

# Dietary patterns in middle age: effects on concurrent neurocognition and risk of age-related cognitive decline

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**Context:** Diet plays a critical role in cognitive integrity and decline in older adults. However, little is known about the relationship between diet and cognitive integrity in middle age. **Objective:** To investigate the relationship between dietary patterns in healthy middle-aged adults and neurocognition both in middle age and later in life. **Data Sources:** Using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, the following electronic databases were searched: Web of Science, Scopus, PubMed, and PsychInfo. **Data Extraction:** Data from eligible articles was extracted by 2 reviewers. **Data Analysis:** Articles included in the systematic review were synthesized (based on the synthesis without meta-analysis reporting guidelines) and assessed for quality (using the Joanna Briggs Institute checklist for randomized controlled trials, cohort studies, and cross-sectional studies) by 2 reviewers. **Results:** Of 1558 studies identified, 34 met the eligibility criteria for inclusion. These comprised 9 cross-sectional studies, 23 longitudinal or prospective cohort studies, and 2 randomized controlled trials. Findings were mixed, with some studies reporting a significant positive relationship between adherence to various “healthy” dietary patterns and neurocognition, but others reporting no such relationship. **Conclusion:** This systematic review demonstrated that adherence to the Mediterranean diet and other healthy dietary patterns in middle age can protect neurocognition later in life.

**Systematic Review Registration:** PROSPERO registration no. CRD42020153179.

## INTRODUCTION

There is growing evidence suggesting that a healthy diet can play a vital role in the maintenance of cognitive

health and in delaying cognitive decline.<sup>1–3</sup> Healthy dietary patterns such as the Mediterranean diet (MedDiet), DASH (Dietary Approaches to Stop Hypertension) diet, and MIND (Mediterranean–DASH Intervention for

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**Key words:** Alzheimer’s disease, cognition, cognitive impairment, cognitive performance, DASH diet, dementia, dietary pattern, healthy diet, Mediterranean diet, mild cognitive impairment, MIND diet

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Neurodegenerative Delay) diet have been found to be protective of cognitive function as people age.<sup>4-8</sup> These dietary patterns are characterized by a high intake of fruits, vegetables, fish, beans, and legumes, with lower amounts of processed foods, red meat, sweets, and discretionary foods. While the dietary patterns share many components, there is some variation, eg, only the MIND and MedDiet specify olive oil as the main source of fat, and the MIND diet only includes berries in the fruit component.<sup>9</sup> Many of the individual food components (such as fruits, vegetables, and nuts,<sup>10</sup> and fatty fish<sup>11,12</sup>) and their nutrient components (such as polyphenols<sup>13</sup> and n-3 polyunsaturated fatty acids<sup>14</sup>) are thought to be protective of neurocognitive function in older age.

These healthy dietary patterns are no longer typical for Western populations in countries such as Australia, the United Kingdom, and the United States. On average, Australians are consuming less than the recommended intake of fruits, vegetables, and legumes, while eating more than the suggested servings of discretionary foods.<sup>15,16</sup> This is consistent with the Western-style diet, which is characterized by a high intake of processed foods, refined sugars, and low intakes of fruits and vegetables.<sup>16,17</sup> Various studies have demonstrated that the typical Western dietary pattern is related to poorer cognitive outcomes.<sup>18-20</sup>

It is commonly acknowledged that cognitive performance naturally declines with age, especially in the domains of memory and processing speed.<sup>21,22</sup> Performance on measures of reaction time, episodic memory, and spatial working memory has already started to decline in midlife.<sup>21</sup> While cognitive decline is a normal component of the aging trajectory, there are great inter-individual differences, which may be due to differences in lifestyle factors such as diet. Experiencing exaggerated cognitive decline is a key risk factor for the development of clinical disorders such as mild cognitive impairment (MCI) and dementia (of which Alzheimer's disease is the most common form<sup>23</sup>). Unfortunately, pharmacological interventions for these disorders have been unsuccessful.<sup>24</sup> Prevention strategies, involving modifiable lifestyle factors such as diet, may be more beneficial compared with later life interventional strategies. They potentially target the risk factors for these disorders before significant pathology has developed in the brain. While research investigating the relationship between diet and cognition is promising in terms of the use of diet as a prevention strategy for cognitive decline, most of the research to date has been conducted in aging populations, and there is a paucity of evidence from randomized controlled trials (RCTs). The current literature suggests that prevention, or at the very least risk reduction, may lead to a delayed onset of cognitive decline, and that this is a more realistic and cost-

effective target.<sup>25</sup> In order to develop appropriate dietary preventative strategies or interventions to protect against cognitive decline, it is necessary to determine whether this relationship is present in middle age, prior to the onset of significant pathology. The first aim of the current review was to summarize the literature of studies investigating the relationship between dietary patterns in middle-aged adults and neurocognition, both in middle and older age. The second aim was to highlight the gaps in the literature on the relationship between diet in midlife and neurocognitive function.

## METHOD

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist that was devised for systematic reviews with observational studies. The review was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42020153179).

### Searches

The following databases were searched for journal articles published until December 2020 investigating the relationships that various dietary patterns have with cognition: Web of Science, Scopus, PubMed, and PsychInfo. Searches combined the following terms “dietary patterns” or “dietary pattern” or “nutrient pattern” or “nutrient patterns” AND “cognit\*” or “memory” or “executive function” or “reaction time” or “neuro\*” AND “elderly” or “older” or “middle age” or “middle aged” or “midlife” or “adult” or “aged” or “geriatric”. Further details on the search strategies is provided in [Supplemental Table 1](#). The bibliography of eligible studies found through these searches was also scanned to identify additional eligible studies.

### Eligibility criteria

Following the PRISMA guidelines, a-priori inclusion and exclusion criteria were used in accordance with the population, intervention, comparison, and study (PICOS) design criteria shown in [Table 1](#). All articles investigating dietary pattern or diet quality, regardless of whether it was the primary outcome or not, were included. Other inclusion criteria were: cognitively healthy human participants (free from a reported diagnosis of a cognitive disorder); articles published in English; articles reporting on at least one outcome or measure of cognition; and mean age at baseline between 40 and 65 years. If the mean age was not reported, the

**Table 1 PICOS criteria for inclusion of studies**

Parameter	Criterion
Participants	Middle-aged adults (40–65 years)
Intervention	Whole dietary pattern or diet quality
Comparison	Any
Outcome	Neurocognitive function, including measures of cognition, brain morphology, and subjective cognitive function
Study design	Longitudinal or prospective cohort studies, randomized controlled trials, or cross-sectional studies

age range of participants at baseline fell between 40–65 years. Due to the limited number of papers in this age range, all study types were included (notably, longitudinal or prospective cohort studies, RCTS, and cross-sectional studies). Papers were also included if the outcome was a measure of brain morphology and subjective cognitive function as an indicator of cognitive health. Papers were excluded if they focused on single foods, single nutrients or a partial diet (eg, low fat, low carbohydrate, low calorie). Papers investigating nutrient patterns were included in the review.

### Study selection and data extraction

One investigator (S.G.) conducted the search and removed duplicates. The titles and abstracts were then screened based on inclusion and exclusion criteria using Rayyan<sup>26</sup> by at least 2 reviewers (S.G. and either L.M.Y., A.S., or L.A.). Articles then underwent full-text review by at least 2 reviewers (S.G. and either L.M.Y. or L.A.). Data from eligible articles were extracted by 2 reviewers (S.G. and either L.A. or L.M.Y.). Data extracted included: study type, country of origin, participant characteristics, sample size, dietary assessment tool used, type of dietary pattern under investigation, and neurocognitive outcomes. The study cohort was also extracted, to prevent repeated publication using the same study participants. Publications utilizing the same cohort were only included in the review if they investigated a different dietary pattern. The mean age of participants at baseline was recorded. If multiple mean ages were recorded, the grand mean of these was calculated or the age range was recorded. The articles and data included in this review were agreed upon by all reviewers. Any discrepancies were discussed and resolved. If more information about an article was needed, the authors were contacted by S.G. This process is outlined in Figure 1.

The data extracted from eligible studies were synthesized based on the Synthesis Without Meta-analysis reporting guideline.<sup>27</sup> Included studies were grouped by study type (in Tables 2–4) and dietary pattern (written results). This was done in order to demonstrate heterogeneity between studies as well as to identify the dietary

patterns with the most evidence for a relationship with various measures of cognition. For each dietary pattern, the intervention effects were reported (this included effect sizes, *Beta Coefficient* [ $\beta$ ], mean difference [MD], odds ratios [ORs], and hazard ratios [HRs]). Vote counting based on the direction of the effect was used to indicate the total evidence, as a meta-analysis was not possible (reported in Table 8). Quality appraisal was used to evaluate the methods of the included studies, and heterogeneity in study outcomes and dietary information were synthesized using informal methods (reported in the data extraction tables).

Evidence for the following dietary patterns were reported in the results: Mediterranean diet (MedDiet; a traditional dietary pattern typically consumed in countries surrounding the Mediterranean Sea; high in olive oil, fish, fruit, vegetables, legumes, and nuts and low in red meat<sup>8</sup>), DASH (which was developed to help protect against the development of hypertension; high in fruits, vegetables, low-fat dairy products, whole grains, poultry, fish, and nuts<sup>28</sup>), Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND; developed by combining the neuroprotective aspects of both the MedDiet and the DASH diet with the addition of leafy green vegetables and berries<sup>4</sup>). Measures of diet quality were also included: the Alternative Healthy Eating Index (aHEI) and Healthy Eating Index (HEI 2005 and 2010) are diet quality scores based on the Dietary Guidelines for Americans<sup>29,30</sup>; a diet screening tool (DST);<sup>31</sup> and the Dietary Guideline Index (DGI-2013).<sup>32</sup> Plant-based dietary patterns were also reported, including the plant-based diet index (PDI), healthful plant-based diet index (hPDI; both the PDI and hPDI were developed based on the consumption of healthy plant-based foods while also taking into account less healthy plant foods<sup>33</sup>), pro-vegetarian diet (PVD),<sup>34</sup> and a carotenoids dietary pattern, which was derived through posteriori methods (carotenoids are natural pigments found in plant-based foods<sup>35</sup>). Other healthy dietary patterns that were scored using posteriori methods were also included: the wholefood dietary pattern,<sup>36</sup> healthy and traditional dietary patterns,<sup>37</sup> a prudent-style diet,<sup>38,39</sup> an alcohol and salads pattern,<sup>40</sup> traditional Chinese,<sup>41</sup> a wheat-based diverse dietary pattern,

