



Protective Role of the Mediterranean Diet against the Development of Age-Related Cognitive Disorders: An Umbrella Review of Meta-Analyses [†]

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Abstract: This umbrella review was aimed at understanding if the Mediterranean diet can have a protective role against the development of age-related cognitive disorders. PubMed, Cochrane Library, Web of Science, EMBASE, Scopus and the DOAJ were systematically searched for relevant meta-analyses published in the last 10 years (up to October 2021). After the article selection process, six research works met the inclusion criteria. Pooled results of these meta-analyses indicated that following a Mediterranean diet can be associated with a reduction in the risk of developing cognitive disorders (mild cognitive impairment, vascular dementia and Alzheimer's disease), although in one study the overall result was not statistically significant. In particular, people following a Mediterranean diet may be up to 40% less likely to develop age-related neurodegenerative disorders associated with impaired cognition. A possible explanation can be found in the antioxidant, anti-inflammatory, cardioprotective, pro-metabolic and prebiotic effects of the Mediterranean diet, rich in fiber, unsaturated fatty acids, micronutrients and natural antioxidants. In consideration of current epidemiological trends that suggest a substantial rise in cognitive disorder prevalence in the near future, promoting the Mediterranean diet can be a useful public health strategy for healthy aging and disease prevention (GRADE 1B). Additional studies are recommended to strengthen current indications.

Keywords: Mediterranean diet; nutrition; dementia; cognitive impairment; Alzheimer's disease; literature review



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1. Introduction

The Mediterranean diet was first studied in the 1970s as a set of eating habits deeply rooted in the food culture of different Mediterranean countries [1], and recently included in the UNESCO list of intangible cultural heritage of humanity [2]. Stemming from a combination of different culinary traditions, some authors have pointed out that there is no unique Mediterranean diet, but diverse Mediterranean-style diets, each of them characterized by specific nutritional features [3]. However, generally speaking, these dietary habits tend to have some main characteristics in common: a shared definition suggests that, every day, a standard Mediterranean diet should include 3-to-9 vegetable servings, up to 2 fruit servings, different starchy foods, olive oil and typical Mediterranean spices (oregano, basil, rosemary, marjoram, thyme, parsley, pepper, garlic, etc.) [4]. The Mediterranean diet is also characterized by high consumption of legumes, nuts and unprocessed cereals, whereas animal-derived products (especially red meat) are consumed far less frequently than in the common Western diet [5] (Figure 1).

Considering the world population ageing and a rising attention to senile disorders such as Alzheimer's dementia, affecting millions of patients worldwide [6], researchers

have started to investigate the preventive role of different lifestyle habits for age-related degenerative conditions associated with cognitive impairment. In recent decades, scientific research has suggested that, thanks to its nutritional composition, the Mediterranean diet can have a protective role against several chronic illnesses, including cardiovascular problems, dysmetabolic conditions, degenerative diseases and even cancer [7]. The useful role of the Mediterranean diet as a pillar of a healthy lifestyle has also been underscored by the World Health Organization in an effort to promote dietary habits capable of reducing the burden of preventable chronic diseases across the globe [8].

The aim of this review is to assess if the Mediterranean diet can contribute to the prevention of age-related cognitive disorders.



Figure 1. Mediterranean food pyramid. Harvard food pyramid of the Mediterranean diet (picture distributed under the public domain license and available online at: <https://www.hsph.harvard.edu/nutritionsource/pyramids.html>, accessed on 1 March 2022).

2. Methods

PubMed, Cochrane Library, Web of Science, EMBASE, Scopus and the Directory of Open Access Journals (DOAJ) were systematically searched for relevant meta-analyses up to 22 October 2021. These keywords were used for the literature survey: “Mediterranean diet”, “dementia”, “cognitive”, “Alzheimer*”. To be eligible for inclusion, meta-analyses had to be published in the last ten years and to report a pooled estimate of the Mediterranean diet impact on the development of age-related cognitive disorders. The following criteria for study inclusion were adopted:

P (population): any adult without neurologic diseases at baseline.

I (intervention): high adherence to the Mediterranean diet, usually measured with a multiple-item scoring system (daily quantity of vegetables, fruits and nuts, legumes, cereals, fish, meat and meat products, dairy products, alcohol, olive oil usage) [9,10].

C (comparison): poor adherence to the Mediterranean diet (usually the typical Western diet).

O (outcomes): the incidence over time of cognitive disorders, including mild cognitive impairment, vascular dementia and Alzheimer's disease.

S (study design): meta-analyses of observational studies or clinical trials.

