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Diet and Alzheimer’s disease risk factors or prevention: the current evidence


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Preventing or postponing the onset of Alzheimer’s disease (AD) and delaying or slowing its progression would lead to a consequent improvement of health status and quality of life in older age. Elevated saturated fatty acids could have negative effects on age-related cognitive decline and mild cognitive impairment (MCI). Furthermore, at present, epidemiological evidence suggests a possible association between fish consumption, monounsaturated fatty acids and polyunsaturated fatty acids (PUFA; in particular, n-3 PUFA) and a reduced risk of cognitive decline and dementia. Poorer cognitive function and an increased risk of vascular dementia (VaD) were found to be associated with a lower consumption of milk or dairy products. However, the consumption of whole-fat dairy products may be associated with cognitive decline in the elderly. Light-to-moderate alcohol use may be associated with a reduced risk of incident dementia and AD, while for VaD, cognitive decline and predementia syndromes, the current evidence is only suggestive of a protective effect. The limited epidemiological evidence available on fruit and vegetable consumption and cognition generally supports a protective role of these macronutrients against cognitive decline, dementia and AD. Only recently, higher adherence to a Mediterranean-type diet was associated with decreased cognitive decline, although the Mediterranean diet (MeDi) combines several foods, micro- and macro-nutrients already separately proposed as potential protective factors against dementia and predementia syndromes. In fact, recent prospective studies provided evidence that higher adherence to a Mediterranean-type diet could be associated with slower cognitive decline, reduced risk of progression from MCI to AD, reduced risk of AD and a decreased all-cause mortality in AD patients. These findings suggested that adherence to the MeDi may affect not only the risk of AD, but also of predementia syndromes and their progression to overt dementia. Based on the current evidence concerning these factors, no definitive dietary recommendations are possible. However, following dietary advice for lowering the risk of cardiovascular and metabolic disorders, high levels of consumption of fats from fish, vegetable oils, nonstarchy vegetables, low glycemic index fruits and a diet low in foods with added sugars and with moderate wine intake should be encouraged. Hopefully this will open new opportunities for the prevention and management of dementia and AD.

**KEYWORDS:** alcohol consumption • Alzheimer’s disease • dairy products • dementia • fruits • Mediterranean diet adherence • mild cognitive impairment • MUFA • predementia syndromes • PUFA • vegetables

Owing to aging populations, dementia and late-life cognitive disorders are reaching epidemic proportions. In Western 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 [1]. AD is a progressive neurodegenerative illness that affects 5.3 million people in the USA [2], with >26 million patients with AD worldwide, and an expected increase to more than 106 million by 2050 [3]. Currently, clinicians use the term AD to refer to a clinical entity that typically presents with a characteristic progressive amnestic disorder with the subsequent appearance of other cognitive, behavioral and neuropsychiatric changes that impair social function and activities of daily living [4]. The initial presentation can also be atypical, with nonamnestic focal cortical cognitive symptoms [5]. AD is both multifactorial and heterogeneous, involving 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 the misprocessing of the amyloid precursor protein (APP), a type-1 transmembrane protein, by β- and γ-secretases to form a toxic β-amyloid (Aβ) peptide of 40–42 amino acids [6] that aggregates and initiates a pathogenic self-perpetuating cascade, ultimately leading to neuronal loss and dementia. According to the updated version of the ‘amyloid cascade hypothesis’ [7], the development of SPs is thought to precede and precipitate the formation of NFTs as a result of the cellular changes invoked, and the oligomeric forms of Aβ1–42 are the main cause of neuronal death in AD [8,9].

The term ‘predementia syndrome’ identified 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 of early stages of dementia [10]. Therefore, this ‘umbrella term’ includes different conditions and, among them, mild cognitive impairment (MCI) is currently the most widely used term to indicate nondemented aged persons with no significant disability and a mild memory or cognitive impairment that cannot be explained by any recognized medical or psychiatric condition [11]. There is now ample evidence that MCI is often a pathology-based condition with a high rate of progression to AD [10]. However, in population-based studies, MCI classification is less consistent than in clinical series, suggesting that MCI is a heterogeneous descriptor and that the outcome at follow-up depends on which population is studied and how MCI is defined, with a quota of MCI subjects remaining cognitively stable or improving after a brief follow-up [10]. Very recently, with the advances in the use of reliable biomarkers of AD that provide in vivo evidence of the disease, new research criteria that reconceptualize the diagnosis around both a specific pattern of cognitive changes and structural/biological evidence of AD pathology were proposed [12].

The International Working Group for New Research Criteria for the Diagnosis of AD proposed a common lexicon as a point of reference for the clinical and research communities. The cornerstone of this lexicon was to consider AD solely as a clinical and symptomatic entity that encompasses both predementia and dementia phases [13]. In this new lexicon, the term MCI is applied to individuals with measurable MCI in the absence of a significant effect on instrumental activities of daily living. This diagnostic label was applied if there was no disease to which MCI can be attributed. It remained a term of exclusion for individuals who were suspected to have but did not meet the proposed new research criteria for AD [12], in that they deviated from the clinico‐biological phenotype of prodromal AD because they had memory symptoms that were not characteristic of AD or because they were biomarker negative [13].

The clinical presentation of VaD varies greatly depending on the causes and location of cerebral damage. Given the definitional heterogeneity of VaD, the term vascular cognitive disorder (VCD) has been proposed by Sachdev [14] and it would become the global diagnostic category for cognitive impairment of vascular origin [15]. VCD includes the group of syndromes and diseases characterized by cognitive impairment resulting from a cerebrovascular etiology. The main categories of VCD are vascular cognitive impairment (i.e., vascular cognitive impairment with no dementia and vascular MCI), VaD and mixed AD plus cerebrovascular disease (CVD), previously termed ‘mixed dementia’ [14,15]. In fact, dementia is more likely to be present when vascular and AD lesions coexist, a situation that is especially common with increasing age [16]. Therefore, particularly in late life, we should be interested in preventing the ‘dementia syndrome’ per se with the distinct components being the neuropathologic changes of AD, vascular changes and possibly other neurodegenerative processes [17,18].

**Dietary & vascular-related factors in dementia syndromes**

In the last decade, advances in understanding the neurobiology of AD have translated into an increase in clinical trials assessing various potential AD treatments [19]. However, drugs currently used for the treatment of AD produce limited clinical benefit and do not treat the underlying causes of the disease [19]. Therefore, at present, prevention appears to still be a mandatory option. The causes of dementia and predementia syndromes are unknown; however, some studies have suggested that it may be preventable [20–24]. In fact, epidemiological evidence supported the hypothesis that modifiable vascular and lifestyle-related factors were associated with the development of dementia and predementia syndromes in late life, opening new avenues for the prevention of these diseases [21]. The vascular and related factors that have been associated with dementia and cognitive decline include hypertension and elevated blood pressure [25], total cholesterol [26], diabetes mellitus [27], BMI [27] and the metabolic syndrome [28]. In addition, the presence of cardiovascular and other chronic diseases [29], depression [30] and low levels of physical activity [21] have been identified as risk factors for cognitive decline. By contrast, physical exercise [21,31] and education [21,32] appear to have clear protective effects on cognitive functioning and a possible reduction in incident dementia. For the latter, whether this is due to education per se or related to lifetime occupation and/or level of cognitive exercise is debatable [32].

Since several dietary factors affect the risk of cardiovascular disease, it can be assumed that they also influence the risk of AD [20,21,33–38]. This concept is further supported by recent evidence that certain diets have been associated with a lower incidence of AD. In fact, recent findings demonstrate that maintaining a healthy diet may impact on many of these possible risk factors for cognitive decline and the model to follow seems to be the Mediterranean diet (MeDi) [20]. The typical dietary pattern of MeDi is characterized by a high intake of vegetables, fruits and nuts, legumes, cereals, fish and monounsaturated fatty acids (MUFA); relatively low intakes of meat and dairy products; and moderate consumption of alcohol. In fact, higher levels of consumption of olive oil, very rich in MUFA, are considered the hallmark of the traditional MeDi, and some recent studies have suggested that dietary fatty acids, particularly high MUFA intake and regular fish and n-3 polyunsaturated fatty acid (PUFA) consumption, may play a role in the prevention of cognitive decline.
associated with aging or dementia [39–42]. Elevated dietary MUFA and PUFA n-3 and high fish consumption, alongside high levels of antioxidants from fruit and vegetables [43,44], and moderate alcohol consumption [45,46] may have a beneficial effect on the risk of dementia.

In this article, we examine the possible role of macronutrients and food nutrients, with a particular focus on the MeDi and the adherence to the Mediterranean dietary pattern in modulating the risk of AD and dementia, as well as the possible mechanisms behind the observed associations, from English literature published before January 2011. We review clinical and epidemiological studies from the international literature, including both cross-sectional and longitudinal studies that provided a description of the diagnostic criteria used for predementia or dementia syndromes. We searched through the PubMed database of NCBI (available at [301]) by author and the following keywords: Mediterranean, diet, Mediterranean dietary pattern, adherence, MUFA, PUFA, alcohol consumption, cereals, fruits, vegetables, dairy products, mild cognitive impairment, dementia, Alzheimer's disease, predementia syndromes and MCI.

**Dietary macronutrients & AD**

One of the most intriguing and appealing links hypothesized in recent years is the association between lifestyle factors, such as diet and dietary habits, and the occurrence of AD [33,35]. Deficiencies of some micronutrients (especially vitamins B1, B2, B6, B12, C and folate) have been described quite frequently in elderly people and found to be significantly associated with cognitive impairment [33]. However, the role of the diet in cognitive decline has not been extensively investigated, with few data available on the role of macronutrient intake in the pathogenesis of predementia and dementia syndromes [20,21,33–38]. In this article, we focus on the possible role of macronutrients from the MeDi in protecting against AD. The MeDi, from the south of Europe, represents the dietary pattern usually consumed among the populations bordering the Mediterranean sea, and it has been widely reported to be a model of healthy eating for its contribution to a favorable health status and a better quality of life [302]. Since the first data from Keys from the Seven Countries’ Study in the 1950s to 1960s [47], several studies in different populations have established a beneficial role for the main components of the MeDi on the occurrence of cardiovascular diseases and chronic degenerative diseases [48,49].

The Mediterranean-style diet is characterized by abundant plant food consumption in the form of fruits, vegetables, breads, other forms of cereals, potatoes, beans, nuts and seeds; fresh fruit as the typical dessert; olive oil as the main source of MUFA; dairy products as principally cheese and yogurt; a low-to-moderate consumption of fish depending on the proximity of the sea; a low-to moderate consumption of poultry; fewer than four eggs consumed per week; and low-to-moderate amounts of red meat and wine consumed, normally during meals [50]. However, there is no single MeDi, but several definitions, because dietary habits vary considerably across the Mediterranean countries bordering the sea [51]. Previous observational studies already indicated that specific foods or nutrients that take part in the traditional MeDi (i.e., fish, unsaturated fatty acids [UFA], antioxidants, such as vitamin E, vitamin B12, folates, carotenoids, flavonoids and moderate alcohol) may have potential protective effect against dementia or cognitive decline [20,52]. In the last few years, the study approach has been to associate single micro- or macro-nutrients to MCI or AD. In this picture, several hallmarks of the MeDi were linked to an increased risk or a protective effect against cognitive impairment and AD [20,53,54].

**Dietary fatty acids, fish consumption & dementia**

Fatty acids can be categorized briefly into saturated fatty acids (SFA) and UFA. SFA, such as stearic acid, are present in products such as meat, dairy products, cookies and pastries. MUFA are most frequently consumed in olive oil. The principal series of PUFA are n-6 (i.e., linoleic acid) and n-3 (i.e., α-linolenic acid, docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]). In the Mediterranean dietary pattern, the main sources of n-6 PUFA are vegetable oils, while the principal sources of n-3 PUFA are fatty fish (salmon, tuna and mackerel). In fact, olive oil contains 70–80% MUFA (oleic acid) and 8–10% PUFA (6–7% linoleic acid and 1–2% α-linolenic acid) [39,41,42].

An increasing number of cross-sectional and longitudinal epidemiological and clinical studies have addressed the link between UFA intake and cognitive function [39,41,42,55–65]. Future studies on this topic will address different constructs of predementia syndromes and subtypes of MCI, while also accounting for the possible role of the apolipoprotein E (APOE) ɛ4 allele in modifying the possible associations between dietary fatty acids and cognitive decline [41,42]. As discussed previously, MUFA represented the most important fat in the MeDi as a consequence of the high consumption of extra-virgin olive oil. In US diets, a major source of MUFA is canola oil, while olive oil consumption is much less frequent. Cumulative evidence suggests that extra-virgin olive oil may have a role in the protection against cognitive decline, as well as against coronary artery disease (CAD) and several types of cancer, because of its high levels MUFA and polyphenolic compounds [39,42]. Recently, in the Three-City (3C) Study, olive oil consumption habits were significantly associated with selective cognitive deficit and cognitive decline, independently of other dietary intakes and after adjusting for potential confounders. Intensive use of olive oil in diet is associated with lower odds of cognitive deficit in visual memory and verbal fluency, even if the relationship is not significant when assessing global cognitive functioning with the Mini-Mental State Examination (MMSE) [65]. In the analyses of 732 participants of the European Prospective Investigation into Cancer and nutrition (EPIC)-Greece cohort, intake of olive oil, MUFA and SFA exhibited a weak, but not significant, positive association with cognitive function as assessed by the MMSE, 6–13 years after enrolment [62].

