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## **TITLE PAGE**

### **Title**

**Mediterranean diet and cognitive function in older adults**

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### **Short running head**

Mediterranean Diet, Cognitive Decline and Dementia

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## **ABSTRACT**

*Purpose of review:* The effectiveness of the Mediterranean diet in reducing the prevalence of cardiovascular and chronic diseases has been largely evidenced. Although nutrition constitutes an interesting approach in preventing age-related brain disorders, the association between the Mediterranean-style diet and cognitive functions has been very occasionally explored.

*Recent findings:* Results are provided from only two recent prospective cohorts of older Americans and French individuals ( $\geq 65$  y) on the relationship of Mediterranean diet to cognitive functions. A high adherence to the Mediterranean diet has been associated with slower cognitive decline, with reduced risk of Mild Cognitive Impairment conversion to Alzheimer's Disease (AD) and with reduced risk of AD.

*Summary:* The possibility that the Mediterranean diet may affect not only the risk for AD, but also the evolution of cognitive performances a long time before the clinical diagnosis of dementia and subsequent disease course constitutes major promising results. Replication of these results in other populations seems necessary to allow their generalization and to propose the Mediterranean diet as a potential preventive approach against cognitive decline or dementia in addition to its expected benefits against many other unfavorable outcomes in a public health perspective.

### **Keywords:**

Mediterranean diet, cognitive functions, aging

## INTRODUCTION

The health benefits of a Mediterranean-style diet are well documented in regard of the abundant literature in the field of nutritional epidemiology. The Mediterranean-style diet has been first associated with a significant decrease in overall mortality among 182 men and women aged 70 years and more in three Greek villages [1-2••]. This result has been recently extended to larger population in Greece (more than 22 000 adults) displaying a significant reduction in total mortality with greater adherence to the traditional Mediterranean diet [3•]. Advantages of a type of diet that adheres to the principles of the traditional Mediterranean one on health were mentioned in a recent meta-analysis in which greater adherence to a Mediterranean-style diet was associated with longer survival, reduced risk for cardiovascular mortality and cancer incidence and mortality [4•]. A growing body of evidence has then emerged and the concept of Mediterranean diet as a healthy eating model has been widely recognized [5].

Whether adherence to a Mediterranean-type diet was associated with brain health has surprisingly only recently been explored although the Mediterranean diet has the special feature to combine several foods and nutrients already separately proposed as potential protective factors against cognitive dysfunctions [6]. Here, we update available knowledge on the relationship between Mediterranean diet and cognitive decline, risk of dementia or Alzheimer's disease based on two prospective cohorts from US and France.

## **TEXT OF REVIEW**

Older adults appear to be at high risk for cognitive impairment and the increased life expectancy observed in developed countries is accompanied by an increasing prevalence of dementia and of its major cause, Alzheimer's disease (AD) [7]. The prevalence of dementia increases with age from approximately 1.0% in the group age 65 to 69 years to 30% at age 90 years and older [8]. The main risk factors of AD, age and possession of the  $\epsilon 4$  allele of the gene of apolipoprotein E (ApoE) for the late-onset or sporadic form of the disease, are only predisposing factors which offer no possibility of prevention. Because of the presently limited efficacy of pharmacological therapies, the search for preventive strategies for cognitive decline or dementia seems of utmost importance. Preventive strategies should aim at delaying the onset of Mild Cognitive Impairment (MCI) [9], an unstable but still potentially reversible stage, or favouring the reversibility to normal cognitive functioning in MCI patients, in order to avoid or delay the conversion to dementia.

Among lifestyle-related factors recently proposed as the first line of defence against the development and progression of cognitive impairment [6, 10], nutrition constitutes an interesting approach. Beyond the potential impact of specific nutrients such as antioxidants, n-3 polyunsaturated fatty acids and homocysteine-related vitamins (vitamin B12 and folate), dietary patterns allow to investigate their additional or synergistic effects. However, few epidemiological studies on elderly individuals have been interested by dietary patterns and their impact on brain aging outcomes so far [11].

