The purpose of this review was to update available knowledge on the relationship between adherence to the Mediterranean diet (MeDi) and cognitive decline, risk of dementia or Alzheimer’s Disease (AD), and to analyse the reasons for some inconsistent results across studies. The traditional MeDi has been recognised by the United Nations Educational Scientific and Cultural Organisation as an Intangible Cultural Heritage of Humanity. This dietary pattern is characterised by a high consumption of plant foods (i.e. vegetables, fruits, legumes and cereals), a high intake of olive oil as the main source of fat, a moderate intake of fish, low-to-moderate intake of dairy products and low consumption of meat and poultry, with wine consumed in low-to-moderate amounts during meals. Beyond the well-known association between higher adherence to the MeDi and lower risk of mortality, in particular from CVD and cancer, new data from large epidemiological studies suggest a relationship between MeDi adherence and cognitive decline or risk of dementia. However, some inconsistent results have been found as well, even in Mediterranean countries. In this review, we analyse the reasons likely to explain these discrepancies, and propose that most of these differences are due to variations in the methodology used to assess MeDi adherence. We also discuss the possibility of residual confounding by lifestyle, that is, greater adherents to the MeDi also have a healthier lifestyle in general, which can favourably affect cognition. In conclusion, large-scale studies in various populations with common methodology are required before considering the MeDi as an optimal dietary strategy to prevent cognitive decline or dementia.
Dementia: a worldwide public health challenge

Dementia and AD, its most frequent form, are responsible for a considerable public health challenge. The prevalence of dementia increases exponentially with age from approximately 1% in the age group 65–69 years to 30% at age 90 years and older(6). Given the longer life expectancy, the prevalence of dementia is expected to increase considerably according to most projections(7). In 2005, more than twenty-four million people suffered from dementia, and it was estimated that 4.6 million new cases of dementia were arising every year(8). There is no aetiological treatment for AD available yet, and the strongest risk factors for dementia and AD are age, and possession of variants of several genes, which are not modifiable(9–11). Hence, finding effective preventive strategies for cognitive decline or dementia is of utmost importance. These preventive strategies should aim at delaying the onset of mild cognitive impairment (MCI)(12), an unstable but still potentially reversible stage, in order to avoid or delay the conversion to dementia.

Although the aetiology of dementia and AD is still partly unknown, a growing body of evidence suggests that complex interactions between genetic factors and environmental conditions, involving multiple pathophysiological mechanisms, probably occur to initiate and exacerbate the neurodegenerative process(13–16). Among environmental factors, cardiovascular risk factors may lead to various lesions in the brain which modify the risk of late-onset dementia(17). In addition, regular physical exercise or other lifestyle risk factors have been associated with dementia risk. However, overall, no definite conclusion on the impact of these factors could be established to date, since results from randomised controlled trials did not corroborate most of the observational findings, highlighting the complexity of this disease(17–19).

Among lifestyle factors, several epidemiological data underscored a possible protective role of nutrition(18,20–25). Most nutrients that have been individually associated with cognitive decline, dementia or AD in preclinical or epidemiological studies are found in the Medi: MUFA, found in large amounts in olive oil (the hallmark of the Medi), long-chain n-3 PUFAs, mainly provided by fish and seafood, vitamins B<sub>12</sub>, folate, and antioxidants (vitamins C and E, carotenoids, flavonoids and selenium) provided by plant foods(22,26–40). However, reports about consumption of single nutrients or foods have been inconsistent and an integrative approach of the diet considering the additive and/or synergistic effects of each food component should be privileged(41–44). Therefore, beyond the study of individual dietary components, there has been an increasing interest in the influence of dietary patterns on cognitive health(5,45,46). This review focused on available epidemiological knowledge on the relationship between adherence to the Medi and cognitive function.

The Mediterranean diet: basic concepts

The Seven-Country study was the pioneer observational study that first described the Mediterranean-style diet in the early 1960s(31). This study evidenced that countries from South Europe (Italy, Yugoslavia and Greece) had a higher life expectancy and lower rates of CHD, cancers and some other chronic diseases(31). Hence, the authors hypothesised that the exceptional health of these populations from the Mediterranean basin may be attributed to their traditional diet(37). The MedDi is characterised by abundant consumption of plant foods such as fresh fruits, vegetables, breads, other forms of cereals, potatoes, beans, nuts and seeds; olive oil as the main source of fats, providing notably monounsaturated lipids; a low-to-moderate intake of dairy products in the form of cheese and yoghurt; 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(38). There is no single MedDi, but several definitions, because dietary habits vary considerably across countries bordering the Mediterranean sea(49,50). Nevertheless, a scientific consensus has been reached on what constitutes a MedDi today(51). At the same time, several indices have been developed to evaluate adherence to a Mediterranean-style diet(52–54).

