Diet and Cognition:

Focus on Macronutrients and the Mediterranean Diet

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Definitions

Nutrients =

A- Micro	B- Macro
1. Vitamins	1. Proteins
2. Minerals: Major: calcium, magnesium, potassium, sodium, etc Trace: iron, copper, zinc, iodine, manganese, chromium, selenium etc	
	2. Carbs
	3. Fat

Definitions cont.

FATS

- **Saturated fats**
- **Monounsaturated fats (MUFA)**
  - Olive oil

- **Polyunsaturated fats (PUFA)**
  - N-3 PUFA (omega-3)

  - N-6 PUFA

Veg. oil

- ***trans* fats**

- Several dietary factors affect the risk of cardiovascular disease
- This also influences the risk of dementia
- Deficiencies of some micronutrients (especially vitamins B1, B2, B6, B12, C) have been described quite frequently in elderly people, and found to be significantly associated with cognitive impairment
- This concept is further supported by recent evidence that certain diets have been associated with a lower incidence of AD

- Dietary fatty acids such as monounsaturated fatty acids (MUFA) intake, and regular fish and n-3 polyunsaturated fatty acid (PUFA) consumption, are suggested to play a role in the prevention of cognitive decline
- Olive oil is rich in MUFA

  (70–80% MUFA; oleic acid) and 8–10% PUFA
- principal sources of n-6 PUFA are vegetable oils,
- principal sources of n-3 PUFA are fatty fish (e.g. salmon, tuna, and mackerel)

Macronutrients and food nutrients found to have favorable effect on cognition

1. High intake of MUFA
2. High intake of PUFA n-3
3. High and regular fish consumption,
4. Antioxidants from fruit and vegetables,
5. Moderated alcohol consumption

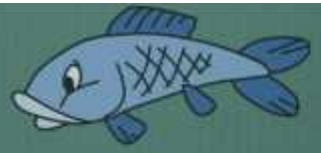
Dietary fatty acids and fish consumption in *pre-dementia* syndromes

Study (year)	Setting and study design (duration)	Subjects	Dietary assessment	Cognitive outcomes	Results and conclusions
Kalmijn *et al.* (1997) The Zutphen Elderly Study, The Netherlands	Longitudinal, population-based (3 y)	476 subjects, aged 69–89 y	Evaluation of dietary intake with the cross-check dietary history method	Cognitive impairment= MMSE score <25 points Cognitive decline= drop of >2 points of MMSE over a 3-years	High linoleic acid intake (type of N6 PUFA) was positively associated with cognitive impairment. High fish consumption was inversely associated with cognitive impairment
Morris *et al.* (2004) The Chicago Health and Aging Project (CHAP), USA	Longitudinal, population-based (6 y)	2560 subjects, aged ≥ 65 y	Evaluation of dietary intake with a 139-item FFQ	Cognitive change at 3-year and 6-year follow-ups measured with Immediate and Delayed Recall of EBMT, MMSE, and SDMT	A diet high in saturated and trans-unsaturated fat, or low in nonhydrogenated unsaturated fats, may be associated with cognitive decline among older people
Morris *et al.* (2005) CHAP, USA	Longitudinal, population-based (6 y)	3718 subjects, aged ≥ 65 y	Evaluation of dietary intake with a 139-item FFQ	Cognitive change at 3-year and 6-year follow-ups measured with Immediate and Delayed Recall of EBMT, MMSE, and SDMT	Dietary intake of fish was inversely associated with a cognitive decline over 6 years. n-3 fatty acids was not consistent, although in the direction of slower decline

Solfrizzi, V., Panza, F., Frisardi, V., Seripa, D., Logroscino, G., Imbimbo, B. P., & Pilotto, A. (2011). Diet and Alzheimer's disease risk factors or prevention: The current evidence. *Expert Review of Neurotherapeutics, 11*(5), 677-708.