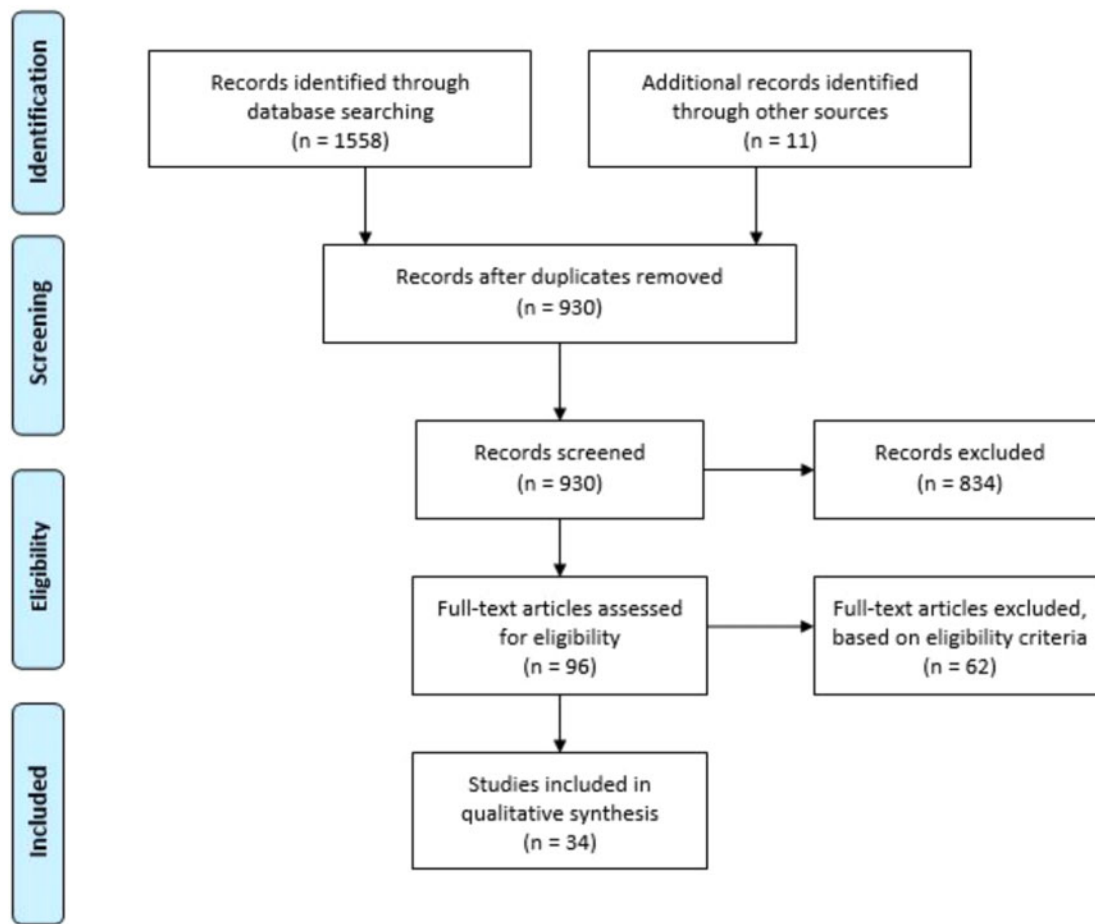


Figure 1 PRISMA diagram depicting the selection process for articles included in this systematic review .

a rice/pork dietary pattern,<sup>42</sup> and the healthy food diet.<sup>36</sup> Finally, unhealthy dietary patterns were also reported, including the dietary inflammatory index,<sup>43</sup> Western and other unhealthy dietary patterns extracted through statistical methods (Western-style diet,<sup>38,39</sup> the convenience pattern, the Southern pattern, the sweets and fats pattern,<sup>40</sup> the protein-rich and starch-rich dietary pattern,<sup>41</sup> the processed food pattern,<sup>36</sup> and the iron-related dietary pattern<sup>44</sup>).

### Quality appraisal

All included articles were assessed for quality using the Joanna Briggs Institute checklist for RCTs, cohort studies, and cross-sectional studies by both S.G. and L.M.Y.<sup>45–47</sup> These tools were used to appraise the methodologies used and to identify and inform the interpretation and synthesis of the results and methodological issues for that need to be addressed in future research. Cross-sectional studies were appraised based on whether there were defined inclusion/exclusion criteria, participant descriptions, the exposure and outcomes were measured in a valid and reliable way, and the

appropriate statistical technique was used. The cohort studies were also appraised based on whether the exposure and outcome were measured in a valid and reliable way, confounding factors were accounted for, the outcome was assessed at baseline, there were sufficient follow-up times (and strategies to address incomplete follow-up time data), and appropriate states were completed. The RCTs were appraised based on randomization and blinding procedures, whether follow-up was complete and outcome assessment was reliable.

## RESULTS

### Included studies

The initial database searches yielded 1558 records, and an additional 11 articles were identified through other sources, see Fig. 1. After duplicates were removed, the titles and abstracts of 930 articles were screened and assessed for eligibility. There were 96 articles reviewed in full text, resulting in 34 studies being included in the qualitative synthesis. In summary, there were 9 cross-sectional studies included (Table 2),<sup>28–31,36,48–56</sup> 23 longitudinal or

Table 2 Cross-sectional studies listed by year of publication.

Study	Country	N	Age (y)	Diet measure and pattern	Covariates	Cognitive outcome	Key findings
Akbaraly et al (2009) <sup>36</sup>	United Kingdom	4693: 1229 females and 3464 males	GM = 61.03	FFQ: a wholefood pattern and processed food pattern were extracted using PCA (posteriori)	Age, gender, energy intake, marital status, smoking habits, physical activity, health status (diabetes, hypertension, CHD, dyslipidemia, BMI, and mental health) and education	A cognitive test battery: short-term verbal memory, verbal and mathematical reasoning, inductive reasoning, word recognition and comprehension, and verbal fluency	Greater adherence to the wholefood diet was associated with decreased odds of cognitive deficit. The processed food pattern was associated with increased odds of cognitive deficit for reasoning. When controlling for education, these relationships were no longer significant.
Crichton et al (2013) <sup>52</sup>	Australia	1183: 751 females and 432 males	M = 50.6 ± 5.8	FFQ: MedDiet score (Trichopoulos method <sup>51</sup> ; a priori)	Age, gender, education, BMI, exercise, smoking, and energy intake	Self-appraised cognitive function (Cognitive Failures Questionnaire)	There were no significant associations between MedDiet and self-appraised cognitive function.
Ye et al (2013) <sup>53</sup>	USA	1269	M = 57.3 ± 7.6	FFQ, MedDiet score (Trichopoulos method <sup>51</sup> ) and HEI-2005 <sup>29</sup> (a priori)	Age, sex, educational attainment, household income, acculturation score, smoking status, physical activity score, supplement use, taking more than 5 types of medications within the last 12 months, BMI, hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol, and triglycerides	Neuropsychological tests: executive function, memory, attention, and global cognitive function. MMSE	Higher adherence to the MedDiet and HEI-2005 were both related to better global cognitive function.
Berti et al (2015) <sup>54</sup>	USA	52: 37 females and 15 males	M = 54 ± 12	FFQ: nutrient patterns were extracted using PCA: NP1 (B vitamins), NP2 (mono-unsaturated and polyunsaturated fats), NP3 (Vit A	Age, energy intake, gender, education, ethnicity, BMI, alcohol consumption, APOE, and family history	Neuroimaging: glucose metabolism (FDG-PET), structural MRI and amyloid beta markers (PIB-PET)	NP4 was positively associated with glucose metabolism and gray matter volume in areas of the brain associated with AD. NP4 was

(continued)

Table 2 Continued

Study	Country	N	Age (y)	Diet measure and pattern	Covariates	Cognitive outcome	Key findings
Wright et al (2017) <sup>55</sup>	USA	2090: 1195 females and 895 males	M = 47.85 ± 9.22	carotenoids, Vit C and fiber), NP4 (B12, Vit D and zinc) and NP5 (saturated, trans-saturated fats, cholesterol, and sodium; posteriori)	Age, race, sex, education, poverty status, CES-D score, current alcohol use, current cigarette smoker, BMI, mean systolic blood pressure, and diabetes status	Neuropsychological tests: verbal learning and memory, nonverbal memory, working memory, attention, cognitive flexibility, visuospatial ability, perceptual speed, and semantic fluency	also negatively associated with amyloid beta markers in these regions. NP2 was positively associated with glucose metabolism and gray matter volume. NP3 was positively associated with glucose metabolism. Higher diet quality was associated with better verbal learning and memory. There was no significant association between HEI-2010 adherence and the other cognitive outcomes measured.
Brouwer-Brolsma et al (2018) <sup>56</sup>	Netherlands	1607: 771 females and 836 males	M = 52.9	FFQ; MedDiet Score (Trichopoulos method <sup>51</sup> ; a priori)	Age, gender, education, BMI, energy intake, physical activity, smoking status, social activities, number of dietary and supplements used	Neuropsychological tests: semantic memory, language production, information processing speed, and everyday memory	The MedDiet was not significantly related to semantic memory or processing speed. However, there was a significant inverse relationship between everyday memory performance and MedDiet.
Hossain et al (2019) <sup>48</sup>	USA	304: 163 females and 141 males	M = 56.90 ± 0.24	24-h diet recalls, HEI-2010, <sup>30</sup> and DASH <sup>28</sup> (a priori)	Age, sex, race, poverty status, education status, BMI, total energy intake, current smoking status, current drug use, depression,	Cognitive test battery and MMSE	None of the dietary patterns were significantly related to cognitive performance after

(continued)

Table 2 Continued

Study	Country	N	Age (y)	Diet measure and pattern	Covariates	Cognitive outcome	Key findings
Estrella et al (2020) <sup>49</sup>	USA	8461: 4738 females and 3723 males	M = 56 ± 0.1	24-h diet recalls, aHEI-2010 <sup>30</sup> (a priori)	diabetes, hypertension, dyslipidemia, cardiovascular disease, inflammatory conditions, and use of non-steroidal anti-inflammatory drugs Age, sex, Hispanic/Latino background, education, annual household income, language preference, energy intake, type 2 diabetes, smoking status, depressive symptoms	Neuropsychological tests: verbal learning, verbal memory, verbal fluency, processing speed	Higher aHEI adherence was associated with higher global cognition, verbal learning, and verbal memory.
Young et al (2020) <sup>50</sup>	Australia	141: 71 females and 70 males	M = 52.84 ± 6.87	Diet quality, diet screening tool <sup>51</sup> (a priori)	Age, gender, BMI, years of education	Cognitive assessment battery (SUCCAB): Stroop processing, reaction and decision speed, visual processing, and spatial working memory	Participants classified with an optimal diet had significantly better Stroop processing than those with a sub-optimal diet. However, this was not significant when diet quality was run as a continuous variable.

Abbreviations: AD = Alzheimer's Disease; aHEI = Alternative Healthy Eating Index; APOE = Apolipoprotein E; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale; CHD = Coronary heart disease; DASH = dietary approaches to stop hypertension; FA = factor analysis; FFO = food frequency questionnaire; GM = grand mean; HEI = healthy eating index; M = mean; Mdn = median, ± standard deviation of age when reported; MMSE = Mini-Mental State Examination; PCA = principal component analysis; SUCCAB = Swinburne University Computerized Cognitive Assessment Battery.

