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Review

Dietary patterns, foods, and food groups: relation to late-life cognitive disorders

C. Custodero[1], V. Valiani[1], P. Agosti[1], A. Schilardi[1], A. D'Introno[1], M. Lozupone[2], M. La Montagna[4], F. Panza[2 3 5], V. Solfrizzi[1], C. Sabbà[1]

[1] Geriatric Medicine-Memory Unit and Rare Disease Centre, University of Bari Aldo Moro, Bari, Italy; [2] Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari Aldo Moro, Bari, Italy; [3] Geriatric Unit & Laboratory of Gerontology and Geriatrics, Department of Medical Sciences, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Foggia, Italy; [4] Psychiatric Unit, Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy; [5] Department of Clinical Research in Neurology, University of Bari Aldo Moro, "Pia Fondazione Cardinale G. Panico", Tricase, Lecce, Italy

The limited efficacy of disease-modifying therapeutic strategies for mild cognitive impairment (MCI) and Alzheimer's dementia (AD) underscores the need for preventive measures to reduce the burden of late-life cognitive impairment. The aim of the present review article was to investigate the relationship among dietary patterns, foods, and food groups and late-life cognitive disorders considering the results of observational studies published in the last three years (2014-2016). In the last decade, the association between diet and cognitive function or dementia has been largely investigated. However, more recently, the National Institute on Aging-Alzheimer's Association guidelines for AD and cognitive decline due to AD pathology introduced some evidence suggesting a direct relation between diet and changes in the brain structure and activity. Several studies focused on the role of the dietary patterns on late-life cognition, with accumulating evidence that combinations of foods and nutrients into certain patterns may act synergistically to provide stronger health effects than those conferred by their individual dietary components. In particular, higher adherence to a Mediterranean-type diet was associated with decreased cognitive decline, although the Mediterranean diet (MeDi) combines several foods, micronutrients, and macronutrients already separately proposed as potential protective factors against dementia and MCI. Moreover, also other emerging healthy dietary patterns such as the Dietary Approach to Stop Hypertension (DASH) and the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND) diets were associated with slower rates of cognitive decline and significant reduction in AD rate. Furthermore, some foods or food groups traditionally considered harmful such as eggs and red meat have been partially rehabilitated, while there is still a negative correlation of cognitive functions with added sugars and trans fatty acids, nutrients also increasing the cardiovascular risk. This would suggest a genesis for the same damage for aging brain.

Key words: Dementia, Alzheimer's disease, MCI, Dietary pattern, Mediterranean diet, Healthy diet, Foods, Food groups

INTRODUCTION

Currently, available drugs for the treatment of Alzheimer's disease (AD) have only symptomatic effects [1], and there is an unmet need of preventing AD onset and delaying or slowing disease progression from mild cognitive impairment (MCI) in absence of disease-modifying therapies. In the last ten years, a large number of studies have investigated the association between diet and cognitive function and dementia [2-4]. However, in the last few years, some changes have emerged in approaching the relationship between diet and cognitive impairment. In fact, the National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines for AD and cognitive decline due to AD pathology [5] introduced

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Correspondence: Vincenzo Solfrizzi, Department of Geriatrics, Center for Aging Brain, Memory Unit, University of Bari, Policlinico, piazza Giulio Cesare 11, 70124 Bari, Italy - Tel. + 39 080 5473685 - Fax + 39 080 5478633 - E-mail: v.solfrizzi@geriatria.uniba.it

some evidence suggesting a direct relation between diet and changes in the brain structure and activity, opening the era of brain imaging biomarkers in nutrition epidemiology. Furthermore, some groups of foods traditionally considered harmful such as eggs and red meat have been partially rehabilitated. Conversely, there is still a negative correlation of cognitive functions with added sugars and trans fatty acids, the same nutrients that increase the cardiovascular risk, suggesting a genesis for the same damage for aging brain. Finally, many studies focused on the role of dietary patterns on late-life cognition, accumulating evidence that combinations of foods and nutrients into certain patterns may act synergistically to provide stronger health effects than those conferred by their individual dietary components. The aim of the present review article was to shed light on the relationship among dietary patterns, foods, and food groups and late-life cognitive disorders considering the results of observational studies published in the last three years (2014-2016).

DIETARY PATTERNS AND LATE-LIFE COGNITION

The Mediterranean diet (MeDi) is a typical dietary pattern of Mediterranean countries, characterized by high consumption of fruits, vegetables, legumes and cereals, olive oil as the main added lipid, moderate consumption of alcohol (mainly wine and during meals) and low consumption of red meat and dairy products. It is doubtless the most analyzed dietary pattern and accumulating evidence support a potential protective role against cognitive decline and dementia, although there are still inconsistencies in the reported data. In particular, the findings from prospective studies and very recent systematic reviews and meta-analyses suggested that adherence to the MeDi fulfilling the whole-diet approach may affect not only the risk of AD, but also of predementia syndromes and their progression to overt dementia [6]. In the last two years, in the EPIC study, in a cohort of Greek elderly population that still adheres to the traditional MeDi, it was demonstrated that closer adherence to MeDi was associated with less decline in Mini Mental State Examination (MMSE) performance over a period of about 7 years, especially in individuals aged 75 years or older (Tab. I) [7].

Other emerging dietary patterns are the Dietary Approach to Stop Hypertension (DASH) and the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND) diets (Tab. I). The DASH diet is characterized by low consumption of saturated fat and commercial pastries and sweets, and higher intake of dairy than in the MeDi. In the last three years, in the Memory and Aging Project (MAP) study, a prospective study on older adults with 4 years of follow-up, the DASH pattern was associated with slower rates of cognitive decline. In particular, a 1-unit-higher DASH score, was equivalent of being at least 4.4 years younger (Tab. I) [8]. These results were in line with those of Morris and colleagues, in the same MAP study, in which higher adherence to DASH diet was related with greater reduction of incident AD rather than higher adherence to MeDi (54% and 39% reduction, respectively) (Tab. I) [9].