Study (year)	Setting and study design (duration)	Subjects	Dietary assessment	Cognitive outcomes	Results and conclusions
Solfrizzi *et al.* (2006) The Italian Longitudinal Study on Aging (ILSA) Italy	Longitudinal, population-based (8.5 y)	278 subjects, 65–84 y	Evaluation of MUFA and PUFA dietary intake with a 77-item FFQ	MMSE	High MUFA, PUFA and total intake were significantly associated with a better cognitive performance in time; remained robust even after adjustment for potential confounding variables, such as age, sex, educational level, BMI
Solfrizzi *et al.* (2006) ILSA, Italy	Longitudinal, population-based (2.6 y)	278 subjects, 65–84 y	Evaluation of MUFA and PUFA dietary intake with a 77-item FFQ	Incident MCI	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 development of MCI
Psaltopoulou *et al.* (2008), European Prospective Investigation into Cancer and Nutrition (EPIC), Greece	Longitudinal, population-based (median 8 y)	732 subjects, ≥ 60 y	Evaluation of dietary intakes with a 150-item FFQ. A dietary composite score (MeDi score)	MMSE	No significant association between MeDi and MMSE scores, whereas a statistically significant inverse association was found w/ some individual dietary components, such as seed oil or PUFA intake
Eskilinen *et al.* (2008) Cardiovascular Risk Factors Aging and Dementia (CAIDE) Finland	Longitudinal, population-based (21 y)	1449 subjects, 65–80 y	Evaluation of dietary intakes with a 208-item FFQ	Mayo Clinic AD Research Center criteria for MCI; MMSE, CFT, Purdue Pegboard, LDST, wordlist episodic; executive function w/ the Stroop test; prospective memory task	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. Frequent fish consumption was associated with better global cognitive function and semantic memory. Higher PUFA:SFA ratio was associated with better psychomotor speed and executive function

Solfrizzi et al, 2011



Dietary fatty acids and fish consumption in *dementia* syndromes

Study (year)	Setting and study design (duration)	Subjects	Dietary assessment	Cognitive outcomes	Results and conclusions
Engelhart *et al.* (2002) The Rotterdam Study, The Netherlands	Longitudinal, population-based (6 y)	5395 subjects, ≥ 55 y	Evaluation of dietary intakes with a 100-item FFQ	Diagnosis of dementia (DSM-III-R criteria), AD (NINCDS–ADRDA criteria), and VaD (NINCDS–AIREN criteria)	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
Luchsinger *et al.* (2002) Washington Heights- Inwood Columbia Aging Project, USA	Longitudinal, population-based (4 y)	980 subjects, mean= 75.3 ± 5.8 y	Evaluation of dietary intake with a 61-item FFQ	Diagnosis of prevalent dementia (DSM-IV criteria) and incident AD (NINCDS–ADRDA criteria)	Higher intake of calories and fats may be associated with higher risk of AD in subjects carrying the ***APOE e4*** **allele**
Morris *et al.* (2003) CHAP, USA	Longitudinal, population-based (3.9 y)	815 subjects, ≥ 65 y	Evaluation of dietary intake with a 154-item FFQ	Incident diagnosis of AD (NINCDS–ADRDA criteria)	Higher intake of n-3 PUFA and weekly fish consumption may reduce the risk of incident AD

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Dietary fatty acids and fish consumption in *dementia* syndromes

Study (year)	Setting and study design (duration)	Subjects	Dietary assessment	Cognitive outcomes	Results and conclusions
Huang *et al.* (2005) Cardiovascular Health Cognition Study (CHCS), USA	Longitudinal, population-based (5.4 y)	5201 participants, ≥ 65 y	Evaluation of dietary intake with a 99-item FFQ	Incident diagnosis of dementia (DSM-IV criteria) and AD (NINCDS–ADRDA criteria)	Fatty fish, such as tuna, was associated with a lower risk of developing dementia and AD with a dose–response relationship, whereas lean, fried fish was not. Non-carriers of ***APOE* e4 allele** had a 35–45% lower risk with consumption of fatty fish, no difference for *APOE* e*4* allele carriers
Laitinen *et al.*, (2006) CAIDE, Finland	Longitudinal, population-based (21 y)	1449 subjects, 65–80 y	Evaluation of dietary intake with a 154-item FFQ	Incident diagnosis of AD (NINCDS–ADRDA criteria)	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* e*4* carriers
Barbeger-Gateau *et al.* (2007) Three-City Study, France	Longitudinal, population-based (4 y)	9294 subjects, ≥ 65	Evaluation of dietary intakes with a FFQ	Incident diagnosis of dementia (DSM-IV criteria) and AD (NINCDS–ADRDA criteria)	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**

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Fruit and Vegetable and Fruit intake in *dementia* and *pre-syndromes*