**Table 3 Longitudinal and prospective cohort studies listed by year of publication**

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Covariates	Neurocognitive outcome	Key findings
Kesse-Guyot et al (2012) <sup>37</sup>	France, SU.VI.MAX	Longitudinal cohort; 13 y	3054: 1642 males and 1412 females	M = 52.1 ± 4.6	24-h diet recalls: a healthy and a traditional diet were extracted using factor analysis (posteriori)	Self-reported memory troubles	Age, gender, follow-up time, intervention group, education, energy intake, number of 24-h records, physical activity, BMI, alcohol intake, tobacco use status, baseline self-reported memory troubles, baseline diabetes mellitus, baseline hypertension, cardiovascular events during follow-up, depression, and (for women) baseline menopausal status	Neuropsychological evaluation assessing global cognitive function: episodic memory, lexical-semantic memory, working memory, and mental flexibility	The healthy dietary pattern was related to better global cognitive performance and verbal memory. However, the positive effect of the healthy pattern on cognition only occurred in participants with low energy intake.
Kesse-Guyot et al (2013) <sup>57</sup>	France, SU.VI.MAX	Longitudinal cohort; 13 y	3083: 1655 males and 1428 females	M = 52 ± 4.6	24-h diet recalls: MedDiet score (Trichopoulos method <sup>51</sup> ; a priori)	None reported	Age, gender, follow-up time, intervention group, education, number of 24-h records, cognitive evaluation, energy intake, BMI, occupational status, tobacco use status, physical activity, memory difficulties at baseline, depressive symptoms, and history of diabetes, hypertension, or cardiovascular disease	Neuropsychological evaluation carried measuring: episodic memory, lexical-semantic memory, short-term and working memory, and mental flexibility	There was only a significant link between a lower MedDiet and poorer short-term memory performance and a link between a lower MSDPS and poorer lexical-semantic memory performance.
			10 670 females	30–55		TICS			

(continued)



**Table 3 Continued**

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Covariates	Neurocognitive outcome	Key findings
Samieri et al (2013) <sup>58</sup>	USA, The Nurses' Health Study	Longitudinal cohort; 15.2 y			FFQ: AHEI <sup>29</sup> and aMED <sup>71</sup> (a priori)		Age, education, marriage status, median income, median house value, family histories of diabetes, cancer, and myocardial infarction, physical activity, energy intake, smoking, multivitamins use, aspirin use, and BMI	Cognitive aging assessed using TICS	Greater adherence to the MedDiet was significantly associated with greater odds of healthy cognitive aging (TICS). The aHEI was not found to be significantly related to healthy cognitive aging.
Kesse-Guyot et al (2014) <sup>35</sup>	France, SU.VI.MAX	Longitudinal cohort; 13 y	381	M = 52.5 <sup>b</sup>	24-h diet recalls: calcium extracted using reduced rank regression (posteriori)	None reported	Age, sex, education, follow-up time between baseline and cognitive evaluation, supplementation group, number of 24-h dietary records, energy intake, BMI, occupational status, tobacco use status, physical activity, reported memory problems at baseline, depressive symptoms, and history of diabetes hypertension, or CVD	Neuropsychological evaluation carried out measuring: episodic memory, lexical-semantic memory, short-term and working memory, and mental flexibility. A composite cognitive score was also calculated.	Participants with a higher carotenoid-rich dietary pattern score had higher composite cognitive scores as well as individual scores on measures of episodic memory, short-term/working memory, mental flexibility, and lexical-semantic memory.

(continued)

Table 3 Continued

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Covariates	Neurocognitive outcome	Key findings
Jacka et al (2015) <sup>38</sup>	Australia, PATH	Longitudinal cohort; 4 y	255: 118 females and 137 males	$M = 62.6 \pm 1.42$	FFQ: prudent and Western dietary patterns were extracted using the principle components analysis (posteriori)	MMSE	Age, gender, education, employment status, depressive symptoms and medication, physical activity, smoking, hypertension, and diabetes	Neuroimaging: hippocampal and amygdala volumes	People adhering to the healthy prudent dietary pattern were found to have a significantly larger left hippocampal volume, while those with a higher consumption of an unhealthy Western dietary pattern had a smaller left hippocampal volume.
Qin et al (2015) <sup>42</sup>	China, CHNS	Prospective cohort; 5.3 y	1650: 829 females and 821 males	$GM = 63.5$	24-h diet recalls: Modified MedDiet (based on Trichopoulos method <sup>51</sup> ; a priori). A wheat-based diverse diet and the rice/pork pattern were extracted using principle components analysis (posteriori)	Modified TICS	Age, gender, region, urbanization index, education, annual household income per capita, current smoking, BMI, hypertension, and history of chronic diseases (including myocardial infarction, stroke, or diabetes), physical activity	Modified- TICS: Global cognition and verbal memory was assessed	No significant associations were found between any dietary pattern and cognitive performance for adults below age 65 y.
Pearson et al (2016) <sup>40</sup>	USA, Regards	Longitudinal cohort; 6.8 y	18 080	$GM = 63.91$	FFQ: A convenience, SIS plant-based, sweets/fats, Southern, alcohol/salads patterns were extracted using principle components analysis (posteriori)	SIS	Age, race, sex, region, total energy intake, income, education, physical activity, smoking status, BMI, hypertensive status, diabetes status, history of	Cognitive test battery: verbal learning and memory domains	Greater adherence of the alcohol/salads pattern was associated with higher cognitive performance and lower odds of developing cognitive

(continued)

**Table 3 Continued**

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Covariates	Neurocognitive outcome	Key findings
Kesse-Guyot et al (2017) <sup>43</sup>	France, SU.VI.MAX	Longitudinal cohort; 13 y	3080	M = 52 ± 4.6	24-h diet recalls: DII (a priori)	None reported	CVD, and depression	Neuropsychological evaluation: episodic memory, lexical-semantic memory, short-term and working memory. A higher DII score was also associated with poorer executive function and mental flexibility. A composite cognitive score was extracted.	impairment. Greater adherence to the plant-based pattern was also associated with better cognitive performance. However, greater consumption of a Southern dietary pattern was associated with lower cognitive performance. A higher DII score (pro-inflammatory diet) was associated with lower global cognitive function. A higher DII score was also associated with poorer executive function and lexical-semantic memory on some tasks.
Bhushan et al (2017) <sup>59</sup>	USA, HPS	Prospective cohort; 22 y	27 842 males	GM = 51.1	FFQ: MedDiet Score (Trichopoulos method <sup>51</sup> ; a priori)	None reported	Age, smoking history, diabetes, hypertension, depression, hypercholesterolemia, physical activity, and BMI	Higher adherence to the MedDiet was significantly associated with a lower likelihood of both moderate and poor SCF. Men in the highest quintile	(continued)

Table 3 Continued

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Covariates	Neurocognitive outcome	Key findings
Akbaraly et al (2018) <sup>60</sup>	UK, Whitehall II imaging sub-study	Prospective cohort; 11 y	459: 88 females and 371 males	M = 59.6 ± 5.3	FFQ: AHEI-2010 <sup>71</sup> (a priori)	None reported	Age, sex, total energy intake, physical activity, smoking status, cardio-metabolic disorders, cognitive impairment, and depressive symptoms	Neuroimaging hippocampal volume	Higher aHEI-2010 scores were found to be significantly related to larger hippocampal volumes. It was also observed that participants who improved their diet or maintained a high aHEI-2010 score had larger hippocampal volumes compared with those who had a low aHEI-2010 score over the 11 y follow-up.
Berti et al (2018) <sup>61</sup>	USA, multiple cohort studies	Longitudinal cohort; 2 y	70: 47 females and 23 males	M = 50 ± 8	FFQ: MedDiet score (Trichopoulos method <sup>51</sup> , a priori)	Neuropsychological evaluation: MMSE, Digit symbol, paired associates, paragraph, designs, object	Age, sex, education, APOE status, BMI, insulin resistance, and hypertension	Neuroimaging: glucose metabolism (FDG-PET), structural MRI, and amyloid beta markers (PiB-	No difference in neuropsychological measures at baseline across high and low diet

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Table 3 Continued

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Covariates	Neurocognitive outcome	Key findings
Xu et al (2018) <sup>41</sup>	China, CHNS	Longitudinal cohort; 10 y	4847	<i>Mdn</i> = 64	24-h recall: traditional Chinese, protein-rich, and starch-rich patterns were extracted using factor analysis (posterofori)	Part of the TCIS naming, WAIS-vocabulary	Age, gender, urbanization index, marital status, work status, education levels, BMI, alcohol drinking, smoking status, survey year, hypertension, and diabetes	Modified TICS: global cognition and verbal memory were assessed.	There was a significant positive association between protein rich dietary pattern and cognitive function. A significant positive association was found between traditional Chinese dietary pattern and cognitive global scores only. Significant negative associations were found between a starch-rich dietary pattern and cognitive function.
Adjibade et al (2019) <sup>62</sup>	France, The NutriNet-Santé study	Prospective cohort; 6 y	6011: 3627 females and 2384 males	<i>M</i> = 64.4 ± 4.3	24-h recall: MIND diet <sup>4</sup> (a priori)	None reported	Age, sex, marital status, educational level,	Subjective memory complaints	No significant relationship was found between

(continued)

Table 3 Continued

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Covariates	Neurocognitive outcome	Key findings
Akbaraly et al (2019) <sup>63</sup>	UK, Whitehall II study	Prospective cohort; 24.8 y	6961	M = 50.2 ± 6.1	FFQ; aHEI <sup>29</sup> (a priori) and healthy food diet and the Western-type diet extracted using PCA (posteriori)	Cognitive assessment was introduced at second follow-up	Age, sex, marital status, occupational position, education level, race/ethnicity, smoking status, alcohol consumption, physical activity, hypertension, dyslipidemia, type 2 diabetes, BMI, coronary heart disease or stroke, medications for cardiovascular disease, depressive symptoms, and APOE genotype	Cognitive test battery: executive function, memory, and fluency (global cognitive score)	The aHEI or Western-type patterns were not significantly associated with cognitive decline. However, a higher score for the healthy food dietary pattern was significantly associated with greater cognitive decline.
Dearborn-Tomazos et al (2019) <sup>39</sup>	USA, ARIC	Longitudinal cohort; 20 y	13 588: 7588 females and 6000 males	M = 54.6 ± 5.7	FFQ; principal components: Western and prudent dietary patterns (posteriori)	Cognitive test battery	Age, age squared, sex, education, race, total energy, apolipoprotein E ε4 status, alcohol use history, smoking history, activity	Cognitive test battery: the Delayed Word Recall, the Digit Symbol Substitution test, and the Word Fluency test. Global cognition	Adherence to the Western-style diet at baseline was found to be associated with lower cognitive scores; adherence to

(continued)

Table 3 Continued

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Covariates	Neurocognitive outcome	Key findings
Hosking et al (2019) <sup>64</sup>	Australia, PATH	Longitudinal cohort; 12 y	1220	GM = 62.5	FFQ: MIND diet and MedDiet (Trichopoulos <sup>51</sup> and Panagiotakos <sup>72</sup> methods; a priori)	Neuropsychological testing and MMSE	Energy intake, age, sex, APOE status, education, mental activity, physical activity, smoking status, depression, heart disease, stroke, diabetes, BMI, and hypertension	and cognitive change	Greater MIND diet adherence was associated with reduced odds of cognitive impairment. There was no significant association between MedDiet, cognitive impairment, and the development of MCI/dementia.
Mattei et al (2019) <sup>65</sup>	USA, Boston Puerto Rican Health Study	Longitudinal cohort; 2 y	711 without diabetes; 523 females and 188 males	M = 56 ± 7.7	FFQ: MedDiet (Trichopoulos <sup>51</sup> ), HEI-2005 <sup>29</sup> , aHEI-2010, <sup>71</sup> and DASH <sup>28</sup> (a priori)	MMSE	Sex, age, marital status, income-to-poverty ratio, educational attainment, food security status, smoking status, psychological acculturation, physical activity score, depressive symptomatology score, hypertension	Neuropsychological battery: MMSE, verbal memory, processing speed, attention, working memory, verbal fluency, visuospatial function, and a global cognitive performance score	All diet scores were significantly associated with cognitive outcomes among participants without type 2 diabetes

(continued)

Table 3 Continued

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Covariates	Neurocognitive outcome	Key findings
Milte et al (2019) <sup>66</sup>	Australia, WELL	Prospective, longitudinal cohort study; 4 y	617	M = 60.2 ± 3.14	FFQ; DGI-2013 <sup>32</sup> (a priori)	None reported	status, homocysteine, CRP, BMI, baseline value, and time Age, sex, education, urban/rural, total physical activity	Modified TICS	There was no significant association between greater adherence to the Australian Dietary Guidelines and cognitive function. However, higher dietary variety was also associated with better cognitive function.
Munoz-García et al (2019) <sup>67</sup>	Spain, SUN	Prospective cohort; 6 y	806: 244 females and 562 males	M = 61 ± 6	FFQ; MedDiet (Trichopoulos <sup>51</sup> ), MEDAS <sup>73</sup> , DASH <sup>28</sup> , MIND, aHEI-2010, <sup>71</sup> and PVD <sup>34</sup> (a priori)	STICS-m	Age, sex, follow-up time, years of university education, APOE 4 smoking, total energy intake, physical activity, BMI, alcohol intake, and prevalent disease at time of recruitment	STICS-m	It was found that higher adherence to the MIND diet and aHEI-2019 was related to improved cognitive performance 6 y later. This was not found to be significant for adherence to the MedDiet, DASH, or PVD dietary patterns.
Shannon et al (2019) <sup>68</sup>	UK, EPIC	Prospective cohort; 13–18 y	8009: 4467 females and 3524 males	M = 55, 49.4–61.7	FFQ; MedDiet scores: MEDAS <sup>73</sup> ; the MEDAS continuous score; MedDiet pyramid score <sup>74</sup> (a priori)	None reported	Age, sex, BMI, waist circumference, marital status, employment status, self-reported medical conditions, self-reported	Global cognitive function: total score from a Short-Form Extended Mental State Exam, verbal episodic memory,	Higher MedDiet adherence (all 3 MedDiet scores) was associated with significantly better global cognitive performance.