Assessment of adherence to a Mediterranean diet

The most commonly used definition to assess adherence to the MedDi is the ‘MedDi score’, first proposed by Trichopoulou et al.(55). In its original form, the MedDi score included eight food groups–dietary components (vegetables, fruits, legumes, cereals, meat, dairy products, MUFA:SFA ratio and alcohol), and ‘fish and seafood’ intake was added as a ninth group, based on growing evidence on the beneficial role of long-chain n-3 PUFAs in health(56). The MedDi score is a sum-score of nine individual binary components (corresponding to the nine aforementioned food groups), and ranges therefore from zero (lower adherence) to nine points (higher adherence). Individual components are calculated as follows: a value of zero or one is assigned to each component, using cut-offs based on sex-specific medians of consumption in the population. For components presumed to be beneficial to health (e.g. vegetables, fruits, legumes, cereals and fish, and MUFA:SFA ratio), individuals whose consumption is below the median are assigned a value of zero; one for the others. For components presumed to be detrimental to health (e.g. meat and dairy products), individuals whose consumption is below the median are assigned one point; zero point for the others. For alcohol intake, where moderate consumption is supposed to be beneficial, more heterogeneity in the scoring system has been observed. Initially, a value of one is assigned to men who consume 10–50 g alcohol (from any source) per d, and to women...
who consume 5–25 g alcohol per d (56). In studies based on populations less adherent to the traditional MeDi, these thresholds have been sometimes modified to better identify moderate drinkers (57). Finally, among the sources of alcohol, red wine also provides polyphenols which may be beneficial for various health outcomes; it has been sometimes separated from other sources of alcohol in the scoring system (58).

An alternate index, the MedDiet score, has been used in relation to cognitive functions (58). In this index, first developed by Panagiotakos et al. (59), food intake is not translated into a binary component according to the median as in the MedDiet score, but is expressed in number of servings (per month, week or d, according to the food group considered). The MedDiet score is a sum-score of eleven individual five-point components: non-refined cereals, vegetables, fruits, olive oil, alcohol and full-fat dairy products (servings per d); legumes, fish, poultry and potatoes (servings per week), and red meat and meat products (servings per month). For components positively associated with the MeDi (i.e. non-refined cereals, potatoes, fruits, vegetables, legumes fish and olive oil), a score from zero, for rare or no consumption, up to five for almost daily consumption was assigned. On the other hand, for components inversely associated with the MeDi (i.e. red meat and products, and poultry and full fat dairy products), opposite scores were assigned (i.e. zero for almost daily consumption to five for rare or no consumption of meat and meat products, poultry and full-fat dairy products). For alcohol, in the original MedDiet score form, five points were assigned for a consumption of less than 300 ml alcohol per d, and zero point for no consumption or for consumption over than 700 ml per d. Thus, the range of the MedDiet score was between zero and fifty-five; higher score indicating greater adherence to a Mediterranean-style diet (59). Advantages of this second index are the weighting of the selected food groups, depending on the frequency of consumption (thresholds are chosen based on a priori hypothesis) and regardless of the consumption of the sample studied.

Altogether, these indices have been considered as efficient tools to assess adherence to the MeDi, whereas a lack of high correlation between both indices has also been reported (54).

Potential biological mechanisms

Foods or nutrients from the MeDi might delay age-related cognitive decline by several underlying biological mechanisms, including vascular, antioxidant and anti-inflammatory pathways (23, 40, 60, 61). A comprehensive review recently published by Frisardi et al. provides an updated state-of-the-art on this issue (62).

First, dementia and cognitive decline have been related to various vascular risk factors (63) and the role of nutrition, and especially of the MeDi, on vascular risk factors and CVD is well documented (4). A greater adherence to the MeDi was associated with a 10% reduced risk of fatal and non-fatal cardiovascular events (4). Dementia and cognitive decline have also been related to the metabolic syndrome, defined as a cluster of cardiovascular risk factors (i.e. having at least three over the five following cardio-metabolic abnormalities: hypertension, high waist circumference, hypertriglyceridaemia, low-HDL-cholesterol and hyperglycaemia) (64–66). A recent meta-analysis of fifty epidemiological studies and trials involving more than 500,000 participants showed that MeDi adherence was inversely associated with the risk of the metabolic syndrome overall, and with each of its individual component (67). For instance, compared with a low-fat diet, the MeDi improved plasma glucose, systolic blood pressure and cholesterol levels in individuals with high risk of CVD (68).

Secondly, oxidative damage have been implicated in the pathogenesis of AD, and the MeDi, rich in antioxidant compounds found in olive oil and wine (sources of polyphenols), fruits and vegetables (sources of vitamins C, E and carotenoids) may help lower oxidative stress in brain age ing. Among individuals with high cardiovascular risk enrolled in the PREDIMED study, a dietary-intervention trial, some components of the MeDi (i.e. total olive oil, walnuts and wine), with antioxidant properties or rich in polyphenols, have been independently associated with better cognitive function (69). Moreover, the MeDi has been inversely associated with markers of oxidative stress (70) and lipid peroxidation (71). In a recent trial, a MeDi enriched in olive oil was found to lower expression of genes related to oxidative stress and inflammatory processes, and to decrease markers of lipid oxidation and systemic inflammation in plasma (72).