Study (year)	Setting and study design (duration)	Subjects	Methods	Results and conclusions
Kang et al. (2005) The Nurses' Health Study, USA	Longitudinal, population- based (10–16 y)	13,388 women, ≥ 70 y	- The TICS and five other cognitive tests (immediate and delayed recalls of the EBMT, category fluency, delayed recall of the TICS and DSB) - evaluation of dietary intake of food with a semiquantitative FFQ	High consumption of vegetables, but not fruit, was associated with less cognitive decline among older woman
Morris et al. (2006) CHAP, USA	Longitudinal, population- based (3–6 y)	3718 subjects, ≥ 65 y	Immediate and delayed recalls of the EBMT, MMSE, and SDMT and evaluation of dietary intake of food with a semiquantitative FFQ	High vegetable, but not fruit, consumption was associated with slower rate of cognitive decline with older age
Dai et al. (2006) The Kame Project, USA	Longitudinal, population- based (6.3 y)	3045 Japanese–Americans, ≥65 y	Diagnosis of incident AD and evaluation of dietary intake of food with a semiquantitative FFQ	Frequent drinking of fruit and vegetable juices was associated with a substantially decreased risk of AD. stronger after adjustments for confounding factors
Hughes et al. (2010) The HARMONY study, Sweden	Longitudinal (30 y)	3779 members of the Swedish Twin Registry	Diagnosis of incident dementia and AD and evaluation of dietary habits	Higher fruit and vegetable intake assessed at midlife was associated with a lower risk of dementia and later AD

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Dietary Dairy products consumption in *pre-syndromes*

Study (year)	Setting and study design (duration)	Subjects	Dietary assessment	Cognitive outcomes	Results and conclusions
Imeida *et al.* (2006) Australia	Longitudinal, population- based (4.8 y)	601 men, ≥ 80 y	Self-report questionnaire, including dietary measures	'Preserved cognitive function': MMSE ≥24 'Preserved mood': GDS ≤5	Consumption of full-cream milk associated with impaired cognitive function and with poor mental health
Vercambre *et al.* (2009) Etude Epidémiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N), France	Longitudinal, population- based (13 y)	4809 women, 76–82 y	Evaluation of dietary intakes with a 208-item FFQ	DECO and IADL	No significant association between milk and yogurt, and cheese consumption with cognitive decline
Eskilinen *et al.* (2008) CAIDE, Finland	Longitudinal, population- based (21 y)	1449 subjects, 65–80 y	Evaluation of dietary intake with a 208-item FFQ	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	High SFA intake from milk products and spreads (>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

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Dietary Dairy products consumption in *dementia syndromes*

Study (year)	Setting and study design (duration)	Subjects	Dietary assessment	Cognitive outcomes	Results and conclusions
Yamada *et al.* (2003) The Adult Health Study Japan	Longitudinal, population- based (25–30 y)	1774 subjects, born before September 1932	Evaluation of dietary intake with a FFQ	Clinical diagnosis of dementia (DSM-IV criteria), CASI, IQCDE (by the caregiver), Hachinski's Ischemic Score, Clinical Dementia Rating	Almost-daily milk intake associated with significantly lower likelihood of VaD, compared with consuming milk less than four-times per week
Laitinen *et al.* (2006) CAIDE, Finland	Longitudinal, population- based (21 y)	1449 subjects, 65–80 y	Evaluation of dietary intake with a 208-item FFQ	Incident diagnosis of AD (NINCDS– ADRDA criteria)	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

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Study (year)	Setting and study design (duration)	Subjects	Methods	Results and conclusions
Dufouil *et al.* (2000) Epidemiology of Vascular Aging (EVA) Study, France	Longitudinal, population-based (4 y)	1389 subjects, 59–71 y	MMSE, evaluation of alcohol consumption, *APOE* genotyping and smoking habits	Alcohol consumption was associated with a decreased risk of cognitive decline in individuals without the *APOE* e*4* allele, whereas moderate drinking increased the risk of decline in *APOE* e*4* allele carriers. In addition, lifetime smoking was a risk factor for cognitive decline in individuals without the *APOE* e*4* allele. The data also suggested a slight protective effect of smoking in *APOE* e*4* allele carriers
Ngandu *et al.* (2007) CAIDE, Finland	Longitudinal, population-based (21 y)	1341 participants, 65–79 y	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	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* e*4* and alcohol, or sex and alcohol were found
Anttila *et al.* (2004), CAIDE, Finland	Longitudinal, population-based study (23 y)	1464 subjects, 65–79 y	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)	Alcohol drinking in middle-age demonstrated a U-shaped relationship with risk of MCI in old age. Only the carriers of *APOE* e*4* had an increased risk of dementia with increasing alcohol consumption
Mukamal *et al.* (2003) The Cardiovascular Health Study (CHS), USA	Nested case-control of a longitudinal, population-based study (6 y)	373 cases w/incident dementia and 373 controls	Diagnosis of incident dementia (AD and VaD), average alcohol consumption and MRI findings	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* e*4* allele, with similar relationships of alcohol use with AD and VaD

