Ageing Research Reviews 63 (2020) 101145

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

The association of dietary patterns with cognition through the lens of neuroimaging—a Systematic review

Belina Rodrigues[a,b,*], Evans A. Asamane[c,d], Ricardo Magalhães[a,b,e,f], Nuno Sousa[a,b], Janice L. Thompson[c], Nadine Correia Santos[a,b]

[a] Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal
[b] ICVS/3B's, PT Government Associate Laboratory, Braga, Guimarães, Portugal
[c] School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, United Kingdom
[d] Keele University, School of Primary, Community and Social Care, Keele, United Kingdom
[e] NeuroSpin, Institut Des Sciences Du Vivant Frédéric Joliot, Commissariat à l'Énergie Atomique Et Aux Énergies Alternatives, 91190, Gif-sur-Yvette, France
[f] Université Paris-Saclay, 91190, Gif-sur-Yvette, France

ARTICLE INFO

Keywords:
Cognition
Neuroimaging
Dietary pattern
Neuropsychological assessment
Middle-aged
Older adults

ABSTRACT

Despite the reported benefits of diet on cognition in older adults, randomized controlled trials (RCT) testing the impact of dietary interventions on cognitive scores have yielded less promising results when cognition was assessed via neuropsychological tests. More recently, neuroimaging has been used to identify more subtle brain-related changes associated to cognition. Hence, employing a combination of neuroimaging techniques with neuropsychological tests could clarify this controversy.

To determine the effect of diet on cognitive performance, we conducted a systematic review of PubMed and Scopus databases for all studies, on middle-aged and older adults, combining neuroimaging, neuropsychological tests, and data on dietary patterns. The inclusion criteria were met by 14 observational studies and no RCTs. The range of brain measures assessed varied from volumes to white matter integrity, functional connectivity, brain glucose metabolism and beta-amyloid deposition. Given the variability of methods used in assessing cognitive performance, diet and brain correlates, conducting a meta-analysis was not possible.

Here the evidence suggests that, in observational studies, dietary patterns may be associated with brain correlates that have been shown to precede cognitive decline. As such, neuroimaging should be included in future RCTs to identify any benefits of diet on brain measures linked with cognitive health.

1. Introduction

Existing evidence suggests that healthy dietary patterns can positively impact on cognitive health in aging. Longitudinal prospective studies have reported slower rates of cognitive decline with higher scores of adherence to healthy dietary patterns (Tangney et al., 2011; Qin et al., 2015; Wengreen et al., 2013; Morris et al., 2015). Conversely, randomized controlled trials (RCTs) have yielded less promising results. Whereas some RCTs have shown that a Mediterranean-type diet (MedDiet) can delay cognitive decline (Valls-Pedret et al., 2015), others have found no statistical difference in cognitive performance between the MedDiet and a habitual diet (Knight et al., 2016; Marseglia et al., 2018). One major limitation of the current published literature is that neurocognitive tests and dietary assessments, alongside neuroimaging, are rarely measured and analyzed in the same study. Employing a combination of neurocognitive and neuroimaging approaches could provide clarification as to discrepant findings reported in observational studies as compared to RCTs.

The debate on dietary patterns and cognitive decline has gained new prominence with the advent of cutting-edge neuroimaging techniques. These can both measure meaningful variations in brain correlates when detectable changes are not captured by neurocognitive tests (Sizonenko et al., 2013; Monti et al., 2015; Zamroziewicz and Barbey, 2016), and predict cognitive trajectories (Reddan et al., 2018). For instance,

* Corresponding author at: Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus Gualtar, 4710-057, Braga, Portugal.

E-mail addresses: belinarodrigues@gmail.com (B. Rodrigues), asamaneevans@yahoo.com (E.A. Asamane), ricardo.magalhaes@cea.fr (R. Magalhães), njcsousa@med.uminho.pt (N. Sousa), J.Thompson.1@bham.ac.uk (J.L. Thompson), nsantos@med.uminho.pt (N.C. Santos).

https://doi.org/10.1016/j.arr.2020.101145
Received 26 March 2020; Received in revised form 30 June 2020; Accepted 10 August 2020
Available online 17 August 2020
1568-1637/

changes in cerebral white matter integrity, studied using diffusion magnetic resonance imaging (MRI), were: (i) associated with cognitive performance (Vernooij et al., 2009; Cremers et al., 2016); (ii) detectable before cognitive impairment (Wang et al., 2012); and (iii) predictive of cognitive decline (Defrancesco et al., 2014). In addition, alterations of specific regional brain volumes were detected prior to the decline of cognitive function (Smith et al., 2007). As such, neuroimaging has the potential to inform whether healthy dietary patterns are associated with beneficial changes in brain measures such as brain glucose uptake, structural connectivity and brain volumes. As shown in studies employing both neuroimaging and neuropsychological tests, dietary interventions focusing on specific nutrients have shown beneficial effects on cognition and brain correlates in older adults with preserved and impaired cognition. For instance, consumption of fish oil supplements (2.2 g/day of long chain omega-3 fatty acids) increased white matter integrity, gray matter volume, reduced the loss of gray matter and enhanced executive performance by 26 % in healthy women (aged 50–75 years), when compared to placebo, after 26 weeks (Witte et al., 2014). Similarly, interventions studying the consumption of dietary flavanol supplements and concentrated grape juice on similar outcomes yielded positive findings (Krikorian et al., 2012; Brickman et al., 2014). These findings suggest that certain nutrients may positively impact on cognitive performance. Yet, as nutrients are not eaten in isolation but consumed in combination, it is most likely that dietary effects on the brain occur as a result of additive/synergistic interactions between nutrients (Zwilling et al., 2019; Scarmeas et al., 2018).

To understand the effect of the breadth of the interactions of dietary patterns, an overview of how these patterns impact on cognition and brain correlates obtained by using several neuroimaging techniques is currently lacking. Thus, to establish whether, and how, dietary patterns associate with cognition, the simultaneous use of neurocognitive tests and neuroimaging could allow for an improved assessment of the cumulative effects of a dietary pattern and provide additional information on the mechanisms impacting on cognition. To the best of our knowledge, no systematic review has been conducted on studies measuring dietary patterns, neuroimaging correlates and neurocognitive tests.

2. Methods

To determine whether dietary patterns are associated with different brain correlates and cognitive domains in middle-aged and older adults, this systematic review considered studies including community dwelling adults aged 50 years or older, with varying levels of adherence to the studied dietary patterns (exposure and comparison group), and the associations with brain correlates and cognitive scores (outcomes). The PICO format was followed (Richardson et al., 1995).

A comprehensive search was conducted in PubMed and Scopus databases. Key terms and medical subject headings (MeSH), used to search titles, abstracts and keywords, included “nutrition” or “eating habits” or “nutrients” or “diet” and “functional MRI” or “MRI” and “cognition”. Additional records identified through manual search were also incorporated (Fig. 1). All study design types with human participants were included. Date of the last search was February 2020. Studies were included if they met the following criteria: 1) included a neurocognitive test or battery of tests; 2) included a measure of dietary patterns as opposed to single nutrients; 3) included participants aged 50 years or older; and 4) included at least one neuroimaging technique. Articles were excluded if they were reviews or protocols, published in languages other than English, or if the effect of the diet itself could not be ascertained (e.g. interventions where a given dietary pattern and exercise were studied together). The screening of titles and abstracts was carried out independently by two reviewers (BR and EAA). The authors met to reach consensus on which articles should be included and conflicts were resolved through discussion.