### **Concept of the Mediterranean diet**

The Mediterranean-style diet was first described in the Seven-Country study in the 1950s to 1960s in the south of Europe where adult life expectancy was among the highest in

the world and rates of coronary heart disease, certain cancers and other nutrition-related chronic diseases were among the lowest [12]. Not a specific pattern but a collection of eating habits traditionally followed by the populations of the Mediterranean basin first defined the Mediterranean diet called “traditional”. This dietary pattern is characterized by abundant plant foods consumption in the form of fruits, vegetables, breads, other forms of cereals, potatoes, beans, nuts and seeds; fresh fruit as the typical dessert; olive oil as the main source of monounsaturated fat; dairy products as principally cheese and yogurt; a low to moderate consumption of fish depending of the proximity of the sea; a low to moderate consumption of poultry; fewer than four eggs consumed per week; low amount of red meat and wine consumed in low to moderate amounts, normally during meals [13]. However, there is no single Mediterranean diet but several definitions, because dietary habits vary considerably across the Mediterranean countries bordering the sea [14•]. Nevertheless, the evaluation of the adherence to a Mediterranean-style diet has conducted to develop scores or indexes called “Mediterranean Diet Scale” or “Mediterranean Diet Score” or “Mediterranean Adequacy Index” or even “Mediterranean–Style Dietary Pattern Score” based on *a priori* hypotheses and intended to be close to the traditional one [15-16]. The Mediterranean diet scale in its original form did not include the consumption of fish [2••] while it was included in more recent studies. The use of the Mediterranean diet score seems especially useful to compare adherence to the so-called “Mediterranean diet” between different populations [17].

The computation of the Mediterranean diet score, as used in studies about cognitive impairments [18••-19••], was close to the method previously described by Trichopoulou et al. [2••-3]. Briefly, a value of 0 or 1 was assigned to each of the nine food groups characterizing the traditional Mediterranean diet (vegetables, fruits, legumes, cereals, the ratio of monounsaturated-to-saturated fatty acid, alcohol and fish presumed to be beneficial; meat and dairy products presumed to be detrimental), using sex-specific median consumption of the

population as cut-offs. Theoretically, the score could range from 0 to 9, with higher scores indicating greater dietary adherence.

### **Potential mechanisms linking the Mediterranean diet to cognitive functions**

Previous observational studies already indicated that specific food or nutrient that take part of the traditional Mediterranean diet (i.e. fish, unsaturated fatty acids, antioxidant as vitamin E, vitamin B12, folates, carotenes, flavonoids, moderate alcohol) may have potential protective effect against dementia or cognitive decline [10]. However, these results about isolated nutrient or food seem so far conflicting [20-22]. Compared with traditional single-food or nutrient methods, the dietary pattern approach is appealing for several reasons. Indeed, the analyses of single nutrients ignore important interactions (additive, synergistic or antagonist effects) between components of diet and more importantly people did not eat isolated nutrients [23].

Different biological mechanisms could be evoked to explain the association between foods or nutrients of the Mediterranean diet and potential better brain health. Indeed, the role of nutrition and notably of the Mediterranean diet on cardiovascular events is well documented [24-25] and a protective effect of the Mediterranean diet against vascular dementia or the vascular component of AD could be expected. Oxidative damages have been implicated in the pathogenesis of AD, and the Mediterranean diet is also a dietary pattern with antioxidant properties [26]. Moreover, inflammation is another mechanism involved in the pathogenesis of AD which is in general reduced with higher adherence to the Mediterranean diet [27-28].

### **Adherence to a Mediterranean diet and cognitive functions**

The association between adherence to a Mediterranean-type diet and the evolution of cognitive functions or incidence of dementia has been explored recently. To date, only two prospective studies from US [19••, 29••-31••] and France [18••] have investigated this relationship and results are in agreement with a beneficial effect of the Mediterranean diet on cognitive functions, despite many differences between the populations studied.