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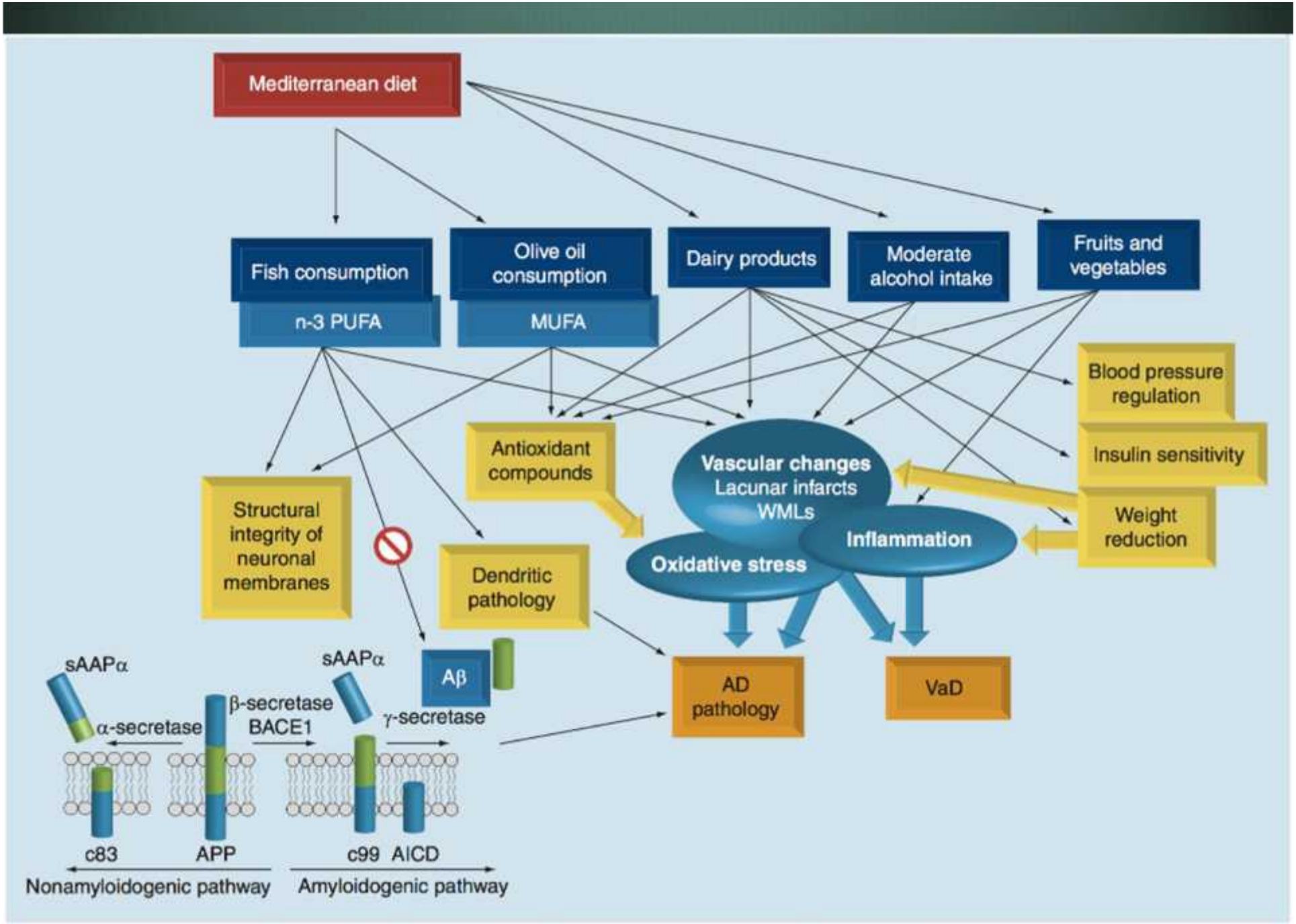
All in the MeDi!!!