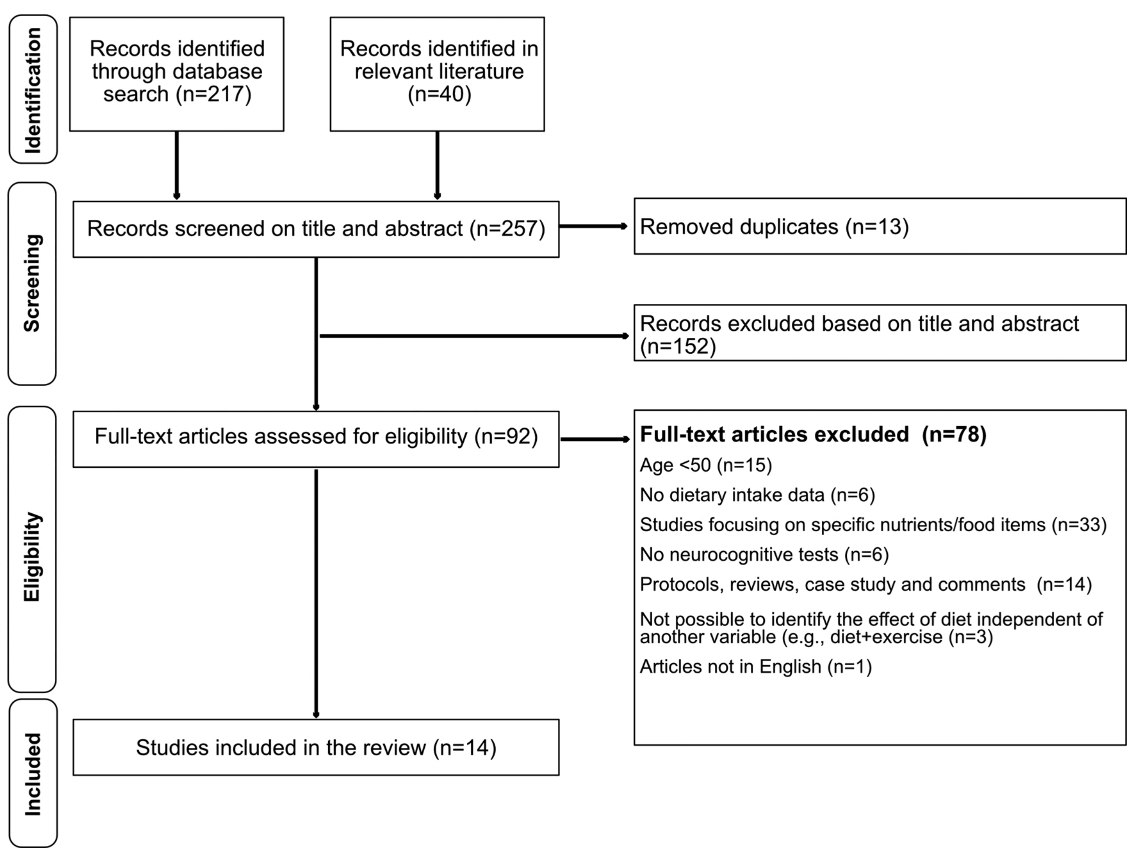

Fig. 1. Flow diagram of the study selection process.

2.1. Quality assessment

To appraise the quality of included studies, the Quality assessment tool for Observational Cohort and Cross-Sectional Studies from the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) was used (National Institute of Health National Heart, 2019). This tool is comprised of 14 questions: 1) is the research question or objective of the paper clearly stated?; 2) was the studied population well specified and defined?; 3) was the participation rate of the eligible population equal or greater than 50 %?; 4) were all participants recruited from the same or similar population?; 5) was the sample size, power description, variances or effect sizes reported?; 6) were the exposures of interest measured prior to the measurement of outcomes?; 7) was the given timeframe enough to expect associations?; 8) were different levels of exposure studied?; 9) were the exposure variables clearly defined, valid, reliable and consistently implemented across all participants?; 10) was the exposure assessment repeated?; 11) were the outcome variables clearly defined, valid, reliable and consistently implemented across all participants?; 12) were the outcome assessors blinded to the exposure status?; 13) was loss to follow-up lower than 20 %?; 14) were the key potential confounders controlled for?

3. Results

Overall, 257 articles were identified, out of which 13 were excluded after identification of duplicates and 152 after screening of the title and abstract. As a result, 92 full-text articles were assessed for eligibility. Of these, 14 were included in this review (Table 1).

3.1. Study design and statistical analyses

Both cross-sectional and longitudinal observational studies met the inclusion criteria for this review. All of the longitudinal studies described the effect of dietary patterns assessed prior to the cognition-related and brain imaging-related outcome, thereafter referred to as past dietary patterns as opposed to concurrent dietary patterns, which were assessed during the study when cognition- and brain-related outcomes were measured. Of the longitudinal studies, except for Gu et al., 2018, all the other longitudinal studies assessed adherence to the MedDiet. Of those which focused on the MedDiet, two studies conducted additional analyses either on the robustness of the applied MedDiet score (Berti et al., 2018) or the stability of the pattern over time (Pelletier et al., 2015). Berti et al., 2018 reproduced the findings with a different MedDiet score, and Pelletier., et al. 2015 confirmed the stability of the pattern. Specifically, over time, those in the high extreme end of the MedDiet score reported a higher consumption of fruits, legumes, vegetables, fish, a moderated alcohol intake, and lower meat intakes (Pelletier et al., 2015).

With regards to statistical analyses, studies reported bivariate relationships, direct and indirect contributions of diet on a given outcome through third-variable effects models, and structural equation modelling to evaluate interdependent relationships. Adherence to the MedDiet scores was studied either as a continuous variable (Titova et al., 2013; Pelletier et al., 2015; Luciano et al., 2017; Mosconi et al., 2014, 2018) or dichotomous variable, i.e. high vs low adherence to the MedDiet (Gu et al., 2015; Karstens et al., 2019; Mosconi et al., 2014; Walters et al., 2018). Except for the study by Gu et al., 2016, in which the authors ranked the loading factors of the relevant cluster of nutrients, all of the remaining studies utilising PCA included the loading factors values as continuous variables.

3.2. Target groups

Only studies with community-dwelling, non-institutionalized participants were considered (Table 2 and 3). Most studies excluded individuals with dementia, except Gu et al., 2016, 2018 and Titova et al., 2013, with the latter two including the participants with some degree of cognitive impairment or dementia in all analyses. The majority of the studies excluded participants with medical conditions or history of conditions that could affect brain structure or function (Berti et al., 2015; Bowman et al., 2012; Zwilling et al., 2019; Karstens et al., 2019; Berti et al., 2018; Mosconi et al., 2014, 2018; Gu et al., 2018; Walters et al., 2018) and Titova et al., 2013 excluded participants whose diseases could induce changes in diet and lifestyle (e.g. diabetes, stroke). Those that did not exclude participants based on these conditions entered these variables into the models as covariates (Pelletier et al., 2015; Gu et al., 2015, 2018; Luciano et al., 2017). Nine of the studies included exclusively older adults (i.e., participants aged 60 years old or older), with 5 studies including also younger adults (i.e., participants aged 25 years or older) as well as older adults (Walters et al., 2018; Mosconi et al., 2018, 2014; Berti et al., 2015, 2018).

3.3. Dietary intake assessment

Several tools were applied to assess dietary patterns (Table 2 and 3). Most of the studies used food frequency questionnaires (FFQ) (Gu et al., 2015; Berti et al., 2015; Gu et al., 2016; Luciano et al., 2017; Gu et al., 2018; Karstens et al., 2019; Mosconi et al., 2014; Berti et al., 2018; Mosconi et al., 2018; Walters et al., 2018). One study combined a FFQ with a 24 h dietary recall (Pelletier et al., 2015), two inferred dietary intake from blood biomarkers (Zwilling et al., 2019; Bowman et al., 2012), and one collected a 7-day non-weighed food diary (Titova et al., 2013). Except for the studies by Luciano et al., 2017 and Mosconi et al., 2014, in which it was not clear who completed the FFQ, trained interviewers administered the dietary assessment tools in all other studies. Intakes of nutritional supplements were not reported in any of the studies.

3.4. Dietary patterns ascertainment

Dietary patterns were ascertained either through principal component analysis (PCA), reduced-rank regression (RRR) or scores/questionnaires assessing the adherence to the dietary pattern (Tables 2 and 3). In the case of the PCA, both food frequency questionnaires (Berti et al., 2015; Gu et al., 2016) and blood parameters (Zwilling et al., 2019; Bowman et al., 2012) were used to determine the clusters of nutrients. The study utilising RRR employed a FFQ to ascertain the dietary intake and used inflammatory blood biomarkers as responsive variables to obtain the nutrients clusters (Gu et al., 2018). As for the studies using scores/questionnaires, only studies focusing on the MedDiet met the inclusion criteria. To assess the adherence to the MedDiet two criteria were used: Trichopoulou et al., 2003 (Titova et al., 2013; Mosconi et al., 2014; Gu et al., 2015; Pelletier et al., 2015; Gu et al., 2016; Luciano et al., 2017; Mosconi et al., 2018; Berti et al., 2018; Walters et al., 2018) and Panagiotakos et al., 2007 (Karstens et al., 2019). Note that studies differed in terms of adjusting for energy intake, cut-offs and studied dietary variables (see supplementary material for an in-depth description).

3.5. Neuropsychological assessment

Cognitive domains that are known to decline with age were the target of the applied neurocognitive testing (Table A.1). As such, general cognition, executive function, memory, attention, language and visuospatial were studied. Except for Luciano et al., 2017, who only studied general cognition through Mini-mental State Examination (MMSE), the remaining studies incorporated a diverse set of tests (Table A.1). Of the studies that applied several questionnaires, five utilized the raw scores of the neurocognitive tests (Berti et al., 2015, 2018; Bowman et al., 2012; Zwilling et al., 2019; Mosconi et al., 2014), four computed a composite score per studied cognitive domain (Gu et al., 2015, 2016; Gu et al., 2018; Karstens et al., 2019), two analyzed both raw and composite

Table 1
Summary of the brain correlates associated with dietary/nutrient patterns.