(continued)



Table 3 Continued

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Covariates	Neurocognitive outcome	Key findings
Shi et al (2019) <sup>44</sup>	China, CHNS	Prospective cohort; 15 y	4685: 2437 females and 2248 males	GM = 63.45	3-day food record: reduced rank regression: iron-related dietary pattern (posteriori)	None reported	Age, gender, energy intake, intake of fat, smoking, alcohol drinking, income, urban city, education, physical activity, BMI, and hypertension	nonverbal episodic memory, attention, simple processing speed, complex processing speed, and visual deficits contributing to cognitive impairment, memory	Higher MedDiet (pyramid score) was associated with lower risk of poor performance in verbal episodic memory, processing speed and prospective memory. Moderate adherence was also associated with lower risk of poor performance on the processing speed task.
Wu et al (2019) <sup>69</sup>	Singapore, The Singapore Chinese Health Study	Prospective cohort; 19.7 y	16 948: 10 033 females and 6915 males	M = 53.5 ± 6.2	FFO: DASH <sup>28</sup> , aHEI <sup>73</sup> , PDI, hPDI <sup>33</sup> and aMED <sup>71</sup> (a priori)	None reported	Age, year of baseline interview, sex, dialect group, marital status, education level, smoking status, physical activity, sleep duration, BMI, total energy intake, alcohol consumption, coffee and tea intake, and history of hypertension, diabetes, cardiovascular	A Singapore-modified version of the MMSE	Compared with those in the lowest quartile, participants in the highest quartile of the dietary pattern scores had a significant reduction in the risk of cognitive impairment.

(continued)

Table 3 Continued

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Covariates	Neurocognitive outcome	Key findings
Zhang et al (2021) <sup>70</sup>	UK, Women's Cohort Study	Longitudinal cohort; 10–15 y	503 females	M = 62 ± 6.6	FFQ; MedDiet (Trichopoulos) <sup>51</sup>	None reported	Age, ethnicity, marital status, socioeconomic status, physical activity, BMI, sleep duration, smoking status, alcohol consumption, and total energy intake	Cognitive test battery: simple reaction time and choice reaction time	No significant relationship was found between MedDiet score and reaction time.

<sup>a</sup> Age is mean age at baseline; b mean age at baseline was calculated by subtracting average follow-up (years) from mean age at follow-up. Abbreviations: aHEI = Alternative Healthy Eating Index; aMED = alternative Mediterranean diet score; APOE = Apolipoprotein E; ARIC = Atherosclerosis Risk in Communities; BMI = body mass index; CHNS = China and Health Nutrition Survey; CVD = Cardiovascular disease; DASH = dietary approaches to stop hypertension; CRP = C-reactive protein; DGI = Dietary Guideline Index; DII = dietary inflammatory index; EPIC = European Investigation into Cancer and Nutrition; FFQ = food frequency questionnaire; GM = grand mean; hPDI = healthful plant-based diet index; HPFS = Health Professionals Follow-up Study; M = mean, Mdn = median, ± standard deviation of age when reported; MCI = Mild Cognitive Impairment; MEDAS = Mediterranean Diet Adherence Screener; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay; MMSE = Mini-Mental State Examination; MSDPS = Mediterranean-Style Dietary Pattern Score; PATH = Personality and Total Health (PATH) Through Life study; PCA = principal component analysis; PDI = plant-based diet index; PVD = pro-vegetarian diet; SCF = subjective cognitive function; SIS = Six-Item Screener; SUN = Seguimiento Universidad de Navarra; S.U.VI.MAX = Suplementation en Vitamines et Minéraux Antioxydants; TICS = Telephone Interview of Cognitive Status; WAIS = Wechsler Adult Intelligence Scale; WELL = Wellbeing, Eating and Exercise for a Long Life.

**Table 4. Randomized controlled trials listed by year of publication**

Study	Country and cohort	Study type and length	N	Age <sup>a</sup>	Diet assessment/intervention	Baseline neurocognitive assessment	Neurocognitive outcome	Key findings
Wade et al (2018) <sup>75</sup>	Australia, MedDairy	RCT, 24-wk parallel crossover design	41: 28 females and 13 males	$M = 60.2 \pm 6.9$	3-day weighed food records: MedDiet Score (adapted from Trichopoulos <sup>51</sup> , a priori) Med Diet intervention supplemented with adequate dairy for 8 wks; control diet was a low-fat diet for 8 wks.	Same as outcome	CANTAB: Attention, processing speed, memory, and planning	A significant improvement was found for processing speed following the MedDairy intervention.
Wade et al (2019) <sup>76</sup>	Australia, MedPork	RCT, 24-wk parallel crossover design	33: 23 females and 10 males	$M = 61.0 \pm 7.1$	3-day weighed food records: MedDiet Score (a priori). Med Diet intervention supplemented with 2–3 weekly servings of fresh, lean pork for 8 wks; control diet was a low-fat diet for 8 wks.	Same as outcome	CANTAB: Attention, processing speed, memory, and planning	The MedPork intervention was associated with a significant improvement in processing speed.

<sup>a</sup> Age is mean age at baseline. Abbreviations: CANTAB = Cambridge Neuropsychological Test Automated Battery;  $M$  = mean,  $\pm$  standard deviation of age; RCT = randomized controlled trial.

prospective cohort studies (Table 3),<sup>4,28,32–35,37–44,51,57–74</sup> and 2 RCTs (Table 4).<sup>75,76</sup> Some studies included in the review utilized the same study sample populations (SU.VI.MAX = 4, CHNS = 3, PATH = 2, Whitehall II = 2). The results of the data extraction are summarized in Tables 2 to 4, respectively.

## Quality appraisal

The results of the quality appraisal are displayed in Tables 5 to 7.<sup>35–44,48–50,52–70,75,76</sup> For the cross-sectional studies, most meet the criteria for quality appraisal. Four studies did not define their inclusion and exclusion criteria,<sup>36,49,52,56</sup> and only 1 study did not provide a detailed description of included participants.<sup>53</sup>

For the longitudinal and prospective cohort studies, 20 studies recruited only 1 cohort group,<sup>35,37–40,42–44,57–60,62–64,66–70</sup> therefore assessing whether the participant groups were similar and recruited from the same population was not applicable for those studies. Sixteen studies did not measure the exposure (dietary patterns) at follow-up as well as baseline.<sup>35,37–43,57,58,61,63,64,67–69</sup> The outcome was also not measured at both time points for 13 studies.<sup>29,31,33,37,39,44,46,47,50,51,54,56,60</sup> Twelve studies failed to report reasons that follow-up was not completed,<sup>35,37,39–44,57,66,68</sup> and another 15 studies did not use any strategies to account for incomplete follow-up.<sup>38,40–42,44,58–64,66,68,69</sup> For the RCTs, the quality appraisal demonstrated a couple of methodological issues. First, for both RCTs, the participants were not blind to the treatment, the researchers delivering the treatment were also not blinded, and finally it was not clear whether the outcome assessors were blind to the treatments.<sup>75,76</sup> Many of the methodological issues highlighted in the quality appraisal are present across a large number of cohort studies, but due to the limited number of studies included in the systematic review, these studies were still included in the data synthesis. The methodological issues should be addressed in future research and taken into consideration when interpreting the results.

## Scoring of dietary studies

There were 2 main differences in the techniques used for scoring dietary patterns. Twenty-three studies utilized a priori scoring methods,<sup>43,49,52,53,55–58,60–62,64,66–70,75,76</sup> which account for predefined nutritional factors that are scored into dietary quality indices (refer to Tables 2–5 for details on the methods). Eight utilized posteriori<sup>35–41,54</sup> scoring methods, which, rather than focusing on specific nutritional factors, instead used statistical methods to investigate correlations among reported food components to provide information regarding global dietary behavior (refer to Tables 5–7 for

details on statistical methods). Two studies utilized both a priori and posteriori techniques.<sup>42,63</sup> A summary of the studies that support or refute an association between diet and neurocognitive function is presented in Table 8.

*Mediterranean diet.* Three of the 9 cross-sectional studies investigated the MedDiet, with contrasting findings.<sup>52,53,56</sup> Brouwer-Brolsma et al (2018) found that, after adjusting for covariates, adherence to the MedDiet was not significantly related to semantic memory or processing speed ( $\beta = 0.022 \pm 0.053$ ,  $P = 0.68$ ;  $\beta = -0.003 \pm 0.097$ ,  $P = 0.98$ ). However, an inverse relationship between a measure of everyday memory and adherence to the MedDiet was detected ( $\beta = -0.107 \pm 0.046$ ,  $P = 0.02$ ), indicating that increased adherence to a MedDiet was associated with poorer memory.<sup>56</sup> After further analysis of the individual food groups, the authors found that this relationship may be driven by the relatively high monounsaturated-to-saturated fatty acids ratio, which was inversely related to cognition. Ye et al (2013) found that higher adherence to the MedDiet was related to better global cognitive function ( $\beta = 0.14$ ,  $SE = 0.05$ ,  $P = 0.012$ ) but was not related to executive function ( $\beta = 0.01$ ,  $SE = 0.02$ ,  $P = 0.52$ ), memory ( $\beta = 0.02$ ,  $SE = 0.02$ ,  $P = 0.39$ ), and attention ( $\beta = 0.03$ ,  $SE = 0.02$ ,  $P = 0.067$ ).<sup>53</sup> Crichton et al (2013) failed to find any relationship between MedDiet and self-reported cognitive function ( $P > 0.30$ ).<sup>52</sup>

An additional 11 longitudinal studies investigated the effect of a MedDiet on cognitive performance.<sup>42,57–59,61,64,65,67–70</sup> A number of these found that MedDiet during midlife was related to neurocognitive outcomes later in life.<sup>58,59,61,68,69</sup> Specifically, higher adherence to the MedDiet was found to be significantly related to better global cognition approximately 13 years later (Pyramid score:  $\beta \pm SE = -0.012 \pm 0.002$ ;  $P < 0.001$ , Mediterranean Diet Adherence Screener (MEDAS):  $\beta \pm SE = -0.004 \pm 0.002$ ;  $P = 0.019$ , MEDAS continuous:  $\beta \pm SE = -0.005 \pm 0.002$ ;  $P = 0.008$ )<sup>68</sup> and to greater odds of healthy cognitive aging in women 15 years later (OR 0.97, 95% CI [0.95, 1.00],  $P = 0.02$ ).<sup>58</sup> Another study found that those in the highest tertile of adherence to the MedDiet also had a 33% reduction in the risk of cognitive impairment as measured by the Mini-Mental State Examination (MMSE) almost 20 years later, compared with those in the lowest tertile (OR 0.67, 95% CI [0.59, 0.77],  $P$  trend  $< 0.001$ ).<sup>69</sup> For each standard deviation increase in adherence to the MedDiet, there was a 16% reduction in the risk of cognitive deficit (OR 0.84, 95% CI [0.80, 0.88]).<sup>69</sup> For specific cognitive domains, the

**Table 5 Quality appraisal cross-sectional studies listed by year of publication**

Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Akbaraly et al (2009) <sup>36</sup>	×	✓	✓	NA	✓	✓	✓	✓
Crichton et al (2013) <sup>52</sup>	×	✓	✓	NA	✓	✓	✓	✓
Ye et al (2013) <sup>53</sup>	✓	X	✓	NA	✓	✓	✓	✓
Berti et al (2015) <sup>54</sup>	✓	✓	✓	NA	✓	✓	✓	✓
Wright et al (2017) <sup>55</sup>	✓	✓	✓	NA	✓	✓	✓	✓
Brouwer-Brolsma et al (2018) <sup>56</sup>	×	✓	✓	NA	✓	✓	✓	✓
Hossain et al (2019) <sup>48</sup>	×	✓	✓	NA	✓	✓	✓	✓
Estrella et al (2020) <sup>49</sup>	✓	✓	✓	NA	✓	✓	✓	✓
Young et al (2020) <sup>50</sup>	✓	✓	✓	NA	✓	✓	✓	✓

Note: Q1 = Were inclusion criteria defined? Q2 = Were detailed descriptions of participants provided? Q3 = Was exposure (diet) measured in a valid and reliable way? Q4 = Were objective, standard criteria used for measurement of the condition? Q5 = Were confounding factors identified? Q6 = Were there strategies to deal with the confounding factors? Q7 = Were outcomes measured in a valid and reliable way? Q8 = Was appropriate statistical analysis used?