Inflammation is another key mechanism in the pathogenesis of AD, and a higher adherence to the MeDi has been associated with lower inflammatory markers (73–75). A meta-analysis comparing Mediterranean to low-fat diets concluded that individuals assigned to a MeDi had more favourable changes in plasma high-sensitivity C-reactive protein and fasting glucose, in total cholesterol and in blood pressure than those assigned to a low-fat diet (76). The anti-inflammatory properties of n-3 fatty acids may also be involved in the relationship between MeDi, inflammation and cognitive function, since higher MeDi adherence has been associated with higher levels of plasma n-3 fatty acids (77), in particular in the Three-City (3C) study (78).

Altogether, these results suggested that the association between MeDi adherence and cognitive functions might be mediated by vascular comorbidity, and underscored that non-vascular biological mechanisms, such as oxidative stress, inflammation and metabolic disorders, should also be considered as possible mediators (62).

Adherence to a Mediterranean diet and cognitive functions

The association between adherence to a Mediterranean-type diet and cognitive function or dementia has been only recently explored. To date, this relationship has been investigated in seven different cohorts, and overall, results mostly converge towards a beneficial effect of the MeDi on cognitive function, despite many differences between the populations studied (Table 1). We provide here a summary...
Table 1. Adherence to a Mediterranean diet (MeDi) and cognitive functions: summary of main longitudinal studies