Using data from the Washington Heights-Inwood Columbia Aging Project (WHICAP), Scarmeas et al. was the first who reported a beneficial effect of the Mediterranean diet on incidence of AD [19••]. Subjects older than 65 years were enrolled in this cohort in 1992 and 1999 and have been followed 4 years in mean (range 0.2 – 13.9). Among subjects free from dementia at baseline, 2258 subjects had a complete assessment of cognitive functions and of dietary habits. Criteria used for the diagnosis of dementia were those of the *Diagnostic and Statistical Manual of Mental disorders, Revised Third Edition* (DSM-III-R) and the subtype of dementia was determined according to the criteria of the *National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association* (NINCDS-ADRDA). The authors identified 262 incident cases of AD during the follow-up. The Mediterranean diet score was computed as early described. Among most interesting results, they observed that the mean Mediterranean diet score at baseline was slightly higher in subjects who remained nondemented compared to those who developed AD over time (4.4 vs. 4.2 in mean respectively,  $P=0.05$ ). Higher adherence to the Mediterranean diet was significantly associated with lower risk for development of AD, even after adjustment for age, sex, ethnicity, education, ApoE genotype, caloric intake, smoking, comorbidity index and body mass index (Hazard Ratio (HR) =0.91,  $P=0.015$ ). Compared with subjects in the lowest tertile of Mediterranean diet score (score 0 to 3, indicating a low adherence to the Mediterranean diet), those in the middle score tertile

(score 4 to 5) had 21 % less risk for development of AD and those in the highest tertile (score 6 to 9, indicating a high adherence to the Mediterranean diet) had 40% less risk for development of AD, with a trend for a dose-response effect, in fully adjusted models.

In a more recent analysis, the same authors confirmed their original finding about a beneficial effect of the Mediterranean diet on cognitive functions in older Americans [31••]. In a sub-sample of the WHICAP constituted by 1393 subjects aged 77 years in mean at baseline, and followed in mean 4.5 years (range 0.9 – 16.4), there were 275 subjects who developed MCI over time. A trend for a beneficial effect of a high adherence to the Mediterranean diet on the risk of MCI over time was observed (HR=0.72,  $P=0.05$ ). Among subjects with MCI at baseline (n=482), 106 developed AD during the follow-up. Compared with MCI patients in the lowest tertile of Mediterranean diet score (score 0 to 3), those in the middle (score 4 to 5) and high (score 6 to 9) tertiles of the Mediterranean diet score had respectively 45% and 48% significant less risk of developing AD over time. The assessment of nutritional data in subjects already suffering from MCI at baseline denoted however a potential bias in these analyses.

Finally, another original analysis from the WHICAP was the investigation of the risk of incident AD according to the adherence to the Mediterranean diet and to the practice of physical exercise, already known as potential protective factor against functional decline [29••]. Briefly, the authors observed that both high Mediterranean-type diet adherence (HR=0.60, 95% CI 0.42 – 0.87) and participating in physical activity (HR=0.67, 95% CI 0.47 – 0.95) were independently associated with lower risk of AD over time.

To our knowledge, there is only one other prospective study to date which reported the association of a Mediterranean diet with change in cognitive performances and risk of dementia in a population near from the Mediterranean basin [18••]. Using data from the

Three-City (3C) Study, a French prospective cohort of older individuals (aged 65 years and over at baseline) starting in 1999, the authors investigated the relationship between adherence to the Mediterranean diet and change in cognitive performances. The sample consisted of 1410 individuals from the Bordeaux center of the 3C study, free from dementia at baseline, aged 75.9 years in mean and followed at least once over 5 years (2002-2007). Cognitive performances were assessed on four neuropsychological tests: Mini-Mental State Examination (MMSE), Isaacs Set Test (IST), Benton Visual Retention Test (BVRT) and Free and Cued Selective Reminding Test (FCSRT) assessing respectively, global cognitive function, semantic verbal fluency, visual memory and verbal episodic memory. An independent committee of neurologists analysed in depth the medical history of each subject to obtain a consensus on the diagnosis and etiology of dementia according to the DSM-Fourth Edition and the NINCDS-ADRDA criteria. The Mediterranean diet score was computed as described above and as in the US study [19••]. Analyses were adjusted for age, gender, education, marital status, energy intake, physical activity, depressive symptomatology, taking 5 drugs/d or more, ApoE genotype, cardiovascular risk factors and stroke. The main original finding was that higher adherence to the Mediterranean diet was significantly associated with better global cognitive performances and episodic memory (MMSE and FCSRT) over time, especially in subjects who remained free from dementia over time. For instance, a women with a low adherence to the Mediterranean diet (score 0 to 3) would lose 1.2 point on the MMSE score and 2.6 points on the FCSRT score over 5 years, whereas a comparable women with a high Mediterranean diet adherence (score 6 to 9) would lose 0.75 points and 1.6 points respectively. Nevertheless, there was no association between the adherence to the Mediterranean diet and risk of dementia (HR=1.06,  $P=0.43$ ) or AD (HR=1.00,  $P=0.96$ ) in older individuals enrolled in this study.

