking Water and its Possible Relationships with the Epidemiology of Some Diseases, Department of Chemistry, Norwegian University of Science and Technology, Trondheim, Norway, 1986.


[244] R.D. Rogers, B.J. Everitt, A. Baldacchino, A.J. Blackshaw, B.G. Chandler, M.A. Rogers, D.G. Simon and M. Thomas, Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, pa-
V. Solfritti et al. / Macronutrients, aluminium from drinking water and foods, and other metals