<table>
<thead>
<tr>
<th>Study, location, authors (reference)</th>
<th>Participants/design</th>
<th>Follow-up (mean (so) and/or range)</th>
<th>MeDi adherence: method of assessment</th>
<th>Special feature of the score computation</th>
<th>Outcomes</th>
<th>Adjustment variables</th>
<th>Main findings</th>
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<tbody>
<tr>
<td>WHICAP, USA, Scarmeas et al. (79)</td>
<td>2258 community-based non-demented individuals aged 65 years and older at baseline</td>
<td>4-year (3.0) on average, range 0.2–13.9 years</td>
<td>Semi-quantitative FFQ and energetic derived residuals to compute the MeDi score (0–9 point scale)</td>
<td>For alcohol consumption, one point was attributed to men and women with consumption &gt;0 and &lt;30 g/d</td>
<td>262 incident AD cases</td>
<td>Cohort, age, sex, ethnicity, education, APOE genotype, energetic intake, smoking, medical comorbidity index and BMI</td>
<td>Higher MeDi adherence (+ 1 unit) was associated with lower risk of AD (HR 0.91, 95% CI 0.83, 0.98, P = 0.015). Individuals with middle MeDi adherence had a HR of 0.85 (0.63, 1.16) and those with high MeDi adherence had a HR of 0.60 (0.42, 0.87) for AD compared with low MeDi adherents (P for trend 0.007)</td>
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<tr>
<td>WHICAP, USA, Scarmeas et al. (80)</td>
<td>1393 cognitively normal participants and 482 individuals with MCI aged 65 years and older at baseline</td>
<td>Cognitively normal: 4.5-year (2.7) on average, range 0.9–16.4 years MCI participants: 4.3-year (2.7) on average, range 1.0–13.8 years</td>
<td>Semi-quantitative FFQ and energetic derived residuals to compute the MeDi score (0–9 point scale)</td>
<td>For alcohol consumption, one point was attributed to men and women with consumption &gt;0 and &lt;30 g/d</td>
<td>275 incident MCI cases among cognitively normal at baseline 106 incident AD cases among MCI individuals at baseline</td>
<td>Cohort, age, sex, ethnicity, education, APOE genotype, energetic intake, smoking, medical comorbidity index, BMI, and time duration between dietary assessment and baseline diagnosis</td>
<td>Among cognitively normal participants, each additional unit of MeDi score was associated with a reduced risk of MCI (HR 0.92 (0.85, 0.99), P = 0.04) Individuals with middle MeDi adherence had a HR of 0.83 (0.62, 1.12) and those with high MeDi adherence had a HR of 0.72 (0.52, 1.00) for MCI compared with low MeDi adherents (P for trend 0.05). Among MCI participants, higher MeDi adherence (+ 1 unit) was not associated with lower risk of AD (HR 0.89 (0.78, 1.02), P = 0.09) Individuals with middle MeDi adherence had a HR of 0.55 (0.34, 0.90) and those with high MeDi adherence had a HR of 0.52 (0.30, 0.91) for AD compared with low MeDi adherents (P for trend 0.02)</td>
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<td>Study, location, authors (reference)</td>
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<td>WHICAP, USA, Scarmeas et al. (81)</td>
<td>1880 community-based non-demented individuals aged 65 years and older at baseline</td>
<td>5.4-year (3.3) on average, Range 0.2–13.9 years</td>
<td>Semi-quantitative FFQ and energetic derived residuals to compute the MeDi score (0–9 point scale) Three categories: - low adherents (scores 0–3) - middle adherents (scores 4–5) - high adherents (scores 6–9)</td>
<td>For alcohol consumption, 1 point was attributed to men and women with consumption &gt;0 and &lt; 30 g/d</td>
<td>282 incident AD cases</td>
<td>Cohort, age, gender, ethnicity, education, APOE genotype, energetic intake, smoking, medical comorbidity index, BMI, depression, leisure activities, baseline clinical dementia rating and physical activity</td>
<td>Individuals with middle MeDi adherence had a HR of 0.98 (0.72–1.33) and those with high MeDi adherence had a HR of 0.60 (0.42–0.87) for AD compared to low MeDi adherents (P for trend 0.008)</td>
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<td>WHICAP, USA, Scarmeas et al. (82)</td>
<td>192 community-based individuals with AD aged 65 years and older at baseline</td>
<td>4.4-year (3.6) on average, range 0.2–13.6 years</td>
<td>Semi-quantitative FFQ and energetic derived residuals to compute the MeDi score (0–9 point scale) Three categories: low adherents (scores 0–3); middle adherents (scores 4–5); and high adherents (scores 6–9)</td>
<td>For alcohol consumption, one point was attributed to men and women with consumption &gt;0 and &lt; 30 g/d</td>
<td>Eighty-five deaths</td>
<td>Period of recruitment, age, sex, ethnicity, education, APOE genotype, smoking, energetic intake and BMI</td>
<td>Higher MeDi adherence (+ 1 unit) was associated with lower risk of death (HR 0.76 (0.65, 0.89, P = 0.001)). Individuals with middle MeDi adherence had a HR of 0.27 (0.10, 0.68) for death compared with low MeDi adherents (P for trend 0.003) and those with high MeDi adherence had a HR of 0.65 (0.38, 1.09)</td>
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<td>Three-City Study, France, Feart et al. (83)</td>
<td>1410 community-based individuals aged 65 years and older at baseline</td>
<td>4.1-year, range 1.6–6.1 years</td>
<td>FFQ and 24 h dietary recall to compute the MedDiet score (0–9 point scale) Three categories: low adherents (scores 0–3); middle adherents (scores 4–5); and high adherents (scores 6–9)</td>
<td>For alcohol consumption, the second quartile of distribution of total alcohol intake was considered as “moderate consumption”: one point was attributed to men whose consumption was between seven and fourteen glasses per week and to women whose consumption was between one and four glasses per week</td>
<td>Ninety-nine incident cases of dementia (sixty-six incident cases of AD)</td>
<td>Age, sex, education, APOE genotype, marital status, physical activity, energetic intake, drug consumption, depressive symptomatology, smoking, BMI, hypertension, hypercholesterolemia, diabetes and stroke history</td>
<td>Higher MeDi adherence (+ 1 unit) was associated with fewer errors on MMSE (β = − 0.006 ± 0.01, – 0.0003, P = 0.04). In individuals free from dementia over time, higher MeDi adherence (+ 1 unit) was associated with fewer errors on MMSE (β = − 0.006 ± 0.01, – 0.007, P = 0.03) and better performances on FCSRT (β = 0.05 (0.005, 0.010), P = 0.03). No association between MeDi adherence and risk of dementia or AD (HR = 1.00 (0.85, 1.19), P = 0.96)</td>
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<tr>
<td>Study, location, authors (reference)</td>
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<td>Mayo Clinic Study of Aging, USA, Roberts et al. (84)</td>
<td>1141 community-based individuals cognitively normal or with MCI at baseline aged 70–89 years at baseline</td>
<td>Median of 2.2 years, Interquartile range 1.7–2.6 years</td>
<td>Semi-quantitative FFQ and caloric derived residuals to compute the MeDi score (0–9 point scale)</td>
<td>For alcohol consumption, 1 point was attributed to men and women with consumption &gt;0 and &lt;30 g/d</td>
<td>116 incident events (93 incident cases of MCI and 23 incident cases of dementia)</td>
<td>Age, gender, education, caloric intake, stroke, APOE genotype, CHD, depressive symptoms, BMI and diabetes</td>
<td>Individuals in the second tertile of MeDi adherence had a HR of 0.79 (0.51–1.21), P = 0.28, and those in the upper tertile of MeDi adherence had a HR of 0.75 (0.46–1.21), P = 0.24 for MCI or dementia compared to individuals in the first tertile of MeDi adherence. These results were unchanged when the (MUFA + PUFA)/SFA ratio was considered.</td>
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<td>PATH Through Life study, Australia, Cherbuin and Anstey (85)</td>
<td>1528 community-based individuals aged 60–64 years at baseline</td>
<td>4-year on average</td>
<td>Semi-quantitative FFQ to compute the MeDi score (0–9 point scale)</td>
<td>Tent incidents cases of MCI, nineteen with incident impairment on the CDR, thirty-seven incident cases with any MCD</td>
<td>Age, sex, education, APOE genotype, BMI, physical activity, stroke, diabetes, hypertension, energetic intake</td>
<td>Adherence to the MeDi was not associated with MCI (OR = 1.41 (0.95, 2.10), P = 0.09), or CDR (OR = 1.18 (0.88, 1.57), P = 0.27), or any-MCD (OR = 1.20 (0.98, 1.47), P = 0.08) (for each additional point of the MeDi score).</td>
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<td>CHAP, USA, Tangney et al. (58)</td>
<td>3790 community-based individuals aged 65 years and over at baseline</td>
<td>7.6-year on average</td>
<td>Semi-quantitative FFQ to compute the MedDiet score (0–55 point scale)</td>
<td>A MedDiet wine score has been developed considering only the consumption of wine instead of that of total alcoholic beverages, and using the same thresholds</td>
<td>Cognitive decline assessed by the global measure of cognitive function based on repeated tests over time (the East Boston tests of immediate and delayed recall, the MMSE and the Symbol Digit Modalities test)</td>
<td>Age, sex, race, education, participation in cognitive abilities, total energy intake and interaction between time and each covariable</td>
<td>The MedDiet score and the MedDiet wine score were both associated with reduced decline in cognitive functions (β = 0.0014, se = 0.0004, P = 0.0004 and β = 0.0014, se = 0.0004, P = 0.0009, respectively, for each point increase of the score). Individuals in the upper tertile of MedDiet score had significantly slower rate of cognitive change over time (β = 0.0117, se = 0.0046, P = 0.0002), as those in the upper tertile of the MedDiet wine score (β = 0.0106, SE = 0.0046, P = 0.021).</td>
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WHICAP, Washington Heights-Inwood Columbia Aging Project; AD, Alzheimer disease; HR, hazard ratio; MCD, mild cognitive disorder; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; IST, Isaacs Set Test; BVRT, Benton Visual Retention Test; FCSRT, Free and Cued Selective Reminding Test; CDR, clinical dementia rating; CHAP, Chicago Health and Aging Project.
of existing prospective published data in this field, to the best of our knowledge to date.