The MIND diet was based on the dietary components of the MeDi and DASH diet with modifications that highlight the foods and nutrients shown to be associated with dementia prevention. Among the MIND diet components, there are 10 brain healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine) and five unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). Hence, MIND diet uniquely specifies consumption of berries and green leafy vegetables and does not specify high fruit consumption (both DASH and MeDi), high dairy (DASH), high potato consumption, or > 1 fish meal per week (MeDi). Other recent findings from the MAP study suggested that higher MIND diet score was associated with slower decline in cognitive abilities (Tab. I) [10]. The rate reduction for persons in the highest tertile of diet scores compared with the lowest tertile was the equivalent of being 7.5 years younger. MIND diet score was also more predictive of cognitive decline than either of the other (DASH and MeDi) diet scores (Tab. I) [10]. Furthermore, in a follow-up of 4.5 years of the MAP study, participants with higher and moderate adherence to MIND diet had statistically significant reduction in AD rate compared with those with lower adherence (53% and 35% respectively) [9]. Instead only the highest tertiles of the DASH and MeDi scores were significantly associated with incident AD reduction (Tab. I) [9].

Despite the promising results of these two diets, to date, we have brain imaging data only on the correlation with the MeDi (Tab. I). The few cross sectional studies carried out on cognitively normal people showed that higher adherence to MeDi was related to greater magnetic resonance imaging (MRI)-based cortical thickness in AD-vulnerable regions and larger brain volumes. MeDi effects on MRI biomarkers were significant in the left, but not in the right hemisphere, and were most pronounced in entorhinal cortex, orbito-frontal cortex and posterior cingulate cortex (Tab. I) [11]. Higher adherence to a Mediterranean dietary pattern was associated with larger MRI measures of cortical thickness and with several individual region of interests (ROIs) that undergo age-related or AD-related neurodegeneration, was marginally associated with temporal and AD signature cortical thickness and was not associated with hippocampal volume (Tab. I) [12]. This finding may be explained with the observation from the Alzheimer's Disease Neuroimaging Initiative in which presymptomatic individuals had significantly reduced cortical thickness in AD vulnerable regions compared to controls but did not differ in regard to hippocampal volume [13]. In the Washington Heights-Inwood Community Aging Project (WHICAP), higher MeDi adherence was associated with less brain atrophy (larger total brain volume, total gray matter volume, total white matter volume), with an effect similar to 5 years of aging (Tab. I) [14].

To date, only one prospective imaging-diet study on older adults was conducted (Tab. I) [15], confirming other results coming from cross-sectional studies. In fact, Jacka and colleagues, in the Personality and Total Health Through Life Study found that healthy "prudent" dietary pattern characterized by intake of fresh vegetables, salad, fruit and grilled fish was associated with a larger left hippocampal volume on MRI over 4 years of follow-up (Tab. I) [15]. In particular, every one standard deviation (SD) increase in healthy "prudent" dietary pattern was associated with a 45.7 mm^3 larger left hippocampal volume [15]. While higher consumption of an unhealthy "Western" dietary pattern characterized by intake roast meat, sausages, hamburgers, steak, chips, crisps and soft drinks was independently associated with a 52.6 mm^3 smaller left hippocampal volume [15]. The difference in hippocampal volume between those classified with a healthy and or unhealthy diet was 203 mm^3, a difference which corresponds to 62% of the average decline in left hippocampal volume observed over the 4-year period. It was found no interaction between right hippocampus volumes and the two dietary factor scores (Tab. I) [15].

Other studies suggested a strong impact of healthy diets on structural connectivity in older subjects, rather than gray and white matter volumes. In fact, through diffusion tensor imaging (DTI) at MRI examination was seen that higher adherence to the MeDi was associated with preserved white matter microstructure in multiple brain areas and appeared to delay cognitive aging by up to 10 years (Tab. I) [16]. None of the individual components was strongly associated with DTI parameters, supporting the hypothesis that overall diet quality may be more important to preserve brain structure than any single food. These results suggested the involvement of vascular pathways rather than neurodegenerative mechanisms in the link between the MeDi and lower risks of cognitive decline and related diseases (Tab. I) [16].

The importance of components of prudent dietary pattern (vegetables, fruit, cooking/dressing oil, cereals and legumes, whole grains, rice/pasta, fish, low-fat dairy, poultry and water) was confirmed by the observation that the MMSE decline associated with Western diet may be attenuated by high adherence to prudent pattern (Tab. I) [17]. In fact, the decline became less pronounced (53.5%) and non-significant among people who had a high adherence to both the prudent and Western patterns. Furthermore, Western dietary pattern score was significantly associated with all-cause mortality in the older age cohorts (Tab. I) [17]. Instead, people who followed healthiest diet were slightly older, more active, less likely to smoke, had a lower body mass index (BMI), normal serum creatinine, and had higher MMSE score (Tab. I) [18]. The healthiest diet was associated with a reduction of about 24% in risk of cognitive decline and in particular was shown a significant association between higher diet quality and reduced risk of decline in 4 components of the MMSE including copying, attention and calculation, registration and writing (Tab. I) [18]. The brain damage related to an unhealthy diet may be based on a pro-inflammatory mechanism. Ozawa and colleagues detected an inflammatory dietary pattern (IDP) characterized by higher intake of red meat, processed meat, peas and legumes and fried food, and lower intake of whole grains which correlated with elevated interleukin(IL)-6 (Tab. I) [19]. It was related with greater decline in reasoning and in global cognition and, in a cross-sectional analysis at baseline, a two times greater risk of having a decline of 3 points or more in MMSE (Tab. I) [19].

FOODS, FOOD GROUPS, AND LATE-LIFE COGNITION

Fish and seafood

The emerging data from the last studies on the correlation between fish and seafood consumption and cognitive decline are conflicting. Significant correlations were found in some particular population subgroups [≥ 65 years and apolipoprotein E (*APOE*) *ε4* carriers]. Age significantly modified the association between fish consumption and cognitive change (Tab. II) [20]. In fact, no association was observed among adults aged 55-64 years. Conversely, adults aged ≥ 65 years, that consuming ≥ 1 servings/week fish (i.e., 100 g) had a reduction of cognitive decline rate [20]. Compared with individuals who consumed < 1 serving/week fish, the mean annual rate of global cognitive decline was reduced by 0.35 point equivalent to the disparity associated with 1.6 years of age. Removing shellfish and/or preserved fish from the total fish did not appreciably alter the results (Tab. II) [20].