The possible relationship between dietary fatty acids intake and risk of dementia and AD has also been evaluated in a series of longitudinal studies with contrasting findings (Table 1) [66–73]. However, the sum of evidence suggested that an increase of SFA could have negative effect on cognitive functions and incident dementia, while a clear reduction of risk for cognitive decline has
Table 1. Principal longitudinal, clinical and epidemiological studies on the relationships among dietary fatty acids, fish consumption and dementia (i.e., Alzheimer’s disease and vascular dementia) or predementia syndromes (i.e., age-related cognitive decline and mild cognitive impairment).

<table>
<thead>
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<tbody>
<tr>
<td>Kalmijn et al. (1997)</td>
<td>The Zutphen Elderly Study, The Netherlands, longitudinal, population-based (3 years)</td>
<td>476 subjects, aged 69–89 years old</td>
<td>Evaluation of dietary intake with the cross-check dietary history method</td>
<td>Cognitive impairment defined as a MMSE score &lt;25 points and cognitive decline as a drop of ≥2 points of MMSE over a 3-year period</td>
<td>High linoleic acid intake (PUFA) was positively associated with cognitive impairment. High fish consumption was inversely associated with cognitive impairment</td>
<td>[57]</td>
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<tr>
<td>Morris et al. (2004)</td>
<td>The Chicago Health and Aging Project (CHAP), USA, longitudinal, population-based (6 years)</td>
<td>2560 subjects, aged 65 years and older</td>
<td>Evaluation of dietary intake with a 139-item FFQ</td>
<td>Cognitive change at 3-year and 6-year follow-ups measured with the EBMT of Immediate and Delayed Recall, the MMSE and the SDMT</td>
<td>A diet high in saturated and trans-unsaturated fat, or low in nonhydrogenated unsaturated fats, may be associated with cognitive decline among older people</td>
<td>[58]</td>
</tr>
<tr>
<td>Morris et al. (2005)</td>
<td>CHAP, USA, longitudinal, population-based (6 years)</td>
<td>3718 subjects, aged 65 years and older</td>
<td>Evaluation of dietary intake with a 139-item FFQ</td>
<td>Cognitive change at 3-year and 6-year follow-ups measured with the EBMT of Immediate and Delayed Recall, the MMSE and the SDMT</td>
<td>Dietary intake of fish was inversely associated with a cognitive decline over 6 years There were no consistent associations with the n-3 fatty acids, although the effect estimates were in the direction of slower decline</td>
<td>[75]</td>
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<td>Solfrizzi et al. (2006)</td>
<td>The Italian Longitudinal Study on Aging (ILSA), Italy, longitudinal, population-based (8.5 years)</td>
<td>278 subjects, aged 65–84 years old, from a cohort of 5632 subjects</td>
<td>Evaluation of MUFA and PUFA dietary intake with a 77-item FFQ</td>
<td>MMSE</td>
<td>High MUFA, PUFA and total energy intake were significantly associated with a better cognitive performance in time. The association between high MUFA and PUFA intake and cognitive performance remained robust even after adjustment for potential confounding variables, such as age, sex, educational level, CCI, BMI and total energy intakes</td>
<td>[60]</td>
</tr>
<tr>
<td>Solfrizzi et al. (2006)</td>
<td>ILSA, Italy, longitudinal, population-based (2.6 years)</td>
<td>278 subjects, aged 65–84 years old, from a cohort of 5632 subjects</td>
<td>Evaluation of MUFA and PUFA dietary intake with a 77-item FFQ</td>
<td>Incident MCI: Diagnostic criteria for MCI: 1.5 SDs below age- and education-adjusted mean on the MMSE and 10th percentile below age- and education-adjusted mean on memory test, without SMC and intact ADL/IADL</td>
<td>Dietary fatty acids intakes were not associated with incident MCI. However, high PUFA intake appeared to have borderline nonsignificant trend for a protective effect against the development of MCI that may be important</td>
<td>[61]</td>
</tr>
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</table>

AD: Alzheimer’s disease; ADL: Activities of daily living; APOE: Apolipoprotein E; CCI: Charlson Comorbidity Index; CFT: Category Fluency Test (semantic memory); DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, third edition (revised); DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EBMT: East Boston Memory Test (immediate and delayed episodic memory); FFQ: Food Frequency Questionnaire; IADL: Instrumental activities of daily living; LDST: Letter Digit Substitution Test (perceptual–motor speed); MCI: Mild cognitive impairment; MedD: Mediterranean diet; MMSE: Mini-Mental State Examination (global cognitive functioning); MUFA: Monounsaturated fatty acids; NINCDS–ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association; NINCDS–AIREN: National Institute of Neurological and Communicative Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences; PMSQ: Pfeiffer’s Mental State Questionnaire (global cognitive functioning); PRBT: Purdue Peg Board task (psychomotor speed); PUFA: Polynsaturated fatty acids; SDMT: Symbol Digit Modalities Test (perceptual–motor speed); SFA: Saturated fatty acids; SMC: Subjective memory complaint; VaD: Vascular dementia.
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<tr>
<td>Psaltopoulou et al. (2008), European Prospective Investigation into Cancer and Nutrition (EPIC), Greece</td>
<td>Longitudinal, population-based (median 8 years)</td>
<td>732 subjects, 60 years or older</td>
<td>Evaluation of dietary intakes with a 150-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi</td>
<td>MMSE</td>
<td>No significant association between MeDi score and MMSE scores, whereas a statistically significant inverse association was found between MMSE performance and some individual dietary components, such as seed oil or PUFA intake</td>
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<tr>
<td>Eskilinen et al. (2008), Cardiovascular Risk Factors Aging and Dementia (CAIDE), Finland</td>
<td>Longitudinal, population-based (21 years)</td>
<td>1449 subjects, aged 65–80 years old</td>
<td>Evaluation of dietary intakes with a 208-item FFQ</td>
<td>The Mayo Clinic AD Research Center criteria were applied for diagnosing MCI; MMSE, CFT, PPBt, LDST, episodic memory with immediate word recall tests; executive function with the Stroop test; and prospective memory with a task by Einstein</td>
<td>Elevated SFA intake at midlife was associated with poorer global cognitive function and prospective memory and with an increased risk of MCI. High intake of PUFA was associated with better semantic memory. In addition, frequent fish consumption was associated with better global cognitive function and semantic memory. Furthermore, higher PUFA:SFA ratio was associated with better psychomotor speed and executive function</td>
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<td>Engelhart et al. (2002), The Rotterdam Study, The Netherlands</td>
<td>Longitudinal, population-based (6 years)</td>
<td>5395 subjects, aged 55 years and older</td>
<td>Evaluation of dietary intakes with a 100-item FFQ</td>
<td>Diagnosis of dementia (DSM-III-R criteria), AD (NINCDS–ADRDA criteria), and VaD (NINCDS–AIREN criteria)</td>
<td>High intakes of total fat, saturated fat, trans fat and cholesterol, and low intake of MUFA, PUFA, n-6 PUFA and n-3 PUFA were not associated with an increased risk of dementia, AD or VaD</td>
</tr>
<tr>
<td>Luchsinger et al. (2002), Washington Heights-Inwood Columbia Aging Project, USA</td>
<td>Longitudinal, population-based (4 years)</td>
<td>980 subjects, mean age: 75.3 ± 5.8 years old</td>
<td>Evaluation of dietary intake with a 61-item FFQ</td>
<td>Diagnosis of prevalent dementia (DSM-IV criteria) and incident AD (NINCDS–ADRDA criteria)</td>
<td>Higher intake of calories and fats may be associated with higher risk of AD in subjects carrying the APOE e4 allele</td>
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AD: Alzheimer’s disease; ADL: Activities of daily living; APOE: Apolipoprotein E; CCI: Charlson Comorbidity Index; CFT: Category Fluency Test (semantic memory); DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, third edition (revised); DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EBMT: East Boston Memory Test (immediate and delayed episodic memory); FFQ: Food Frequency Questionnaire; IADL: Instrumental activities of daily living; LDST: Letter Digit Substitution Test (perceptual–motor speed); MCI: Mild cognitive impairment; MeDi: Mediterranean diet; MMSE: Mini-Mental State Examination (global cognitive functioning); MUFA: Monounsaturated fatty acids; NINCDS–ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association; NINCDS–AIREN: National Institute of Neurological and Communicative Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences; PMSQ: Pfeiffer’s Mental State Questionnaire (global cognitive functioning); PPBt: Purdue Peg Board task (psychomotor speed); PUFA: Polyunsaturated fatty acids; SDMT: Symbol Digit Modalities Test (perceptual–motor speed); SFA: Saturated fatty acids; SMC: Subjective memory complaint; VaD: Vascular dementia.
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<td>Morris et al. (2003) Chicago Health and Aging Project (CHAP), USA</td>
<td>Longitudinal, population-based (3.9 years)</td>
<td>815 subjects, aged 65 years and older</td>
<td>Evaluation of dietary intake with a 154-item FFQ</td>
<td>Incident diagnosis of AD (NINCDS–ADRDA criteria)</td>
<td>Higher intake of n-3 PUFA and weekly fish consumption may reduce the risk of incident AD</td>
<td>[70]</td>
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<tr>
<td>Huang et al. (2005) Cardiovascular Health Cognition Study (CHCS), USA</td>
<td>Longitudinal, population-based (5.4 years)</td>
<td>5201 participants, aged 65 years and older</td>
<td>Evaluation of dietary intake with a 99-item FFQ</td>
<td>Incident diagnosis of dementia (DSM-IV criteria) and AD (NINCDS–ADRDA criteria)</td>
<td>Fatty fish, such as tuna or 'other fish', was associated with a lower risk of developing dementia and AD with a dose–response relationship, whereas lean, fried fish was not. Those without an APOE e4 allele had a 35–45% lower risk with consumption of fatty fish, whereas there was little or no difference for APOE e4 allele carriers</td>
<td>[78]</td>
</tr>
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<td>Laitinen et al., (2006) Cardiovascular Risk Factors Aging and Dementia (CAIDE), Finland</td>
<td>Longitudinal, population-based (21 years)</td>
<td>1449 subjects, aged 65–80 years</td>
<td>Evaluation of dietary intake with a 154-item FFQ</td>
<td>Incident diagnosis of AD (NINCDS–ADRDA criteria)</td>
<td>Moderate intake of PUFA at midlife was protective, whereas a moderate intake of SFA may increase the risk of dementia and AD, especially among APOE e4 carriers</td>
<td>[72]</td>
</tr>
<tr>
<td>Barbeger-Gateau et al. (2007) Three-City Study, France</td>
<td>Longitudinal, population-based (4 years)</td>
<td>9294 subjects, aged 65 years and older</td>
<td>Evaluation of dietary intakes with a FFQ</td>
<td>Incident diagnosis of dementia (DSM-IV criteria) and AD (NINCDS–ADRDA criteria)</td>
<td>Frequent consumption of fruits and vegetables, fish and n-3-rich oils may decrease the risk of dementia and AD, especially among APOE e4 noncarriers</td>
<td>[73]</td>
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</table>

AD: Alzheimer’s disease; ADL: Activities of daily living; APOE: Apolipoprotein E; CCI: Charlson Comorbidity Index; CFT: Category Fluency Test (semantic memory); DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, third edition (revised); DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EBMT: East Boston Memory Test (immediate and delayed episodic memory); FFQ: Food Frequency Questionnaire; IADL: Instrumental activities of daily living; LDST: Letter Digit Substitution Test (perceptual–motor speed); MCI: Mild cognitive impairment; MeDi: Mediterranean diet; MMSE: Mini-Mental State Examination (global cognitive functioning); MUFA: Monounsaturated fatty acids; NINCDS–ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association; NINCDS–AIREN: National Institute of Neurological and Communicative Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences; PMSQ: Pfeiffer’s Mental State Questionnaire (global cognitive functioning); PPBt: Purdue Peg Board task (psychomotor speed); PUFA: Polyunsaturated fatty acids; SDMT: Symbol Digit Modalities Test (perceptual–motor speed); SFA: Saturated fatty acids; SMC: Subjective memory complaint; VaD: Vascular dementia.
been found in population samples with elevated fish consumption, and high intake of MUFA and PUFA, particularly n-3 PUFA [42]. In fact, fish, particularly fatty fish (e.g., herring, mackerel, salmon or trout), is the principal source of n-3 PUFA in the MeDi. Very recently, the baseline data from the Older People And n-3 Long-chain polyunsaturated fatty acid (OPAL) study suggested that higher fish consumption is associated with better cognitive function in later life [74]. Epidemiological, longitudinal, observational studies reporting associations of fish consumption with cognitive function have demonstrated mixed results; some longitudinal studies have reported a positive association with higher fish consumption [63,75–77], while others have found no association [57]. Nevertheless, a lower risk of incident dementia in subjects consuming more fish has been reported in several other independent prospective cohort studies [69,71,73,78]. Therefore, despite these contrasting findings, there is now considerable evidence suggesting that fatty acid intake and fish consumption may influence dementia and AD risk, but the direction (protection or risk) and the level of this effect remain unclear [42]. Finally, some recent randomized controlled trials (RCTs) assessed the cognitive or functional effect of n-3 PUFA supplementation on patients with VaD, AD, MCI or age-related cognitive decline (ARCD) in cognitively unimpaired older subjects [79–85]. These RCTs suggested a positive effect of this intervention only in very mild AD or MCI patients, or in subgroups (e.g., APOE-ε4 carriers), for cognitive performance in nondemented subjects or for neuropsychiatric symptoms in mild- to-moderate AD patients [79]. Supplemental DHA may not necessarily be recommended when the decline is more severe, possibly because additional DHA may contribute to degenerative processes in the brain related to lipid peroxidation [41].