**Results from the Washington Heights-Inwood Columbia Aging Project**

The first association between greater adherence to a Mediterranean-style diet and lower incidence of AD was reported by Scarmeas et al.\(^{(79)}\). Beginning in 1992, 2258 US individuals older than 65 years free from dementia were enrolled in the Washington Heights-Inwood Columbia Aging Project (WHICAP) and followed for 4 years on average (range 0–2–13.9). During this follow-up, 262 incident cases of AD were identified. Adherence to a Mediterranean-style diet was assessed at baseline using the MeDi score (range 0–9), as described earlier. A higher adherence to the MeDi was associated with a reduced risk of AD (hazard ratio (HR) = 0.91, 95% CI 0.83–0.98 for each additional point of MeDi score, \(P = 0.015\)), taking into account major potential confounders. Compared with individuals in the lowest tertile of MeDi score (scores 0–3), indicating a low adherence to the MeDi), those in the middle tertile of score (scores 4 or 5) had a 21% lower risk of AD and those in the highest tertile (scores 6–9) had a 40% lower risk of AD, with a significant trend for a dose–response effect (\(P\) for trend = 0.007), in fully adjusted models.

This key result was extended to MCI\(^{(80)}\). In a subsample of 1393 individuals of the WHICAP followed for 4–5 years on average, 275 individuals developed MCI. A borderline significant association between greater adherence to the MeDi and lower risk of MCI was observed (HR = 0.72, 95% CI 0.52–1.00, for one additional point of MeDi score, \(P = 0.05\)). Moreover, among 482 individuals with MCI at baseline, 106 developed AD during the follow-up. MCI patients with moderate (scores 4 or 5) or high (scores 6–9) MeDi adherence at baseline had, respectively, 45 and 48% lower risks of AD than those with lower MeDi adherence (scores 0–3; \(P\) for trend = 0.02). A potential bias could yet not be dismissed in these analyses in which assessment of nutritional habits was performed among individuals with memory deficits.

A more global healthy lifestyle was then studied in the WHICAP, combining dietary habits and physical exercise in relation to the risk of AD\(^{(81)}\). Among 1880 individuals with information for diet and physical activity and non-demented at baseline, 282 individuals were diagnosed with AD during follow-up (5–4 years on average). Independent inverse associations between physical exercise, MeDi adherence and the risk of AD were found (HR for much v. no physical activity = 0.67, 95% CI 0.47–0.95, \(P = 0.02\); HR for high (scores 6–9) v. low MeDi adherence (scores 0–3) = 0.60, 95% CI 0.42–0.87, \(P = 0.007\)).

Finally, the same authors investigated in the WHICAP the relation between adherence to the MeDi and mortality in AD patients\(^{(82)}\). Among 192 subjects diagnosed with AD at baseline in the WHICAP and followed for 4–4 years on average, eighty-five died. Compared with AD patients in the lowest tertile of MeDi score at baseline (scores 0–3), those in the highest tertile of the MeDi score (scores 6–9) had a significant lower mortality risk (HR = 0.27, 95% CI 0.10–0.69, \(P\) for trend = 0.003), with a longer survival of 3–9 years on average. This result suggests that adherence to the MeDi may affect not only risk for AD but also subsequent disease course.