Interestingly, Morris and colleagues showed that, in *APOE ε4* carriers, seafood consumption ≥ 1 meals/

Table I. Observational studies on the relationship among dietary patterns and late-life cognitive disorders (2014-2016).

References	Study design	Sample	Outcome	Cognitive and nutritional assessment	Principal results
			Dietary patterns		
Trichopoulou et al., 2015 [7]	Prospective cohort study Follow-up: average 6.6 years	n = 401 older subjects from EPIC-Greece cohort (mean age 74 years)	Association of MeDi or any particular MeDi component with cognitive decline	FFQ (150 items) MeDi score MMSE; MMSE change (cMMSE)	Decline in MMSE performance inversely associated with adherence to traditional MeDi. Only vegetable consumption, showed significant inverse association with cognitive decline
Tangney et al., 2014 [8]	Prospective cohort study Follow-up: mean of 4.1 years	n = 826 older persons (mean age 81.5 years)	Association between DASH diet or MeDi and cognitive decline	MAP FFQ (144 item) DASH diet MeDi Score Global composite score of 19 cognitive tests	DASH and MeDi patterns associated with a slower rate of global cognitive decline
Morris et al., 2015 [9]	Prospective cohort study Follow-up: mean of 4.5 years	n = 923 participants (58 to 98 years old)	Association of MIND diet, DASH diet and MeDi with incident AD	AD diagnosis at each annual evaluation FFQ (144 items) MIND diet score DASH diet score MeDi score	High adherence to all three diets may reduce AD risk. Moderate adherence to the MIND diet may also decrease AD risk
Morris et al., 2015 [10]	Prospective cohort study Follow-up: mean of 4.7 years	n = 960 participants (mean age 81.4 years)	Association of MIND diet score with cognitive decline Comparing the estimated effects of MIND diet to those of the MeDi and DASH diet	Annual cognitive assessments, global and composite scores of 5 domains FFQ (144 items) at each annual clinical evaluation MIND diet score DASH diet score MedDiet score	The MIND score positively associated with slower decline in global cognitive score and with each of five cognitive domains. The MIND diet score more predictive of cognitive decline than either of the other diet scores
Mosconi et al., 2014 [11]	Cross-sectional study	n = 52 clinically and cognitively normal subjects (mean age 54 years)	Associations between adherence to a MeDi and structural MRI-based brain atrophy in key regions for AD	Semiquantitative FFQ (61-item) MeDi score MRI CT measures for 5 ROIs	Subjects with higher MeDi adherence showed greater thickness of AD-vulnerable ROIs as compared to subjects with lower MeDi adherence
Staubo et al., 2016 [12]	Cross-sectional study	n = 672 cognitively normal participants (mean age: 79.8 years)	Association of MeDi score and MeDi components with MRI measures of CT for the four lobes separately and averaged	FFQ (128 items) MeDi score MRI CT measures	Higher MeDi score associated with larger CT. Higher legume, fish, vegetables, whole grains or cereals intakes were associated with larger CT
Gu et al., 2015 [14]	Cross-sectional study	n = 674 elderly adults without dementia (mean age 80.1 years)	Association between higher adherence to MeDi with larger MRI measured brain volume or CT	FFQ MeDi score MRI scans for TBV, TGMV, TWMV and mCT	Higher MeDi adherence associated with larger TBV, TGMV and TWMV. Higher fish intake associated with larger TGMV and mCT. Lower meat intake associated with larger TGMV and TBV

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References	Study design	Sample	Outcome	Cognitive and nutritional assessment	Principal results
Dietary patterns					
Jacka et al., 2015 [15]	Prospective cohort study Follow-up: 4 years	n = 255 older adults (mean age 62.6 years)	Association between dietary patterns and hippocampal volume Association between diet and differential rates of hippocampal atrophy over time	FFQ "Prudent" (healthy) diet and "Western" (unhealthy) diet. Two MRI scans	Lower intakes of nutrient-dense foods and higher intakes of unhealthy foods each independently associated with smaller left hippocampal volume. No evidence that dietary patterns influenced hippocampal volume decline
Pelletier et al., 2015 [16]	Prospective cohort study Follow-up: MRI performed mean of 8.9 years after dietary assessment	n = 146 non-demented participants (mean age 73.0 years)	Association between higher adherence to the MeDi and preserved brain GM volume and WM microstructure	FFQ (148 items) MeDi score MRI Brain GM and WM volumes, and WM microstructure Cognitive assessment	Adherence to the MeDi significantly associated with preserved WM microstructure in extensive areas, a gain in structural connectivity related to strong cognitive benefits
Shakersain et al., 2016 [17]	Population-based longitudinal study Follow-up: 6 years.	n = 2223 dementia-free older adults (mean age 70.6 years)	Impact of dietary patterns on cognitive decline	MMSE Semiquantitative FFQ (98 items) Two dietary patterns: 1) the "Western", 2) the "prudent"; factor scores for each dietary pattern categorized into quintiles	Highest adherence to prudent pattern related to less MMSE decline, whereas the highest adherence to Western pattern was associated with more MMSE decline. Decline associated with Western diet, attenuated by high adherence to prudent pattern
Smyth et al., 2015 [18]	Prospective cohort study Follow-up: 56 months	n = 27860 patients (mean age 66.2 years)	Association of dietary factors and cognitive decline in a population at high risk of cardiovascular disease	MMSE FFQ (20 items) mAHEI	Highest quintile of mAHEI (healthiest diet) associated with a reduced risk of cognitive decline
Ozawa et al., 2016 [19]	Prospective cohort study Follow-up: 10 years	n= 5083 patients (mean age 56 years)	Investigate dietary patterns associated with inflammation Association of such diet with cognitive decline	Alice Heim 4-I, short-term verbal memory, phonemic and semantic fluency, MMSE FFQ (127 item) Serum IL-6 IDP	Dietary pattern with higher intake of red and processed meat, peas, legumes and fried food, and lower intake of whole grains associated with higher inflammatory markers and accelerated cognitive decline