Different pathways could contribute to the neuroprotective, as well as the neurotrophic, properties of UFA (Figure 1) [38,39,42]. An underlying biological mechanism for the observed association between UFA and dementia and predementia syndromes is currently unknown. In particular, the prolonged protection of MUFA intake against ARCD and AD may be linked to the relevant quota of antioxidant compounds in olive oil, including low-molecular-weight phenols (Figure 1) [38,39,42]. Moreover, substitution of caloric energy from SFA with UFA has been demonstrated to lower low-density lipoprotein (LDL) cholesterol levels and increase

**Figure 1.** Overview of the principal underlying mechanisms linking the Mediterranean diet and its principal components to Alzheimer’s disease and vascular dementia.

Aβ: β-amyloid; AD: Alzheimer’s disease; AICD: APP intracellular domain; APP: Amyloid precursor protein; BACE1: β-site APP-cleaving enzyme 1; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; sAPPα: Soluble amyloid precursor protein α; sAPPβ: Soluble amyloid precursor protein β; VaD: Vascular dementia; WML: White matter lesion.
high-density lipoprotein (HDL) cholesterol levels [86]. Other studies have found that high-fat/high-cholesterol diets increased, and cholesterol-lowering drugs decreased, Aβ peptide deposition and AD-related abnormalities [41,42]. The neuroprotective effects of dietary UFA could also rely on their impact on membrane architecture: maintaining the structural integrity of neuronal membranes, determining the fluidity of synaptosomal membranes and thereby regulating neuronal transmission (Figure 1). Furthermore, essential fatty acids can modify the activity of certain membrane-bound enzymes (phospholipase A2, protein kinase C and acetyltransferase), and the function of the neurotransmitter receptors. Moreover, free fatty acids, lipid metabolites and phospholipids modify the function of membrane proteins, including ion channels [38,39,42]. Fatty acid composition of neuronal membranes in advancing age also demonstrated an increase in MUFA content and a decrease in PUFA content [38,39,42]. In adult rats, learning and cognitive behavior are related to brain DHA status, which, in turn, is related to the levels of the dietary n-3 PUFA [87]. In fact, administration of DHA seems to improve learning ability in Aβ-infused rats [88] and inhibit decline in avoidance learning ability in the AD model rats, which was associated with an increase in the corticohippocampal n-3:n-6 ratio, and a decrease in neuronal apoptotic products [89]. In other transgenic AD mouse models, DHA also protects against dendritic pathology [90], prevents neuronal apoptosis induced by soluble Aβ peptides [91], increases synaptic protein and phospholipid densities [92], reduces the intraneuronal accumulation of both Aβ and tau protein [93], and inhibits degradative endopeptidase activities [94]. Some experimental evidence suggests that essential n-3 PUFA effectively lower Aβ production in transgenic mice, as reported in studies from several laboratories (Figure 1) [92,95,96].

There are several published studies on human infant subjects in which breastfeeding – which leads to higher DHA concentrations in the brain – or n-3 PUFA supplementation, is related to better cognitive performance at a later age [38,39,42]. The n-3 PUFA from fish may be inversely associated with dementia because it lowers the risk of thrombosis, stroke, cardiovascular disease and cardiac arrhythmia, reducing the risk of thrombembolism in the brain and consequently of lacunar and large infarcts that can lead to VaD and AD [38,39,42]. Furthermore, the n-3 PUFA may be important as lipids in the brain, particularly for the possible influence of DHA on the physical properties of the brain that are essential for its function [38,39,42]. Furthermore, fish oil was a better source than α-linolenic acid for the incorporation of n-3 PUFA into rat brain phospholipid subclasses [38,39,42]. On the contrary, high linoleic acid intake (n-6 PUFA) may increase the susceptibility of LDL cholesterol to oxidation, which makes it more atherogenic, even if the association between linoleic acid and atherosclerosis is controversial [38,39,42]. Therefore, the ratio of dietary n-3:n-6 PUFA intake may influence the potential role of PUFA on cognitive decline and dementia, and the optimal ratio of n-6:n-3 for a healthier diet should be <5:1 [38,39,42]. At present, similar indications for cognitive decline or dementia are not available, but n-3 PUFA, particularly DHA status, should not be considered independently of n-6 PUFA intake [80]. Finally, a high dietary intake of SFA and cholesterol increases the risk for cardiovascular disease, and therefore for cognitive decline, VaD and AD [38,39,42]. A diet high in SFA and cholesterol may increase hippocampal accumulation of Aβ [9]. In addition, a diet high in fat/SFA may lead to cognitive impairment through its effects on, for example, hyperinsulinemia [86], oxidative stress or endothelial damage [38,39,42]. In experimental studies, SFA have decreased the levels of hippocampal brain-derived neurotrophic factor (BDNF) that are relevant for neuronal plasticity and the maintenance of cognitive functions [97]. On the contrary, treatment for 4 weeks with a Mediterranean-inspired diet rich in n-3 PUFA decreased blood lipids in healthy individuals with a low-risk profile for cardiovascular disease, with a beneficial effect also on vascular function and oxidative stress [98]. Finally, the inverse relationship between fish consumption and dementia could be explained by the biological hypothesis that the potentially protective active ingredients are the n-3 PUFA content in fish, with fatty fish containing considerably greater amounts of n-3 PUFA than white fish: approximately 2 g and 0.3 g n-3 PUFA per 100 g of average fish, respectively [99]. However, other constituents of fish could prevent dementia. For instance, fish is also a good source of selenium, a powerful antioxidant, and fatty fish traditionally consumed in Northern Europe are not only rich in n-3 PUFA, but also in vitamin D, which is a recently recognized neurosteroid hormone [100,101]. Vitamin D is essential for neurophysiological function, regulation of neurotransmitters or neurotrophic factors, and cerebral antioxidant, anti-inflammatory and anti-ischemic mechanisms [100,101]. A recent systematic literature review suggested that vitamin D insufficiency may instead cause neuropathological dysfunction, such as cognitive impairment [100]. Therefore, the apparent protective effect of fish consumption against dementia could be explained by the impact of a health-promoting lifestyle or by the fish itself. In this view, the intake of n-3 PUFA, antioxidant compounds and vitamin D should be taken into account.

In conclusion, epidemiological evidence has suggested a possible association among fish consumption, MUFA and PUFA (particularly, n-3 PUFA) and reduced risk of cognitive decline, AD and dementia. However, due to the small number of studies that inform this topic, further research is necessary before a strong conclusion can be drawn. Based on the current evidence from human and animal studies, it is not possible to make definitive dietary recommendations in relation to the AD risk on fish consumption and the lower intake of saturated fat from meat and dairy products [102], as well as on UFA consumption or lower intake of saturated fat in relation to the risk for dementia and cognitive decline. However, a high consumption of fats from fish, vegetable oils, vegetables and nuts should be encouraged as this dietary advice is in accordance with recommendations for lowering the risk of cardiovascular disease, obesity, diabetes and hypertension [42,102].

**Dairy products & risk of cognitive impairment & Alzheimer’s disease**

While positive associations have been shown between a number of macronutrients and cognitive performance, little attention has been paid to the potential role of dairy foods in modulating...
the risk of cognitive impairment or AD [103]. This is despite recent epidemiological, observational and interventional studies providing evidence for the role of dairy products in improving cardiovascular risk factors and lowering the prevalence of the metabolic syndrome [103]. Dairy consumption may reduce the likelihood of cognitive decline, either directly, or via mediating effects on cardio-metabolic health [103]. Among the cross-sectional epidemiological studies (Table 2) [104–106], one report suggested that women with poor cognitive function had significantly lower intakes of milk and dairy products than those with inadequate or normal cognitive function [104], and another study reported that higher cheese intake was associated with a reduced likelihood of cognitive impairment, while milk intake was not associated with cognitive impairment [108]. Among longitudinal studies (Table 2) [63,64,72,107,108], only one out of the five principal prospective reports found a beneficial effect from dairy consumption in regards of cognitive function or MCI/dementia risk [108]. In fact, a Japanese prospective study indicated that milk intake was associated with a significantly lower likelihood of VaD in older age amongst both men and women [108]. On the other hand, three longitudinal studies found adverse effects on cognitive function from dairy fat [63,64,72]. The Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) study did not examine dairy intake per se, but evaluated associations of the fat from milk products and spreads with the risk of MCI, dementia, AD and a number of cognitive domains [63,72]. High saturated or total fat intakes were associated with an increased risk for MCI, poorer global cognitive function and poorer psychomotor speed [63], but not with risk of dementia or AD [72]. Similarly, an Australian study on older men demonstrated that whole-fat milk consumption was associated with impaired cognitive function [107], while the final study reported that higher consumption of dairy desserts and ice cream was associated with an increased risk of cognitive decline amongst elderly French women [64]. No significant associations were found between milk and yogurt, or cheese consumption and cognitive decline [64]. A very recent systematic review on the possible association between dairy consumption and cognitive function concluded that methodological variability and study limitations did not enable conclusions to be drawn regarding optimal dairy intake and cognitive performance [103]. The limited available literature supported the concept that high dairy consumption may be associated with a lower likelihood of cognitive impairment; however, high intakes of full-fat dairy and/or dairy fats may be associated with declines in cognitive performance [103]. Dairy foods may reduce the risk for cognitive impairment by modifying vascular factors linked to detrimental brain changes, particularly via weight reduction (Figure 1). Epidemiological studies, animal studies and a small number of randomized trials provide evidence for an antiobesity effect of calcium and dairy foods [109–111]. In addition to calcium, bioactive compounds derived from whey protein in dairy may contribute to accelerating weight and fat loss [109,111]. Furthermore, dairy products are the primary dietary source of vitamin D [112], which, through its role in regulating calcium homeostasis, may improve insulin sensitivity and glucose homeostasis [112]. Phosphorus and magnesium contained in dairy foods are involved in blood pressure regulation [113]. Magnesium may also modulate vascular function through its antioxidant and anti-inflammatory properties [114], and increasing dietary intake of magnesium may help reduce cholesterol and triglycerides [115], and improve diabetes control, owing to its role in glucose homeostasis [116]. The beneficial effects of these components of dairy foods on vascular disease may also be mediated by an improvement in the inflammatory state. Individuals with greater adiposity have an increased inflammatory state in comparison to their leaner counterparts [117], which has been linked with adverse cognitive function [118]. Any decrease in inflammation (via weight loss or improved regulation of glucose and blood pressure) may subsequently reduce the risk for cognitive decline (Figure 1) [103].

**Alcohol consumption in predementia & dementia syndromes**

An additional interesting link between diet and AD is in relation to alcohol intake. Recent studies with older samples have indicated that a U- or J-shaped curve may best describe the relationship between the level of alcohol consumption and cognitive performance [119–123]. In fact, in several cross-sectional studies, moderate drinking, from up to one drink per day (up to 14 g of alcohol) to four drinks per day (52 g of alcohol) has been associated with better function in many cognitive domains compared with nondrinking [124–127]. Furthermore, in cross-sectional studies, both greater [128–132] and poorer [133] cognitive performances have been observed with higher levels of alcohol drinking. The studies that have assessed changes in cognition prospectively have had contradictory results (Table 3) [46]. Drinkers have been proposed to have a greater decrease in global cognitive function [134] and attention [135], compared with nondrinkers, but moderate drinkers (~one drink, or less than 15 ml of alcohol per day) have less decline in general cognition [136] or psychomotor speed [137] than nondrinkers. Furthermore, some studies demonstrated no association at all [123,130,138,139]. In particular, the association between current cognitive performance and alcohol drinking 5–24 years earlier have also been studied, with contrasting results. In fact, the global cognitive function may be poorer among both alcoholics and past drinkers, compared with nondrinkers or moderate drinkers [121], and better among moderate drinkers and poorer among heavy drinkers as compared with nondrinkers [140]. Moreover, smoking or the APOE e4 allele often modified the association between alcohol drinking and cognitive functions [46,141].