Higher levels of consumption of olive oil, very rich in MUFA, is considered the hallmark of the traditional Mediterranean Diet (MeDi)

The typical dietary pattern of MeDi is characterized by a high intake of:

- MUFA
- vegetables,
- fruits and nuts,
- Cereals,
- Fish
- Legumes (peas, chickpeas, lentils, soybeans, peanuts),
- relatively low intakes of meat and dairy products,
- moderated consumption of alcohol



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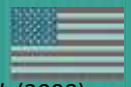
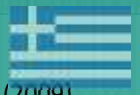
Study (year)	Setting and study design (duration)	Subjects	Dietary assessment	Cognitive outcomes	Results and conclusions
Scarmeas *et al.* (2006) Washington Heights-Inwood Columbia Aging Project (WHICAP), USA	Longitudinal, population-based (4 y)	2258 subjects, ≥ 65 y	Evaluation of dietary intake with a 61-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi	Diagnosis of incident AD	Higher adherence to MeDi reduced risk for probable AD, either with or without coexisting stroke
Scarmeas *et al.* (2007) WHICAP, USA	Longitudinal, population-based (4.4 y)	192 community-based indiv., ≥65 y, diagnosed with AD	Evaluation of dietary intake with a 61-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi	All-cause mortality	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
 Psaltopoulou *et al.* (2008) (EPIC), Greece	Longitudinal, population-based (median 8 y)	732 subjects, ≥ 60 y	Evaluation of dietary intakes with a 150-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi	MMSE	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
 Scarmeas *et al.* (2009) (WHICAP), USA	Longitudinal, population-based (4.5 y)	2258 subjects, ≥ 65 y	Evaluation of dietary intake with a 61-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi	Incidence of MCI and progression from MCI to AD	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
Scarmeas *et al.* (2009) WHICAP, USA	Longitudinal, population-based (5.4 y)	2247 subjects, ≥ 65 y	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	Diagnosis of incident AD	Both higher Mediterranean-type diet adherence and higher physical activity were independently associated with reduced risk for AD

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Study (year)	Setting and study design (duration)	Subjects	Dietary assessment	Cognitive outcomes	Results and conclusions
Gu *et al.* (2010) WHICAP, USA	Longitudinal, population-based (4 y)	1219 subjects, ≥ 65 y	Evaluation of dietary intake with a 61-item FFQ. A dietary composite score (MeDi score) evaluated adherence to MeDi	Diagnosis of incident AD	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
Tangney *et al.* (2011) CHAP, USA	Longitudinal, population-based (3 y)	3790 subjects, ≥ 65 y	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	Immediate and delayed recalls of the EBMT, MMSE and SDMT	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

Solfrizzi et al, 2011

Misanalyses and Systematic Reviews

Singh, B., Parsaik, A. K., Mielke, M. M., Erwin, P. J., Knopman, D. S., Petersen, R. C., & Roberts, R. O. (2014). Association of Mediterranean Diet with Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Journal Of Alzheimer's Disease*, *39*(2), 271-282. doi:10.3233/JAD-130830

Petersson, S. D., & Philippou, E. (2016). Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review of the Evidence. *Advanced Nutrition, 7*(5), 889-904. doi:10.3945/an.116.012138

Wu, L., & Sun, D. (2017). Adherence to Mediterranean diet and risk of developing cognitive disorders: An updated systematic review and meta-analysis of prospective cohort studies. *Scientific Reports*, *7*, 41317. doi:10.1038/srep41317

Loughrey, D. G., Lavecchia, S., Brennan, S., Lawlor, B. A., & Kelly, M. E. (2017). The impact of the Mediterranean diet on the dognitive dunctioning of healthy older adults: A systematic review and meta-analysis. *Advances in Nutrition (Bethesda, Md.)*, *8*(4), 571-586. doi:10.3945/an.117.015495

Radd-Vagenas, S., Flood, V. M., Fiatarone Singh, M. A., Duffy, S. L., Naismith, S. L., & Brew, B. J. (2018). Effect of the Mediterranean diet on cognition and brain morphology and function: a systematic review of randomized controlled trials. *The American Journal of Clinical Nutrition, 107*(3), 389-404. doi:10.1093/ajcn/nqx070

(1)Metaanlysis (2014)

- Search of the major databases and hand-searched proceedings of major neurology, psychiatry, and dementia conferences through November 2012.
- Included prospective cohort studies examining the MeDi with longitudinal follow-up of at least 1 year and reporting outcomes of cognitive impairment or AD
- Studies included were high quality, longitudinal, population-based studies with the total NOS score ≥ 8
- all the studies were adjusted for age, sex, education and Apolipoprotein E (APOE) status
- There was no significant heterogeneity
- Out of the 664 studies screened, five studies met eligibility criteria.