Author, year	Dietary variables	Brain correlates: Volume/density	WMH	White Matter Integrity	Functional connectivity	Glucose Metabolism	PiB Retention	Association between dietary pattern and cognitive score? (cognitive domain)
Gu, 2016	**Vit E and PUFA**	–	–	Increased FA	–	–	–	Yes (L, M, SE, VS)[#]
Berti, 2015	**Vit E and PUFA**	No[a]	–	–	–	↑ medial, inferior, lateral frontal cortex	No	No
	Antioxidants and Fibers	No[a]	–	–	–	↑ middle frontal, cingulate cortex (L);	No	No
	Fats (saturated, trans-saturated, cholesterol)[1]	↓GM of frontal cortex[a]	–	–	–	↓ middle and inferior temporal cortex, frontal cortex (R), and parietal cortex (L)	No	No
	Vit B12 and D	↑ GM of temporal and frontal cortex (R)[a]	–	–	–	↑ superior and medial temporal areas	↓ parietal, frontal and posterior cingulate cortex	No
Zwilling, 2019	**Vit B12 and D[1]**	–	–	–	↓WP fronto-parietal and default networks	–	–	Yes (EXE)
	n-6	–	–	–	↑ WP somatomotor and ventral attention networks	–	–	Yes (EXE)[#]
	n-3	–	–	–	↑ WP visual network	–	–	Yes (EXE)
	Carotene	–	–	–	↑ WP limbic network	–	–	No
	Lycopene				No			Yes (M, EXE[#])
	MUFA:SFA	–	–	–	↓WP ventral attention	–	–	Yes (EXE)
Gu, 2018	**Low Ca, Vit D, A, E, B, Ca, n-3 and antioxidants + high cholesterol**	↑ TBV, TGMV, and TWMV	No	–	–	–	–	YES (VS) [#]
Bowman, 2012	**vitamins B, C, D, and E**	Larger TBV	No	–	–	–	–	Yes (G, EXE, ATT, VS)
	marine -3 FA	No	↓ WMH	–	–	–	–	Yes (EXE)
	Trans-fat	Smaller TBV	No	–	–	–	–	Yes (G, ATT, M, L, PS)
Pelletier, 2015	**MedDiet**	No[a]	No	Lower diffusivity values	–	–	–	No*
Berti, 2018	**(low) MedDiet**	No[a]	–	–	–	↓ temporal and PCC/precuneus	↑ frontal cortex and left parietal cortex	No
Mosconi, 2018	**MedDiet**	↑ thickness of EC, PCC, OFC, inferior and middle temporal gyrus[2]. [b]	–	–	–	–	–	No
Walters, 2018	**(Low) MedDiet**	No[b]	–	–	–	↓ PCC	No	No
Karstens, 2019	**(high) MedDiet**	Larger GM of the dentate gyrus[b]	No		–	–	–	Yes (M, Lr)
Mosconi, 2014	**(high) MedDiet**	Thicker OFC, EC and PCC[b]	–	–	–	–	–	No
Titova, 2013	**MedDiet**	No[a]	–	–	–	–	–	No
	Meat	TBV[a]	–	–	–	–	–	Yes (composite)
Gu, 2015	**MedDiet/(high) MedDiet**	↑TBV, TGMV, and TWMV, cingulate cortex, PL, TL, HP and CT of the superior-frontal region[b]	–	–	–	–	–	No
	(high) Fruit	↓GMV of temporal lobe and hippocampus[b]	–	–	–	–	–	–
	(low) Meat	↑TBV, TGMV, cingulate cortex, PL, TL, and CT of the superior-frontal region[b]	–	–	–	–	–	–
	(high) Fish		–	–	–	–	–	–

(*continued on next page*)

Table 1 (*continued*)

Author, year	Dietary variables	Brain correlates						Association between dietary pattern and cognitive score? (cognitive domain)
		Volume/density	WMH	White Matter Integrity	Functional connectivity	Glucose Metabolism	PiB Retention	
		↑TGMV and mean CT, cingulate cortex, PL, TL, HP and CT of the superior-frontal region[b]						
Luciano, 2017	**(High) MedDiet**	↓ reduction of total brain volume but not GMV[a]	–	–	–	–	–	No

The included studies and reported dietary patterns were ordered to facilitate comparison between patterns and associations with cognitive domains and brain correlates. The reported brain correlates are bilateral if not indicated otherwise (R = right, L = Left). Null associations are indicated with a "No", non-studied links with a hyphen (-).
Abbreviations: ATT attention, CT cortical thickness, EC entorhinal cortex, EXE executive, FA fractional anisotropy, G global cognitive function, HP hippocampus, L language, Lleft, M memory, OFC orbitofrontal cortex, PL parietal lobe, PCC posterior cingulate cortex, PS processing speed, R right, SE Speed/executive, TBV total brain volume, TGMV total gray matter volume, TL temporal lobe TWMV total white matter volume, VS visuospatial, WMH - white matter hyperintensities, WP – world propensity.
[1]Nutrient patterns denomination altered from the original denomination to facilitate interpretation of the table.
[2]A latent factor of brain structure was generated by combining the ROI thickness measures using CFA to represent that construct.
↑ increased/higher; ↓ decreased/lower.
[#]mediation analyses.
*Lower MD and higher FA in the region that appeared preserved by the MedDiet were generally strongly associated with higher cognitive scores.
[a]voxel-based morphometry; [b]surface-based morphometry.

scores (Pelletier et al., 2015; Mosconi et al., 2018) and two combined all cognitive scores into one composite (Titova et al., 2013; Walters et al., 2018). According to reported study methods, all questionnaires were applied by experienced psychologists/trained research assistants. Whereas 7 studies mentioned that neuropsychological tests were applied several times (Pelletier et al., 2015; Luciano et al., 2017; Bowman et al., 2012; Gu et al., 2015, 2016; Berti et al., 2018; Walters et al., 2018), 7 studies did not report whether that was the case (Titova et al., 2013; Berti et al., 2015; Mosconi et al., 2014, 2018; Gu et al., 2018; Karstens et al., 2019; Zwilling et al., 2019). As for the applied tools, MMSE was the most widely used across the included studies to assess general cognition. Other cognitive domains were assessed using a variety of tests (Table A.1).

3.6. *Confounding variables*

Several non-dietary factors were included in the models. Age was either controlled for or, as in one study, all participants were aged 70 years (Titova et al., 2013). Likewise, education and gender were accounted for in the models. Physical activity was not reported or controlled for in 7 of the studies (Berti et al., 2015; Bowman et al., 2012; Gu et al., 2015, 2016; Luciano et al., 2017; Gu et al., 2018; Karstens et al., 2019). Similarly, carriers of ApoE4 were identified in 7 studies (Berti et al., 2015; Pelletier et al., 2015; Mosconi et al., 2014; Berti et al., 2018; Gu et al., 2018; Mosconi et al., 2018; Walters et al., 2018). Depression and depressant symptomatology were either controlled for or used as exclusion criteria (Berti et al., 2015; Bowman et al., 2012; Mosconi et al., 2014; Berti et al., 2018; Mosconi et al., 2018; Walters et al., 2018). Other confounding variables less frequently included in the models were body mass index, cardiovascular risk factors, ethnicity, occupation, socioeconomic status, cognitive enrichment activities, presence of a family history of Alzheimer's disease, the Homeostasis Model Assessment (HOMA, a proxy indicator of beta call function and insulin resistance), and intellectual activities. Analyses in all but one study (Zwilling et al., 2019) were corrected for the total intracranial volume.

3.7. *Neuroimaging techniques and brain correlates*

A wide range of neuroimaging techniques and brain markers were used (Tables 2 and 3). Whereas 8 studies examined cerebral macrostructural integrity such as volumes and presence of white matter hyperintensities (WMH) (Titova et al., 2013; Bowman et al., 2012; Luciano et al., 2017; Gu et al., 2015; Mosconi et al., 2014; Gu et al., 2018; Karstens et al., 2019; Mosconi et al., 2018), Zwilling et al., 2019 explored functional networks, and Gu et al., 2016 assessed white matter integrity. In addition, 6 studies combined two or more neuroimaging techniques. Pelletier et al., 2015; Karstens et al., 2019 and Bowman et al., 2012 focused on volumes and white matter integrity. Berti et al., 2015, 2018 and Walters et al., 2018, measured volumes, glucose metabolism and ^{11}C-Pittsburgh compound-B retention. All studies used magnetic resonance imaging to study the brain, with the exception of Berti et al., 2015, 2018 and Walters et al., 2018, in which PET was also used (see supplementary material for an in-depth description of the methodologies used to compute brain volumes and studied brain areas).

3.8. *Outcomes - results*

The included studies described associations of dietary patterns with both brain markers and cognitive scores (Table 2 and 3). The reported findings are presented as follows: 1) the MedDiet; 2) food groups/components from the MedDiet scores; and 3) nutrient patterns.

3.8.1. *MedDiet association with brain correlates and cognitive scores*

Higher adherence to the MedDiet correlated with larger total and regional brain volumes and higher white matter integrity. When total

Table 2
Summary of the studies assessing concurrent dietary/nutrient patterns.