MedDiet was found to be related to better verbal episodic memory for one measure of the MedDiet (Pyramid score:  $\beta \pm SE = -0.009 \pm 0.002$ ;  $P < 0.001$ , MEDAS:  $\beta \pm SE = -0.003 \pm 0.002$ ;  $P = 0.139$ , MEDAS continuous:  $\beta \pm SE = -0.004 \pm 0.002$ ;  $P = 0.052$ ), simple processing speed (Pyramid score:  $\beta \pm SE = -0.002 \pm 0.001$ ;  $P = 0.013$ , MEDAS:  $\beta \pm SE = -0.001 \pm 0.001$ ;  $P = 0.423$ , MEDAS continuous:  $\beta \pm SE = -0.001 \pm 0.001$ ;  $P = 0.079$ ).<sup>68</sup> Greater adherence to the MedDiet was found to be significantly related to memory function 2 years later in individuals free from diabetes ( $\beta = 0.047$ ,  $SE = 0.020$ ,

$P = 0.016$ ); however, it was not significantly related to global cognitive function or executive function ( $P > 0.05$ ).<sup>65</sup>

In addition, the MedDiet was associated with reduced levels of neuroimaging markers associated with Alzheimer’s disease at baseline and after a follow-up of 2 years ( $P < 0.001$ ).<sup>61</sup> Greater adherence to the MedDiet in a large male cohort was found to be significantly related to better subjective cognitive function 22 years later.<sup>59</sup> Further, compared with individuals in the lowest adherence quartile, those in the highest adherence quartile had a 36% reduction in the odds of poor self-

**Table 6 Quality appraisal longitudinal and cohort studies listed by year of publication**

Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Kesse-Guyot et al (2012) <sup>37</sup>	NA	NA	×	✓	✓	Unsure	✓	✓	×	✓	✓
Kesse-Guyot et al (2013) <sup>57</sup>	NA	NA	×	✓	✓	Unsure	✓	✓	×	✓	✓
Samieri et al (2013) <sup>58</sup>	NA	NA	×	✓	✓	Unsure	✓	✓	✓	×	✓
Kesse-Guyot et al (2014) <sup>35</sup>	NA	NA	×	✓	✓	Unsure	✓	✓	×	✓	✓
Jacka et al (2015) <sup>38</sup>	NA	NA	×	✓	✓	✓	✓	✓	✓	×	✓
Qin et al (2015) <sup>42</sup>	NA	NA	×	✓	✓	✓	✓	✓	×	×	✓
Pearson et al (2016) <sup>40</sup>	NA	NA	×	✓	✓	✓	✓	✓	×	×	✓
Kesse-Guyot et al (2017) <sup>43</sup>	NA	NA	×	✓	✓	Unsure	✓	✓	×	✓	✓
Bhushan et al (2017) <sup>59</sup>	NA	NA	✓	✓	✓	Unsure	✓	✓	✓	×	✓
Akbaraly et al (2018) <sup>60</sup>	NA	NA	✓	✓	✓	×	✓	✓	Unsure	×	✓
Berti et al (2018) <sup>61</sup>	✓	✓	×	✓	✓	✓	✓	✓	✓	×	✓
Xu et al (2018) <sup>41</sup>	✓	✓	×	✓	✓	✓	✓	✓	×	×	✓
Hosking et al (2019) <sup>64</sup>	NA	NA	×	✓	✓	✓	✓	✓	✓	×	✓
Wu et al (2019) <sup>69</sup>	NA	NA	×	✓	✓	Unsure	✓	✓	✓	×	✓
Shannon et al (2019) <sup>68</sup>	NA	NA	×	✓	✓	Unsure	✓	✓	×	×	✓
Adjibade et al (2019) <sup>62</sup>	NA	NA	✓	✓	✓	Unsure	✓	✓	✓	×	✓
Akbaraly et al (2019) <sup>63</sup>	NA	NA	×	✓	✓	✓	✓	✓	✓	×	✓
Dearborn-Tomazos et al (2019) <sup>39</sup>	NA	NA	×	✓	✓	Unsure	✓	✓	×	✓	✓
Mattei et al (2019) <sup>65</sup>	✓	✓	Unsure	✓	✓	✓	✓	✓	✓	×	✓
Milte et al (2019) <sup>66</sup>	NA	NA	✓	✓	✓	Unsure	✓	✓	×	×	✓
Munoz-Garcia et al (2019) <sup>67</sup>	NA	NA	×	✓	✓	✓	✓	✓	Unsure	✓	✓
Shi et al (2019) <sup>44</sup>	NA	NA	✓	✓	✓	Unsure	✓	✓	×	×	✓
Zhang et al (2021) <sup>70</sup>	NA	NA	Unsure	✓	✓	Unsure	✓	✓	✓	×	✓

Note: Q1 = Were the 2 groups similar and recruited from the same population? Q2 = Were the exposures measured similarly to assign people to both exposed and unexposed groups? Q3 = Was the exposure (diet) measured in a valid and reliable way? Q4 = Were confounding factors identified? Q5 = Strategies to deal with confounding factors? Q6 = Were the groups/participants free of the outcome at the start of the study? Q7 = Were the outcomes measured in a valid and reliable way? Q8 = Was the follow-up time reported and sufficient to be long enough for outcomes to occur? Q9 = Was follow-up complete and, if not, were the reasons for loss to follow-up described and explored? Q10 = Were strategies to address incomplete follow-up utilized? Q11 = Was appropriate statistical analysis used?

**Table 7 Quality appraisal randomized controlled trials**

Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Wade et al (2018) <sup>75</sup>	✓	✓	✓	×	×	Unsure	✓	✓	✓	✓	✓	✓	✓
Wade et al (2019) <sup>76</sup>	✓	✓	✓	×	×	Unsure	✓	✓	✓	✓	✓	✓	✓

Note: Q1 = Was true randomization used for assignment of participants to treatment groups? Q2 = Was allocation to treatment groups concealed? Q3 = Were treatment groups similar at the baseline? Q4 = Were participants blind to treatment assignment? Q5 = Were those delivering treatment blind to treatment assignment? Q6 = Were outcomes assessors blind to treatment assignment? Q7 = Were treatment groups treated identically other than the intervention of interest, Q8 = Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed? Q9 = Were participants analyzed in the groups to which they were randomized? Q10 = Were outcomes measured in the same way for treatment groups? Q11 = Were outcomes measured in a reliable way? Q12 = Was appropriate statistical analysis used? Q13 = Was the trial design appropriate, and any deviations from the standard randomized controlled trial design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

**Table 8 Vote count of significant findings for each dietary pattern**

Dietary pattern	Significant positive			Significant negative			Null <i>P</i> > 0.05
	<i>P</i> < 0.05	<i>P</i> < 0.01	<i>P</i> < 0.001	<i>P</i> < 0.05	<i>P</i> < 0.01	<i>P</i> < 0.001	
MedDiet	5	1	4	1			5
DASH		1	1				2
MIND	2						1
Diet quality	4	3	1				4
Plant based			2				2
Other healthy	1	2	2		1		2
Nutrient			1				
Inflammatory						1	
Western						3*	4

\*One of these studies also found a significant positive association at *P* < 0.001\*.

reported cognitive function; this was estimated to be equivalent to being 1.3 years younger (OR 0.64, 95% CI [0.55, 0.75], *P* < 0.001).<sup>59</sup>

Not all longitudinal studies found a significant relationship between MedDiet and measures of cognition. Both Hosking et al (2019) and Munoz-Garcia et al (2019) failed to find an association between greater adherence to the MedDiet and risk of cognitive impairment (Munoz-Garcia et al  $\beta = 0.43$ , 95% CI [-0.40, 1.26], *P* for trend = 0.28 and  $\beta = 0.32$ , 95% CI [-0.23, 0.88], *P* for trend = 0.26; Hosking et al OR 1.30, 95% CI [0.79, 2.15], *P* for linear trend = 0.29 and OR 0.77, 95% CI [0.43, 1.39], *P* for linear trend = 0.40).<sup>64,67</sup> Qin et al (2015) also found no significant relationship between MedDiet and cognitive performance 5 years later in individuals under 65 years of age (no statistics reported), and Zhang et al (2020) failed to find a significant relationship between MedDiet and reaction time (linear trend *P* = 0.222 and *P* = 0.739).<sup>42,70</sup>

Kesse-Guyot et al (2013) found that greater MedDiet adherence was associated with better performance on a measure of cognition (MD = -0.73, 95% CI [-1.55, 0.09], *P* for linear relation = 0.02); however, this relationship no longer remained significant after fully adjusting for covariates (sex, age, education, occupation, geographic region, smoking status, physical activity, memory troubles, and medication use; MD = 0.41, 95% CI [-1.23, 0.40], *P* for linear relation = 0.12).<sup>57</sup> There was, however, a significant difference between lower and higher MedDiet adherence,

favoring the latter, for short-term memory and lexical-semantic memory performance 13 years later (MD = -0.64, 95% CI [-1.60, 0.32], *P* for linear relation = 0.003 and MD = -1.00, 95% CI [-1.85, -0.15], *P* for linear relation = 0.048).<sup>57</sup>

Only 2 RCTs were conducted assessing the impact of a MedDiet intervention on cognitive performance.<sup>75,76</sup> One of these supplemented the Mediterranean diet with dairy and the other with lean pork. Both studies reported significantly improved (faster) processing speed after 8 weeks of intervention when compared with the low-fat diet group (MedDairy, *d* = 1.3, *P* = 0.04 and MedPork, MD = 0.32, 95% CI [0.08, 0.57], *P* = 0.01).<sup>75,76</sup>

When considering the results of the quality appraisal, only 1 study measured the MedDiet across the study period;<sup>59</sup> therefore, it cannot be assumed that all participants were still adhering to the MedDiet when their neurocognitive function was assessed. For many studies, neurocognitive function was also not assessed at baseline; thus, the cognitive health of the participants at baseline was not clear.<sup>57-59,68</sup>

**DASH diet.** Only 1 cross-sectional study investigated the relationship between the DASH diet and neurocognition in midlife, and no significant relationship was observed (MMSE:  $\beta = 0.02$ , SE = 0.09, *P* = 0.80, California Verbal Learning Test:  $\beta = -0.20$ , SE = 0.24, *P* = 0.40, Free Recall Long Delay:  $\beta = -0.25$ , SE = 0.24, *P* = 0.28, Benton Visual Retention Test:  $\beta = -0.20$ ,