Knowing the beneficial impact of the Mediterranean diet on cardiovascular events and the contribution of cardiovascular risk factors in AD risk, Scarmeas et al. hypothesized that there might be an attenuation of the association between the Mediterranean diet adherence and the risk of AD when vascular risk factors (history of stroke, diabetes, hypertension, heart disease and lipids levels) were simultaneously introduced in the statistical model [30•]. As previously described, they confirmed that a higher adherence to the Mediterranean diet was associated with lower risk of AD. However, a surprising finding was that the introduction of the vascular variables did not change the magnitude of this association. Interestingly, in the 3C study, similar results were observed [18••]. The association between a Mediterranean diet and cognitive decline was not attenuated when adjusting for stroke and cardiovascular risk factors. Altogether, these results suggested that the association was not mediated by vascular comorbidity while other biological mechanisms, such as oxidation and inflammation, may contribute to this association.

Altogether, results from the first US [19••] and the French [18••] studies may seem inconsistent while important differences between these studies could explain such discrepancies, as discussed by Féart et al. [18••] and Knopman in the related editorial [32]. First, in the design of these studies, difference in length of follow-up was observed, the US study being longer (range 0.2 to 13.9 vs. 1.6 to 6.1 years). Second, the computation of the Mediterranean diet score was based on sex-specific median of consumption of nine food groups which characterized each study sample and was therefore not exactly comparable. Therefore, low French consumers could be considered as high US consumers for a particular food group, leading to a decreased chance to observe similar results. Moreover, the Mediterranean diet score did not consider other food groups that could reflect specific health concerns and behaviours, such as the consumption of dietary supplements. Another

explanation to these inconsistent results was related to cognitive decline in the prodromal phase preceding diagnosis of dementia [33]. Féart and collaborators suggested that the beneficial effect of the Mediterranean diet observed on cognitive decline would be efficient only at least 5 years before the clinical diagnosis of dementia. After this window of opportunity, in the very last years preceding dementia, the neurodegenerative processes of dementia could be too advanced to be reversed by diet. Controlling for late-life risk factors cannot be sufficient to stand for lifelong exposure as well [32].

Finally, food choices and dietary habits which reflect individual food preferences are highly sensitive to culture, education, socio-economic status, socio-demographic characteristics, environmental and lifestyle determinants, as well as to age- or nutrition-related diseases. Therefore, a Mediterranean-style diet pattern probably does not fully explain the better health of persons who adhere to it but it likely contributes directly. This dietary pattern may also indirectly constitute an indicator of a complex set of favorable social and lifestyle factors that contribute to global better health.

## CONCLUSION

The evaluation of a Mediterranean diet on health outcomes seems of particular interest [34]. To date, only two recent prospective studies focused on brain health and results seem really promising. A high adherence to the Mediterranean diet has been associated with slower cognitive decline, with trend for a reduced risk for developing MCI, with reduced risk of MCI conversion to AD and with reduced risk for AD. Altogether, these results suggest that adherence to the Mediterranean diet may affect not only the risk for AD, but also the evolution of cognitive performances over time and subsequent disease course. Further research is needed to allow the generalization of these results to other populations and to propose the Mediterranean diet as a potential preventive approach against dementia or cognitive decline in addition to its expected benefits against many other unfavorable outcomes in a public health perspective.

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