AUTHOR, YEAR	NEUROIMAGING	DIETARY ASSESSMENT	TARGET GROUP[1], age M±SD, (N)	FINDINGS
Bowman, 2012	**EQ**: 1.5 T **Correlates**: total cerebral brain volume, white matter hyperintensities volume.	**Tool/method**: Nutrients blood biomarkers **Index:** Nutrient patterns through principal component analysis (PCA) **Energy adjustment Method:** Not applicable	≥65y, 87y±10, (n=104)	**A – Study of the brain parameters and dietary variables** - Participants with higher vitamin B, C, D and E scores had larger total cerebral brain volume, and those with high trans-fat scores had smaller total cerebral brain volume. - Marine n-3 scores were negatively associated with white matter hyperintensities volumes when adjusted for gender, education and APOE4. Yet, when controlled for depression and hypertension, the significance was lost. **B – Study of the neuropsychological tests and dietary variables** - Higher vitamins B, C, D and E scores had better global cognitive function (executive, attention and visuospatial function). - Higher marine n-3 scores had better executive function and those with higher lutein had higher memory scores. - Higher trans-fat scores had worse global cognitive function (attention, memory, language and processing speed.) - Higher n-6 scores had worse memory and language scores.
Mosconi, 2014	**EQ:** 1.5T **Correlates:** cortical thickness for entorhinal cortex, inferior parietal lobe, middle temporal gyrus, orbitofrontal cortex, and posterior cingulate cortex.	**Tool/method**: 61-item version of Harvard/Willett's semi-quantitative FFQ **Index:** MedDiet score adapted from Trichopoulu et al., 2003[2], cut-off ≥5 *Alterations*: - Fat intake: a ratio of daily consumption of monounsaturated to saturated fats - Alcohol intake - alcohol consumption was dichotomized into 1) mild to moderate alcohol consumption (>0 drinks per week) but <2 drinks per day in the previous year) and 2) no consumption (0 g/day) or more than moderate intake (>2 drinks per day). **Energy adjustment Method:** regressed caloric intake prior to scoring.	25-72 y, 54y±12, (n=52)	**A – Study of the brain parameters and dietary variables** - When compared to participants with low adherence to the MedDiet, participants with high adherence had overall greater thickness of AD-vulnerable ROIs (cortical thickness for entorhinal cortex, inferior parietal lobe, middle temporal gyrus, orbitofrontal cortex and posterior cingulate cortex. **B – Study of the neuropsychological tests and dietary variables** - There were no significant associations between the MedDiet score and neuropsychological measures.
Berti, 2015	**EQ**: 1.5T, PET **Correlates**: gray matter volumes (VBM), 11C-Pittsburgh compound-B (PiB; a marker of fibrillar amyloid-β, Aβ) and 18F-fluoro-deoxyglucose (FDG; a marker of glucose metabolism)	**Tool/method**: Harvard/Willet Food Frequency Questionnaire (applied by trained interviewers) **Index:** Nutrient patterns derived from PCA **Energy adjustment Method:** regressed caloric intake	25–72 y, 54±12, (n=52)	**A – Study of the brain parameters and dietary variables** - VitB12 and D pattern was positively associated with 1) glucose metabolism in several temporal regions, including superior and medial temporal areas, bilaterally and 2) GMV in temporal and frontal cortex, mostly of the right hemisphere. Conversely, VitB12 and D pattern was negatively associated with 1) PiB retention in parietal, frontal and posterior cingulate cortex. - Fats patternwas negatively associated with 1) glucose metabolismin middle and inferior temporal cortex, bilaterally, right frontal cortex, and left parietal cortex and 2) GMV in frontal cortex. - VitE and PUFA patternwas positively associated with 1) glucose metabolismin medial, inferior and lateral frontal cortex, bilaterally. - Antioxidants and Fibers pattern was positively associated with glucose metabolismin middle frontal and cingulate cortex of the left hemisphere; **B – Study of the neuropsychological tests and dietary variables** - No association regarding neuropsychological tests and the derived nutrient patterns.
Gu, 2015	**EQ**: 1.5 T **Correlates**: total brain volume, total gray	**Tool/method**: Harvard/Willet Food Frequency Questionnaire (applied by trained interviewers)	≥65y, 80.1±5.6, (n= 674)	**A – Study of the brain parameters and dietary variables** - Higher adherence was associated with larger

(*continued on next page*)

Table 2 (*continued*)

AUTHOR, YEAR	NEUROIMAGING	DIETARY ASSESSMENT	TARGET GROUP[1], age M±SD, (N)	FINDINGS
	matter volume, total white matter volume, mean cortical thickness.	**Index:** MEDDIET score adapted from Trichopoulu et al., 2003[2], continuous variables and cut-off ≥5 *Alterations:* - Fat intake: a ratio of monounsaturated fats to saturated fats, - Alcohol intake: Mild to moderate alcohol consumption (>0 to <30 g/day) assigned one point. Otherwise the score would be zero. **Energy adjustment Method:** regressed caloric intake prior to scoring.		total brain volume, total gray matter volume and total white matter volume. - Higher fish and lower meat intakes were associated with larger total gray matter volume. Lower meat intake was also associated with larger total brain volume. Higher fish intake was associated with larger mean cortical thickness. - Gray matter volumes of cingulate cortex, parietal lobe, temporal lobe, hippocampus and cortical thickness of the superior-frontal region were associated with adherence to the MedDiet and higher consumption of fish. Similarly, low meat intake was also associated with larger gray matter volumes of the previous regions except for hippocampus. In turn, higher fruit intake was associated with lower temporal and hippocampus volume. **B – Study of the neuropsychological tests and dietary variables** - Participants with lower MedDiet adherence did not differ from those with higher adherence in terms of any cognitive score.
Mosconi, 2018	**EQ:**3 T **Correlates:** Cortical thickness entorhinal of cortex, posterior cingulate cortex, orbitofrontal cortex, inferior and middle temporal gyrus.	**Tool/method**: Harvard/Willet Food Frequency Questionnaire **Index:** MedDiet score adapted from Trichopoulu et al., 2003 [2], continuous variable *Alterations* - fat intake: a ratio of daily consumption of monounsaturated to saturated fats, - alcohol intake: alcohol consumption was dichotomized into 1) mild to moderate alcohol consumption (>0 drinks per week but <2 drinks per day in the previous year) and 2) no consumption (0 g/day) or more than a moderate intake (>2 drinks per day). **Energy adjustment Method:** regressed caloric intake prior to scoring	30-60y, 50y±6, (n= 116)	**A – Study of the brain parameters and dietary variables** - MedDiet significantly and independently predicted brain structure (latent construct composed by the cortical thickness of the following areas: entorhinal of cortex, posterior cingulate cortex, orbitofrontal cortex, inferior and middle temporal gyrus) **B – Study of the neuropsychological tests and dietary variables** - MedDiet was not associated with cognitive function.
Gu, 2016	**EQ**: 1.5 T **Correlates**: fractional anisotropy	**Tool/method**: Harvard/Willet Food Frequency Questionnaire (applied by trained interviewers) **Index:** Nutrient patterns derived from PCA **Energy adjustment Method:** regressed caloric intake	≥65y, 84.1y±5.1, (n=239) (n=28 met the diagnostic criteria for dementia at neuroimaging visit).	**A – Study of the brain parameters and dietary variables** - Nutrient pattern-6, characterized by high intakes of n-3 and n-6 PUFAS and vitamin E was positively associated with fractional anisotropy. **B – Study of the neuropsychological tests and dietary variables** - Fractional anisotropy mediated the relationship between nutrient pattern-6 and memory, language, visuospatial, speed/ executive function, and mean cognitive scores.
Zwilling, 2019	**EQ**: 3T **Correlates**: small world organization of the intrinsic connectivity network maps: visual, somatosensory, limbic, default mode, dorsal attention, ventral attention and frontoparietal	**Tool/method**: Nutrients blood biomarkers **Index:** Nutrient patterns through PCA **Energy adjustment Method:** Not applicable	65-75y, 69y±3.2, (n=116)	**A – Study of the brain parameters and dietary variables** - N-6 pattern was positively associated with the somatomotor and the ventral attention networks. - N-3 pattern was positively associated with the visual network. - Carotene pattern demonstrated a positive association with the limbic network. - Vitamin BD pattern was negatively associated with the fronto-parietal networks. - MUFA:SFA ratio pattern was negatively associated with ventral attention. **B – Study of the neuropsychological tests and dietary variables** - The n-3/n-6 mixture was positively associated with two measures of memory: WMS auditory and WMS delayed. - Lycopene was positively associated with three measures of memory: WMS auditory, WMS immediate and WMS delayed.