Abbreviation: MeDi: mediterranean diet; FFQ: food frequency questionnaire; MMSE: mini-mental state examination; DASH: dietary approach to stop hypertension; MIND: mediterranean-DASH diet intervention for neurodegenerative delay; AD: Alzheimer's disease; MRI: magnetic resonance imaging; CT: cortical thickness; ROI: region of interest; TBV: total brain volume; TGMV: total gray matter volume; TWMV: total white matter volume; mCT: mean cortical thickness; GM: gray matter; WM: white matter; mAHEI: modified alternative healthy eating index; IL-6: interleukin-6; IDP: inflammatory dietary pattern

week was correlated with lesser burden of brain AD neuropathology, including lower density of neuritic plaques, less severe and widespread neurofibrillary tangles, and lower neuropathologically defined AD (Tab. II) [21]. Furthermore, some studies demonstrated an association between fish consumption and MRI biomarkers (Tab. I) [12 14]. In the Mayo Clinic Study of Aging, higher fish intake was associated with larger cortical thickness summary measures for parietal and average lobar cortical thickness and marginally associated with AD signature cortical thickness, temporal and frontal cortical thickness, and also associated with several individual

Table II. Observational studies on the relationship among foods, food-groups, and late-life cognitive disorders (2014-2016).

References	Study design	Sample	Outcome	Cognitive and nutritional assessment	Principal results
Foods and food-groups					
Qin et al., 2014 [20]	Prospective cohort study Follow-up: mean 5.3 years.	n = 1566 community-dwelling adults (mean age 63 years).	Association of fish consumption with decline in cognitive function.	Diet measured by 3-d 24-h recalls TICSm: global and composite cognitive scores	Age significantly modified the association between fish consumption and cognitive change. At least 1 serving/wk fish predicted slower cognitive decline among ≥ 65 years
Morris et al., 2016 [21]	Cross-sectional analyses	n = 286 autopsied brains (mean age at death 89.9 years)	Relation of seafood consumption with brain mercury levels Association of seafood consumption or brain mercury levels with brain neuropathologies	Brain autoptical assessment Mercury and selenium brain tissue concentrations FFQ for consumption of seafood and n-3 fatty acids in the 4.5 years before death	Seafood consumption (> 1 meal[s]/week) significantly correlated with less AD pathology. Seafood consumption correlated with higher brain levels of mercury, these levels not correlated with brain neuropathology
Danthiir et al., 2014 [22]	Cross-sectional study	n = 390 community-dwelling cognitively normal older adults (mean age 73.1 years)	Associations between multiple domains of cognition and erythrocyte membrane n-3 PUFA proportions and historical and contemporary fish intake in older adults	n-3 FA analysis in erythrocyte membranes Fish consumption (current: FFQ, historical: LDQ) Cognitive tests	No evidence that higher proportions of long-chain n-3 fatty acids or fish intake benefits cognitive perfomances. Negative effect of fish intake in childhood and older age on older-age cognitive functions
Dong et al., 2016 [23]	Cross-sectional study	n = 894 Chinese adults, normal and with mild cognitive impairment (mean age 62.9 years)	Association between nuts, vegetables and fruit-rich diet and the risk of cognition impairment	MoCA FFQ of 13 food groups totally 41 items	The nuts and cooking oil intake of MCI patients were less than the normal subjects. Fruit and vegetable intake will benefit orientation, name and attention ability. Fruit and vegetable juice drinking will benefit abstraction ability
Pastor-Valero et al., 2014 [24]	Cross-sectional population-based study	n = 1849 low-income elderly subjects with CI (n = 147, mean age 77.5 years) and without (n = 1702, mean age 71.5 years)	Association between fruit and vegetable intake and cognitive impairment	CSI-D FFQ: 10 vegetables items, and 17 fruit and natural juices items Monthly consumption of fish	Daily intakes of fruit and vegetable ≥ 400 grams/day associated with decreased prevalence of cognitive impairment. Fish consumption not associated with cognitive impairment
Zhao et al., 2015 [25]	Cross-sectional study	n = 404 patients, aged 60 years old or above, with or without MCI	Association of dietary and lifestyle patterns with MCI	MoCA FFQ	Higher daily intake of eggs and marine products significantly decreased odds of suffering from MCI

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References	Study design	Sample	Outcome	Cognitive and nutritional assessment	Principal results
Foods and food-groups					
Xu et al., 2015 [26]	Cross-sectional study	n = 517 Chinese elderly with possible dementia (22.1%, mean age 73.8 years) and without CI (77.9% mean age 65.7 years)	Effect of weekly tofu intake on cognitive performance	HVLT IR FFQ	High intake of tofu negatively related to cognitive performance. Consumption of meat and green vegetables independently associated with better memory function
O'Brien et al., 2014 [28]	Population-based prospective cohort study. Follow-up: 6 years	n = 16010 women without a history of stroke (mean age 74 years); final sample n = 15467	Association of long-term intake of nuts with cognition	FFQ TICS, immediate and delayed recalls, category fluency, delayed recall of the TICS 10-word list and the digit span backwards test	Increasingly higher total nut intake (≥ 5 nuts/week vs never < 1/month) related to increasingly better overall cognition at older ages
Solfrizzi et al., 2015 [30]	Population-based prospective cohort study Follow-up: 3.5 years	5632 subjects, aged 65-84 year old; final sample n = 1445	Association between change or constant habits in coffee consumption and the incidence of MCI	FFQ MCI diagnosis	Cognitively normal older individuals who increased their coffee consumption had a higher rate of developing MCI, while a constant in time moderate coffee consumption was associated to a reduced rate of the incidence of MCI
Araújo et al., 2015 [31]	Cross-sectional study	n = 14563 public service workers (mean age 51.9 years)	Relation of coffee consumption to performance on specific domains of cognition	Cognitive tests from CERAD battery FFQ Type of coffee, caffeine content, additional items added	Coffee consumption associated with better cognitive performance on memory and efficiency of searching in long-term memory only in elderly, but without a dose response relationship
Beydoun et al., 2014 [32]	Prospective cohort study Follow-up: ~2 visits/person each ~2 years intervals	n= 628-1305 subjects free of dementia (mean age 66.8 years)	Association of caffeine and alcohol intake with cognitive performance	MMSE, BVRT, CVLT, VFT-L, VFT-C, TMT A and B, DS-F, DS-B 7-d dietary records for caffeine and alcohol intakes NAS	Stratum-specific associations by sex and baseline age, between caffeine and alcohol intake and cognition. Putative beneficial effects of caffeine and NAS on global cognition, verbal memory, and attention, and mixed effects of alcohol on letter fluency, attention, and working memory