Singh, B., Parsaik, A. K., Mielke, M. M., Erwin, P. J., Knopman, D. S., Petersen, R. C., & Roberts, R. O. (2014). Association of Mediterranean Diet with Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Journal Of Alzheimer's Disease*, *39*(2), 271-282. doi:10.3233/JAD-130830

Author year country	N (%male)	Age, mean (SD) or median (IQR)	Follow-up, yrs, mean (SD) or median (IQR)	Subject selection	Outcome definition (N)	Adjustment
Scarmeas, 2006, USA	2226 (32)	77.2 (6.6)	4.0 (3.0)	Cognitively normal subjects (≥ 65 y)	AD (262)	Cohort, age, sex, ethnicity, education, APOE, caloric intake, smoking, comorbidity index and BMI
Feart, 2009, France	1410 (37)	75.9	Median = 4.1	Cognitively normal subjects (≥ 65 y)	AD (66)	Age, sex, marital status, education, APOE, total energy intake, physical exercise, taking ≥5 medications/day, CES depression scale, BMI, hypertension, hypercholesterolemia, diabetes and tobacco use
Scarmeas, 2009, USA	482 (32)	77.5 (6.6)	4.3 (2.7)	MCI (≥ 65 y)	AD(106)	Age, sex, ethnicity, education, APOE, caloric intake, BMI and time between first dietary assessment and the first cognitive assessment
Scarmeas, 2009, USA	1393 (32)	76.7 (6.5)	4.5 (2.7)	Cognitively normal subjects (≥ 65 y)	MCI (275)	Age, sex, ethnicity, education, APOE, caloric intake, BMI and time between first dietary assessment and the first cognitive assessment
Roberts, 2010, USA	1141 (53)	Event = 83.3 (78.7– 86.2); No event = 79.7 (75.6–84.2)	Median (IQR): 2.2 (1.7–2.6)	Cognitively normal or had MCI (70–89 y)	MCI (93) and dementia (23)	Age, Sex, education, total energy intake, APOE, stroke, coronary heart disease and depressive symptoms
Cherbuin, 2011, Australia	1367	NA	8	Cognitively normal subjects (60–64 y)	MCI (NA)	Age, sex, education, APOE, BMI, total caloric intake, physical activity, stroke, hypertension, and diabetes

Singh et al, 2014

- One point increase in the MeDi score is associated with an 8% reduced risk of developing cognitive impairment in both adjusted and unadjusted models, with no heterogeneity
- Subjects in the highest MeDi tertile had 33% less risk of cognitive impairment (MCI or AD) as compared to the lowest MeDi score tertile.
- Among cognitively normal individuals, higher adherence to the MeDi was associated with a reduced risk of MCI
- Further prospective-cohort studies with longer follow-up and randomized controlled trials are warranted to consolidate the evidence

Singh, B., Parsaik, A. K., Mielke, M. M., Erwin, P. J., Knopman, D. S., Petersen, R. C., & Roberts, R. O. (2014). Association of Mediterranean Diet with Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Journal Of Alzheimer's Disease*, *39*(2), 271-282. doi:10.3233/JAD-130830

(2)Systematic Review(2016)

- Five databases were searched—PubMed, Embase, CINAHL, CENTRAL, and PsycINFO (1806 to 25 May 2015)—
- Heterogeneity precluded a metaanalysis
- Thirty-two studies from 25 unique cohorts, including 5 RCTs and 27 observational studies, met the inclusion criteria.

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- The majority of studies showed that the MeDi was associated with improved cognitive function, a decreased risk of cognitive impairment, or decreased risk of dementia, or AD
- Three studies found no correlation between the MeDi and AD,
- Three studies found no association between the MeDi and cognitive impairment,
- Five found no association between the MeDi and cognitive function

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TABLE 1 Description of included studies[1]