In order to investigate the hypothesis of a vascular mediation, Scarmeas et al. tested whether the association between MeDi and the risk of AD was attenuated when vascular risk factors (i.e. history of stroke, diabetes, hypertension, heart disease and lipids levels) were added in their statistical models\(^{(86)}\). Surprisingly, the magnitude of the association between the MeDi score and AD risk was virtually unchanged when adding vascular factors in the models, suggesting that vascular factors/disease may not act as strong mediators in this relationship. Nevertheless, more recently, the same authors reported among 707 WHICAP participants (aged 80 years on average) that higher MeDi adherence was associated with lower cerebrovascular disease burden in the brain, as assessed by high-resolution structural MRI\(^{(87)}\). Interestingly, MeDi adherence was associated with less MRI infarcts, markers of large vessel disease, but not with less white matter hyperintensities volumes, markers of small vessel disease. This result thus suggested that large vessel disease could be in the biological pathway between MeDi and AD\(^{(87)}\). To discuss the inconsistency between this finding and their previous mediation study\(^{(86)}\), the authors argued that self-reported history of stroke might be less accurate than markers of cerebrovascular disease provided by MRI\(^{(87)}\). Finally, the association between MeDi adherence and AD was also not attributable to inflammatory or metabolic markers since the introduction of high-sensitive C-reactive protein, fasting insulin or adiponectin as adjustment variables, did not modify the inverse association between MeDi adherence and incident AD observed in the WHICAP\(^{(75)}\).

Altogether, these results suggest that vascular and inflammatory pathways explored in the WHICAP may be, at best, only partial mediators in the MeDi–AD association, and that other pathways may also be involved. Most of the aforementioned results from the WHICAP performed at Columbia University have been recently reviewed\(^{(19)}\).

**Results from the Three-City study**

To our knowledge, there is only one prospective study to date which examined the association of a MeDi cognitive change and risk of dementia in Europe\(^{(83)}\). Using data from the 3C Study, a French prospective cohort of older individuals (aged 65 years or over at baseline)\(^{(88)}\), the authors investigated the relationship between adherence to the MeDi at baseline, using the MeDi score (range 0–9), and change in cognitive performances assessed every 2–3 years using four neuropsychological tests. The 3C study was the first to analyse the relationship between MeDi adherence and cognitive decline assessed longitudinally. A total of 1410 individuals free from dementia at baseline were followed-up for 5 years. Global cognitive function was assessed using the Mini Mental State Examination, and the Isaacs Set Test, the Benton Visual Retention Test and the Free and Cued Selective Reminding Test assessed semantic verbal fluency, visual memory and verbal episodic memory, respectively. During the
follow-up, ninety-nine incident cases of dementia (including sixty-six AD) were identified. After multivariable adjustment, higher adherence to the MeDi was significantly associated with better trajectories of global cognition and episodic memory (Mini Mental State Examination and Free and Cued Selective Reminding Test, respectively), especially in individuals who remained free from dementia over 5 years. However, no association was found between greater MeDi adherence and the risk of dementia (HR = 1.06, 95% CI 0.92, 1.21, P = 0.43) or AD (HR = 1.00, 95% CI 0.85, 1.19, P = 0.96). These results may suggest that the MeDi prevents brain ageing early in the prodromal phase of dementia(89), rather than in the very last few years preceding dementia diagnosis. However, the null association found between MeDi adherence and dementia risk in this study could also be explained by a lack of power due to a relatively short length of follow-up and a limited number of incident cases of dementia. As already observed in the WHICAP, additional adjustments for cardiovascular risk factors and reported history of stroke did not attenuate the negative relationship between MeDi adherence and cognitive decline in the 3C study(82).

Combined results from the WHICAP and the 3C study were summarised in a meta-analysis which concluded that a two-point increase of the MeDi score was associated with a 13% reduced risk of neurodegenerative disease(4).

Investigators from the 3C study further examined the association between MeDi adherence and the onset of disability, which is a necessary condition for the diagnosis of dementia(90). Among 1410 individuals from the 3C study, basic and instrumental activities of daily living were assessed by Lawton-Brody and Katz scales(91). MeDi adherence, assessed by the MeDi score, was inversely associated with the risk of incident disability in basic and instrumental activities of daily living in women (n 185 incident cases), but not in men (n 90 incident cases). Women with the highest MeDi adherence (scores 6–9) had a 50% reduction of incident disability in basic and instrumental activities of daily living than women with the lowest MeDi adherence (scores 0–3; P = 0.003). These findings suggested that adherence to a Mediterranean-style diet could contribute to slow down of the disablement process, at least in women.

Results from The Mayo Clinic Study of Aging
The relationship between adherence to the MeDi and the risk of MCI and dementia has also been investigated among 1141 individuals enrolled in The Mayo Clinic Study of Aging in the USA(84). After 2 years of follow-up, a non-significant 25% reduced risk of MCI (n 93 incident cases) or dementia (n 23 incident cases) was observed in individuals with greater MeDi adherence v. those with lower adherence (P = 0.24). However, with only 116 events recorded during a short follow-up, this study may have been underpowered to detect associations.