(*continued on next page*)

Table 2 (*continued*)

AUTHOR, YEAR	NEUROIMAGING	DIETARY ASSESSMENT	TARGET GROUP[1], age M±SD, (N)	FINDINGS
				-The n-3 pattern was positively associated with three measures of executive function: DKEFS switch, DKEFS switch minus search and DKEFS switch minus an aggregate score for numbers and letters. - DKEFS switch minus search: the vitamin BD pattern demonstrated a positive association while the MUFA:SFA ratio has a negative association. **C - Moderation of nutrient patterns on the relationship between brain parameters and cognitive function** - N-6 NBP moderates the dorsal attention network in predicting DKEFS switch measure of executive function. - Lycopene NBP moderates the dorsal attention network in predicting DKEFS switch measure of executive function.
Karstens, 2019	**EQ**: 3T **Correlates:** hippocampus and the dentate gyrus volumes and white matter hyperintensities volume.	**Tool/method**: Block 2005 Food frequency questionnaire by a trained research assistant **Index:** MedDiet scoresadapted from Panagiotakos et al., 2007. **Energy adjustment Method:** regressed caloric intake	>60y, 68.8y±6.9, (n=82)	**A – Study of the brain parameters and dietary variables** - High MedDiet group had significantly larger dentate gyrus volumes when compared with the Low MedDiet group. There was no significant effect of the MedDiet group on log-transformed WMH volumes or total white matter volume. **B – Study of the neuropsychological tests and dietary variables** - High MedDiet group had significantly better Leaning and memory composite scores when compared with the Low MedDiet group. There was no significant effect of the MedDiet group on information processing or executive functioning.

Abbreviations: DKEFS - Delis-Kaplan Executive Function System, EQ- equipment, FDG - 18F-fluorodeoxyglucose, FFQ – food frequency questionnaire, PCA – principal component analysis, PiB – Pittsburgh compound B, T – Tesla, WMS - Wechsler Memory Scale.

1– If not indicated otherwise, studies recruited participants living in the community free of dementia.

2 – The adherence to the MedDiet score ranges from 0 to 9, with higher values indicating higher adherence to this dietary pattern (Trichopoulou et al., 2003). To compute the final score, after determining the sex-specific median of the relevant food groups, the scoring applies. For the beneficial dietary variables, a 1 is assigned to those individuals whose intake is above the median, and a zero to those whose intake is below. For the detrimental dietary variables, the reverse scoring took place. If the studies reported an adaptation of the original score, those alterations were described.

brain volumes and/or total gray matter volumes differed significantly with different levels of adherence to the MedDiet, no association was found with cognitive scores (Titova et al., 2013; Gu et al., 2015). Conversely, a positive correlation was found with gray matter volumes of specific brain areas such as the dentate gyrus (Karstens et al., 2019) and thickness of orbitofrontal cortex, entorhinal cortex and posterior cingulate cortex (Mosconi et al., 2014, 2018), but not with others such as the hippocampus (Gu et al., 2015). As for the white matter hypersensitivities (WMH), no difference was detected between high and low adherence to the MedDiet (Karstens et al., 2019; Pelletier et al., 2015). In contrast to WMH, high adherence to the MedDiet was associated with lower diffusivity, which in turn was associated with higher cognitive scores (Pelletier et al., 2015). Likewise, no differences in brain volumes were recorded between low and high adherence to the MedDiet, but low adherence to the MedDiet was associated with steeper declines of glucose metabolism in the temporal cortex (Berti et al., 2018) and posterior cingulate cortex (Walters et al., 2018; Berti et al., 2018). It is worth noting that low adherence to the MedDiet was associated with increased B-amyloid in the left frontal parietal cortex (Berti et al., 2018).

3.8.2. *Food groups/components derived from MedDiet scores association with brain correlates and cognitive scores*

As for the components of the MedDiet, the results were inconsistent. For instance, no correlations were found between high fish intake, brain volumes and cognition (Luciano et al., 2017). In contrast, Gu et al., 2015, found that high fish intake was associated with larger total GMV, and cortical thickness of several brain regions but not with cognitive scores (Gu et al., 2015). Likewise, whereas meat intake was negatively associated with total brain volume and cognition (Titova et al., 2013), as well as cingulate, parietal and temporal GMV (Gu et al., 2015), meat intake was not associated with total brain volume or total gray matter volume (Luciano et al., 2017). Interestingly, Titova et al., 2013 observed that the meat food group was negatively associated with brain correlates and cognition rather than the MedDiet score (Titova et al., 2013).

3.8.3. *Clusters of nutrients association with brain correlates and cognitive scores*

When analyzing clusters of nutrients, all identified patterns were associated with both cognitive scores and brain markers, except in the studies by Berti et al., 2015 and Berti et al., 2018. The B vitamins, vitamins C, D and E cluster correlated with larger total brain volumes and higher cognitive scores as opposed to the high trans-fat cluster (Bowman et al., 2012). The PUFA and vitamin E pattern was associated with memory, language, visuospatial and speed/executive function, and mean cognitive scores were mediated by FA (Gu et al., 2016). The omega-3 nutrient pattern moderated the relationship between frontal, parietal network and Wechsler Adult Intelligence Scale (representative of general cognition), whereas the omega-6 cluster and lycopene cluster moderated the dorsal attention network in predicting executive function (Zwilling et al., 2019). The omega-6 pattern was positively associated with the somatomotor and ventral attention networks, and the dorsal attention network was positively associated with executive functioning.

Table 3
Summary of the studies assessing past dietary/nutrient patterns.

AUTHOR, YEAR	NEUROIMAGING	DIETARY ASSESSMENT	LENGTH	TARGET GROUP[1], age M±SD, (N)	FINGINDS
Titova, 2013	**EQ**: 1.5 T **Correlates:** total brain volumes, gray matter volume, white matter volume (VBM)	**Tool/method**: 7-day food diary **Index:** MedDiet score adapted from Trichopoulu et al., 2003[2], continuous variable. *Alterations* **-** Alcohol intake:1 was assigned to those falling within moderate consumption: 10-50g/day for males and 5-25/day for females. - Fat intake: PUFA were replaced by monosaturated fat, and nuts and seeds were excluded, and pulses added to the vegetables score. - Cereals intake: Potato was added to the cereals item. **Energy adjustment Method:** Residual adjusted method prior to scoring	5y	75y, 75.3±0.01 (n=193) (mostly cognitively normal individuals, cognitive impairment and dementia, n=8)	**A – Study of the brain parameters and dietary variables** - No associations between the MedDiet score and volumes of gray matter, white matter, or their sum. - A negative association between the self -reported intake of meat and meat products and total brain volume. **B – Study of the neuropsychological tests and dietary variables** - The MedDiet score was positively associated with global cognitive score in the model controlled for age, but not in the fully adjusted model. - Higher intakes of meat were associated with lower global cognitive scores in both models.
Pelletier, 2015	**EQ**: 3T **Correlates:** GM and WMvolumes (VBM), fractional anisotropy, axial diffusivity, radial diffusivity, mean diffusivity represents a global measure of diffusion.	**Tools and methods**: FFQ and 24h recall by a trained dietitian. Food groups were derived from the FFQ, whereas the 24h recall allowed to estimate nutrient and total energy intake and the ratio of monounsaturated-to-saturated fatty acids. **Index**: MedDiet score adapted from Trichopoulu et al., 2003, continuous variable. *Alterations* - Alcohol intake: 1 point was given for consumption between 4 and 15 glasses/week in men and 0 and 2 glasses in women. **Energy adjustment Method:** regressed caloric intake	9y	67.7-83.2y, 73y (n=146)	**A – Study of the brain parameters and dietary variables** - MedDiet was not associated with white matter volumes nor grey matter volumes in any studied brain area. - Higher MedDiet score was associated with 1) lower diffusivity values in the whole corpus callosum (genu, body, and splenium), anterior and posterior thalamic radiations, paracingulate gyrus cingulum, and parahippocampal fornix and 2) higher FA values in the corpus callosum, anterior and posterior thalamic radiations. **B - Study of neuropsychological tests, dietary variables and brain parameters** - Higher fractional anisotropy values in the region that appeared preserved by the MedDiet were generally strongly associated with higher cognitive scores.
Luciano, 2017	**EQ**: 1.5 T **Correlates**: mean cortical thickness, total gray matter volume (VBM); total brain volume.	**Tools**: The Scottish Collaborative Group 168-item Food Frequency Questionnaire. **Index**: MedDiet score adapted from Trichopoulu et al., 2003[2], cut-off ≥5 *Alterations* - Alcohol intake: Moderate alcohol consumption was defined for men as between 10 and 50 g alcohol per day and for women between 5 and 25 g per day. **Energy adjustment Method:** Residual adjusted method prior to scoring and exclusion of individuals with extreme energy intakes (<2.5th or >97.5th centile).	3y	70 y, 72.7y±0.7, (n=562) .	**A – Study of the brain parameters and dietary variables** - Lower adherence to the MedDiet was associated with greater 3-year reduction in total brain volume, but not gray matter volume. - Cross-sectional associations between the MedDiet and baseline gray matter volumes or cortical thickness were not significant. - Meat and fish consumption were not associated with total brain volume or total gray matter volume. **B – Study of the neuropsychological tests and dietary variables** - Global cognition scores did not differ between low and high adherence to the MedDiet.
Berti, 2018	**EQ:** 3T, PET **Correlates**: gray matter volumes (VBM), 11C-Pittsburgh compound-B (PiB; a marker of fibrillar amyloid-β, Aβ) and 18F-fluorodeoxyglucose (FDG; a marker of glucose metabolism)	**Tool**: Harvard/Willet Food Frequency Questionnaire (applied by trained interviewers) **Index** - MedDiet score adapted from Trichopoulu et al., 2003[2], cut-off ≥5 *Alterations* - Fat intake: a ratio of monounsaturated fats to saturated fats, - Alcohol intake: mild to moderate alcohol consumption (>0 to <30 g/ day) assigned one point. Otherwise the score would be zero. **Energy adjustment Method:** Residual adjusted method prior to scoring.	2y	30-60 y, 50y±8 (n=52)	**A – Study of the brain parameters and dietary variables** - No group differences in grey matter volumes were observed at neither cross-sectional nor longitudinal analyses. - At baseline, the low MedDiet group showed reduced glucose metabolism in temporal cortex bilaterally compared to the high MedDiet group. - Low MedDiet group showed higher rates of glucose metabolism declines compared to the high MedDiet group in temporal and posterior cingulate cortex/ precuneus. - At baseline, the low MedDiet group showed higher PiB uptake in the frontal