3. Results

After database search, 748 items were retrieved (PubMed: $n = 343$; Cochrane Library: $n = 23$; Web of Science: $n = 92$; EMBASE: $n = 50$; Scopus: $n = 139$; DOAJ: $n = 101$) and 6 meta-analyses were included in this literature overview [11–16]. A summary of quantitative evidence about the protective role of the Mediterranean diet against cognitive disorders can be found in Table 1. All but one meta-analysis [14] reported that following the Mediterranean diet can be associated with significant reduction in the risk of developing age-related cognitive disorders. In one case, the Mediterranean diet still showed a protective role, but the overall effect did not reach the threshold for statistical significance, which was set at $p < 0.05$ [14]. The number of primary studies included in each meta-analysis ranged from 5 to 9, and the number of study participants varied from 6652 to 34,168. Adherence to Mediterranean dietary habits was often assessed with a 9-point score, and most meta-analyses estimated the effect of this nutritional regime on the risk of developing either mild cognitive impairment or dementia (Table 1). The majority of meta-analyses were reported in compliance with internationally recognized methodological standards (PRISMA or MOOSE).

Table 1. Summary of quantitative evidence about the relationship between Mediterranean dietary habits and risk of developing cognitive disorders.

Studies (Sample Size)	Follow-Up Duration	Cognitive Disorders	Pooled Analysis	Guidelines	Year	Ref.
9 studies ($n = 10,278$)	1–14 years	MCI or AD (9 studies of any design)	RR = 0.60 [95% CI: 0.43; 0.83] *	MOOSE	2013	[11]
6 studies ($n = 6652$)	>4 years	MCI or AD (6 cohort studies)	HR = 0.67 [95% CI: 0.55; 0.81] *	PRISMA	2014	[12]
5 studies ($n = \text{NR}$)	2–5 years	Dementia due to any cause (5 studies)	RR = 0.69 [95% CI: 0.57; 0.84] *	-	2016	[15]
9 studies ($n = 34,168$)	4–12 years	MCI (5 study arms), AD (5 study arms), VD (3 study arms)	RR = 0.79 [95% CI: 0.70; 0.90] *	-	2017	[13]
7 studies ($n = \text{NR}$)	4–12 years	MCI (3 study arms)	RR = 0.89 [95% CI: 0.73; 1.09]	MOOSE	2021	[14]
		AD (5 study arms)	RR = 0.95 [95% CI: 0.88; 1.02]			
8 studies ($n = \text{NR}$)	4–12 years	MCI (2 study arms)	RR = 0.91 [95% CI: 0.85; 0.97] *	PRISMA	2021	[16]
		AD (9 study arms)	RR = 0.89 [95% CI: 0.84; 0.93] *			

* = significant result ($p < 0.05$) in favor of a high adherence to the Mediterranean diet. Legends: AD = Alzheimer's disease, CI = Confidence Interval, HR = Hazard Ratio, MCI = Mild Cognitive Impairment, MedDiet = Mediterranean Diet, NR = Not Reported, RR = Risk Ratio/Relative Risk.

4. Discussion

The main results of meta-analyses summarized in Table 1 indicate that following the Mediterranean diet can be a protective factor for age-related dementia, with an average risk ratio always inferior to 1. Recent data from included studies are in line with two meta-analyses published in 2008 and 2010 about the impact of the Mediterranean diet on any neurodegenerative disorders, including Parkinson's disease (sometimes, although not always, associated with dementia) [17,18]. Pooled estimates of these two meta-analyses

suggested an average result of $RR = 0.87$ ($p < 0.05$), thus indicating a significant protective role of intervention.

In general, it is demonstrated that high adherence to the Mediterranean diet can be beneficial for maintaining older adults' global cognition and physical performance [14,19]. This is also suggested by retrospective studies about modifiable predictors of dementia, among which nutritional habits play a fundamental role, both directly and indirectly [20]. Additionally, the Mediterranean diet seems not only to reduce the risk of developing dementia, but also to diminish Alzheimer's disease mortality with a possible dose-response effect, depending on individual degree of adherence to this nutritional regime [21]. As expected, the best results are obtained when the Mediterranean diet is included in a globally healthy lifestyle, characterized by regular physical activity (at least 150 min/week), no-smoking habit and engagement in cognitive/social tasks [22].

It has largely been debated what the health benefits of the Mediterranean diet can be attributed to, and most accredited explanations point toward a combined physiological and pharmacological effect of all the nutrients found in this dietary regime. In particular, it seems that high consumption of fruits, vegetables and sources of mono- and poly-unsaturated fatty acids (olive oil, fish, seeds and nuts), along with a sufficient nutritional intake of vitamin D and very low consumption of sources of saturated fatty acids, can have a protective role against age-related cognitive decline and impairment [23,24]. A possible explanation can be found in the anti-inflammatory, antioxidant, cardioprotective, pro-metabolic and prebiotic effects of the Mediterranean diet, capable of reducing advanced glycation end-products, improving lipid levels (especially high-density lipoproteins or HDL), slowing down the progression of vascular aging and modulating intestinal microbiota in a healthy way [25–27]. These effects are probably due to an optimal intake of fiber, unsaturated fatty acids, vitamins, minerals and natural antioxidants, including polyphenols, flavonoids, anthocyanins, quercetin, resveratrol, catechins, beta-carotene, lycopene and allium sulfur compounds [27–29].