Alcohol drinking is also one of the possible determinants of clinical dementia [46,133,135,137,138]. Epidemiological studies have reported an association between red wine consumption and the incidence of AD and dementia in cross-sectional and longitudinal studies (Table 3) [142,143]. These results were consistent with the findings from some cohort studies [144–147], but not with others [133,135,137,138,148,149]. Other population-based, prospective studies, with longer follow-up periods, have studied the effects of different patterns of alcohol intake on dementia [150–152]. For predementia syndromes, in 1445 noncognitively impaired individuals aged 65–84 years from the Italian Longitudinal Study on Aging (ILSA), patients with MCI who consumed up to one
<table>
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<tr>
<th>Study (year)</th>
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<th>Subjects</th>
<th>Dietary assessment</th>
<th>Cognitive outcomes</th>
<th>Results and conclusions</th>
<th>Ref.</th>
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<tr>
<td>Dietary dairy products &amp; predementia syndromes</td>
<td>Almeida et al. (2006) Australia</td>
<td>Longitudinal, population-based (4.8 years)</td>
<td>601 men, aged 80 years and older</td>
<td>Self-report questionnaire, including dietary measures</td>
<td>‘Preserved cognitive function’: MMSE ≥24</td>
<td>Consumption of full-cream milk associated with impaired cognitive function and with poor mental health</td>
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<td>Vercambre et al. (2009) etude Epidémiologique de Femmes de la Mutuelle Générale de l’Education Nationale (E3N), France</td>
<td>Longitudinal, population-based (13 years)</td>
<td>4809 elderly women, 76–82 years old</td>
<td>Evaluation of dietary intakes with a 208-item FFQ</td>
<td>DECO and IADL</td>
<td>No significant association between milk and yogurt, and cheese consumption with cognitive decline</td>
</tr>
<tr>
<td></td>
<td>Eskilinen et al. (2008) Cardiovascular Risk Factors Aging and Dementia (CAIDE), Finland</td>
<td>Longitudinal, population-based (21 years)</td>
<td>1449 subjects, aged 65–80 years</td>
<td>Evaluation of dietary intake with a 208-item FFQ</td>
<td>The Mayo Clinic AD Research Center criteria were applied for diagnosing MCI: MMSE, CFT, PPBt, LDST, episodic memory with immediate word recall tests; executive function with the Stroop test; and prospective memory with a task by Einstein</td>
<td>High SFA intake from milk products and spreads (&gt;21.6 g) associated with increased risk for MCI compared with those with lower intakes. High SFA from milk products associated with poorer global cognitive function (MMSE). High total fat from milk products and spreads associated with poorer psychomotor speed</td>
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<td>Yamada et al. (2003) The Adult Health Study Japan</td>
<td>Longitudinal, population-based (25–30 years)</td>
<td>1774 subjects, born before September 1932</td>
<td>Evaluation of dietary intake with a FFQ</td>
<td>Clinical diagnosis of dementia (DSM-IV criteria), CASI, IQCDE (by the caregiver), Hachinski’s Ischemic Score, Clinical Dementia Rating</td>
<td>Almost-daily milk intake associated with significantly lower likelihood of VaD, compared with consuming milk less than four-times per week</td>
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<td></td>
<td>Laitinen et al. (2006) CAIDE, Finland</td>
<td>Longitudinal, population-based (21 years)</td>
<td>1449 subjects, aged 65–80 years</td>
<td>Evaluation of dietary intake with a 154-item FFQ</td>
<td>Incident diagnosis of AD (NINCDS–ADRSA criteria)</td>
<td>Fat intake from milk products (milk and sour milk) not significantly associated with risk of dementia or AD. Moderate intakes of PUFA from spreads associated with decreased risk of dementia. Moderate intake of SFA from spreads associated with increased risk of dementia and AD</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; CASI: Cognitive Ability Screening Instrument; CFT: Category Fluency Test (semantic memory); DECO: Deterioration Cognitive Observéé scale (observed cognitive deterioration); DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EBMT: East Boston Memory Test (immediate and delayed episodic memory); FFQ: Food Frequency Questionnaire; GDS: Geriatric Depression Scale; IADL: Instrumental activities of daily living; IQCDE: Informative Questionnaire on Cognitive Decline in the Elderly; LDST: Letter–Digit Substitution Test (perceptual–motor speed); MCI: Mild cognitive impairment; MMSE: Mini-Mental State Examination (global cognitive functioning); MUFA: Monounsaturated fatty acids; NINCDS–ADRSA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease Related Disorders Association; PPBt: Purdue Peg Board task (psychomotor speed); PUFA: Polynsaturated fatty acids; SFA: Saturated fatty acids; VaD: Vascular dementia.
Table 3. Principal longitudinal clinical and epidemiological studies on the relationship between alcohol consumption and dementia (i.e., Alzheimer’s disease and vascular dementia) or predementia syndromes (i.e., age-related cognitive decline and mild cognitive impairment) (cont.).

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Setting and study design (duration)</th>
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<th>Methods</th>
<th>Results and conclusions</th>
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</tr>
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<tbody>
<tr>
<td>Launer et al. (1996)</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>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>
<td>[123]</td>
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<tr>
<td>Elias et al. (1999)</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 (two to four drinks/day) demonstrated superior performance in many cognitive domains relative to abstainers. For men, superior performance was found within the range of four to eight drinks/day, although fewer significant relations were observed. These results were confirmed by prospective analyses of 24-year drinking history</td>
<td>[124]</td>
</tr>
<tr>
<td>Dufouil et al. (2000)</td>
<td>Longitudinal, population-based (4 years)</td>
<td>1389 subjects, aged 59–71 years</td>
<td>MMSE, evaluation of alcohol consumption, APOE genotyping and smoking habits</td>
<td>Alcohol consumption was associated with a decreased risk of cognitive decline in individuals without the APOE e4 allele, whereas moderate drinking increased the risk of decline in APOE e4 allele carriers. In addition, lifetime smoking was a risk factor for cognitive decline in individuals without the APOE e4 allele. The data also suggested a slight protective effect of smoking in APOE e4 allele carriers</td>
<td>[134]</td>
</tr>
<tr>
<td>Ngandu et al. (2007)</td>
<td>Longitudinal, population-based (21 years)</td>
<td>1341 participants, aged 65–79 years</td>
<td>MMSE and neuropsychological tests evaluating episodic memory, semantic memory, psychomotor speed, executive function, prospective memory and subjective memory. Evaluation of alcohol intake, smoking habits and APOE genotyping</td>
<td>The nondrinkers, both at midlife and later, had a poorer cognitive performance than drinkers, especially in the domains related to fluid intelligence – that is, executive function, psychomotor speed, as well as episodic memory – whereas the other cognitive functions showed little association with alcohol drinking. No interactions between APOE e4 and alcohol, or sex and alcohol were found</td>
<td>[141]</td>
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<td>Anttila et al. (2004)</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 demonstrated a U-shaped relationship with risk of MCI in old age. Only the carriers of APOE e4 had an increased risk of dementia with increasing alcohol consumption</td>
<td>[154]</td>
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<tr>
<td>Espeland et al. (2005)</td>
<td>Longitudinal, population-based study (4.2 years)</td>
<td>4451 community-dwelling women, aged 65–79 years</td>
<td>Diagnosis of incident MCI and dementia, and annual modified MMSE. Subjects classified as abstainers, &lt;one drink/day and &gt;one drink/day</td>
<td>Moderate alcohol intake was associated with an approximately 50% reduced risk of combined probable-dementia and/or MCI. Significant decline in global cognition was less common among women who reported alcohol intake at baseline, and also after adjustment for both demographic/social and clinical factors</td>
<td>[155]</td>
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</table>

A.D: Alzheimer’s disease; APOE: Apolipoprotein E; CVD: Cerebrovascular disease; MCI: Mild cognitive impairment; MMSE: Mini-Mental State Examination; OR: Odds ratio; VaD: Vascular dementia.
### Table 3. Principal longitudinal clinical and epidemiological studies on the relationship between alcohol consumption and dementia (i.e., Alzheimer’s disease and vascular dementia) or predementia syndromes (i.e., age-related cognitive decline and mild cognitive impairment) (cont.).

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<tr>
<td>Solfrizzi et al. (2007)</td>
<td>Longitudinal, population-based study (3.5 years)</td>
<td>1445 men and women, aged 65–84 years</td>
<td>Diagnosis of incident MCI and progression from MCI to dementia; subjects classified as abstainers, zero to one drink/day, one to two drink/day, and &gt;two drink/day</td>
<td>In patients with MCI, up to one drink/day of alcohol or wine may decrease the rate of progression to dementia. No significant associations were found between any levels of drinking and the incidence of MCI in noncognitively impaired individuals versus abstainers.</td>
<td>[153]</td>
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<tr>
<td><strong>Alcohol consumption &amp; dementia syndromes</strong></td>
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<tr>
<td>Yoshitake et al. (1995)</td>
<td>Longitudinal, population-based (7 years)</td>
<td>828 subjects, aged 65 years and over</td>
<td>Diagnosis of dementia, AD and VaD; evaluation of alcohol consumption</td>
<td>Multivariate analysis demonstrated that age, systolic blood pressure, drinking habits and prior stroke episodes were significant independent precursors of VaD.</td>
<td>[133]</td>
</tr>
<tr>
<td>Orgogozo et al. (1997)</td>
<td>Longitudinal, population-based (3 years)</td>
<td>3777 subjects, aged 65 years and over</td>
<td>Diagnosis of dementia and AD; evaluation of alcohol intake</td>
<td>In the 318 moderate drinkers, the ORs were respectively 0.19 for incident dementia and 0.28 for AD as compared with the 971 nondrinkers, and after adjusting for possible confounders. Among the 922 mild drinkers, the relative risk for AD was reduced significantly with respect to the abstainers.</td>
<td>[142]</td>
</tr>
<tr>
<td>Ruitenberg et al. (2002)</td>
<td>Longitudinal, population-based study (6 years)</td>
<td>5395 subjects, aged 55 years and older</td>
<td>Diagnosis of AD, VaD or other dementia; evaluation of alcohol intake and APOE genotyping</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 was found that the relationship between alcohol and dementia varied by type of alcoholic beverage</td>
<td>[144]</td>
</tr>
<tr>
<td>Mukamal et al. (2003)</td>
<td>Nested case-control of a longitudinal, population-based study (6 years)</td>
<td>373 cases with incident dementia and 373 controls</td>
<td>Diagnosis of incident dementia (AD and VaD), average alcohol consumption and MRI findings</td>
<td>Compared with abstention, consumption of one to six drinks weekly was 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 e4 allele, with similar relationships of alcohol use with AD and VaD.</td>
<td>[165]</td>
</tr>
<tr>
<td>Deng et al. (2006)</td>
<td>Longitudinal, population-based study (2 years)</td>
<td>3286 subjects, aged 60 years and older</td>
<td>Diagnosis of incident dementia, AD and VaD and evaluation of alcohol intake</td>
<td>Light-to-moderate drinkers had a lower risk of dementia than nondrinkers, but a nonsignificant increased risk was observed in heavy drinkers.</td>
<td>[147]</td>
</tr>
<tr>
<td>Mehlig et al. (2008)</td>
<td>Longitudinal, population-based study (34 years)</td>
<td>1462 women, aged 38–60 years</td>
<td>Diagnosis of dementia; evaluation of alcohol intake and smoking habits</td>
<td>Wine was protective for dementia, and the association was strongest among women who consumed wine only. By contrast, consumption of spirits at baseline was associated with a slightly increased risk of dementia.</td>
<td>[152]</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; APOE: Apolipoprotein E; CVD: Cerebrovascular disease; MCI: Mild cognitive impairment; MMSE: Mini-Mental State Examination; OR: Odds ratio; VaD: Vascular dementia.


Diet & Alzheimer's disease

Review

...drink of alcohol per day had a reduction in the rate of progression to dementia, in comparison with patients with MCI who never consumed alcohol. Overall, patients with MCI who consumed less than one drink of wine per day versus nondrinkers had a decrease in the rate of progression to dementia of approximately 85%. No significant association was found between any levels of drinking and the incidence of MCI in noncognitively impaired individuals versus abstainers [153]. Only a few other studies have examined the effect of alcohol consumption on the risk for the incidence of MCI [154,155]. After an average follow-up of 23 years, nondrinkers and frequent drinkers were both more than twice as likely to have MCI in old age than occasional drinkers [154]. However, the APOE genotype seemed to modify the relationship, such that the risk of old age dementia increased with increasing midlife alcohol consumption only among carriers of the APOE ε4 allele [154]. On the other hand, the findings from the ILSA were consistent with those obtained in the Women's Health Initiative Memory Study with a 4.2-year follow-up, which found that moderate alcohol intake (one drink per day) was associated with an approximately 50% reduced risk of combined probable dementia and MCI [155]. However, after adjusting for demographic and socioeconomic factors and baseline Modified Mini-Mental State Examination (3MSE), the significance disappeared [155].