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References	Study design	Sample	Outcome	Cognitive and nutritional assessment	Principal results
			Foods and food-groups		
Travassos et al., 2015 [33]	Cross-sectional multicentre study	n = 88 patients with AD (58%) or MCI (42%) (mean age 66.3 years)	Association of caffeine consumption with the CSF biomarkers, particularly Aβ	FFQ Caffeine and main active metabolites in the CSF and plasma $A\beta_{1-42}$, total tau and phosphorylated tau in the CSF	Caffeine consumption not modify the levels of CSF biomarkers. Theobromine associated with a favorable Aβ profile in the CSF
Kesse-Guyot et al., 2014 [34]	Prospective cohort study Follow-up: mean 13.6 years	n = 2983 middle-aged adults from the SU.VI.MAX 2 study (mean age at cognitive evaluation 65.5 years)	Association between a CDP and cognitive performance	Plasma concentrations of carotenoids 24 h dietary record every 2 months RRR statistical method 6 neuro-psycholo gical tests	Positive correlation between CDP and consumption of orange- and green-coloured fruits and vegetables, vegetable oils and soup. Positive association between a CDP and cognitive function (executive functioning and episodic memory)

Abbreviation: TICSm: telephone interview of cognitive status modified; FFQ: food frequency questionnaire; AD: Alzheimer's disease; PUFA: polyunsaturated fatty acids; LDQ: lifetime diet questionnaire; MoCA: Montreal cognitive assessment; MCI: mild cognitive impairment; CSI-D: community screening instrument for dementia; HVLT IR: Hopkins verbal learning test immediate recall; CERAD: consortium to establish a registry for Alzheimer's disease; MMSE: mini-mental state examination; BVRT: Benton visual retention test; CVLT: California verbal learning test; VFT-L and VFT-C: verbal fluency tests - letter and categorical; TMT A and B: trail making test parts A and B; DS-B and DS-F: digit span forward and backward tests; NAS: nutrient adequacy score; CSF: cerebrospinal fluid; Aβ: β-amyloid; CDP: carotenoid-rich dietary pattern; RRR: reduced rank regression

cortical thickness measures: precuneus, superior parietal, posterior cingulate, supramarginal, middle temporal, and inferior parietal and marginally associated with fusiform CT [12]. Higher fish consumption was also related with larger total gray matter volume [14].

Fish consumption was associated with a slower decline in composite and verbal memory scores (Tab. II) [20]. Other studies did not suggest evidence that higher fish intake may impact positively cognitive performance in cognitively normal older adults [24 25] or in those with cognitive impairment (Tab. II) [23 24]. However, Dong and colleagues found that cognitively normal Chinese older subjects consumed more fish than mild cognitive impairment (MCI) subjects [23] and Zhao and colleagues found that higher consumption of marine products was associated with a significantly decreased probability of suffering from MCI (Tab. II) [25]. Of note, Danthiir and colleagues demonstrated that more frequent consumption of total fish (oily and white) was associated with slower cognitive speed for the constructs of inhibition, simple/choice reaction time, reasoning speed, and memory scanning (Tab. II) [22]. More frequent consumption of oily fish significantly associated with worse inhibitory processes, similarly, consumption of white fish significantly and negatively predicted simple/choice reaction time (Tab. II) [22]. Danthiir and colleagues [22] hypothesized that the negative trends observed between cognitive performance and fish consumption were due to neurotoxic contaminants in fish, such as methylmercury. However, as seen above, Morris and colleagues found that higher brain levels of mercury were not correlated with brain neuropathology (Tab. II) [21].

Fruit and vegetables

In Greece, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, among the components of MeDi, only vegetable consumption exhibited a significant inverse association with cognitive decline (Tab. I) [7]. The diet-low in fruit and vegetable might increase the risk of cognitive function decline in older adults (Tab. II) [23]. In fact, adherence to WHO recommendations for daily intakes of fruit and vegetable, that are eating 5 or more portions of fruit and/or vegetables a day (≥ 400 g/day), were significantly associated with a 47% decreased prevalence of cognitive impairment (Tab. II) [24]. In contrast to these findings, Xu and colleagues found that among older adults (≥ 68 years of age) being vegetarian (not eating meat), the risk for cognitive impairment increased almost 4-fold (Tab. II) [26]. Imaging data in older cohort showed that higher intake of total vegetables was associated with larger dorsolateral prefrontal and superior parietal cortical thickness, while vegetables without legumes were associated with larger middle temporal, superior parietal, and dorsolateral prefrontal cortical thickness (Tab. I) [12]. In contrast, fruit consumption was negatively associated with inferior parietal, supramarginal, superior parietal, parietal, and precuneus cortical thickness (Tab. I) [12]. These findings are in keeping with result of another study in which higher fruit intake was associated with lower temporal and hippocampal volumes (Tab. I) [14]. This is probably due to high content of simple sugars and a high glycemic index of several fruits and so the effects of carbohydrate component on increased risk of MCI [27]. In older adults, fruit intake would benefit name ability and attention level, while vegetables intake would benefit orientation ability (Tab. II) [23]. Finally, consumption of green vegetables was independently associated with better memory function and among older elderly (≥ 68 years of age) it reduced the risk for cognitive impairment by almost 20% (Tab. II) [26].