(*continued on next page*)

Table 3 (*continued*)

AUTHOR, YEAR	NEUROIMAGING	DIETARY ASSESSMENT	LENGTH	TARGET GROUP[1], age M±SD, (N)	FINGINDS
					cortex compared to the high MedDiet group - Longitudinally, both groups showed increased PiB uptake in frontal regions. The low MedDiet group showed additional clusters of increasing PiB uptake in the parietal cortex of the right hemisphere **B – Study of the neuropsychological tests and dietary variables** - There were no group differences for clinical and neuropsychological measures.
Gu, 2018	**EQ: 1.5T** **Correlates**: total brain volume (TBV), total gray matter volume (TGMV), and total white matter volume (TWMV), White matter hyperintensity volumes	**Tool**: Harvard/Willet Food Frequency Questionnaire (applied by trained interviewers) **Index** Reduced Rank Regression model using inflammatory markers (CRP, IL-6) as response variables. **Energy adjustment Method:** regression residual method	4.5y and 5.3y[3]	≥65y, 79y±5.8, (n=330)	**A – Study of the brain parameters and dietary variables** - The inflammatory nutrient pattern was associated with lower visuospatial z-score. **B – Study of the neuropsychological tests and dietary variables** The inflammatory nutrient pattern was associated with smaller TBV, TGMV, and TWMV. **C - Mediation of nutrient patterns on the relationship between brain parameters and cognitive function** - TGMV mediated the association between inflammatory nutrient pattern with visuospatial cognitive score.
Walters, 2018	**EQ**: 3 T **Correlates**: Cortical thickness of entorhinal cortex and posterior cingulate cortex, and PiB uptake and FDG of PCC and frontal cortex.	**Tool/method**: Harvard/Willet Food Frequency Questionnaire **Index:** MedDiet score adapted from Trichopoulu et al., 2003[2], continuous variable *Alterations* - fat intake: a ratio of daily consumption of monounsaturated to saturated fats,- alcohol intake: alcohol consumption was dichotomized into 1) mild to moderate alcohol consumption (>0 drinks per week but <2 drinks per day in the previous year) and 2) no consumption (0 g/day) or more than a moderate intake (>2 drinks per day). **Energy adjustment Method:** caloric intake-adjusted daily gram	3y	30-60y, 49y±8, (n= 70)	**A – Study of the brain parameters and dietary variables** - MedDiet was neither associated with PiB intake nor with cortical thickness at baseline and follow-up. - Lower MedDiet adherence at baseline was associated with faster rates of FDG declines on the posterior cingulate cortex. **B – Study of the neuropsychological tests and dietary variables** - Both at baseline and follow up, MedDiet was not associated with cognitive scores.

Abbreviations: CRP - C-reactive Protein, EQ - equipment, FDG - 18F-fluorodeoxyglucose, FFQ - food frequency questionnaire, IL6 - Interleukin-6, PCA - principal component analysis, PiB -Pittsburgh compound B, T - Tesla, VBM - voxel-based morphometry.

1- If not indicated otherwise, studies recruited participants living in the community who were free of dementia.

2 - The adherence to the MedDiet score ranges from 0 to 9, with higher values indicating higher adherence to this dietary pattern (Trichopoulou et al., 2003). To compute the final score, after determining the sex-specific median of the relevant food groups, the following scoring applies: 1) for the beneficial dietary variables, a 1 is assigned to those individuals whose intake is above the median, and a zero to those whose intake is below; 2) for the detrimental dietary variables, the reverse of this scoring was used. If the studies reported an adaptation of the original score, those alterations are described in the table.

3 - The MRI scans and cognitive assessment were performed on average 4.5 (±0.9) years after the blood samples were collected, and 5.3 (±2.7) years after the dietary assessment.

However, the omega-6 and lycopene pattern moderated the dorsal attention network in predicting executive function rather than the somatomotor and ventral attention network. The inflammatory nutrient pattern, characterized by low intakes of calcium and vitamin D, antioxidants such as vitamins E and A, several B vitamins, and n-3 PUFA, and high intake of cholesterol, was negatively associated with TBV, TGMV, and TWMV and visuospatial domain (Gu et al., 2018). The remaining patterns identified were neither associated with brain correlates nor with cognitive scores (Gu et al., 2016; Zwilling et al., 2019; Bowman et al., 2012).

3.8.4. Brain regions/white matter bundles

Both global and regional volumes were studied. Of those focusing on total brain volumes, TBV was positively associated with nutrient pattern Vitamins B, C, D and E (Bowman et al., 2012) and high MedDiet (Gu et al., 2015), and negatively associated with trans-fat (Bowman et al., 2012), meat intake (Gu et al., 2015; Titova et al., 2013) and the inflammation-related nutrient pattern (Gu et al., 2018). Total gray matter volume was positively associated with the MedDiet and fish intake and negatively associated with meat consumption (Gu et al., 2015) and the inflammation-related nutrient pattern (Gu et al., 2018). Total white matter volume was positively linked with the MedDiet (Gu et al., 2015) and negatively associated with the inflammation-related nutrient pattern (Gu et al., 2018). As for regional brain volumes, temporal gray matter volume was positively correlated with vitamins B12 and D (Berti et al., 2015), the MedDiet and fish intake, and negatively associated with fruit and meat consumption (Gu et al., 2015). Regional gray matter of frontal cortex was positively correlated with vitamins B12 and D and negatively correlated with saturated fat, trans-fat and dietary cholesterol (Berti et al., 2015). Parietal lobe GM was also associated with the MedDiet and fish and meat intake (Gu et al., 2015). Specific cortical regions volumes were also tested. More specifically, cingulate cortex, orbitofrontal cortex, posterior cingulate cortex, entorhinal cortex, dentate gyrus and hippocampus (Mosconi et al., 2014; Gu et al., 2016; Mosconi et al., 2018; Karstens et al., 2019). Similarly, temporal cortical thickness was also associated with the MedDiet (Mosconi et al., 2018). Additionally, cortical thickness of superior frontal regions was positively associated with the MedDiet and fish consumption, and negatively associated with meat intake (Gu et al., 2015).

As for the white matter integrity, whereas Gu et al., 2016 reported that 26 white matter tracts had an overall increase of FA with Vitamin E and PUFA (Gu et al., 2016), Pelletier et al., 2015 reported that higher intake of dairy products was associated with higher RD and lower FA values, and moderate alcohol intake with lower diffusivity of specific white matter bundles. That is, these alterations of the WH integrity were limited to the genu and body of corpus callosum. As for the Mediterranean diet, higher scores of the MedDiet were associated with lower diffusivity in the whole corpus callosum, anterior and posterior thalamic radiations, paracingulate gyrus cingulum and parahippocampal fornix (Pelletier et al., 2015).

3.9. Quality appraisal

According to the NIH quality assessment, the quality of the included studies ranged from fair to good (Table A.2). None of the studies reported whether the assessors of the outcomes were blinded to the exposure status.

4. Discussion

This systematic review identified 14 studies that simultaneously assessed cognition, dietary patterns and neuroimaging correlates in middle-aged to older adults. The variety of questionnaires to assess cognitive status, methods to ascertain dietary patterns and available neuroimaging techniques precludes the ability to conduct a meta-analysis. As such, a narrative synthesis of the eligible/included studies was conducted. In addition to highlighting the wide variability of methodologies used in the included studies, this review provides unique insights into how dietary patterns may be associated with changes in brain correlates, and in turn could influence cognition scores in later life. The evidence from this review supports the presence of an association between diet and vascular and neurodegenerative pathways, which in turn relate to brain markers. Specifically, the MedDiet and other nutrient patterns were associated with white matter integrity, functional connectivity, total and regional brain volumes and glucose metabolism. In addition, in the included studies, associations of dietary patterns with cognitive scores were consistently described in association with an alteration of at least one brain correlate. This suggests that studies reporting no effect of dietary interventions on cognitive health (as assessed via neurocognitive tests) should not be interpreted as evidence of a lack of effect of dietary intake on brain health.