SE = 0.25,  $P = 0.41$ , Clock Command test:  $\beta = -0.05 \pm 0.05$ ,  $P = 0.31$ , Brief Test of Attention:  $\beta = -0.07 \pm 0.10$ ,  $P = 0.49$ , Trail-making Test, Part A:  $\beta = -3.41$ , SE = 2.55,  $P = 0.18$ , Trail-making Test, Part B:  $\beta = 7.95$ , SE = 7.80,  $P = 0.31$ , Digits Span, Forward:  $\beta = -0.07$ , SE = 0.08,  $P = 0.40$ , Digits Span, Backward:  $\beta = -0.07$ , SE = 0.08,  $P = 0.34$ , Card Rotation test:  $\beta = 0.26$ , SE = 0.76,  $P = 0.74$ , Identical Pictures:  $\beta = 0.07$ , SE = 0.25,  $P = 0.77$ , Verbal fluency:  $\beta = -0.11$ , SE = 0.21,  $P = 0.61$ ).<sup>48</sup>

Three longitudinal studies investigated adherence to the DASH diet in midlife and cognitive function.<sup>65,67,69</sup> One study found that those in the highest quartile of adherence to the DASH diet and other healthy dietary patterns had a significant reduction in the risk of cognitive impairment later on in life (after 20 years) when compared with those in the highest quartile (OR 0.71, 95% CI [0.62, 0.81],  $P$  for linear trend < 0.001).<sup>69</sup> Adherence to the DASH diet was found to be significantly related to better memory functioning 2 years later, in participants free from diabetes ( $\beta = 0.024$ , SE = 0.008,  $P = 0.003$ ); however, this was not significant for global cognitive function or executive functioning ( $P > 0.05$ ).<sup>65</sup> On the other hand, Munoz-Garcia et al (2019) did not find that adherence to the DASH diet was significantly associated with cognitive function after 6 years ( $\beta = 0.30$ , 95% CI [-0.35, 0.96],  $P$  for trend = 0.43).<sup>67</sup> The quality appraisal highlighted that these studies only assessed adherence to the DASH diet at baseline,<sup>67,69</sup> and one only assessed cognition at follow-up;<sup>69</sup> therefore, the results need to be interpreted with this in consideration.

*MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet.* Three of the cohort studies investigated the effects of the MIND diet on neurocognitive function.<sup>62,64,67</sup> These each had conflicting results. Adjibade et al (2019) did not find the MIND diet to be related to measures of subjective cognitive complaints after 6 years follow-up (HR 0.98, 95% CI [0.93, 1.02],  $P$  for linear relation = 0.32). However, the MIND diet was significantly related to subjective cognitive complaints in individuals older than 70 years (HR 0.87, 95% CI [0.78; 0.98],  $P$  for linear relation = 0.02). In contrast, Hosking et al (2019) found the highest tertile of adherence to the MIND diet to be related to reduced odds of developing cognitive impairment, MCI, and dementia after 12 years (OR 0.47, 95% CI [0.24, 0.91],  $P$  for linear trend = 0.026).<sup>64</sup> Munoz-Garcia et al (2019) also found that higher adherence to the MIND diet was related to improved cognitive function 6 years later: for each 1 standard deviation increase in MIND score there was a 0.27 increase in the cognitive outcome ( $\beta = 0.27$ , 95% CI [0.05, 0.48],  $P < 0.05$ ).<sup>67</sup> The quality

appraisal demonstrated that only Adjibade et al (2019)<sup>62</sup> measured the MIND diet across the follow-up period; however, both Munoz-Garcia et al (2019)<sup>67</sup> and Hosking et al (2019)<sup>64</sup> assessed baseline cognition.

*Diet quality.* Five cross-sectional studies investigated the relationship between diet quality (aHEI, DST, and HEI-2010) and measures of neurocognitive function at mid-life.<sup>48-50,53,55</sup> Greater adherence to the aHEI was found to be associated with higher global cognitive performance (this was only significant between the second and fourth quintiles;  $\beta = 0.48$  95% CI [0.17, 0.80],  $P$  trend = 0.042), verbal learning ( $\beta = 0.88$ , 95% CI [0.18, 1.58],  $P$  trend = 0.020), and verbal memory ( $\beta = 0.46$ , 95% CI [0.01, 0.72],  $P$  trend = 0.007).<sup>49</sup> Ye et al (2013) also found that greater diet quality (HEI-2005 score) was significantly related to cognitive performance ( $\beta = 0.25$ , SE = 0.10,  $P$  trend = 0.011): a 10-point increase in HEI-2005 was found to be equivalent to being cognitively 5 years younger. In contrast, the HEI-2010 was not significantly related to executive function ( $\beta = 0.04$ , SE = 0.03,  $P$  trend = 0.23), memory ( $\beta = 0.06$ , SE = 0.03,  $P$  trend = 0.059), or attention ( $\beta = 0.05$ , SE = 0.03,  $P$  trend = 0.10).<sup>53</sup> The HEI-2010 was also not found to be related to any measures of cognition by Hossain and colleagues in 2019 (MMSE:  $\beta = -0.01$ , SE = 0.01,  $P = 0.60$ , California Verbal Learning Test:  $\beta = -0.034$ , SE = 0.03,  $P = 0.23$ , Free Recall Long Delay:  $\beta = -0.03$ , SE = 0.03,  $P = 0.28$ , Benton Visual Retention Test:  $\beta = 0.01$ , SE = 0.03,  $P = 0.80$ , Clock Command test:  $\beta = -0.001$ , SE = 0.01,  $P = 0.90$ , Brief Test of Attention:  $\beta = -0.01$ , SE = 0.01,  $P = 0.35$ , Trail-making test, Part A:  $\beta = 0.01$ , SE = 0.31,  $P = 0.97$ , Trail-making test, Part B  $\beta = 0.02$ , SE = 0.96,  $P = 0.98$ , Digits Span, Forward:  $\beta = 0.02$ , SE = 0.01,  $P = 0.06$ , Digits Span, Backward:  $\beta = -0.01$ , SE = 0.01,  $P = 0.21$ , Card Rotation test:  $\beta = -0.02$ , SE = 0.09,  $P = 0.81$ , Identical Pictures:  $\beta = -0.01$ , SE = 0.03,  $P = 0.69$ , Verbal fluency:  $\beta = -0.002$ , SE = 0.03,  $P = 0.93$ ).<sup>48</sup> Wright et al (2017) found diet quality as measured by the HEI-2010 to be significantly related to verbal learning ( $B = 0.05$ , SE = 0.02,  $P < 0.01$ , and  $B = 0.01$ , SE = 0.002,  $P < 0.05$ ). However, they failed to find an association between diet quality and measures of nonverbal memory, working memory, attention, visuospatial ability, perceptual speed, or semantic fluency ( $P > 0.05$ ).<sup>55</sup> Finally, participants who were classified with an optimal diet using the DST have been found to have better Stroop processing than those with a sub-optimal diet ( $M = 0.19$  vs  $M = -0.10$ ,  $P = 0.013$ ),<sup>50</sup> though no significant relationship was found for reaction or decision speed, visual processing, or spatial working memory ( $P > 0.177$ ).<sup>50</sup>

Seven longitudinal studies examined the relationship between the diet quality (aHEI,<sup>36,58,65,67,69</sup> HEI,<sup>65</sup>

and DGI<sup>66</sup>) and various measures of neurocognitive function. The aHEI was not significantly associated with greater odds of healthy cognitive aging 15 years later in middle-aged women (OR 0.99, 95% CI [0.97, 1.01],  $P$  trend = 0.09)<sup>58</sup>; however, a study by Munoz-Garcia et al (2019) found that those in the highest tertile of aHEI scores had better cognitive performances than those in the lowest tertile ( $\beta = 0.81$ , 95% CI [0.17, 1.45],  $P$  trend = 0.03). Adherence to both the HEI and aHEI were both significantly related to memory function 2 years later in participants free from diabetes ( $\beta = 0.011$ , SE = 0.003,  $P = 0.002$  and  $\beta = 0.012$ , SE = 0.004,  $P = 0.001$ ); however, neither reached significance for global cognitive function or executive function ( $P > 0.05$ ).<sup>65</sup> Further, Wu et al (2019) found that those with lower adherence to the aHEI had greater cognitive decline after 20 years as measured by the MMSE when compared with those with greater adherence (OR 0.75, 95% CI [0.66, 0.85],  $P$  trend < 0.001).<sup>69</sup> Compared with those in the lowest tertile, those in the highest tertile were found to have a 25% reduction in risk of cognitive deficit. One standard deviation increase in adherence was associated with an 11% reduction in risk of cognitive impairment after a 19.7-year follow-up.<sup>69</sup> In addition to these measures of cognitive function, Akbaraly et al (2018) found that higher aHEI scores were significantly related to larger hippocampal volumes 11 years later ( $\beta = 0.11$ , 95% CI [0.02, 0.21],  $P < 0.05$ ).<sup>60</sup> Contrary to these findings, Akbaraly et al (2019) failed to find an association between aHEI and cognitive decline ( $P = 0.62$ ). Milte et al (2019) also failed to find an association between diet quality and cognitive performance: in the fully adjusted module, adherence to the DGI-2013 was not found to be associated with cognitive function 4 years later ( $B = 0.00$ , 95% CI [-0.01, 0.03],  $P > 0.05$ ).<sup>66</sup> The results from the quality appraisal suggest that the findings from 2 of the longitudinal cohort studies need to be interpreted with caution, because diet was not assessed at follow-up<sup>58,67</sup> Further, the baseline cognitive status of participants was not confirmed for 4 studies.<sup>58,60,66,69</sup>

*Plant-based dietary patterns.* Four longitudinal studies investigated plant-based dietary patterns and neurocognitive function.<sup>35,40,67,69</sup> It was found that, compared with those in the lowest quartile, participants in the highest quartiles of adherence to the PDI and hPDI had, respectively, a significant 18% and 22% reduction in the risk of cognitive impairment as measured by the MMSE after a follow-up of 19.7 years (OR 0.82, 95% CI [0.71, 0.94],  $P$  trend < 0.001 and OR 0.78, 95% CI [0.68, 0.90]  $P$  trend < 0.001, respectively).<sup>69</sup> For each 1 standard deviation increase in PDI scores, there was a 7% decrease in risk of cognitive deficit. Similarly, for the

hPDI, for every 1 standard deviation increase in hPDI scores, there was an 8% reduction in risk for cognitive decline.<sup>69</sup> Higher adherence to the carotenoid-rich dietary pattern was associated with increased cognitive performance on the composite score 13 years later (MD = 0.58, 95% CI [0.27, 0.90],  $P < 0.001$ ).<sup>35</sup> Higher adherence was related to better episodic memory, semantic fluency, working memory, and executive function (MD = 0.59, 95% CI [0.25, 0.92],  $P = 0.001$ ; MD = 0.59, 95% CI [0.26, 0.91],  $P = 0.001$ ; MD = 0.39, 95% CI [0.06, 0.72],  $P = 0.02$ ; and MD = 0.51, 95% CI [0.19, 0.82],  $P = 0.002$ , respectively).<sup>35</sup>

Pearson et al (2016) also scored a plant-based dietary pattern: after adjusting for demographic factors and energy intake, higher consumption of the plant-based dietary pattern was found to be associated with lower odds of cognitive impairment after 6.8 years (OR 0.81, 95% CI [0.67, 0.98],  $P = 0.02$ ).<sup>40</sup> However, after also adjusting for socio-economic status and other cognitive risk factors, this was attenuated and was no longer significant (OR 0.89, 95% CI [0.73, 1.10],  $P$  trend = 0.23).<sup>40</sup> Munoz-Garcia et al (2019) also failed to find a significant relationship between PVD and cognitive performance ( $\beta = 0.41$ , 95% CI [-0.56, 1.38],  $P = 0.22$ ).<sup>67</sup> All of the studies investigating the plant-based diet had methodological issues that need to be addressed, eg, diet was not assessed at the same time point as cognition,<sup>35,67,69</sup> and only 1 study investigated baseline neurocognitive health.<sup>67</sup>