Nuts

Nuts are rich in polyunsaturated fatty acids (PUFA) (omega 3 and 6) and monounsaturated fatty acids (MUFA), and also contain a significant amount of minerals such as phosphorus, potassium, magnesium, calcium, iron and sulfur, and vitamin such as B1, B2, B6 and E. It was found the nut intake of MCI patients was less than that of cognitively normal subjects (Tab. II) [23]. In fact, a study performed on older women found that higher total nut intake (i.e., ≥ 5/week) over the long term was associated with modestly better cognitive performance (Tab. II) [28]. Increasingly higher total nut intake was related to increasingly better overall cognition at older ages. Considering that one year of age was associated with a mean decline of 0.04 standard units on both the global and verbal composite scores, therefore, the mean differences comparing the highest to lowest categories of nut intake were equivalent to approximately two years of cognitive aging (Tab. II) [28]. In the same study, it was found a suggestion that those who consumed walnuts 1 to 3 times per month had better cognition than those who consumed walnuts less than once per month, but there was no overall trend of increasingly better cognitive performance with increasing walnut intake (Tab. II) [28]. Dong and colleagues also showed that nut intake would benefit delayed memory (Tab. II) [23].

Coffee and caffeine intake

As summarized in a recent systematic review, several cross-sectional and longitudinal population-based studies suggested a protective effect of coffee, tea, and caffeine use against late-life cognitive impairment/decline, although the association was not found in all cognitive domains investigated and there was a lack of a distinct dose-response association, with a stronger effect among women than men [29]. The findings on the association of coffee, tea, and caffeine consumption or plasma caffeine levels with incident MCI and its progression to dementia were too limited to draw any conclusion [29]. Furthermore, for dementia and AD prevention, some studies with baseline examination in midlife pointed to a lack of association, although other case-control and longitudinal population-based studies with briefer follow-up periods supported favorable effects of coffee, tea, and caffeine consumption against AD [29]. Recent findings from the Italian Longitudinal Study on Aging (ILSA) suggested that cognitively normal older individuals who increased their coffee consumption had a higher rate of developing MCI, while a constant in time moderate coffee consumption was associated to a reduced rate of the incidence of MCI (Tab. II) [30]. Among older adults in Brasil, coffee consumption was associated with better cognitive performance on memory and efficiency of searching in long-term memory (drinking 2-3 cups of coffee per day was associated with about a 3% increase in the mean number of words remembered on the learning, recall and word recognition tests) (Tab. II) [31]. Also, drinking ≥ 3 cups/day of coffee was associated with an increase of about 1.23 words in the mean number of words pronounced in the semantic verbal fluency test [31]. However, in this Brasilian study, Araujio and colleagues did not find indication of a dose response relationship in these associations [31]. In another Chinese study on cognitively normal and MCI adults, no significant association was detected between drinking of coffee and cognitive function (Tab. II) [23]. Another aspect of coffee assumption is the role of its component such as the caffeine. Coffee is a rich source of caffeine, which acts as a psychoactive stimulant. In a cross sectional analysis, Beydoun and colleagues found that caffeine intake was associated with better global cognitive function (MMSE) at baseline for patients ≥ 70 years (Tab. II) [32]. However, in a study that evaluated the association of caffeine consumption with the cerebrospinal fluid (CSF) biomarkers, particularly β-amyloid (Aβ), in AD and MCI patients, no significant difference was found in daily consumption of caffeine between MCI and AD patients, with no correlation between caffeine consumption and Aβ42 in the CSF (Tab. II) [33]. In the same study, theobromine, xanthine formed upon caffeine metabolism and also directly ingested from chocolate products, was associated with a favorable Aβ profile in the CSF (Tab. II) [33]. Interestingly, theobromine in the CSF did not correlate with caffeine consumption, theobromine consumption, or the levels of caffeine and other xanthines in the plasma, but instead it correlated with levels of caffeine, theophylline, and paraxanthine in the CSF, suggesting that it may be formed by central metabolic pathways [33].

Eggs

Eggs have a high content of proteins and lipids in particular cholesterol. For this reason, they are traditionally considered an unhealthy food. However, eggs have also a significant amount of vitamins A, B6, B12, riboflavin, folic acid, choline, iron, calcium, phosphorus and potassium.

In a recent study, higher daily intake of eggs reduced of about 3% the odds of suffering from MCI (Tab. II) [25]. Instead, in the Chinese study of Dong and colleagues, no significant association was detected between intake of eggs with cognitive function in normal and MCI adults (Tab. II) [23].

Tofu

Tofu is a common food in most of the Far East. It is obtained from curdling of the juice extracted from soybeans. It has a high proteins and PUFA content. Higher weekly intake of tofu was associated with worse memory performance, furthermore among older elderly (≥ 68 years of age), high tofu intake increases the risk (of almost 30%) of cognitive impairment indicative of dementia (Tab. II) [26].

Meat

Red meat is a classical element of Western diet that, as mentioned previously, was associated with worse cognitive performance in several studies (Tab. I) [15 17 19]. Consistent with these findings, a negative association of red meat with inferior and superior parietal cortical thickness was found (Tab. I) [12]. However, this concept should be partially reviewed. In fact, in the last years, eating meat (not being vegetarian) was independently associated with better memory function and in older age (≥ 68 years of age) with a four-fold decrease in risk of possible dementia (Tab. II) [26]. Furthermore, Staubo and colleagues also observed that higher red meat intake was associated with larger entorhinal cortical thickness (Tab. I) [12]. This it could relate to some beneficial components of lean red meat (iron, protein, MUFA, PUFA, cobalamine) and beneficial effects in increasing satiety and reducing weight gain. In the Chinese study of Dong and colleagues, no significant association was detected between intake of light or red meat with cognitive function in normal and MCI adults (Tab. II) [23].