Recently, a systematic review with meta-analysis was carried out to investigate any relationship between incident cognitive decline or dementia in the elderly and alcohol consumption between 1995 and March 2006, with only longitudinal studies of subjects aged ≥65 years included [156]. Definitions of outcomes varied with some studies reporting on dementia, or AD alone, or AD and dementia, or VaD, or AD and VaD, or all dementia, VaD and AD [156]. This meta-analysis suggested that, at least in epidemiological studies, light-to-moderate alcohol use was associated with a 38% reduced risk of unspecified incident dementia. In the studies included in this meta-analysis, there was also no close agreement as to the optimal level of alcohol consumption and the classification of light-to-moderate drinking varied very widely. In fact, for dementia, benefit was shown for more than one drink per day, weekly or monthly wine consumption, 250–500 ml (usually wine) or more, which is equivalent to three drinks per day, and from 1 to 28 units per week [46]. For AD, light-to-moderate alcohol was associated with a significantly reduced risk of 32%, defining optimal amounts as weekly consumption of wine, 1–6 units or more than two drinks per week, or more than three drinks/250–500 ml per day (usually wine), or where studied by gender, one to three per day in males [46]. Although the point estimates were also in a similar direction for VaD and cognitive decline (0.82 and 0.89, respectively), the results were not statistically significant [156]. With regard to cognitive function, results for optimal consumption were mixed, either above, below or equal to one drink a month or day, in subjects with cardiovascular disease or diabetes, one to two drinks per week, while for VaD, one to three drinks per day in males appeared to be beneficial [46]. Finally, another very recent meta-analysis included 15 prospective studies (follow-ups ranged from 2 to 8 years), with samples including 14,646 participants evaluated for AD, 10,225 participants evaluated for VaD and 11,875 followed for any type of dementia [157]. This meta-analysis indicated that light-to-moderate alcohol intake was associated with a 25–28% reduction in risk of AD, VaD and any dementia compared with alcohol abstinence in older adults. Heavy drinking was not associated with increased risk of dementia in the present study [157].

The mechanism by which low-to-moderate alcohol intake could be protective against cognitive impairment or decline in older age or against predementia and dementia syndromes is, at present, unclear. Given that drinking alcohol influenced measures of psychomotor speed, episodic memory and executive function, in particular, it was supposed that white matter lesions (WMLs) would play a neuropathological role. In fact, alcohol drinking has been associated with fewer brain infarcts and was demonstrated to have a U-shaped relationship with WMLs [158]. WMLs and infarcts, in turn, may reflect a vascular mechanism responsible for the observed association between alcohol and cognitive functions (Figure 1). Furthermore, different mechanisms may underlie the adverse effects of heavy drinking and the potential beneficial effects of low-to-moderate drinking. In fact, higher doses of alcohol may affect cognitive functioning through increased release of acetylcholine from the hippocampus [159], which was linked to problems with memory and attention [160]. On the other hand, animal evidence indicated that low doses of alcohol may stimulate the release of hippocampal acetylcholine [161]. Finally, moderate alcohol consumption was associated with reduced cardiovascular risk factors [162] and may be protective against ischemic stroke [163], lowering rates of cardiovascular disease, protecting brain vasculature and preventing subclinical strokes, resulting in better cognitive performance. Moreover, light-to-moderate alcohol use is associated with a lower prevalence of MRI-defined WMLs and subclinical infarcts [164], although MRI abnormalities, HDL cholesterol levels and fibrinogen levels only marginally influenced the association of alcohol consumption and dementia in the Cardiovascular Heart Study [165]. The suggested protection of low-to-moderate alcohol use against CVD may also explain the possible protection against VaD. In the Rotterdam study, the protective effect of alcohol consumption was mainly found for VaD, and the authors suggested that moderate alcohol intake may protect against dementia via a reduction in vascular risk factors [144]. In fact, moderate doses of alcohol may increase prostacyclin concentrations, reduce the generation of thromboxane A2 and inhibit platelet function [46]. They may increase plasma levels of endogenous tissue-type plasminogen activator, a serine protease that regulates intravascular fibrinolysis and fibrinolytic activity, while decreasing plasma fibrinogen levels [46]. It is also known that alcohol is associated with increased levels of HDL cholesterol, its subfractions HDL2 and HDL3, and its associated apolipoproteins A-I and A-II [46]. The association with HDL cholesterol is deemed to account for up to half of the reduction in coronary events associated with moderate alcohol consumption [46].

While the above-cited factors affect the risk of unspecified dementia and, probably, of VaD, other experimental and clinical findings may partly explain the suggested protection of...
low-to-moderate alcohol consumption against AD. In fact, small amounts of alcohol have been reported to be associated with a lower prevalence of vascular brain findings and, in APOE ε4 carriers, with hippocampal and amygdalar atrophy as assessed by MRI [164]. Experimental studies found that ethanol initially increases hippocampal acetylcholine release, which could conceivably improve memory performance [165]. Processes that originate, modulate or precipitate the deposition of Aβ in the brain (e.g., oxidative stress) rather than vascular processes, may better explain the development of AD and the vascular effects of the alcohol component of alcoholic beverages may not be enough to explain the protective effects of the moderate intake of alcohol from dementia. Wine consumption may exert a protective effect, either through alcohol intake itself, through the antioxidant effects of polyphenols richly represented in red wine [46] or through both (Figure 1).

The latter effects, of course, are independent of alcohol and, in fact, have been also associated with alcohol-free red wine [166]. The constituents of red wine also have potentially beneficial vascular effects, enhance endothelial nitric oxide release and reduce atherosclerosis in APOE-deficient mice [46]. Red wine polyphenols are a complex mixture of flavonoids (mainly anthocyanins and flavan-3-ols) and nonflavonoids (such as resveratrol and gallic acid). Flavan-3-ols are the most abundant, with oligomeric and polymeric procyanidins (condensed tannins) often representing 25–50% of the total phenolic constituents [167]. Given the link between VaD, vascular risk and the increasing body of evidence suggesting that AD may be influenced by vascular factors [21], it may be concluded that the vascular protection associated with wine consumption decreases the risk of incident dementia/AD. In fact, in the 5-year follow-up Persons Agés QUID (PAQUID) cohort, a significant inverse association between flavonoid intake and the risk of dementia was found [168]. It has also been suggested that the antioxidant properties of the flavonoids in wine may help prevent the oxidative damage implicated in dementia. In fact, oxidative stress may also develop in the brain, leading to neuronal death by various mechanisms such as formation of Aβ, DNA damage, mitochondrial dysfunction and abnormal tau protein [169,170]. The presence in wine of nonalcoholic components, such as particular antioxidants, could explain a differential effect of wine on dementia. In fact, liquor has been demonstrated to have less antioxidant activity than wine [171]. Nonetheless, in some studies on the neuroprotective role of moderate alcohol consumption, the most typically consumed alcohol types were beer and spirits [105,119]. Finally, sirtuins, conserved proteins with a crucial role in oxidative stress, survival and metabolism, including the sirtuin SIRT1, are probably involved in the development of AD and the vascular effects of the alcohol component of alcoholic beverages [172].

In conclusion, low-to-moderate alcohol drinking has been proposed as a protective factor against MCI and dementia in several longitudinal studies, but contrasting findings also exist [46]. In fact, many of these studies were limited by cross-sectional design, restriction by age or sex, or incomplete ascertainment. Moreover, different outcomes, beverages, drinking patterns or follow-up periods, or possible interactions with other lifestyle-related (i.e., smoking) or genetic factors (i.e., APOE genotyping) may be sources of great variability. In fact, the body of evidence within the last 10 years suggested that low-to-moderate alcohol use may be associated with a reduced risk of unspecified incident dementia and AD, while for VaD, cognitive decline and predementia syndromes the current evidence is only suggestive of a protective effect [46]. Therefore, at present, the preferable outcomes for these kind of studies appear to be unspecified dementia and AD, given the small number of studies reporting VaD as an outcome and the difficulties in the classification of cognitive decline and pure VaD; often including cases with vascular factors in the AD category. On the other hand, the cardiovascular mechanisms behind the protective effects of alcohol may have an even greater effect on VaD. For the different types of beverages, several studies suggest that low-to-moderate wine consumption may be protective against dementia and cognitive decline and not total alcohol intake, beer or spirits, with strong but not conclusive evidence [46]. In this context, it would be desirable to differentiate red and white wine, but this information is not currently available. Whether the present divergent findings can be explained by drinking patterns has not been extensively investigated, and studies with long follow-up periods are few [46]. Therefore, the role of alcohol drinking for cognitive functions may be somewhat different at different time points. Nonetheless, the current evidence suggests that alcohol consumption in old age is substantially in agreement with midlife consumption in relation to cognitive decline [46]. At present, there is no evidence indicating that starting to drink at a later age would be beneficial against predementia or dementia syndromes. Therefore, as interventional studies are not feasible in this area, the best evidence comes from an overview of epidemiological studies. At present, there is no indication that low-to-moderate alcohol drinking would be harmful to cognition and dementia. However, it is not possible to define a specific beneficial level of alcohol intake in relation to cognitive functions and dementia. Taking into account the well-known harms related to heavy alcohol drinking and the lack of long-term follow-up studies or RCTs, it would be too early to recommend alcohol to abstainers to prevent cognitive decline or predementia syndromes or delay the onset of dementia. In moderate-to-heavy alcohol drinkers experiencing memory difficulty, or with suggested diagnoses of MCI or early AD [175], among management options, given the challenge in achieving total abstinence, a viable alternative option could also be low-to-moderate drinking [176].
High intakes of cereals, fruits & vegetables in AD

In vitro and in vivo findings demonstrated that chronic accumulation of reactive oxygen species (ROS) in the brain may exhaust antioxidant capacity, including antioxidant vitamins, and lead to the onset and progression of AD [189,190]. Therefore, antioxidant vitamins from dietary fruits and vegetables may also play a role in delaying the onset of AD. Some findings demonstrated that older African-Americans [177] and Japanese individuals living in the USA have a much higher prevalence of AD (6.24 and 4.1%, respectively) [178] than those still living in their ethnic homelands (<2%), suggesting that the prevalence of AD is more greatly influenced by diet and nutrition, environment and/or lifestyle, than by genetics. However, the simple comparison of prevalence data may be misleading, since there is large difference in selective survival and other cultural effects. A more valuable comparison would be that of the overall dementia rate between different countries, after it had been culturally adjusted. In a cross-sectional study on AD, regression analyses have been performed in the 65+ age populations of 11 countries obtained from 18 community-wide studies versus the components of the national diets [33,34]. The primary finding is that fat and total caloric supply have the highest correlations with AD prevalence rates. A significant inverse correlation was found between the fraction of calories derived from cereals and AD prevalence [33,34]. 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 a low fat supply have a high cereal supply, rather than to a direct therapeutic effect of the cereals. These ecological findings on the possible role of cereals as a risk reduction factor were confirmed in a 4-year cohort study in New York (USA), the Washington Heights–Inwood Columbia Aging Project (WHICAP), that also found that dietary fat was an important risk factor for AD for those with the APOE ε4 allele, but not for those without that allele [179].

Given the possible role of vascular factors in contributing to cognitive decline [21], high intake of fruits and vegetables appear to decrease the risk of CAD [180] and stroke [181], and thus may also decrease cognitive decline. In fact, bioactive compounds, such as antioxidants, mostly contained in fruits and vegetables, are important for the protection against oxidative and nitrosative stress, and these micronutrients have been related with aging itself and the pathophysiology of some age-related illnesses, including cognitive impairment and dementia [182]. While a growing body of knowledge demonstrates both the importance of oxidative stress in the etiology of dementia and the efficacy of antioxidant treatment in animal and cellular models, studies in humans are presently inconclusive [183,184]. In fact, epidemiological studies have demonstrated that dietary intake of natural or synthetic products with a putative antioxidant effect, mainly vitamin E, improve cognitive function and reduce the risk of AD [185,186]. Moreover, antioxidant intervention studies in animal models of AD-like amyloidosis demonstrate a significant reduction in oxidative stress, Aβ deposition and behavioral improvements [187,188]. However, intervention trials of antioxidant supplementation have demonstrated no major benefit against cognitive impairment [185,189]. In AD clinical trials, antioxidants have demonstrated only a marginal positive effect on disease progression [190,191], and a recent MCI trial with antioxidants indicated that vitamin E ingestion over 3 years has no benefit on the risk of progression to AD [192]. There are several reasons explaining this discrepancy. As recently reviewed [185,193], the failure of these trials probably arises from a combination of factors, including not monitoring the drug levels and surrogate markers for the in vivo therapeutic effect of the drug of interest and starting the therapy very late in the disease stage. In accordance with convergent data, oxidative stress is a very early event in AD, occurring in presymptomatic phases, and so antioxidant strategies should start years before the dementia age risk.