Results from the Chicago Health and Aging Project
In the Chicago Health and Aging Project, adherence to the MeDi was assessed with a novel tool, the MedDiet score (range 0–55)(58) (see description aforementioned), which takes into account daily, weekly or monthly intakes of eleven food groups. This index was computed according to the traditional MeDi and the definition of the thresholds used was therefore not specific of the consumption of the population studied(59). In this study, Tangney et al. investigated whether MeDi adherence was associated with cognitive change in older adults (n 3790) aged 65+ years at baseline. Four cognitive tests were administered to the participants, up to five times, for 7–6 years on average. The East Boston Memory test (immediate and delayed recalls), the Mini Mental State Examination and the Symbol Digit Modalities test were used to define a global measure of cognition. Interestingly, after multivariable adjustment, the MedDiet score was associated with slower rates of cognitive decline; the results were mostly unchanged in sensitivity analyses excluding persons with heart disease or stroke. Regarding the MedDiet score expressed in tertiles, participants in the highest tertile of MeDi score (range 30–45) had a significant slower rate of cognitive change (P = 0.0002). This result was also observed when only wine was considered in the computation of the MeDi score, instead of all alcoholic beverages. By contrast, the Healthy Eating Index-2005, developed to measure the dietary quality of an individual compared with recommendations of the 2005 Dietary guidelines(92), was not associated with rate of cognitive decline in this study.

Results from the PATH Through Life study
An Australian study investigated whether MeDi adherence was associated with cognitive change among 1528 individuals aged 60–64 years participating in the PATH Through Life study(85). These individuals were followed-up for 4 years and a dietary survey allowed us to compute the MeDi score (range 0–9) at baseline. Clinical assessments allowed us to identify sixty-six individuals (ten MCI, nineteen with impairment on the Clinical Dementia Rating, thirty-seven with any mild cognitive disorder) who transitioned from a normal cognitive stage at baseline to a cognitive impairment at the end of follow-up. In this study, a greater adherence to a MeDi was not associated with cognitive impairment, each disorder being separately studied. Here again, the small number incident cases due to a short length of follow-up could in part explain the lack of significant association. Although the corresponding data were not presented in this paper, we can assume that the pooled analyses, considering all individuals with incident cognitive impairment, whatever the sub-type, added no relevant information.

Results from the Women’s Antioxidant Cardiovascular Study
A recent report examined the association between MeDi adherence and cognitive decline among women enrolled in the Women’s Antioxidant Cardiovascular Study, a trial of secondary prevention of CVD(93). These women (n 2504, aged 65+ years at baseline) had a history of CVD or risk factors and were therefore at higher risk of cognitive decline. The initial cognitive assessment, performed on
average 3.5 years after the dietary survey, consisted of five cognitive tests administered by telephone. Repeated cognitive evaluation was performed every 2 years for 5 years on average. Adherence to the MeDi at baseline (i.e. 3.5 years before initial cognitive interview) was evaluated with the MeDi score (range 0–9) and the MedDiet score (range 0–55). In spite of a large sample and a prospective design with a similar length of follow-up than previous studies, no association was observed between adherence to the MeDi and 5-year cognitive decline. These results suggest that the prevention of cognitive decline might be more challenging in individuals with prevalent vascular disease or risk factors, and overall, strengthen the hypothesis that the MeDi may exert beneficial properties at early disease stages.

**Results from the European Prospective Investigation into Cancer and Nutrition Greek cohort**

The association of MeDi adherence to cognitive function was assessed in the Greek sample of the European Prospective Investigation into Cancer and Nutrition cohort (94). Among 732 individuals, aged 60+ years at baseline, adherence to a MeDi was evaluated by the MeDi score (range 0–9). Six to 13 years after the dietary survey, the Mini Mental State Examination was administered to assess global cognitive function; since there were no cognitive evaluations at the time of dietary assessment, this study cannot be considered as a truly prospective study. In spite of the Mediterranean origin of the population, likely highly adherent to the traditional MeDi, only a weak non-significant association was observed between MeDi adherence and global cognition. However, the lack of repeated assessment of cognition to evaluate cognitive decline limited the scope of these results.

**Possible reasons for some inconsistent results across studies**

There is a strong biological rationale for a protective role of the MeDi in brain ageing. Indeed, this dietary pattern combines antioxidants, B vitamins, n-3 fatty acids and other compounds that have been inversely related to cognitive decline and to the risk of dementia (95). It also likely captures additive or synergistic effects of several nutrients consumed together (44). Yet, some discrepancies remain between studies on MeDi adherence and cognitive health worldwide.

**Assessment of Mediterranean diet adherence**

One of the reasons for these inconsistent results may rely on the method used to compute the MeDi score, which limits the generalisation of the results and prevents definite conclusions.