Oil

Dong and colleagues, in their Chinese cohort, found that oil intake of MCI patients was less than the normal subjects (29.76 *vs* 35.20 mL cooking oil per day), in particular would have a positive impact on visual-spatial ability (Tab. II) [23]. Vegetable oils are rich in carotenoids, and in the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study carotenoids were associated with higher cognitive performance (Tab. II) [34]. Extra-virgin olive oil (EVOO) is one of the main elements of MeDi, and clinical trials and population studies indicated that this dietary pattern and its main lipid component EVOO could have a protective role against AD [35].

Legumes

Dong and colleagues, in their Chinese cohort, showed that normal subjects consumed more legumes and legume products than MCI subjects, demonstrating that intake of legumes and legume product would benefit overall cognition level (Tab. II) [23]. These data were confirmed by imaging biomarkers, in fact, Staubo and colleagues also found that higher intake of legumes was associated with larger parietal and occipital cortical thickness, and with larger thickness in ROIs for superior parietal, inferior parietal, precuneus, and lingual cerebral cortex (Tab. I) [12].

Grain

In their imaging biomarker study, Staubo and colleagues also showed that intake of whole grains or cereals was associated with larger temporal pole and superior temporal cortical thickness (Tab. II) [12]. Conversely, lower intake of whole grains was associated with higher inflammatory markers (IL-6) and accelerated cognitive decline at older age in the Whitehall II prospective cohort study (Tab. II) [19]. However, in the Chinese cohort of Dong and colleagues, no significant association was detected between intake of whole grain and cognitive function in normal and MCI adults (Tab. II) [23].

Alcohol

Recent findings from the Baltimore Longitudinal Study of Aging suggested that alcohol intake was associated with slower improvement on letter fluency and global cognition among those aged < 70 years at baseline (Tab. II) [32]. Conversely, alcohol intake was associated with better attention and working memory performance, particularly among men and individuals ≥ 70 years at baseline (Tab. II) [32]. Compared with moderate consumption (14 to 28 g/d), individuals with higher alcohol intake (> 28 g/d) had faster decline or slower improvement on the MMSE, particularly among women and in the older group. Overall, among men, and for those aged ≥ 70 years, lower alcohol intake (< 14 g/d) compared with moderate consumption (14 to 28 g/d) was associated with poorer performance in working memory (Tab. II) [32]. In the younger group, consuming < 14 g/day was associated with slower decline or faster improvement in the letter fluency compared with a moderate intake of 14 to 28 g/day. Similar pattern was showed also for attention and executive functioning (Tab. II) [32].

CONCLUSIONS AND FUTURE DIRECTIONS

In the last three years, the association between diet and cognitive function or dementia has been largely investigated. However, more recently, the NIA-AA guidelines for AD and cognitive decline due to AD pathology introduced some evidence suggesting a direct relation between diet and changes in the brain structure and activity. Several studies focused on the role of the dietary patterns on late-life cognition, with accumulating evidence that higher adherence to a Mediterranean-type diet was associated with decreased cognitive decline, although the MeDi combines several foods, micronutrients, and macronutrients already separately proposed as potential protective factors against dementia and MCI. Moreover, also other emerging healthy dietary patterns such as the DASH and the MIND diets were associated with slower rates of cognitive decline and significant reduction in AD rate. Furthermore, some food groups traditionally considered harmful such as eggs and red meat have been partially rehabilitated, while there is still a negative correlation of cognitive functions with added sugars and trans fatty acids, nutrients also increasing the cardiovascular risk.
However, some limits should be reported for this review article. Heterogeneity exists in the quantification of individual items as well among the different diets background of the populations investigated, especially in view of different geographical areas, setting of dietary patterns such as the Mediterranean countries in which a large segment of the population still adheres to MeDi. Heterogeneity in time between the two assessments, among studies using paired assessments (or a single assessment) several years after study population enrollment. Nevertheless, these data represent a brick in the construction of the building of the causal link between dietary habits and cognitive impairment.
The absence of causal etiological therapies against AD leads to seek multimodal alternative strategies, increasing the interest in the potential for prevention of dementia by targeting modifiable risk factors. It is now evident that dietary habits influence diverse cardiometabolic risk factors, including not only obesity and low-density lipoprotein cholesterol, but also blood pressure, glucose-insulin homeostasis, lipoprotein concentrations and function, oxidative stress, inflammation, endothelial health, hepatic function, adipocyte metabolism, pathways of weight regulation, visceral adiposity, and the microbiome. Whereas decades of dietary recommendations focused on dietary fat and single vascular risk factors (e.g., hypertension, blood cholesterol etc.) and current dietary discussions are often worried about total calories and obesity, the full health impact of diet extends far beyond these pathways. Considering strategies of prevention of AD could be complicated and take to negative results. A second key lesson is the importance to point out on specific foods and overall diet patterns, rather than single isolated nutrients, for cognitive impairment. A food-based approach also better facilitates public guidance and minimizes industry manipulation. Nevertheless the complexity of the stake, the correction of modifiable risk factors to expect 'the compression of cognitive morbidity' still remains a desirable goal of public health. Larger observational studies with longer follow-up periods should be encouraged, addressing other potential bias and confounding sources, so hopefully opening new ways for diet-related prevention of dementia and AD.

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Conflict of Interest

The authors declare no conflicts of interest.

References

1 Panza F, Seripa D, Solfrizzi V, et al. *Emerging drugs to reduce abnormal β-amyloid protein in Alzheimer's disease patients*. Expert Opin Emerg Drugs 2016;21:377-91.

2 Solfrizzi V, Panza F, Capurso A. *The role of diet in cognitive decline*. J Neural Transm 2003;110:95-110.

3 Tangney CC. *DASH and Mediterranean-type dietary patterns to maintain cognitive health*. Curr Nutr Rep 2014;3:51-61.

4 Xu W, Tan L, Wang HF, et al. *Meta-analysis of modifiable risk factors for Alzheimer's disease*. J Neurol Neurosurg Psychiatry 2015;86:1299-306.