As is evident from the combination of neuroimaging, neuropsychological tests and dietary assessment employed in studies in the present review, the influence of diet on cognition should not be examined using only neuropsychological tests. In this review, dietary patterns were associated with a wide range of brain markers and, in some cases, these differences were reflected in cognitive scores both through direct association and mediation/moderation analyses. These findings indicate that diet, and its components, could potentially impact the brain through several brain correlates that were reported to contribute to and precede cognitive decline. Specifically, changes in glucose metabolism (Camandola and Mattson, 2017; Cunnane et al., 2011), white matter integrity (Bennett and Madden, 2014; van Leijsen et al., 2018; Ly et al., 2014), functional connectivity (Reijmer et al., 2015; Marstaller et al., 2015), and brain volumes (Tondelli et al., 2012; Smith et al., 2007) have been shown to precede cognitive decline. In addition, several dietary components have been shown to be associated with these brain correlates. For instance, vitamin D appears to promote white matter integrity by protecting against axonal loss (Nystad et al., 2018), omega-3 fatty acids were associated with individual differences in functional connectivity (Talukdar et al., 2019), and docosahexaenoic acid (DHA) has been shown to control GLUT1 expression and glucose transport into the brain (Cunnane et al., 2009). The evidence shows a wide range of brain markers associated with diet, yet the association with cognitive scores is inconsistent. A possible explanation for this inconsistency is the effect of each individual's cognitive reserve, i.e. the capacity of the brain to deal with damage (Stern, 2002). Indeed, factors known to contribute to cognitive reserve, such as engagement in leisure activities, were not accounted for in the included studies (Scarmeas and Stern, 2003).

The results from this systematic review provide some support for both the neurodegeneration and vascular hypotheses through which diet has been reported to impact on cognition. While the vascular hypothesis posits that diet can preserve brain function through its effects on the vasculature such as lowering blood pressure, inflammation and serum triglycerides levels, as well as the risk of thrombosis (Tan et al., 2012; Zamroziewicz et al., 2015), the neurodegenerative pathway suggests that brain atrophy is due to axonal damage, increased amyloid-B production and deposition, and increased neuroinflammation and oxidative stress (Tan et al., 2012; Zamroziewicz et al., 2015). In our review, three aspects support both hypotheses. First, dietary patterns were reported to be associated with brain markers of both neurodegeneration and vascular damage. Neurodegeneration was both indicated by higher PiB retention, i.e., a specific marker of amyloid B, associated with lower adherence to the MedDiet (Berti et al., 2018), larger brain volumes linked with a plasma profile high in vitamins C, E and D and B vitamins (Bowman et al., 2012) and smaller total brain volume associated with the inflammation-related nutrient pattern (Gu et al., 2018). Vascular mechanisms were suggested by the negative association of the marine omega-3 fatty acids with hyperintensities volumes but not with total brain volumes (Bowman et al., 2012). Second, lower cognitive scores were associated with less preserved white matter in the absence of brain atrophy (Pelletier et al., 2015), implying a link between vascular mechanism and cognitive performance. In fact, impaired microstructural integrity has been shown to precede conversion into white matter hypersensitivities (van Leijsen et al., 2018) and white matter atrophy (Ly et al., 2014). Note that white matter lesions are a surrogate of small-vessel vascular disease that is predictive of cognitive performance (Prins and Scheltens, 2015) and cognitive decline, even in the absence of volume changes (O'Brien et al., 2003). Third, vascular mechanisms were also implied by mediation analyses conducted on the association of diet with cognition. Specifically, despite the MedDiet being associated with cognitive scores and larger GM of the dentate gyrus, brain volume losses did not mediate the relationship between the MedDiet and cognitive scores. This suggests that the identified association between the MedDiet and cognitive scores was possibly influenced by vascular rather than a neurodegenerative mechanism (Karstens et al., 2019). Indeed, recent studies support the role of vascular factors on cognitive scores without brain volume loss (Samieri et al., 2018). Conversely, the association of the inflammation-related nutrient pattern with the visuospatial cognitive domain was mediated by the total gray matter volume (Gu et al., 2018) which suggests a neurodegenerative mechanism. Taken together, these findings suggest that dietary patterns could impact on cognition through different nutrients and different mechanisms, supporting the need to apply multimodal approaches to comprehensively study if, and how, diet exerts its effects on cognition.

For this review, only studies assessing dietary patterns were included as they better reflect the concept of food synergy, i.e. additive or more than additive influences of foods and food constituents on health (Jacobs and Tapsell, 2013). The reviewed studies employed two methods to assess dietary intake: subjective (self-report) and objective (biomarkers). Subjective methods obtain data on aspects of diet through the participant's accounts. As a result, aspects such as misreporting of food items and portions, desirability bias, and recall bias represent limitations (Potischman, 2003; Shim et al., 2014). To minimize the impact of misreporting, methods such as the exclusion of participants whose reported energy consumption is above or below defined thresholds or control for energy intake were applied (Willett et al., 1997). In this review, several tools were applied to collect the dietary data: the food frequency questionnaire (FFQ) exclusively or combined with 24 h recall and 7-day food diaries. FFQs are designed to assess habitual food intake and take into consideration seasonal food items. However, FFQs do not include all food items one may consume (Berti et al., 2015). Food diaries can minimize recall bias if appropriately recorded, as well as provide a detailed description of amounts and brands of foods and methods of preparation. However, it is well-recognized that recording dietary intake can alter one's diet, and the assessment of food items eaten less than once or twice per week may not be accurate (Willett et al., 1997).

Biomarkers, as an objective method, overcome some of the limitations aforementioned (Potischman, 2003; Shim et al., 2014). Yet, biomarker values should be interpreted with caution, taking into consideration several factors. First, even though a nutritional biomarker is a sound measure of the available amount of a given nutrient after absorption and metabolism, it does not always relate closely to the amount of a nutrient present in the diet (Potischman, 2003). Several factors explain this difference such as interactions during absorption, age-related alterations in tissue turnover and excretion, and medical aspects such as diseases, inflammation or current medication (Potischman, 2003; Blanck et al., 2003). Second, whereas plasma and serum biomarkers reflect the short-term intake from a few days to one month, questionnaires such as FFQs capture long-term general intakes (Potischman, 2003). As both have strengths and weaknesses, one solution might be to combine biomarkers along with dietary data. This combination of methods has been effectively used to minimize the aforementioned limitations and reduced the sample size by 20–50 % of those required to improve accuracy via conventional analyses of self-reported intake (Freedman et al., 2010).

Besides the aspects related to diet assessment, the methods through which dietary patterns were derived warrant a detailed examination. In this review, studies reported either a MedDiet score or nutrient patterns derived from PCA or RRR. While these methods are more readily translatable into practical guidance for the public (Hu and Willett, 2018), they do not allow comparison among the studies resorting to the same method. For instance, concerning the MedDiet score, except for Karsterns et al., 2019, all the other studies assigned 0 or 1 according to the within population sex-specific median, i.e., if in study A the sample reported a median of 200 g of vegetables and in study B the median was 130 g, 1 would be assigned to different amounts of vegetables. This scoring method makes it difficult to compare results between studies. In addition, cut-offs for scoring fats and alcohol differed among studies. Likewise, PCA and RRR focus on the combination of foods/nutrients and therefore more closely approximate the population's dietary exposures (Michels and Schulze, 2005), but do not allow comparisons as the computed factor loadings are sample-specific. Note that while the aim is the same, i.e. generate relevant nutrient/food clusters, the method differs. That is, whereas PCA clusters best explain the variations in intake, RRR best explains the variations in outcome variables, as for its computation it requires a response variable, e.g. CRP blood levels (Michels and Schulze, 2005). Another important aspect is related to the fact that eating indexes might mask the effects of specific dietary components (Titova et al., 2013) by including items that are not relevant. In fact, when the MedDiet and its components were studied, slightly different results were yielded. For example, while meat consumption was negatively associated with brain volumes and cognition, the same was not true for the MedDiet score (Titova et al., 2013). As a result, despite the advantages of exploring the effects of dietary pattern due to the interactions between nutrients, the study of each component can add interesting insights.