The limited epidemiological evidence available on fruit and vegetable consumption and cognition generally supported a protective role of these macronutrients against cognitive decline (Table 4). Associations between greater intake of fruits and vegetables and better cognitive performance have been found in two cross-sectional studies [43,194]. In the Nurses’ Health Study, when fruit and vegetable intake in relation to cognitive function and decline among aging women were prospectively followed from 1976 to 2003 with biennial telephone questionnaires, women in the highest quintile of cruciferous vegetable consumption declined slower compared with the lowest quintile [195]. In the same study, women consuming the highest quantity of green leafy vegetables also experienced slower decline than women consuming the smallest amount [195]. These findings were consistent with those from a subset of subjects participating in the Chicago Health and Aging Project (CHAP) [196] — a high vegetable consumption was associated with a slower rate of cognitive decline over 6 years. Of the different types of vegetables, green leafy vegetables had the strongest association. Fruit consumption was not associated with cognitive change [196]. High intake of β carotene, flavonoids, vitamins C and E, thiamine and folate from dietary fruit and vegetables was also associated with a lower risk of AD in the Rotterdam Study [186]. Furthermore, in the Kame Project cohort (a population-based prospective study on 1836 Japanese–Americans aged 65 years or older based in King County, WA, USA) follow-up surveys found that 63 participants had developed AD after an average of 6 years. After adjusting for age, sex, education and other relevant factors, those who reported drinking at least three glasses of juice a week had a 76% lower risk of developing AD than those who reported drinking juice less than once a week [43]. Data from the 3C Study demonstrated that a diet rich in fish, n-3 PUFA-rich oils, fruits and vegetables could contribute to decrease the risk of dementia and AD in older persons, whereas consumption of n-6-rich oils could exert detrimental effects when not counterbalanced by sufficient n-3 intake. These effects seem more pronounced among APOE ε4 noncarriers [73]. Finally, among the 3779 members of the Swedish Twin Registry who completed a diet questionnaire approximately 30 years before cognitive screening and full clinical evaluation for dementia as part of the study of dementia in Swedish Twins (HARMONY) study, a medium or great proportion of fruits and vegetables in the diet, compared with no or small, was associated with a decreased risk of dementia and AD. This effect was observed among women and individuals with angina [197].
Table 4. Principal longitudinal, clinical and epidemiological studies on the relationships between fruit and vegetable intake and dementia (i.e., Alzheimer’s disease) or predementia syndromes (i.e., age-related cognitive decline).

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Setting and study design (duration)</th>
<th>Subjects</th>
<th>Methods</th>
<th>Results and conclusions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang et al. (2005) The Nurses’ Health Study, USA</td>
<td>Longitudinal, population-based (10–16 years)</td>
<td>13,388 women, aged 70 years and over</td>
<td>The TICS and five other cognitive tests (immediate and delayed recalls of the EBMT, category fluency, delayed recall of the TICS and DSB) and evaluation of dietary intake of food with a semiquantitative FFQ</td>
<td>High consumption of vegetables, but not fruit, was associated with less cognitive decline among older women</td>
<td>[195]</td>
</tr>
<tr>
<td>Morris et al. (2006) Chicago Health and Aging Project (CHAP), USA</td>
<td>Longitudinal, population-based (3–6 years)</td>
<td>3718 subjects, aged 65 years and older</td>
<td>Immediate and delayed recalls of the EBMT, MMSE, and SDMT and evaluation of dietary intake of food with a semiquantitative FFQ</td>
<td>High vegetable, but not fruit, consumption was associated with slower rate of cognitive decline with older age</td>
<td>[196]</td>
</tr>
<tr>
<td>Dai et al. (2006) The Kame Project, USA</td>
<td>Longitudinal, population-based (6.3 years)</td>
<td>3045 Japanese–American subjects, aged 65 or over</td>
<td>Diagnosis of incident AD and evaluation of dietary intake of food with a semiquantitative FFQ</td>
<td>Frequent drinking of fruit and vegetable juices was associated with a substantially decreased risk of AD. This inverse association was stronger after adjustments for potential confounding factors</td>
<td>[43]</td>
</tr>
<tr>
<td>Hughes et al. (2010) The HARMONY study, Sweden</td>
<td>Longitudinal (30 years)</td>
<td>3779 members of the Swedish Twin Registry</td>
<td>Diagnosis of incident dementia and AD and evaluation of dietary habits</td>
<td>These findings suggested that higher fruit and vegetable intake assessed at midlife was associated with a lower risk of dementia and later AD</td>
<td>[197]</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; DSB: Digit Span Backward; EBMT: East Boston Memory Test; FFQ: Food Frequency Questionnaire; MMSE: Mini-Mental State Examination; SDMT: Symbol Digit Modalities Test; TICS: Telephone Interview for Cognitive Status.

One important unanswered question relates to the largely unexplored relationship between intake of fruits and vegetables, antioxidant micronutrient status, a condition of oxidative stress and cognitive performance in healthy subjects [198]. In a very recent cross-sectional study, 193 healthy community dwellers consuming a diet rich in fruits and vegetables had higher plasma levels of lipophilic antioxidant micronutrients, lower levels of biomarkers related to oxidative stress and better scores on neuropsychological evaluation compared with subjects with low intakes of fruits and vegetables. This result was independent of gender, education, BMI, lipid profile and albumin levels but, most importantly, was independent of age. Therefore, micronutrient levels appeared to be a good indicator for fruit and vegetable intake and important in influencing the in vivo oxidant/antioxidant balance in healthy subjects [199]. Furthermore, individuals who consume a diet high in fruits and vegetables, as well as nuts or fish, would probably have other lifestyle characteristics that may be effective in reducing AD or VaD risk (e.g., physical activity) [200].

Fruits and vegetables reflect distinct food groups in the MeDi and in the American Diabetes Association food pyramid, and the benefits of these food groups could be provided through the antioxidant properties that foods in this class provide [201]. In fact, fruits and vegetables are rich sources of antioxidant nutrients and bioactive compounds, such as flavonoids, that are thought to be involved in neurodegenerative processes. This is in accordance with previous finding of a protective effect for higher consumption of dietary flavonoids against dementia [168] and cognitive decline [202] in the PAQUID study. However, in the full Adult Changes in Thought (ACT) cohort, the use of supplemental vitamin E and C, alone or in combination, was not associated with reduced risk for dementia over 5.5 years of follow-up [203]. Examining brains from the same cohort, typical antioxidant supplement use was not associated with suppressed basal or increased levels of free radical damage to the cerebral cortex from AD, microvascular brain injury or smoking [204]. Evidence suggested that the combined intake of tocopherol forms may be important for AD protection, especially the combination of α- and γ-tocopherol [205]; thus, dietary sources of vitamin E may be preferred over supplementation. In contrast to supplemental antioxidant use, more evidence exists for a protective effect of dietary antioxidants for AD development [168,186,206], although study results remain conflicting. Therefore, future clinical trials for AD should consider dietary sources rather than supplements, other antioxidants, combinations or doses other than those used by ACT participants [203]. Furthermore, there is growing evidence indicating that oxidative damage caused by the Aβ peptide in the pathogenesis of AD may be hydrogen peroxide (\(H_2O_2\))-mediated [207]. Recent studies have shown that flavonols, a class of flavonoids, from apple...
and citrus juices, such as quercetin, are able to cross the BBB [208] and demonstrate neuroprotection against H₂O₂ [209] in human neuroblastoma cells, which may or may not behave like neurons in the intact brain, also preventing Aβ-induced calcium influx and apoptosis, each of which results, in part, owing to increased ROS. The effect of flavonols from citrus is similar to vitamin C, but quercetin from apple juice confers stronger neuroprotection than vitamin C [210]. Early in vitro studies reported that polyphenol flavonols, such as quercetin, protect mammalian and bacterial cells from toxicity induced by H₂O₂, but that α-tocopherol is not effective [211]. Recent in vitro studies demonstrate that many polyphenols, including flavonols (e.g., quercetin and others), protect mouse hippocampal cells from oxidative glutamate and H₂O₂ toxicity [209]. Additional animal studies demonstrate that chronic administration of flavonols or apple juice protects against aging and cognitive impairment induced by lipopolysaccharide, genetic and dietary vitamin deficiency in animal models [212,213]. However, the Nurses’ Health study [199] and the CHAP [196] found a protective effect for higher vegetable consumption, but not for higher fruit consumption, against cognitive decline. A partial explanation of this finding could be that vegetables contain more vitamin E than fruits, and this antioxidant nutrient was previously demonstrated to be inversely related to risk of cognitive decline in the CHAP study population [214]. This explanation is supported by the fact that green leafy vegetables (which generally contain more vitamin E than other vegetable types) had the strongest inverse relationship with cognitive decline in the CHAP [196]. Vegetables, but not fruits, are also typically consumed with added fats (e.g., salad dressings, mayonnaise, margarine or butter), and fats increase the absorption of vitamin E and other fat-soluble antioxidant nutrients, such as carotenoids and flavonoids [196].

Other possible mechanisms linking fruit and vegetable intake with neuroprotection could be of vascular origin. In fact, a meta-analysis demonstrated that regular consumption of fruits and vegetables decreased the risk for stroke [215], which could explain their protective effect against the vascular component of dementia. In addition to antioxidant and vascular mechanisms, anti-inflammatory mechanisms have been invoked as contributing protective components, such as folate and minerals [222], and a high serum level of folate was found to be associated with a decreased risk of AD [223].

**AD risk & the whole-diet & dietary pattern approaches to the Mediterranean diet model**

In the last 5 years, research interest on diet and nutrition in relation to the occurrence of AD has been focused in exploring whole types of foods (e.g., tomatoes, fruits and vegetables) and whole dietary patterns rather than a single nutrient [53]. Among the broad spectrum of dietary patterns analyzed with this aim, a special role has been assigned to the MeDi [51]. In fact, the MeDi could be 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, n-3 PUFAs, fish and olive oil consumption, cereals and red wine) in contrasting cognitive impairment. The evidence reviewed thus far is based on the hypothesis that individual nutrients contained in foods may have effects on predementia and dementia syndromes, neglecting the possible importance of the additive or synergistic effects of other nutrients within and across particular foods that form part of a diet [33–38]. However, as seen extensively above, the results regarding isolated nutrients or foods appear to be conflicting. Compared with traditional single-food or nutrient methods, the whole-diet or dietary pattern approach is appealing for several reasons. Indeed, the analyses of single nutrients ignore important interactions (additive, synergistic or antagonist effects) between components of diet and, more importantly, people do not eat isolated nutrients [224,225]. The evaluation of the adherence to a Mediterranean-style diet was conducted to develop scores or indexes named the ‘Mediterranean Diet Scale’ or ‘Mediterranean Diet Score’ or ‘Mediterranean Adequacy Index’ or even ‘Mediterranean-Style Dietary Pattern Score’ based on a priori hypotheses and intended to be close to the traditional one [224,226,227]. In particular, a scale indicating the degree of adherence to the traditional MeDi was constructed by Trichopoulou and colleagues [228], revised to include fish intake [229], and used in recent studies investigating cognitive decline on US, French and Greek cohorts [62,230–236]. A value of 0 or 1 was assigned to each of nine indicated components (vegetables, fruits, legumes, cereals, the ratio of MUFA to SFA, alcohol and fish presumed to be beneficial; meat and dairy products presumed to be detrimental) with the use of a sex-specific median as the cut-off. The total MeDi score ranged from 0 (minimal adherence to the traditional MeDi) to 9 (maximal adherence).

The use of diet-scoring systems, such as the MeDi score, have undeniable advantages in understanding the role of diet in chronic disease [237]. Scarmeas and colleagues, using data from...
the WHICAP with an inclusive dietary score (MeDi score) but studying a population with a substantial difference in dietary habits compared with Greek (European Prospective Investigation into Cancer and Nutrition [EPIC]) [62], Italian (ILSA) [60,61], and French (3C Study) [234] cohorts, found that a higher adherence to the MeDi is associated with a trend for reduced risk of incident MCI and also with reduced risk of MCI progression to AD (Table 5) [233]. Individuals older than 65 years of age were enrolled in the WHICAP in 1992 and 1999 and have been followed on average for 4 years. Among individuals free from dementia at baseline, 2258 individuals had a complete assessment of cognitive functions and of dietary habits (Table 5). These findings confirmed previous reports from the WHICAP in which higher adherence to the MeDi reduced the risk of developing AD [230,231], and was associated with lower mortality in AD (Table 5) [232]. They may account for the complex biological interactions between different components of a composite dietary pattern, such as MeDi, that may be difficult to detect in analyses focusing on only the individual components. The potentially beneficial effect of the MeDi for cognitive decline may be the result of some of its individual food components. For example, as seen above, potentially beneficial effects for MCI and its progression to dementia and AD or dementia have been reported for alcohol [46], fish consumption [42], PUFA [42] and lower SFA [42]. Interestingly, in other studies, alcohol and PUFA have failed to be associated with protection against MCI, its progression to dementia and AD or dementia [42,46]. These contrasting findings about the impact of MeDi score or individual macronutrients on predementia and dementia syndromes may suggest an approach not only confined to cognitive skills, but extended to functional status and comorbidity. However, we should not renounce a priori the work for a correct estimate of the validity of the MeDi score for cognitive impairment as a criterion. While several prospective cohort studies have consistently indicated that adherence to the traditional MeDi is associated with longevity or specific health outcomes, no study has investigated the relative importance of individual components of the MeDi score in the generation of this association. Very recent findings from the EPIC on mortality suggested that the contribution of the nine components of the MeDi to the apparent protective effect of the score assessing adherence to traditional Mediterranean diet is approximately additive. The dominant components of the MeDi score as a predictor of lower mortality were moderate consumption of alcohol, low consumption of meat and meat products, and high consumption of vegetables, nuts and olive oil and legumes [238]. However, the evidence about the role of the whole MeDi on cognitive decline is still scarce [224].