5 McKhann GM, Knopman DS, Chertkow H, et al. *The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease*. Alzheimers Dement 2011;7:263-9.

6 Solfrizzi V, Panza F. *Mediterranean diet and cognitive decline. A lesson from the whole-diet approach: what challenges lie ahead?* J Alzheimers Dis 2014;39:283-6.

7 Trichopoulou A, Kyrozis A, Rossi M, et al. *Mediterranean diet and cognitive decline over time in an elderly Mediterranean population*. Eur J Nutr 2015;54:1311-21.

8 Tangney CC, Li H, Wang Y, Barnes L, et al. *Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons*. Neurology 2014;83:1410-6.

9 Morris MC, Tangney CC, Wang Y, et al. *MIND diet associated with reduced incidence of Alzheimer's disease*. Alzheimers Dement 2015;11:1007-14.

10 Morris MC, Tangney CC, Wang Y, et al. *MIND diet slows cognitive decline with aging*. Alzheimers Dement 2015;11:1015-22.

11 Mosconi L, Murray J, Tsui WH, et al. *Mediterranean diet*

and magnetic resonance imaging-assessed brain atrophy in cognitively normal individuals at risk for Alzheimer's disease. J Prev Alzheimers Dis 2014;1:23-32.

12 Staubo SC, Aakre JA, Vemuri P, et al. *Mediterranean diet, micronutrients and macronutrients, and MRI measures of cortical thickness*. Alzheimers Dement 2017;13:168-77.

13 Sabuncu MR, Desikan RS, Sepulcre J, et al. *The dynamics of cortical and hippocampal atrophy in Alzheimer disease*. Arch Neurol 2011;68:1040-8.

14 Gu Y, Brickman AM, Stern Y, et al. *Mediterranean diet and brain structure in a multiethnic elderly cohort*. Neurology 2015;85:1744-51.

15 Jacka FN, Cherbuin N, Anstey KJ, et al. *Western diet is associated with a smaller hippocampus: a longitudinal investigation*. BMC Medicine 2015;13:215.

16 Pelletier A, Barul C, Feart C, et al. *Mediterranean diet and preserved brain structural connectivity in older subjects*. Alzheimers Dement 2015;11:1023-31.

17 Shakersain B, Santoni G, Larsson SC, et al. *Prudent diet may attenuate the adverse effects of Western diet on cognitive decline*. Alzheimers Dement 2016;12:100-9.

18 Smyth A, Dehghan M, O'Donnell M, et al. *Healthy eating and reduced risk of cognitive decline: a cohort from 40 countries*. Neurology 2015;84:2258-65.

19 Ozawa M, Shipley M, Kivimaki M, et al. *Dietary pattern, inflammation and cognitive decline: the Whitehall II prospective cohort study*. Clin Nutr 2017;36:506-12.

20 Qin B, Plassman BL, Edwards LJ, et al. *Fish intake is associated with slower cognitive decline in Chinese older adults*. J Nutr 2014;144:1579-85.

21 Morris MC, Brockman J, Schneider JA, et al. *Association of seafood consumption, brain mercury level, and APOEε4 status with brain neuropathology in older adults*. JAMA 2016;315:489-97.

22 Danthiir V, Hosking D, Burns NR, et al. *Cognitive performance in older adults is inversely associated with fish consumption but not erythrocyte membrane n-3 fatty acids*. J Nutr 2014;144:311-20.

23 Dong L, Xiao R, Cai C, et al. *Diet, lifestyle and cognitive function in old Chinese adults*. Arch Gerontol Geriatr 2016;63:36-42.

24 Pastor-Valero M, Furlan-Viebig R, Rossi Menezes P, et al. *Education and WHO recommendations for fruit and vegetable intake are associated with better cognitive function in a disadvantaged Brazilian elderly population: a population-based cross-sectional study*. PLoS One 2014;9:e94042.

25 Zhao X, Yuan L, Feng L, et al. *Association of dietary intake and lifestyle pattern with mild cognitive impairment in the elderly*. J Nutr Health Aging 2015;19:164-8.

26 Xu X, Xiao S, Rahardjo TB, et al. *Tofu intake is associated with poor cognitive performance among community-dwelling elderly in China*. J Alzheimers Dis 2015;43:669-75.

27 Roberts RO, Roberts LA, Geda YE, et al. *Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia*. J Alzheimers Dis 2012;32:329-39.

28 O'Brien J, Okereke O, Devore E, et al. *Long-term intake of nuts in relation to cognitive function in older women*. J Nutr Health Aging 2014;18:496-502.

29 Panza F, Solfrizzi V, Barulli MR, et al. *Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: a systematic review*. J Nutr Health Aging 2015;19:313-28.

30 Solfrizzi V, Panza F, Imbimbo BP, et al; Italian Longitudinal Study on Aging Working Group. *Coffee consumption habits and the risk of mild cognitive impairment: the italian longitudinal study on aging*. J Alzheimers Dis 2015;47:889-99.

31 Araújo LF, Giatti L, Padilha dos Reis RC, et al. *Inconsistency of association between coffee consumption and cognitive function in adults and elderly in a cross-sectional study (ELSA-Brasil)*. Nutrients 2015;7:9590-601.

32 Beydoun MA, Gamaldo AA, Beydoun HA, et al. *Caffeine and alcohol intakes and overall nutrient adequacy are associated with longitudinal cognitive performance among U.S. adults*. J Nutr 2014;144:890-901.

33 Travassos M, Santana I, Baldeiras I, et al. *Does caffeine consumption modify cerebrospinal fluid amyloid-β levels in patients with Alzheimer's disease?* J Alzheimers Dis 2015;47:1069-78.

34 Kesse-Guyot E, Andreeva VA, Ducros V, et al. *Carotenoid-rich dietary patterns during midlife and subsequent cognitive function.* Br J Nutri 2014;111:915-23.

35 Casamenti F, Stefani M. *Olive polyphenols: new promising agents to combat aging-associated neurodegeneration.* Expert Rev Neurother 2017;17:345-58.