Source	Study design	Sample size, *n*	Mean age, y	Female, %	Participant source	Country of origin	Participant cognitive status at baseline
Chan et al., 2013 (29)	Cross-sectional	3670	72	48	Cohort from Hong Kong	China	Mixed cognitive health status
Crichton et al., 2013 (30)	Cross-sectional	1183	40–65*	64	South Australian electoral rolls	Australia	Mixed cognitive health status
Gardener et al., 2012 (31)	Cross-sectional	652	72	58	AIBL Study of Ageing	Australia	Mixed healthy controls and participants with MCI and AD
Katsiardanis et al., 2013 (32)	Cross-sectional	557	65	57	Residents of Valestino	Greece	Mixed cognitive health status
Ye et al., 2013 (33)	Cross-sectional	1269	57	Not reported	Boston Puerto Rican Health Study	United States	Mixed cognitive health status
Scarmeas et al., 2006 (34)	Cross-sectional, case-control	1984	76	68	WHICAP project	United States	Subjects with AD and nondemented subjects
Cherbuin and Anstey, 2012 (35)	Longitudinal	1528	64	51	PATH study	Australia	Cognitively healthy
Corley et al., 2013 (36)	Longitudinal	882	70	50	Lothian Birth Cohort 1936 study	Scotland	Mixed cognitive health status
Feart et al., 2009 (37)	Longitudinal	1410	76	63	Three-City study	France	Elderly without diagnosis of dementia
Kesse-Guyot et al., 2013 (38)	Longitudinal	3083	52	46	SU.VI.MAX	France	Cognitively healthy participants
Koyama et al., 2015 (39)	Longitudinal	2326	75	51	Health ABC study	United States	No cognitive assessment at baseline
Olsson et al., 2015 (40)	Longitudinal	564	70	0	Uppsala longitudinal study	Sweden	Cognitively healthy participants
Psaltopoulou et al., 2008 (41)	Longitudinal	732	60	65	EPIC–Greece study	Greece	No cognitive assessment at baseline
Samieri et al., 2013 (42)	Longitudinal	10,670	59	100	Nurses' Health Study	United States	Cognitively healthy participants
Samieri et al., 2013 (43)	Longitudinal	6174	66	100	Women's Health Study	United States	Cognitively healthy participants
Samieri et al., 2013 (44)	Longitudinal	16,058	74	100	Nurses' Health Study	United States	Cognitively healthy participants
Scarmeas et al., 2009 (45)	Longitudinal	282	77	68	WHICAP project	United States	Subjects with AD and nondemented subjects
Scarmeas et al., 2009 (46)	Longitudinal	1875	77	68	WHICAP project	United States	Participants with MCI and cognitively healthy subjects
Scarmeas et al., 2006 (47)	Longitudinal	2258	77	69	WHICAP project	United States	Cognitively healthy participants

Source	Study design	Sample size, *n*	Mean age, y	Female, %	Participant source	Country of origin	Participant cognitive status at baseline
McMillan et al., 2011 (59)	RCT	25	21	27	Australian residents	Australia	No information on cognitive status at baseline
Wardle et al., 2000 (60)	RCT	176	53	52	London and Southeast England residents	England	No cognitive assessment at baseline
Tangney et al., 2014 (48)	Longitudinal	826	82	74	MAP project	United States	No cognitive assessment at baseline
Titova et al., 2013 (49)	Longitudinal	194	70	48	PIVUS study	Sweden	Mixed cognitive health status
Tsivgoulis, 2013 (50)	Longitudinal	17,478	64	57	REGARDS	United States	Cognitively healthy participants
Vercambre et al., 2012 (51)	Longitudinal	2504	>65*	100	Women's Antioxidant Cardiovascular Study	United States	Cognitively healthy participants
Wengreen et al., 2013 (52)	Longitudinal	3831	65	57	CCMS	United States	Cognitively healthy participants
Gu et al., 2010 (53)	Longitudinal/ cross-sectional	1219	77	67	WHICAP project	United States	Cognitively healthy participants
Roberts et al., 2010 (54)	Longitudinal/ cross-sectional	1233	70–89*	49	Rochester Epidemiology Project	United States	No cognitive assessment at baseline
Tangney et al., 2011 (55)	Longitudinal/ cross-sectional	3790	75	62	CHAP project	United States	No cognitive assessment at baseline
Martínez-Lapiscina et al., 2013 (56)	RCT	522	75	55	PREDIMED RCT	Spain	No cognitive assessment at baseline
Martínez-Lapiscina et al., 2013 (57)	RCT	285	67	55	PREDIMED RCT	Spain	No cognitive assessment at baseline
Martínez-Lapiscina et al., 2014 (58)	RCT	522	67	44	PREDIMED RCT	Spain	No cognitive assessment at baseline

(Continued)

- Large heterogeneity, and studies differed with regard to quality.
- majority of findings come from epidemiologic studies providing correlational evidence between the MeDi and cognition but not for a cause-and-effect relation.
- concludes that adherence to the MeDi is associated with better cognitive performance, but more controlled trials are required to establish a causational relation.

Petersson, S. D., & Philippou, E. (2016). Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review of the Evidence. *Adv Nutr, 7*(5), 889-904. doi:10.3945/an.116.012138

(3)Metaanalysis (2017)

- Searched the PubMed and the Embase
- 9 cohort studies involving 34,168 participants
- Highest Mediterranean diet score was inversely associated with developing cognitive disorders,
- pooled RR (95% CI) was 0.79 (0.70, 0.90)
- MeDi score of the median category was not significantly associated with cognitive disorders.
- Dose-response analysis indicated a trend of a nearly linear relationship of the MeDi score with the incident risk of cognitive disorders.
- Further RCTs are warranted to confirm the observed association in different populations.