*Other healthy dietary patterns.* Only one cross-sectional study investigated the relationship between a wholefood dietary pattern and cognitive performance.<sup>36</sup> After controlling for marital status, health behaviors, and health status, individuals with greater adherence to the wholefood dietary pattern had lower odds of cognitive deficit on all cognitive tasks except phonemic fluency (memory: OR 0.74, 95% CI [0.59, 0.93],  $P$  trend = 0.03; reasoning: OR 0.69, 95% CI [0.57, 0.84],  $P$  trend < 0.001; vocabulary: OR 0.54, 95% CI [0.44, 0.66],  $P$  trend < 0.001; phonemic fluency: OR 0.80, 95% CI [0.66, 0.98],  $P$  trend = 0.06; semantic fluency: OR 0.59, 95% CI [0.50–0.72],  $P$  trend < 0.001).<sup>36</sup> However, after controlling for education, this finding attenuated and only remained significant for vocabulary and semantic fluency performance (OR 0.75, 95% CI [0.60, 0.92],  $P$  trend = 0.02 and OR 0.72, 95% CI [0.59, 0.88],  $P$  trend = 0.002).<sup>36</sup>

Similar results were observed in 7 longitudinal, prospective cohort studies investigating the relationship between other healthy dietary patterns and cognitive performance.<sup>37–42,63</sup> Pearson et al (2016) found that when adjusting for demographic factors, energy intake, and socio-economic status, the alcohol/salads dietary



pattern was found to have lower odds of cognitive impairment after 6.8 years (OR 0.68, 95% CI 0.56, 0.84,  $P$  trend < 0.001).<sup>40</sup> Individuals with greater adherence to the prudent-style diet were found to have larger left hippocampal volumes, 4 years later ( $\beta$  [SE] = 48.7 [22.8],  $P = 0.032$ ).<sup>38</sup> Dearborn-Tomazos et al (2019) also scored adherence to the prudent-style diet; however, after adjusting for covariates, adherence was no longer significantly related to global cognitive performance 20 years later (MD = -0.01, 95% CI [-0.06, 0.04],  $P$  trend = 0.60).<sup>39</sup>

A significant positive association was found between adherence to the traditional Chinese dietary pattern and a measure of global cognition 10 years later ( $\beta = 1.32$ , 95% CI [0.90, 1.73],  $P$  trend < 0.001), but this was not significant for verbal memory scores ( $\beta = 0.44$ , 95% CI [0.14, 0.74],  $P$  trend = 0.77).<sup>41</sup> Kesse-Guyot et al (2012) found that those with the highest adherence to the healthy food diet performed better on a measure of global cognitive performance compared with individuals with the lower adherence after a follow-up period of 13 years ( $M = 50.1 \pm 0.7$  vs  $M = 48.9 \pm 0.7$ ;  $P = 0.001$ ); the traditional dietary pattern was not related to cognition ( $M = 49.9 \pm 0.7$  vs  $M = 50.1 \pm 0.7$ ;  $P = 0.68$ ). This positive relationship between the healthy dietary pattern and cognition was only found in those with low energy intakes.<sup>37</sup> For each 1 standard deviation increase in adherence to the healthy dietary pattern, there was an increase in cognitive decline ( $\beta = -0.03$ , 95% CI [-0.05, -0.01],  $P = 0.007$ ).<sup>63</sup> Qin et al (2015) used factor analysis to extract data for 2 traditional diets from a Chinese population: a wheat-based diverse dietary pattern and a rice/pork dietary pattern: neither of these dietary patterns were found to be related to cognitive performance in individuals under the age of 65 years (MD = 0.020, 95% CI [-0.205, 0.246],  $P$  trend = 0.89 and MD = -0.063, 95% CI [-0.296, 0.169],  $P$  trend = 0.21).<sup>42</sup> The quality appraisal demonstrated that 7 of the studies discussed here failed to assess diet at the time of neurocognitive assessment,<sup>37-42,63</sup> and 2 studies did not assess cognitive health at baseline.<sup>37,39</sup>

**Nutrient-defined patterns.** Only 1 cross-sectional study investigated the roll of nutrient patterns.<sup>54</sup> Berti et al assessed how different nutrient patterns were related to 3 different neuroimaging outcome measures of brain health and Alzheimer's disease pathology; ie, glucose metabolism, gray matter volume, and amyloid beta markers.<sup>54</sup> One nutrient pattern high in Vitamin B12, Vitamin D, and zinc was found to be significantly related to all 3 outcome measures: higher intake of those nutrients was associated with reduced amyloid beta ( $P < 0.001$ ), greater glucose metabolism ( $P < 0.001$ ), and increased gray matter volume ( $P < 0.001$ ). Another

nutrient intake pattern high in saturated fat, cholesterol, and sodium was negatively associated with metabolic activity and gray matter volume ( $P < 0.001$ ).<sup>54</sup> Overall, only one nutrient pattern (B vitamins: B1, B2, B3, B6, and B9) was not associated with any of the biomarkers ( $P > 0.05$ ). The nutrient intake patterns found to be protective of brain health were also associated with higher intake of fruits and vegetables, whole grains, fish, and low-fat dairy.<sup>54</sup>

**Unhealthy dietary patterns.** Of the studies reviewed, 7 investigated the relationship between unhealthy dietary patterns and measures of neurocognitive function and brain morphology.<sup>36,38-41,43,63</sup> The main unhealthy dietary patterns explored included inflammatory dietary patterns, Western dietary patterns, and "other" unhealthy dietary patterns.

### Inflammatory dietary patterns

One longitudinal study investigated an inflammatory dietary pattern.<sup>43</sup> This pattern was scored using the dietary inflammatory index (DII), which was developed using a scoring algorithm that incorporated foods that have been found to increase inflammation.<sup>77</sup> Higher DII score in middle age was significantly related to worse global cognitive performance 13 years later (MD -1.76, 95% CI [-2.81, -0.72],  $P$  trend = 0.002).<sup>43</sup> For the individual cognitive assessments, higher DII adherence was related to worse performance on a task of episodic memory performance and 2 lexical-semantic memory tasks (MD = -1.38, 95% CI [-2.50, -0.27],  $P$  trend = 0.01; MD = -2.57, 95% CI [-3.67, -1.48],  $P$  trend < 0.001; MD = -1.42, 95% CI [-2.52, -0.33],  $P$  trend = 0.04), whereas no relationship between DII adherence and performance on tasks of mental flexibility or short-term memory were found (MD = 0.07, 95% CI [-1.05, 1.18],  $P$  trend = 0.87; MD = -0.86, 95% CI [-1.96, 0.25],  $P$  trend = 0.13; MD = -0.61, 95% CI [-1.67, 0.45],  $P$  trend = 0.31).<sup>43</sup> The quality appraisal demonstrated that this study only assessed diet at baseline.<sup>43</sup>

### Western dietary patterns and other unhealthy diets

Only 1 cross-sectional study extracted a dietary pattern similar to the Western-style diet, ie, the processed food pattern.<sup>36</sup> After controlling for marital status, health behaviors, and health status, individuals with high adherence to the processed food diet had cognitive deficits for a number of cognitive tasks compared with individuals with low adherence (memory, OR 1.26, 95% CI [0.95, 1.67],  $P$  trend = 0.26; reasoning, OR 1.55, 95% CI [1.21, 1.98],  $P$  trend < 0.001; vocabulary, OR 2.36, 95%

CI [1.84, 3.04],  $P$  trend < 0.001; phonemic fluency, OR 1.70, 95% CI [1.33, 2.19],  $P$  trend < 0.001; semantic fluency, OR = 1.58, 95% CI [1.25, 2.01],  $P$  trend < 0.001. However, all the results were attenuated after controlling for education and only remained significant for vocabulary performance and phonemic fluency (OR 1.63, 95% CI [1.25, 2.13],  $P$  trend < 0.001 and OR 1.34, 95% CI [1.04, 1.74],  $P$  trend = 0.02, respectively).<sup>36</sup>

Six cohort studies examined the Western dietary pattern or another unhealthy diet and their relationship with measures of cognitive function, such as brain structure<sup>38</sup> and cognitive deficit.<sup>39–41,44,63</sup> The Western-style diet was found to be related to smaller left hippocampal volume after 4 years ( $\beta = -52.6$ , SE = 26.9,  $P = 0.05$ ).<sup>38</sup> In contrast, Akbaraly et al (2019) failed to find a significant association between the Western-type diet and cognitive decline after 18 years ( $P = 0.62$ ). Further, Dearborn-Tomazos et al (2019) also failed to find an relationship between adherence to the Western-style diet and cognitive performance after 20 years (MD = 0.03, 95% CI, [-0.03, 0.08],  $P$  trend = 0.37).<sup>39</sup> Another study investigated the relationship of 3 dietary patterns similar to the Western dietary pattern to cognitive performance over 6.8 years: the “convenience” pattern, the “Southern” pattern, and the “sweets and fats” pattern.<sup>40</sup> There was no relationship between measures of cognitive performance and either “convenience” or the “sweets and fat” dietary patterns (OR 0.87, 95% CI [0.70, 1.08],  $P$  trend = 0.14; OR 1.19, 95% CI [0.95, 1.49],  $P$  trend = 0.31, respectively). Individuals with higher adherence to the Southern pattern (high in added fats, fried food, eggs, processed meats, and sugar-sweetened beverages) were found to have higher odds of cognitive impairment compared with those with lower adherence after 6.8 years (OR 1.46; 95% CI [1.19, 1.78],  $P$  trend < 0.001), however after controlling for socio-economic status and other cognitive risk factors this relationship was no longer significant (OR 1.16, 95% CI [0.93, 1.45],  $P$  trend = 0.05).<sup>40</sup> Xu et al (2018) extracted data for protein-rich and starch-rich dietary patterns and found that higher adherence to the protein-rich pattern was positively related to global and verbal cognition after 10 years ( $\beta = 2.28$ , 95% CI [1.80, 2.78]  $P$  trend < 0.001), whereas greater intake of the starch-rich pattern was negatively related to cognitive function after 10 years ( $\beta = -0.31$ , 95% CI [-0.70, 0.08],  $P$  trend = 0.001).<sup>41</sup> Finally, 1 study investigated adherence to an iron-related dietary pattern and found higher adherence to be significantly related to worse cognitive performance 15 years later (global cognition, regression coefficient = -0.79, 95% CI [-1.25, -0.32],  $P$  trend < 0.001; verbal memory score, regression coefficient = -0.37, 95% CI [-0.70, -0.04],  $P$  trend = 0.02).<sup>44</sup> The quality appraisal suggested,

however, that the results should be interpreted with caution, as diet was only assessed at baseline for 5 studies,<sup>38–41,63</sup> and cognition was not assessed at baseline for 2 studies.<sup>39,44</sup>

## DISCUSSION

This is the first systematic review to examine the relationship between dietary patterns in middle age and concurrent or later neurocognitive function and brain health. It revealed that diet at middle age (40–65 years) may be related to cognitive function and brain morphology, both in midlife and later in life. Nine cross-sectional studies, 23 longitudinal or prospective cohort studies, and 2 RCTs met the criteria for inclusion in the review. Table 8 demonstrates that most of the available evidence supports a protective effect of the MedDiet on cognitive function later in life. This is true, albeit to a lesser extent, for other measures of diet quality, and healthy posteriori patterns. Most of the available evidence synthesized here is from longitudinal, prospective cohort studies, and more RCTs are needed. There was some inconsistency in the findings, which may be due to the heterogeneity in cognitive outcomes and the method of diet assessment. Despite this, the results of this review are largely consistent with previous findings across a range of ages (20–90 years).<sup>2,78</sup> This suggests that diet at midlife appears to have an impact on later life cognition.