Recently, a report from the 3C Study from over a 5-year period in a sample of older community dwellers in France suggested that higher adherence to a MeDi was associated with slower cognitive decline (MMSE score), while it was not associated with a lower risk of incident dementia or AD (Table 5) [234]. These findings were compared with those of the WHICAP from the USA on the possible role of adherence to a Mediterranean dietary pattern on the risk of MCI and AD [230,233]. However, some concern could be expressed regarding the analysis and discussion of the study findings. Our first concern was on the comparison between the French and US findings. In fact, from a methodological point of view, French data were left-truncated (in contrast to the US data), and the results of the MeDi score of the 3C Study and WHICAP were noncomparable (the medians used as cut-offs are generally study-specific). Moreover, from a clinical point of view, the French findings were on ARCD, which was measured by MMSE performance, and the US findings had incident MCI as a primary outcome [233], which is a more structured clinical construct and not just a cognitive test. The second concern regards the role of drop-out dependence on the outcome of interest that was not addressed, particularly because the slower MMSE performance across time was only borderline significant, and follow-up was over 5 years. Féart and colleagues correctly acknowledged among potential limitations of their study that, as already reported in the non-Mediterranean population of the WHICAP [230,233], they found a relatively low ratio of MUFA to SFA [234]. The hallmark of the traditional MeDi is a high consumption of olive oil, leading to a high ratio. In the 3C Study, it was verified that consumption of olive oil was positively correlated with the diet score and with the ratio (data available on request). Nonetheless, these positive associations did not give any indication about the adherence to the MeDi pattern. The ratio of MUFA to SFA intake in the context of other parameters of the MeDi score could be very useful as a marker of adherence to the MeDi pattern.

Other original findings from the WHICAP suggested that both high Mediterranean-type diet adherence and participating in physical activity were independently associated with a lower risk of AD over time [235]. Very recently, findings from the CHAP suggested that another dietary index based on the traditional MeDi [239] was associated with slower rates of cognitive decline, while the Healthy Eating Index (HEI)-2005 dietary quality index, a 12-component measure reflecting diet-related recommendations of the 2005 US Dietary Guidelines [240], was not associated with cognitive change [241]. Finally, in an analysis of food combination from the WHICAP, a dietary pattern that explained variation of AD-related nutrients strongly protective against the development of AD was identified. This dietary pattern reflected a diet rich in n-3 PUFA, n-6 PUFA, vitamin E and folate, but with lower SFA and vitamin B12 [242]. Furthermore, dietary habits of subjects adhering more to this dietary pattern were characterized by a high intake of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits and dark and green leafy vegetables and low intake of high-fat dairy, red meat, organ meat and butter. Notwithstanding the undeniable advantages of the whole-diet approach, using such a score in a US and a multiethnic population may not adequately represent conformity with the traditional MeDi. Furthermore, these recent findings from the WHICAP further underlined the possible protective role against cognitive decline of both n-3 and n-6 PUFA intake and the detrimental role of SFA. In fact, taken together with the recent findings from the WHICAP and the ILSA [60,61,242], it should be advisable to include elevated PUFA (both n-3 and n-6) intake, and lower MUFA:SFA ratio or SFA intake, in the food combination presumed to be beneficial against AD and cognitive decline.
### Table 5. Principal epidemiological studies on the relationship between adherence to the Mediterranean diet and dementia (i.e., Alzheimer’s disease) or predementia syndromes (i.e., age-related cognitive decline and mild cognitive impairment) in older people.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Setting and study design (duration)</th>
<th>Subjects</th>
<th>Dietary assessment</th>
<th>Cognitive outcomes</th>
<th>Results and conclusions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarmeas et al. (2006) Washington Heights-Inwood Columbia Aging Project (WHICAP), USA</td>
<td>Longitudinal, population-based (4 years)</td>
<td>2258 subjects, aged 65 years and over</td>
<td>Evaluation of dietary intake with a 61-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi</td>
<td>Diagnosis of incident AD</td>
<td>Higher adherence to MeDi reduced risk for probable AD, either with or without coexisting stroke</td>
<td>[230]</td>
</tr>
<tr>
<td>Scarmeas et al. (2007) Washington Heights-Inwood Columbia Aging Project (WHICAP), USA</td>
<td>Longitudinal, population-based (4.4 years)</td>
<td>192 community-based individuals, aged 65 years and older, who were diagnosed with AD</td>
<td>Evaluation of dietary intake with a 61-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi</td>
<td>All-cause mortality</td>
<td>Higher adherence to the MeDi was associated with lower mortality in AD. The gradual reduction in mortality risk for higher MeDi adherence tertiles suggested a possible dose–response effect</td>
<td>[232]</td>
</tr>
<tr>
<td>Psaltopoulou et al. (2008) European Prospective Investigation into Cancer and nutrition (EPIC), Greece</td>
<td>Longitudinal, population-based (median 8 years)</td>
<td>732 subjects, aged 60 years or older</td>
<td>Evaluation of dietary intakes with a 150-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi</td>
<td>MMSE</td>
<td>No significant association between MeDi score and MMSE scores, whereas a statistically significant inverse association was found between MMSE performance and some individual dietary components, such as seed oil or PUFA intakes</td>
<td>[62]</td>
</tr>
<tr>
<td>Scarmeas et al. (2009) Washington Heights-Inwood Columbia Aging Project (WHICAP), USA</td>
<td>Longitudinal, population-based (4.5 years)</td>
<td>2258 subjects, aged 65 years and over</td>
<td>Evaluation of dietary intake with a 61-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi</td>
<td>Incidence of MCI and progression from MCI to AD</td>
<td>Higher adherence to the MeDi was associated with a trend for reduced risk of developing MCI and with reduced risk of MCI progression to AD</td>
<td>[233]</td>
</tr>
<tr>
<td>Scarmeas et al. (2009) Washington Heights-Inwood Columbia Aging Project (WHICAP), USA</td>
<td>Longitudinal, population-based (5.4 years)</td>
<td>2247 subjects, aged 65 years and over</td>
<td>Evaluation of dietary intake with a 61-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi. Two slightly different versions of the Godin leisure time exercise questionnaire were also used</td>
<td>Diagnosis of incident AD</td>
<td>Both higher Mediterranean-type diet adherence and higher physical activity were independently associated with reduced risk for AD</td>
<td>[235]</td>
</tr>
<tr>
<td>Féart et al. (2009) Three-City Study, France</td>
<td>Longitudinal, population-based (5 years)</td>
<td>1410 subjects, aged 65 years and older</td>
<td>Evaluation of dietary intakes with a FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi</td>
<td>Cognitive performance was assessed with MMSE, IST, BVRT and FCSRT. Incident cases of dementia were also diagnosed</td>
<td>Adherence to a Mediterranean-type diet was associated with slower decline on the MMSE, but not other cognitive tests, and was not associated with the risk for incident dementia over 5 years of follow-up</td>
<td>[234]</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; BVRT: Benton Visual Retention Test; EBMT: East Boston Memory Test; FCSRT: Free and Cued Selective Reminding Test; FFQ: Food Frequency Questionnaire; HEI-2005: Healthy Eating Index 2005; IST: Isaacs Set Test; MCI: Mild cognitive impairment; MeDi: Mediterranean diet; MMSE: Mini-Mental State Examination (global cognitive functioning); SDMT: Symbol Digit Modalities Test.
Table 5. Principal epidemiological studies on the relationship between adherence to the Mediterranean diet and dementia (i.e., Alzheimer’s disease) or predementia syndromes (i.e., age-related cognitive decline and mild cognitive impairment) in older people (cont.).

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Setting and study design (duration)</th>
<th>Subjects</th>
<th>Dietary assessment</th>
<th>Cognitive outcomes</th>
<th>Results and conclusions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gu et al. (2010)</td>
<td>Longitudinal, population-based (4 years)</td>
<td>1219 subjects, aged 65 years and older</td>
<td>Evaluation of dietary intake with a 61-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi</td>
<td>Diagnosis of incident AD</td>
<td>Greater adherence to a Mediterranean-type diet was significantly associated with lower risk for AD. Introduction of the high-sensitivity C reactive protein, fasting insulin, adiponectin or combinations of them into the COX model did not change the magnitude of the association between Mediterranean-type diet and incident AD</td>
<td>[236]</td>
</tr>
<tr>
<td>Tangney et al. (2011)</td>
<td>Longitudinal, population-based (3 years)</td>
<td>3790 subjects, aged 65 years and older</td>
<td>Evaluation of dietary intake of food with a semiquantitative FFQ; a dietary composite score (MedDiet and MedDiet–wine scores) evaluated adherence to MeDi; the HEI-2005 evaluated dietary quality reflecting diet-related recommendations of the 2005 Dietary Guidelines</td>
<td>Immediate and delayed recalls of the EBMT, MMSE and SDMT</td>
<td>A dietary index based on the traditional Mediterranean diet was associated with slower rates of cognitive decline. By contrast, the HEI-2005 dietary quality index was not associated with cognitive change</td>
<td>[241]</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; BVRT: Benton Visual Retention Test; EBMT: East Boston Memory Test; FCSRT: Free and Cued Selective Reminding Test; FFQ: Food Frequency Questionnaire; HEI-2005: Healthy Eating Index 2005; IST: Isaacs Set Test; MCI: Mild cognitive impairment; MeDi: Mediterranean diet; MMSE: Mini-Mental State Examination (global cognitive functioning); SDMT: Symbol Digit Modalities Test.
with important antioxidant properties, such as olive oil [261], wine, fruits and vegetables, vitamins C and E, and carotenoids [262–264], are found in high concentrations in the typical components of the MeDi [265]. Typical Mediterranean meals [266] or meals rich in typical Mediterranean food elements, such as olive oil [267] or pomegranate juice [268], have been demonstrated to increase enzymes with antioxidant properties, such as paraoxonase and plasma carotenoids [266]. Food intervention studies with either different tomato products, a very commonly used food in Mediterranean areas [268], or a typical Mediterranean dish such as gazpacho—a cold vegetable soup that contains approximately 75% vegetables (tomato, cucumber, pepper), 2–10% olive oil and other minor components (onion, garlic, wine vinegar and sea salt) [269]—have indicated significant reductions of markers of oxidative stress, such as isoprostanes. Therefore, the MeDi could be capturing the composite effect of dietary antioxidants and this could, at least partially, explain the association with a lower risk of dementia and predementia syndromes. Finally, inflammation is another mechanism involved in the pathogenesis of dementia and predementia syndromes that is, in general, reduced with a higher adherence to the MeDi [270,271]. In fact, inflammation is another potential mechanism for AD pathogenesis [272,273] and has been found to be associated with a higher risk for AD, VaD and cognitive decline [28], and links between MCI and higher inflammatory states have been also demonstrated [274–276]. In fact, CRP, an inflammatory marker that has been detected in SPs and NFTs in the brains of patients with AD [277,278] and is upregulated in AD brains [279,280] and serum [281], has been proposed as a possible biomarker for AD [282], MCI and nonamnestic MCI [283]. Higher adherence to the MeDi has been associated with lower CRP levels in both observational [284,285] and interventional studies [255,256]. Furthermore, IL-6, a cytokine that mediates inflammatory reactions, has been consistently detected in diffuse early SPs without neuritic pathological abnormalities of cortical regions of patients with AD [282], and has been associated with greater cognitive decline [286] and an increased risk of dementia during follow-up [287]. Tyrosol and caffeic acid, both found in extra-virgin olive oil and in wine (which are essential components of the MeDi), have been demonstrated to significantly reduce IL-6 production from peripheral blood mononuclear cells of healthy volunteers [288]. In the ATTICA study, subjects in the highest tertile of MeDi adherence have been reported to have 17% lower IL-6 serum levels [244], and in the Nurses’ Health Study, there was a 16% reduction in IL-6 levels for subjects belonging to the upper quintile of a MeDi adherence index [288]. In a clinical trial, as compared with subjects assigned to the control diet, the subjects assigned to the MeDi had significantly reduced levels of IL-6 [255]. Higher adherence to the MeDi is in general associated with a significant reduction in a series of other inflammatory markers, including white blood cell counts and others [244]. Thus, it is possible that the MeDi may, at least partially, lower the risk for dementia and predementia syndromes by affecting inflammatory processes. It is also possible that moderate lifestyles in general, which obviously vary according to different cultural environments, protect from cognitive impairment. Thus, it may not be the direct effect of the MeDi or MeDi components (UFA, elevated fish consumption, moderate alcohol intake and fruit and vegetable intake) or specific substances in MeDi components (antioxidant or anti-inflammatory compounds) that provide the protection, but the higher adherence to the MeDi may be an indicator of a complex set of favorable social and lifestyle factors. In fact, very recent findings from the WHICAP demonstrated that high-sensitivity CRP, fasting insulin and adiponectin (as biomarkers of metabolic abnormalities) did not mediate the association between MeDi and AD risk (Table 5) [264]. These results suggest that greater adherence to MeDi may not be associated with reduced risk for AD via inflammatory or metabolic pathways.