Wu, L., & Sun, D. (2017). Adherence to Mediterranean diet and risk of developing cognitive disorders: An updated systematic review and meta-analysis of prospective cohort studies. *Scientific Reports*, *7*, 41317. doi:10.1038/srep41317

(4)Metaanalysis (2017)

- Included 15 cohort studies with 41,492 participants and 2 RCTs with 309 and 162 participants in intervention and control groups.
- primary outcome was cognitive function, divided into domains of 1) memory and 2) executive function.
- Meta-analysis of ***cohort studies*** revealed a significant association between MeDi and older adults' episodic memory (n = 25,369, $P = 0.03$) and global cognition (n = 41,492, P = 0.001),
- but not working memory (n = 1487, P = 0.93) or semantic memory (n = 1487, r = 0.08, P = 0.28).
- Meta-analysis of ***RCTs*** revealed that compared with controls, the MeDi improved delayed recall (n = 429, P = 0.01), working memory (n = 566, P = 0.03), and global cognition (n = 429, P = 0.047), but not episodic memory (n = 566, P = 0.15), immediate recall (n = 566, P = 0.17), paired associates (n = 429, P = 0.20), attention (n = 566, P = 0.69), processing speed (n = 566, P = 0.35), or verbal fluency (n = 566, P = 0.12).
- strongest evidence effect of the MeDi on older adults' global cognition.

Loughrey, D. G., Lavecchia, S., Brennan, S., Lawlor, B. A., & Kelly, M. E. (2017). The impact of the Mediterranean diet on the dognitive dunctioning of healthy older adults: A systematic review and meta-analysis. *Advances in Nutrition (Bethesda, Md.)*, *8*(4), 571-586. doi:10.3945/an.117.015495

(5)Systematic Review (2018)

9 databases from inception, final update December 2017 for **RCTs** , 66 cognitive tests and 1 brain function outcome from 5 studies (*n* = 1888)

MeDi compared with alternate diet for cognitive or brain morphology and function outcomes

Prescribed MeDi varied considerably between studies, particularly with regards to quantitative food advice. Data limitations precluded a meta-analysis

Only 8/66 (12.1%) of individual cognitive outcomes significantly favored a Medi for cognitive performance, with effect sizes ranging from small (0.32) to large (1.66), 2 outcomes favored controls

Of 8 domain composite cognitive scores from 2 studies, the 3 (Memory, Frontal, and Global function) from PREDIMED (PREvención con DIeta MEDiterránea) were significant, with ESs ranging from 0.39 to 1.29.

A posttest comparison at a second PREDIMED site found that the MeDi modulates the effect of several genotypes associated with dementia risk for some cognitive outcomes, with mixed results.

Finally, the risk of low-plasma brain- derived neurotrophic factor was reduced by 78% in those who consumed a MeDi compared to control diet at 3 y.

The data are mostly nonsignificant, with small ESs. However, the significant improvements in cognitive domain composites in the most robustly designed study warrant additional research

Radd-Vagenas, S., Flood, V. M., Fiatarone Singh, M. A., Duffy, S. L., Naismith, S. L., & Brew, B. J. (2018). Effect of the Mediterranean diet on cognition and brain morphology and function: a systematic review of randomized controlled trials. *The American Journal of Clinical Nutrition*, *107*(3), 389-404. doi:10.1093/ajcn/nqx070

Conclusions

- Saturated fats are consistently associated with poorer cognition and higher risk of AD
- MUFA, PUFA (especially N-3), and fish consumption have all been associated with lower risk of AD, stronger evidence for fish
- 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
- This may not apply to APOE 4 carriers
- 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

Conclusions - 2

- Evidence on association between MeDi adherence and cognition is good and survived several meta-analyses and reviews after adjustment for demographics and other variables
- However, the number of longitudinal studies specifically addressing MeDi is still small in number and causational relationship cannot be assumed
- Analyzing RCTs and longitudinal studies separately better demonstrates results
- RCT are limited, and shows weaker evidence, especially poor of it's effect on incident of AD
- Best effects seen are on global congtion
- It is not clear whether the diet overall or specific components helps cognition, although there are evidence for each component

NHS EatWell Guide

Source: Public Health England in association with the Welsh government, Food Standards Scotland and the Food Standards Agency in Northern Ireland

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