### Summary of the evidence

Specific findings from the cross-sectional studies reveal significant relationships between posteriori-defined dietary patterns and outcomes of cognitive performance and neuroimaging. There were only 2<sup>53,56</sup> studies that found a significant relationship between adherence to the MedDiet and cognitive performance. However, for 1 study this was an inverse relationship between everyday memory performance and MedDiet.<sup>56</sup> Due to the paucity of research assessing the concurrent relationship between MedDiet and neurocognitive function in midlife, more research is needed. On the other hand, a number of longitudinal and prospective cohort studies reported a significant positive relationship between adherence to the MedDiet and neurocognitive outcomes.<sup>58,59,61,65,68,69</sup> These significant findings suggest that adherence to the MedDiet in midlife may protect later life cognition and that the protective benefits of adhering to the MedDiet may be cumulative and observed only after adherence for relatively long periods. However, it should be noted that none of the studies assessing the MedDiet assessed dietary adherence at follow-up. Therefore, these findings need to be confirmed

by future research assessing both dietary adherence and cognition at multiple time points. The 2 RCTs included in this review evaluated the effects of adherence to versions of the MedDiet on cognitive performance, using a crossover design; both studies found that only processing speed improved after only 8 weeks intervention, favoring adherence to the MedDiet compared with the low-fat control diet.<sup>75,76</sup> Not all studies found a significant positive relationship between neurocognition and MedDiet adherence. In one longitudinal study, the MIND diet (related but not identical to the MedDiet) was found to protect against development of cognitive deficit.<sup>64</sup> The MIND Diet comprises the food groups from the MedDiet and the DASH with most evidence for neuroprotection. Further, adherence to the MIND diet was also found to be related to fewer subjective memory complaints after 6 years.<sup>62</sup> Importantly, this diet was developed directly for brain health: it may have the highest clinical utility for cognitive protection and reducing the risk of developing cognitive decline or dementia.

Findings from reviewed studies investigating diet quality and other healthy dietary patterns also showed evidence of improved neurocognitive outcomes. A longitudinal study exploring various healthy dietary patterns (DASH, aHEI, PDI, and MedDiet) found that these diets reduced the odds of cognitive impairment as measured by the MMSE.<sup>69</sup> Adherence to the healthy dietary patterns was also found to be related to enhanced measures of global cognitive performance (healthy dietary pattern)<sup>37</sup>; measures of episodic memory, semantic fluency, working memory, and executive function (carotenoid-rich pattern)<sup>35</sup>; and greater hippocampal volume (the hippocampus is an area of the brain associated with memory and the development of Alzheimer's disease<sup>79</sup>; prudent pattern<sup>38</sup> and aHEI-2010<sup>60</sup>). These different dietary patterns all share common features, such as a high intake of fruits, vegetables, omega-3 fatty acids, and polyunsaturated fatty acids, as well as a low intake of red meat, processed foods, and refined sugars. This suggests that it may be these key components that are important for neuroprotection, rather than one specific dietary pattern. In addition to these neuroprotective dietary patterns, there is evidence for a relationship between unhealthy dietary patterns (such as the inflammatory and Western diet patterns) and both reduction in global cognitive performance<sup>40,43</sup> and smaller hippocampal volumes.<sup>38</sup> These unhealthy dietary patterns are all high in processed foods, added sugar, saturated fat, and red meat, suggesting these are the food groups that should be avoided to protect cognitive and brain health.<sup>18,80</sup> Relative to the number of healthy dietary patterns reviewed, only a few unhealthy

dietary patterns were explored. This is a limitation in the research, as the majority of people in Western countries are adhering to unhealthy diets that may have a negative impact on their brain health.<sup>81,82</sup>

### Variation in the methods of scoring dietary patterns

There was a wide variety of dietary patterns explored in this systematic review. In addition, there were different methods of scoring adherence to the different dietary patterns, and these could be categorized into 2 main types: a priori and posteriori. A priori patterns are pre-defined dietary scores based on previous research; these scores are validated and tend to be reliable (examples include the MedDiet, MIND, and DASH dietary patterns).<sup>83</sup> Use of these scores allows comparison between the different studies that investigate the same dietary pattern. However, even in studies that investigate the same dietary pattern, there was inconsistency in the scoring methods used. For example, in the current review, 7 different methods of scoring adherence to the MedDiet were used. This makes it difficult to compare the results between the studies and between the dietary patterns. In addition to this, many studies utilized posteriori methods of dietary assessment, which are statistically derived patterns that reflect the dietary habits of the sample being investigated.<sup>83</sup> Posteriori methods also mean comparison from study to study is difficult, because each dietary pattern is defined within its own cohort. Future studies should use consistent validated measures of dietary adherence, such as the 14-item Mediterranean Diet Adherence Screener and assessment tool.<sup>84</sup> Validated tools such as this are easy to administer, economical, time efficient, allow for more accurate comparison of the results from study to study, and transition well into clinical settings.

### Variation in the neurocognitive outcomes measured

Furthermore, there was a wide variety of outcomes for assessing cognitive and brain health, including measures of global cognitive performance,<sup>41,42,58,69</sup> performance on specific cognitive domains,<sup>35-37,40,43,56,57,63,64,68</sup> subjective cognitive performance,<sup>52,59,62</sup> and brain structure, as well as neuroimaging of biomarkers.<sup>38,54,60</sup> This diversity made collating the results difficult, as not all cognitive domains are equally sensitive to the changes associated with aging.<sup>21</sup> Some measures of cognitive performance (such as global measures like the MMSE) are insensitive to changes associated with the early stages of cognitive decline.<sup>85</sup> The cognitive domains found to be most sensitive to aging include spatial working memory and

episodic memory.<sup>21</sup> There is evidence that both spatial working memory and episodic memory have already started to decline in midlife.<sup>21,86</sup> The specific cognitive domains found to be related to diet at midlife in the current review were executive functioning,<sup>35</sup> semantic fluency,<sup>35,36</sup> reasoning,<sup>35</sup> vocabulary,<sup>28</sup> processing speed,<sup>68,75,76</sup> and memory.<sup>35,43,65,68</sup>

Overall, the results of this review highlighted that the measures of global cognitive performance, including measures of specific cognitive domains, were significantly positively associated with adherence to a “healthy” dietary pattern in midlife.<sup>35,37,40,68</sup> This is encouraging, as it indicated that cognitive faculties sensitive to age-associated cognitive decline are potentially amenable to change. Adherence to various healthy dietary patterns was also associated with global measures of cognitive function such as subjective cognitive functioning,<sup>59</sup> cognitive aging (measured by telephone interview to determine cognitive status<sup>41,58</sup>), and the MMSE.<sup>69</sup> However, some studies only found a significant relationship in people over the age of 65, suggesting that more sensitive measures may be needed to observe the relationship between diet and cognitive function at midlife, or that this relationship is only present later in life.<sup>42,62</sup> The heterogeneity of the findings of the studies reviewed can possibly be explained by the compounding effects of the differences in the methodologies, the dietary patterns investigated, the scoring methods used for the dietary patterns, and the cognitive outcomes measured.

### **Strengths, limitations, and future directions**

The quality appraisal highlighted that there are some methodological issues that need to be addressed in future studies. One of the commonly identified methodological issues concerned the timing of dietary measurement. Many of the studies reviewed measured diet at baseline only; in some cases this was up to 20 years before the cognitive outcomes were assessed. This is problematic as diet may fluctuate across the life span due to aging and lifestyle changes.<sup>87,88</sup> Future research should address this by assessing diet at multiple time points. However, this limitation should not result in the significant findings in this review being ignored, as it is possible that individuals may adhere to a similar dietary pattern across their lifespan.<sup>87</sup> The quality appraisal also highlighted that a number of longitudinal studies failed to measure cognitive status at baseline. This prevented cognitive decline from being assessed, and limited learnings regarding cognitive performance. Future studies should take this into account and measure both cognition and diet at both time points. There were only 2 RCTs conducted in this age range. Future

studies also need to address this gap in the literature, conducting larger RCTs assessing the efficacy of diet as a preventative strategy for the development of cognitive decline.

Strengths in the studies reviewed include large sample sizes and long follow-up periods. Studies were geographically diverse, indicating that this research area is of growing concern globally. The wide variety of dietary patterns that have been explored demonstrates that there are many options for dietary intervention when targeting the prevention of cognitive decline.

The strengths of this review include its conforming to the PRISMA method. Further, this review is novel in that it investigated the relationship between dietary patterns and cognitive performance in a specific age range (40–65 years). The evidence available for the relationship between diet and neurocognitive function at middle age suggests that there is a continuing association from middle age into older age. This means that interventions at middle age may be effective in preventing neurocognitive decline. The present review also had a number of limitations: the studies reviewed were heterogeneous in methodology, including sample populations, length of follow-up, and variation in the dietary patterns and neurocognitive outcomes explored. This prevented a meta-analysis from being conducted. Another limitation of this systematic review is the inclusion of studies from the same cohort. This may have contributed to biasing the results, as the same participants were examined across different studies, even though the studies investigated different dietary patterns.

The findings of this systematic review highlight the gaps in the literature investigating diet and cognitive health in middle age. First, there is very limited data from randomized RCTs in this age range. Second, none of the studies included in this review assessed diet using nutrient biomarkers; all reported using self-reported measures of diet, including food frequency questionnaires, 24-h diet recalls, and diet interviews. Self-reported diet measures are subject to social desirability bias, such as over-reporting healthy foods and under-reporting unhealthy foods.<sup>89,90</sup> Future research should address this bias by utilizing more objective measures of diet, such as nutrient biomarkers. Finally, the methodological issues highlighted in this review need to be addressed, including measuring both cognition and diet at both time points for longitudinal studies. Other factors, such as genetics and gender differences, could also play a role in the complex relationship between diet and neurocognitive function; these should be examined in future research as they were out of the scope of this current review. Furthermore, additional research is needed to understand the mechanisms of how diet may impact

neurocognitive health. Some of the proposed mechanisms include cardio-metabolic health,<sup>91,92</sup> inflammation and oxidative stress,<sup>93</sup> and gut microbiota.<sup>94</sup> In addition to the use of subjective measures of nutrient status and dietary intake, studies should utilize comprehensive nutrient biomarkers and assess possible mechanisms in order to better understand how diet may impact cognitive health in middle age.

## CONCLUSION

This systematic review evaluated the available evidence from studies that have assessed the relationship between adherence to various dietary patterns at middle age and measures of brain health and cognition. Due to the increasing aging population and limited interventional strategies for cognitive decline, there is an increasing need to develop strategies that will aid the prevention of cognitive decline associated with aging. This systematic review provides evidence that diet may be an effective target for change, as research suggests that diet at middle life is related to cognition later in life. Specifically, adhering to the MedDiet was found to have the most evidence for protecting later life cognitive function among middle-aged people. More research is needed to confirm these findings, including more longitudinal studies that assess diet and cognitive performance at both baseline and follow-up. As there was only 9 cross-sectional studies, more research is needed to assess the relationship between cognitive function and diet at middle age. The paucity of RCTs of dietary interventions in this area was also striking and should be addressed. Additional studies investigating the detrimental effects of the Western-style diet and other “unhealthy” dietary patterns are also warranted. Overall the evidence demonstrates that dietary intervention in middle age may be a feasible intervention strategy to help prevent the onset of age-associated cognitive decline.

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## Supporting Information

[Appendix S1. PRISMA checklist](#)

[Appendix S2. MOOSE checklist](#)

[Table S1. Search strategy.](#)

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