Expert commentary

At present, there is no curative treatment for dementia and AD, or a therapeutic approach to prevent the conversion of MCI to dementia. Given the very limited therapeutic value of drugs currently used in the treatment of cognitive impairment and dementia, it remains necessary to potentially individualize new strategies able to prevent and to slow down the progression of predementia and dementia syndromes. Recently, higher adherence to a Mediterranean-type diet was associated with cognitive decline, although the MeDi combines several foods and nutrients already separately proposed as potential protective factors against dementia and predementia syndromes. Epidemiological evidence suggested a possible association among fish consumption, MUFA and PUFA (particularly, n-3 PUFA) and reduced risk of cognitive decline and dementia. Furthermore, light-to-moderate alcohol use may be associated with a reduced risk of incident dementia and AD, while for VaD, cognitive decline and predementia syndromes the current evidence is only suggestive of a protective effect. Finally, some lines of evidence have suggested that older healthy subjects consuming a diet rich in fruits and vegetables have higher plasma levels of lipophilic antioxidant micronutrients, lower levels of biomarkers related to oxidative stress and better scores on neuropsychological evaluation compared with subjects with low intakes of fruits and vegetables. On the basis of this evidence, the evaluation of the MeDi on cognitive outcomes seems of particular interest and recent prospective studies focused on dementia and predementia syndromes appeared to be promising. In fact, higher adherence to a Mediterranean-type diet has been associated with slower cognitive decline, with a trend towards a reduced risk for developing MCI, reduced risk of progression from MCI to AD, decreased risk for AD and a reduced all-cause mortality in AD patients. These findings suggested that adherence to the MeDi may affect not only the risk for AD, but also that for predementia syndromes, probably influencing the evolution of cognitive performances over time and subsequent disease progression.

However, while for the vascular hypothesis there was clear evidence about a protective role of MeDi and its nutrients in preventing all cardiovascular conditions linked to dementia, for the other possible mechanisms it is only possible to suggest hypothetical biological pathways, taking into account the results from animal studies. Therefore, the lack of reproducibility in some results and the speculative aspect of the biological pathways presented, suggest
caution. However, although it is difficult to define the real impact of these biological findings, these studies provided another possible explanation of the neuroprotective effect of the MeDi and its micro- and macro-nutrients that are not only linked to inflammatory and oxidative-related mechanisms. In fact, the efficacy of nutritionally derived compounds as neuroprotective agents is increasingly supported by empirical evidence. Plant-derived molecules, including polyphenols, have demonstrated neuroprotective activities in cell culture and animal models. However, the molecular mechanisms underlying their protective effects are generally not completely understood and further investigation will be essential to provide links between MeDi nutrients and brain function in a mechanistic, dynamic and quantitative way. Based, in part, on the evidence discussed in this article, it appears possible that in the near future we may consider employing dietary intervention in preventative and possibly therapeutic strategies for dementia and predementia syndromes. Nonetheless, at present, no definitive dietary recommendations are possible. However, high levels of consumption of fats from fish, vegetable oils, nonstarchy vegetables and low glycemic index fruits, and a diet low in foods with added sugars and with moderate wine intake should be encouraged. In fact, this dietary advice provides a variety of antioxidant nutrients, is in accordance with recommendations for lowering the risk of cardiovascular disease, obesity, diabetes and hypertension, and may open new routes for the prevention and management of cognitive decline and dementia to supplement existing symptomatic approaches.

Five-year view

In previous years, extensive research has increased our knowledge of the etiology of AD, other dementing disorders and predementia syndromes and several hypotheses have already emerged from the epidemiological research. The reviewed evidence supports the hypothesis that dietary-related factors may be associated with the development of dementia and predementia syndromes in late life, opening new avenues for the prevention of these diseases. However, many questions remain for future research, addressing possible confounders. For example, if a change of dietary habits may play a major part, what is the role of genetic risk factors, and will these associations valid in populations with different dietary patterns? Other questions address the underlying mechanisms and which is the most relevant component, among dietary micro- and macro-nutrients and their possible interactions. Answers to these questions will help us to better define the target populations for future preventive and therapeutic strategies. Therefore, in the future, addressing possible interactions in different populations with genetic factors and other possible confounders, and whether change in dietary patterns may protect against cognitive decline and AD would require longitudinal studies on larger populations and RCTs.

Among different dietary patterns, studies in support of MeDi as an optimal diet for prevention of cardiovascular and major chronic diseases has rapidly evolved. As discussed extensively above, the association between a high adherence to the MeDi and lower risk of AD and cognitive decline may be mediated by the composite effect of some of its beneficial components. Some of the inconsistencies regarding the above dietary elements and risk for AD in the existing literature may be a result of failure to consider possible additive and interactive (antagonistic or synergistic) effects among nutritional components, which may be captured in a composite dietary pattern, such as the MeDi. Focusing on single MeDi macronutrients, recommendations regarding future research on the effects of n-3 PUFA supplementation on predementia syndromes and very mild AD include properly designed RCTs that are sufficiently powered and with an adequate length (e.g., 3–5 years of follow-up). In particular, the future RCTs on PUFA supplementation should address the effects of different types of n-3 PUFA (i.e., DHA, EPA, arachidonic acid and total n-3 PUFA), as well as the ratio of n-6 to n-3 PUFA. Finally, these RCTs should be designed to include a baseline assessment of dietary n-3 and n-6 PUFA intake and to evaluate the effect of dose, treatment duration and the sustainment of effect after discontinuation of n-3 PUFA consumption. In particular, the dose of n-3 PUFA that might work for prevention may be very high. Furthermore, moderate alcohol consumption seems to be associated with a decreased risk of predementia and dementia syndromes, but, at present, it is still questionable whether the effect of alcohol may be due to social and lifestyle factors. Furthermore, studies on the interaction between smoking and drinking alcohol have yielded inconclusive results [46]. The effect of alcohol on cognition may be modified by the presence of the APOE ε4 allele, but the patterns of interaction suggested have yielded different results. Some studies investigating the effect of different types of alcohol on the cognitive function found no beverage-specific differences. There is evidence that binge drinking is associated with negative cardiovascular outcomes, and possibly also with an increased risk of dementia. The role of drinking patterns for the development of cognitive impairment needs to receive more attention in the future: trying to understand whether starting to drink at a later age would be beneficial and the role of the interaction between APOE ε4 allele and alcohol consumption. Finally, the long-term effect of alcohol drinking on cognitive functions has not been extensively investigated. Therefore, we need studies to collect information on alcohol drinking collected from 5 to 20 years earlier, while also examining possible interaction with APOE ε4 and other lifestyle factors.

In future studies on the MeDi and AD, it would be indicated, along with measuring this effect by a dietary composite score, to also report the estimates and the impact of the individual components of the diet (particularly fats) versus the whole-diet approach, to better understand if the whole MeDi is important and not as only sources of beneficial fats (e.g., MUFA and n-3 PUFA). At present, only the EPIC cohort has been studied for a whole-diet approach, plus individual nutrients analysis, with no significant association found between MeDi score and global cognitive scores, whereas a statistically significant inverse association was found between cognitive performance and some individual dietary components [62]. In a very recent reanalysis from the ILSA cohort, high PUFA were associated with reduced risk of incident MCI among those who consumed a low MUFA:SFA ratio intake [289]. In fact, while an increasing body of evidence suggested that elevated fish consumption and high intake of n-3 PUFA may be protective...
against ARCD and MCI, the traditional Cretan diet, although strongly dependent on high olive oil intake, was never centred on fish consumption [290]. In this context, n-6 PUFA could potentially exert some health benefits. In fact, in the MeDi, some foods are rich in n-6 PUFA (e.g., walnuts, almonds and hazelnuts), while other foods, although poor in n-6 PUFA, are highly consumed, such as cereals, legumes and, in a lesser amount, some types of meat (pork) and poultry. Furthermore, olive oil contains n-6 and n-3 PUFA in a ratio of 10:1. Therefore, it should be advisable to include PUFA in the MeDi score as well as the other individual macronutrients (i.e., MUFA:SFA ratio), among the components presumed to be beneficial, in evaluating the relationship between adherence to the MeDi and ARCD or MCI. Future studies on this topic should probably address different constructs of predementia syndromes and subtypes of MCI, while also accounting for the possible role of the APOE ε4 allele, a major genetic risk factor for AD, in modifying the possible associations between the MeDi and cognitive decline. Further research is also needed to allow the generalization of these results to other populations and to propose the MeDi as a potential preventive approach against dementia and AD. Recommendations regarding future research on the effects of adherence to the MeDi on predementia and dementia syndromes include properly designed RCTs that are sufficiently powered and with an adequate length, although this approach could have some potential limitations. In fact, given the long preclinical phase of dementia, it may be difficult to execute appropriate RCTs over a long enough time period and with large enough samples to draw accurate and repeatable conclusions.

Financial & competing interests disclosure
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No writing assistance was utilized in the production of this manuscript.

Key issues
- Vascular- and dietary-related factors appeared to be associated with increased risk or protection against predementia syndromes and Alzheimer’s disease (AD).
- Among dietary factors, epidemiological evidence suggested a possible association among fish consumption, monounsaturated fatty acids and polyunsaturated fatty acids (PUFA; particularly, n-3 PUFA) and reduced risk of cognitive decline and dementia.
- Limited epidemiological evidence suggested that poorer cognitive function and an increased risk for vascular dementia (VaD) were found to be associated with a lower consumption of milk or dairy products, while whole-fat dairy products may be associated with late-life cognitive decline.
- Light-to-moderate alcohol use may be associated with a reduced risk of incident dementia and AD, while for VaD, cognitive decline and predementia syndromes, the current evidence is only suggestive of a protective effect.
- The limited epidemiological evidence available on fruit and vegetable consumption and cognition generally supported a protective role of these macronutrients against cognitive decline, dementia and AD.
- Among different dietary patterns, recent prospective studies provided evidence that a higher adherence to a Mediterranean-type diet could be associated with slower cognitive decline, reduced risk of progression from MCI to AD, reduced risk of AD and decreased all-cause mortality in AD patients.
- Although this impressive amount of convincing epidemiological evidence, at present, no definitive dietary recommendations for preventing dementia and AD are possible.
- In accordance with recommendations for lowering the risk of cardiovascular and metabolic disorders, high levels of consumption of fats from fish, vegetable oils, nonstarchy vegetables and low glycemic index fruits, and a diet low in foods with added sugars and with moderate wine intake should be encouraged, possibly opening new routes for the prevention and management of cognitive decline and dementia.

References
Papers of special note have been highlighted as:
• of interest
** of considerable interest


• Update on a cross-sectional study on Alzheimer’s disease (AD), suggesting that fat and total caloric supply have the highest correlations with AD prevalence rates. A significant inverse correlation was found between the fraction of calories derived from cereals and AD prevalence.


• In this randomized double-blind trial, after the treatment period the authors found that the supplementation did not delay the rate of cognitive decline but, in the group of 32 patients with the most mild AD (Mini-Mental State Examination [MMSE] ≥27, Clinical Dementia Rating Score 0.5–1), n-3 polyunsaturated fatty acid supplementation slowed the decline in MMSE scores.


• Comprehensive and unique review on the possible association between dairy intake and cognitive functioning.


Diet & Alzheimer's disease


- First article in which alcohol drinking in middle age demonstrated a U-shaped relationship with risk of mild cognitive impairment in old age. Only the carriers of apolipoprotein E ε4 had an increased risk of dementia with increasing alcohol consumption.


- First systematic review with meta-analysis carried out to investigate any relationship between incident cognitive decline or dementia in the elderly and alcohol consumption, with only longitudinal studies of subjects aged ≥65 years included.


Findings

- Higher fruit and vegetable intake assessed at midlife was associated with a lower risk of dementia and AD in late life.


Websites

301 National Center for Biotechnology Information

   http://health.gov/dietaryguidelines/