5. Conclusions

In conclusion, the Mediterranean diet can contribute to healthy aging. On average, people following the Mediterranean diet may be 5 to 40% less likely to develop mild cognitive impairment or Alzheimer's disease if compared with those who opt for a typical Western diet. In consideration of current epidemiological trends, promoting the Mediterranean diet can be a useful public health strategy for age-related neurodegenerative disease prevention and well-being promotion (strength of recommendation: GRADE 1B). Additional studies are recommended to strengthen current indications and to better estimate the preventive role of this dietary intervention for neurodegenerative disorders.

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References

1. Keys, A.; Keys, M. *How to Eat Well and Stay Well the Mediterranean Way*; Doubleday: New York, NY, USA, 1975; ISBN 9780385009065.
2. UNESCO-Mediterranean Diet. Available online: <https://ich.unesco.org/en/lists> (accessed on 24 October 2021).
3. Noah, A.; Truswell, A.S. There Are Many Mediterranean Diets. *Asia Pac. J. Clin. Nutr.* **2001**, *10*, 2–9. [CrossRef] [PubMed]

4. Davis, C.; Bryan, J.; Hodgson, J.; Murphy, K. Definition of the Mediterranean Diet; a Literature Review. *Nutrients* **2015**, *7*, 9139–9153. [CrossRef] [PubMed]
5. Trichopoulou, A.; Martínez-González, M.A.; Tong, T.Y.; Forouhi, N.G.; Khandelwal, S.; Prabhakaran, D.; Mozaffarian, D.; de Lorgeril, M. Definitions and Potential Health Benefits of the Mediterranean Diet: Views from Experts around the World. *BMC Med.* **2014**, *12*, 112. [CrossRef] [PubMed]
6. Mayeux, R.; Stern, Y. Epidemiology of Alzheimer Disease. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a006239. [CrossRef]
7. Dinu, M.; Pagliai, G.; Casini, A.; Sofi, F. Mediterranean Diet and Multiple Health Outcomes: An Umbrella Review of Meta-Analyses of Observational Studies and Randomised Trials. *Eur. J. Clin. Nutr.* **2018**, *72*, 30–43. [CrossRef]
8. World Health Organization. Fostering Healthier and More Sustainable Diets—Learning from the Mediterranean and New Nordic Experience. 2018. Available online: <http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/news/news/2018/5/fostering-healthier-and-more-sustainable-diets-learning-from-the-mediterranean-and-new-nordic-experience> (accessed on 1 March 2022).
9. Stefler, D.; Malyutina, S.; Kubinova, R.; Pajak, A.; Peasey, A.; Pikhart, H.; Brunner, E.J.; Bobak, M. Mediterranean Diet Score and Total and Cardiovascular Mortality in Eastern Europe: The HAPIEE Study. *Eur. J. Nutr.* **2017**, *56*, 421–429. [CrossRef]
10. Hosking, D.E.; Eramudugolla, R.; Cherbuin, N.; Anstey, K.J. MIND Not Mediterranean Diet Related to 12-Year Incidence of Cognitive Impairment in an Australian Longitudinal Cohort Study. *Alzheimers Dement.* **2019**, *15*, 581–589. [CrossRef] [PubMed]
11. Psaltopoulou, T.; Sergentanis, T.N.; Panagiotakos, D.B.; Sergentanis, I.N.; Kosti, R.; Scarmeas, N. Mediterranean Diet, Stroke, Cognitive Impairment, and Depression: A Meta-Analysis. *Ann. Neurol.* **2013**, *74*, 580–591. [CrossRef] [PubMed]
12. Singh, B.; Parsaik, A.K.; Mielke, M.M.; Erwin, P.J.; Knopman, D.S.; Petersen, R.C.; Roberts, R.O. Association of Mediterranean Diet with Mild Cognitive Impairment and Alzheimer’s Disease: A Systematic Review and Meta-Analysis. *J. Alzheimers Dis.* **2014**, *39*, 271–282. [CrossRef]
13. Wu, L.; Sun, D. Adherence to Mediterranean Diet and Risk of Developing Cognitive Disorders: An Updated Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Sci. Rep.* **2017**, *7*, 41317. [CrossRef]