A major limitation of the original MeDi score proposed by Trichopoulou et al. (55) is the use of thresholds based on medians of intake of each MeDi component, which are, per se, population-specific. Therefore, a MeDi score is, by definition, population-specific and cannot be compared with a MeDi score computed in a different sample. This may have led to misclassifications, since low consumers from one cohort could be considered as high consumers in another cohort for a particular food group and vice versa (Fig. 1). Therefore, the use of sex-specific cut-off points to develop the MeDi score does not measure adherence to a universal traditional Mediterranean dietary pattern, but rather to a specific pattern (96). The MedDiet score proposed by Panagiotakos et al., aimed at addressing this limitation, since the frequency of consumption of each food group part of the index was used as cut-off with respect to the traditional MeDi (59) and whatever the population studied.

Another limitation common to both indices is that a same score could be a reflection of several dietary patterns. For instance, a MeDi score of 4 could be assigned to an individual with a high intake of vegetables, fruits, fish and a high MUFA:SFA ratio (but a low consumption of legumes, cereals, a high consumption of meat and dairy products and a non-moderate alcohol intake). However, a MeDi score of 4 could also be assigned to an individual with a high consumption of cereals and fish and a low consumption of meat and dairy products (but a low consumption of fruits, vegetables, legumes, a low MUFA:SFA ratio and non-moderate alcohol intake). Obviously, these dietary patterns, simply summarised by a value of 4 for the MeDi score, are significantly different. Hence, several dietary patterns coexist in a single category of MeDi adherents (identified as low, moderate or high).

Finally, the scoring system used in both indices does not consider other food groups that could be relevant to the traditional MeDi or a more modern definition; for example, the use of supplements is not considered in these indices. Nevertheless, the indices already available showed satisfactory performances in assessing adherence to the MeDi, while the need to reach a consensus on the components to be included is still required (54).

**Design of studies on diet and cognitive health**

Studies on the relationship between MeDi adherence and cognitive health should be interpreted with caution. In a slowly evolving dementia syndrome, successive emergence of cognitive deficits appear more than 10 years before the diagnosis of dementia (89). Therefore, imposing a reasonable delay (i.e. several years) between dietary assessment and cognitive evaluation is of utmost importance to avoid reverse causation, that is, cognitive impairment lead to a change in dietary habits, and not the reverse. In the 3C study, the benefit of a higher MeDi adherence on verbal episodic memory was observed at least 5 years before the clinical diagnosis of dementia, suggesting that after a window of opportunity, in the very last few years preceding dementia, neurodegenerative processes may be too advanced to be reversed by diet (83).

Moreover, in most studies, dietary habits are assessed at a single occasion (i.e. at the beginning of cognitive evaluation, or before) and are therefore assumed a good marker of long-term habits. In the WHICAP, adherence to a MeDi was remarkably stable over 8 years (79,86); similar results were observed in the Chicago Health and Aging Project (58). However, there is still a possibility that diet assessed in late-life is a poor marker of midlife dietary...
habits, and midlife is likely the most relevant period to study risk factors for cognitive decline which evolve for years, if not decades.

It is also possible that the MeDi may not be relevant to cognitive health overall, but that the association between the MeDi and cognitive decline and dementia is actually driven by a limited number of specific foods. This issue was addressed in the WHICAP and in the PATH Through Life study. Among WHICAP participants, a mild-to-moderate alcohol consumption and higher vegetable consumption were independently associated with a reduced risk of AD after adjustment for all other individual components used to calculate the MeDi score (79). Despite a lack of association between MeDi adherence and incident cognitive impairment in the PATH Through Life study, significant associations were found between higher MUFA, dairies and alcohol consumptions and increased risk of MCI(85); unexpectedly, a higher fish consumption was associated with a higher risk of cognitive disorder. However, these analyses were not controlled for all the food groups’ part of the MeDi. Altogether, these results underscored the limits of the single food approach and the difficulty to understand the interactions of all components of the food matrix.

Finally, MeDi adherence is also part of a healthier lifestyle in general, especially in countries far from the Mediterranean basin, which can favourably affect cognition. By insufficiently controlling for lifestyle confounders, it is possible that some residual confounding persists in studies on MeDi and cognition. Besides, controlling for late-life risk factors cannot be sufficient to stand for life-long exposure, which remains an issue (97).

Conclusion

Overall, although a growing body of scientific evidence suggests that the MeDi may promote healthy brain ageing, there are still some controversies among epidemiological studies. The replication of analyses presented here is therefore needed to encompass some limitations and to allow their generalisation (98). Specifically, large-scale studies in various populations with common methodology are required before considering the MeDi as an optimal dietary strategy to prevent cognitive decline or dementia.

Dietary habits reflect individual food preferences which are closely related not only to culture, education and socio-economic background but also to health status. The whole being more than the sum of its part, the promotion of the healthy Mediterranean-type dietary pattern, rather than individual food or nutrients, should be extended, in particular because MeDi would be the best known model to fulfil nutrient requirements (99,100). This seems to be of particular importance since traditional food choices are changing with the progressive globalisation of food supply in young generations (49).

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