14. Coelho-Júnior, H.J.; Trichopoulou, A.; Panza, F. Cross-Sectional and Longitudinal Associations between Adherence to Mediterranean Diet with Physical Performance and Cognitive Function in Older Adults: A Systematic Review and Meta-Analysis. *Ageing Res. Rev.* **2021**, *70*, 101395. [CrossRef] [PubMed]
15. Cao, L.; Tan, L.; Wang, H.-F.; Jiang, T.; Zhu, X.-C.; Lu, H.; Tan, M.-S.; Yu, J.-T. Dietary Patterns and Risk of Dementia: A Systematic Review and Meta-Analysis of Cohort Studies. *Mol. Neurobiol.* **2016**, *53*, 6144–6154. [CrossRef] [PubMed]
16. García-Casares, N.; Fuentes, P.G.; Barbancho, M.Á.; López-Gigosos, R.; García-Rodríguez, A.; Gutiérrez-Bedmar, M. Alzheimer’s Disease, Mild Cognitive Impairment and Mediterranean Diet. A Systematic Review and Dose-Response Meta-Analysis. *J. Clin. Med. Res.* **2021**, *10*, 4642. [CrossRef] [PubMed]
17. Sofi, F.; Cesari, F.; Abbate, R.; Gensini, G.F.; Casini, A. Adherence to Mediterranean Diet and Health Status: Meta-Analysis. *BMJ* **2008**, *337*, a1344. [CrossRef]
18. Sofi, F.; Abbate, R.; Gensini, G.F.; Casini, A. Accruing Evidence on Benefits of Adherence to the Mediterranean Diet on Health: An Updated Systematic Review and Meta-Analysis. *Am. J. Clin. Nutr.* **2010**, *92*, 1189–1196. [CrossRef]
19. Loughrey, D.G.; Lavecchia, S.; Brennan, S.; Lawlor, B.A.; Kelly, M.E. The Impact of the Mediterranean Diet on the Cognitive Functioning of Healthy Older Adults: A Systematic Review and Meta-Analysis. *Adv. Nutr.* **2017**, *8*, 571–586. [CrossRef]
20. Cooper, C.; Sommerlad, A.; Lyketsos, C.G.; Livingston, G. Modifiable Predictors of Dementia in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. *Am. J. Psychiatry* **2015**, *172*, 323–334. [CrossRef]
21. Scarmeas, N.; Luchsinger, J.A.; Mayeux, R.; Stern, Y. Mediterranean Diet and Alzheimer Disease Mortality. *Neurology* **2007**, *69*, 1084–1093. [CrossRef]
22. Dhana, K.; Evans, D.A.; Rajan, K.B.; Bennett, D.A.; Morris, M.C. Healthy Lifestyle and the Risk of Alzheimer Dementia: Findings from 2 Longitudinal Studies. *Neurology* **2020**, *95*, e374–e383. [CrossRef]
23. Buckinx, F.; Aubertin-Leheudre, M. Nutrition to Prevent or Treat Cognitive Impairment in Older Adults: A GRADE Recommendation. *J. Prev. Alzheimers Dis.* **2021**, *8*, 110–116. [CrossRef]
24. Kelly, M.E.; Loughrey, D.G.; Power, J.M.; McEvoy, C.; Sheerin, C.; Pennie, B. The Impact of Adherence to the Traditional Mediterranean Diet and Sex Differences on Global Cognitive Functioning: A Systematic Review and Meta-Analysis. *J. Cogn. Enhanc.* **2020**, *4*, 179–191. [CrossRef]
25. Radd-Vagenas, S.; Duffy, S.L.; Naismith, S.L.; Brew, B.J.; Flood, V.M.; Fiatarone Singh, M.A. Effect of the Mediterranean Diet on Cognition and Brain Morphology and Function: A Systematic Review of Randomized Controlled Trials. *Am. J. Clin. Nutr.* **2018**, *107*, 389–404. [CrossRef] [PubMed]
26. Grao-Cruces, E.; Varela, L.M.; Martin, M.E.; Bermudez, B.; Montserrat-de la Paz, S. High-Density Lipoproteins and Mediterranean Diet: A Systematic Review. *Nutrients* **2021**, *13*, 955. [CrossRef] [PubMed]
27. Nagpal, R.; Shively, C.A.; Register, T.C.; Craft, S.; Yadav, H. Gut Microbiome-Mediterranean Diet Interactions in Improving Host Health. *F1000Research* **2019**, *8*, 699. [CrossRef] [PubMed]
28. Billingsley, H.E.; Carbone, S. The Antioxidant Potential of the Mediterranean Diet in Patients at High Cardiovascular Risk: An in-Depth Review of the PREDIMED. *Nutr. Diabetes* **2018**, *8*, 13. [CrossRef]
29. El-Sabban, F. The Antioxidant Advantage of the Mediterranean Diet in Cardiovascular Disease. *Nutr. Diet. Suppl.* **2014**, *6*, 35–40. [CrossRef]