As with all studies, there are limitations that offer opportunities for further research. None of the included studies were designed to establish causal relationship. Studies were either cross-sectional which cannot exclude reverse causation, or observational longitudinal studies where residual confounding is inherent. In addition, only studies focusing on the MedDiet met the inclusion criteria. As such, it remains to be explored the extent to which other dietary patterns may impact on brain correlates and cognition. Similarly, other brain-related mechanisms are still to be explored. For instance, cerebral blood flow (CBF) is a brain correlate that could be studied given the promising results of vegetables-derived nitrate in both CBF and cognitive performance (Presley et al., 2011; Wightman et al., 2015). Nitrate-induced changes in cerebral flow and the consequent impact on cognitive performance appears to be mediated by the vasodilator effect of nitric oxide (Kitaura et al., 2007) that is naturally converted upon ingestion (Lundberg et al., 2008). In the studies in which there was a delay between initial dietary assessment, neuroimaging, and neuropsychological assessments, not all studied the stability of the pattern. It is also important to note that the study of dietary patterns is not specific as to the particular nutrients accountable for the observed differences (Hu, 2002). Furthermore, publication bias cannot be entirely discounted, as studies showing positive results are more likely to be published. Finally, studies published in non-English language journals were excluded which could have introduced a systematic bias.

Despite these limitations, to our knowledge this is the first comprehensive examination of the associations between dietary patterns with cognition and a multimodal neuroimaging approach. Given the interactions between nutrients, the study of dietary patterns yields more actionable findings. Thus, understanding the changes on brain correlates in a field where changes can take decades to reflect on neuropsychological test performance is a major benefit (Fig. 2). This review underlines the importance of complementing nutrition and ageing research with neuroimaging.

The challenge for future research will be to develop studies where cognitively healthy individuals are either followed-up for a suitable amount of time, or subjected to interventions where each individual is periodically assessed by a comprehensive protocol. Specifically, at each time point, objective dietary biomarkers complemented with self-report dietary data, multimodal neuroimaging techniques and sensitive neuropsychological testing data could help advance the field. In addition, the monitoring of physical activity and physical function, as well as other relevant outcomes should not be overlooked.

5. Conclusion

Combining neuropsychological assessment with neuroimaging techniques to study the association of dietary patterns with cognitive performance has the advantage of providing additional insights into the relationship between diet and cognition and potential mechanisms. In this review, dietary patterns and nutrient patterns/clusters were associated with a wide range of brain markers and, in some cases, these differences were reflected in cognitive scores. Studies including mediation analyses or applying a multimodal neuroimaging approach to study specific nutrient clusters also provided important information on mechanisms by suggesting that both neurodegeneration and vascular mechanisms are likely involved. Thus, the evidence provided by this review supports the need to include neuroimaging techniques in cognition-related studies, and suggests that a healthy diet should be included in recommendations to promote a healthy brain.

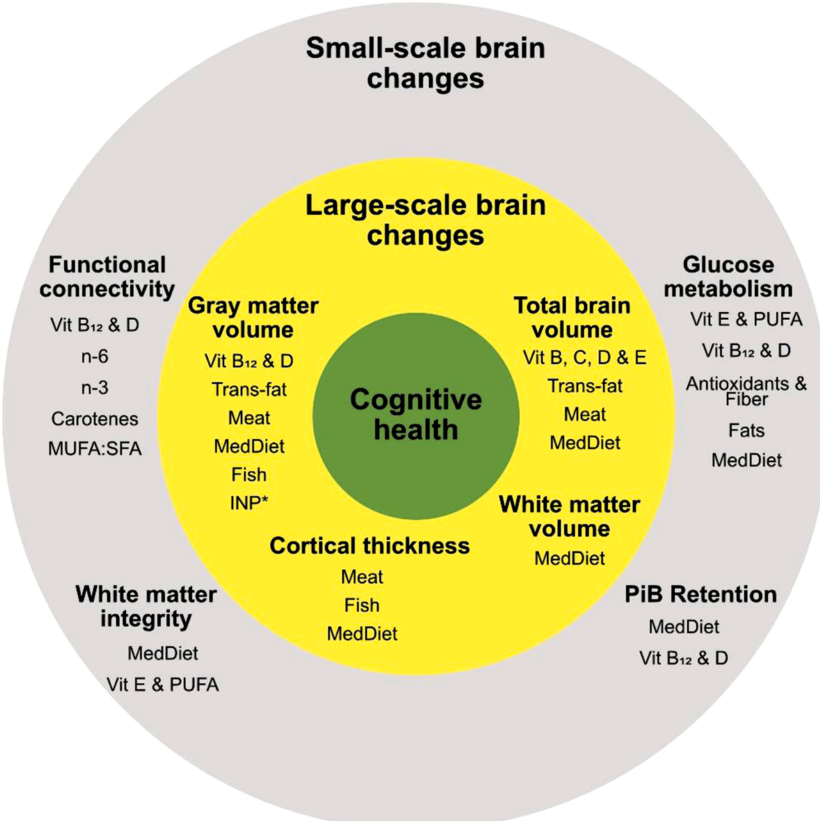

Fig. 2. Summary of the findings. This review found several dietary variables associated with small-scale brain changes or changes of the cerebral microstructure and large-scale brain changes or changes of the cerebral macrostructure. For instance, an increased brain glucose metabolism was associated with several nutrient patterns (e.g. Vitamin E and PUFA and Vit B12 and D) and with dietary patterns such as the Mediterranean diet (MedDiet). Similarly, other small-scale brain changes were associated with other dietary patterns. Besides the cerebral microstructure changes, large-brain changes such as the reduction of gray matter volume or total brain volume were also associated with dietary components or patterns. Both microstructure and macrostructure changes have been reported to be associated with the cognitive health of older adults. Abbreviations: INP - inflammation-related Nutrient Pattern.

Author's contributions

BR and NCS conceptualized the paper. BR wrote the first draft of the paper. BR and EAA conducted the screening of the articles. The paper was revised by EAA, RM, NS, JLT and NCS. BR prepared the figures and tables. All the authors approved the final version of the manuscript.

Funding

This work (BR and EAA) was supported by European Commission, Horizon 2020 under the scope of the Physical Activity and Nutritional INfluences In ageing (PANINI) Innovative Training Network [Grant number: 675003]. BR and EAA are Marie Curie Early Stage Researchers, and JLT, and NS and NCS their respective doctoral supervisors. R.M. was financed by the MrROBOT project (Multi-Regional Research on Brain – Optimized Therapy) supported by the Cancéropôle Île-de-France and the French National Cancer Institute ('PAIR pédiatrie' 2017 program). This work was also funded through the Foundation for Science and Technology (FCT) - project UIDB/50026/2020 and UIDP/50026/2020; and by the projects NORTE-01−0145-FEDER-000013 and NORTE-01−0145-FEDER-000023, supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2020.101145.

References

Bennett, I.J., Madden, D.J., 2014. Disconnected aging: cerebral white matter integrity and age-related differences in cognition. Neuroscience 276, 187–205. https://doi.org/10.1016/j.neuroscience.2013.11.026.

Berti, V., Murray, J., Davies, M., Spector, N., Tsui, W.H., Li, Y., Williams, S., Pirraglia, E., Vallabhajosula, S., McHugh, P., Pupi, A., de Leon, M.J., Mosconi, L., 2015. Nutrient patterns and brain biomarkers of Alzheimer's disease in cognitively normal individuals. J. Nutr. Health Aging 19, 413–423. https://doi.org/10.1007/s12603-014-0534-0.

Berti, V., Walters, M., Sterling, J., Quinn, C.G., Logue, M., Andrews, R., Matthews, D.C., Osorio, R.S., Pupi, A., Vallabhajosula, S., Isaacson, R.S., de Leon, M.J., Mosconi, L., 2018. Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. Neurology 90, e1789–e1798. https://doi.org/10.1212/WNL.0000000000005527.

Blanck, H.M., Bowman, B.A., Cooper, G.R., Myers, G.L., Miller, D.T., 2003. Laboratory issues: use of nutritional biomarkers. J. Nutr. 133, 888S–894S. https://doi.org/10.1093/jn/133.3.888S.

Bowman, G.L., Silbert, L.C., Howieson, D., Dodge, H.H., Traber, M.G., Frei, B., Kaye, J.A., Shannon, J., Quinn, J.F., 2012. Nutrient biomarker patterns, cognitive function, and MRI measures of brain aging. Neurology 78, 241–249. https://doi.org/10.1212/WNL.0b013e3182436598.

Brickman, A.M., Khan, U.A., Provenzano, F.A., Yeung, L.-K., Suzuki, W., Schroeter, H., Wall, M., Sloan, R.P., Small, S.A., 2014. Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults. Nat. Neurosci. 17, 1798. https://doi.org/10.1038/nn.3850.

Camandola, S., Mattson, M.P., 2017. Brain metabolism in health, aging, and neurodegeneration. EMBO J. 36, 1474–1492. https://doi.org/10.15252/embj.201695810.

Cremers, L.G.M., de Groot, M., Hofman, A., Krestin, G.P., van der Lugt, A., Niessen, W.J., Vernooij, M.W., Ikram, M.A., 2016. Altered tract-specific white matter microstructure is related to poorer cognitive performance: the Rotterdam Study. Neurobiol. Aging 39, 108–117. https://doi.org/10.1016/j.neurobiolaging.2015.11.021.

Cunnane, S.C., Plourde, M., Pifferi, F., Bégin, M., Féart, C., Barberger-Gateau, P., 2009. Fish, docosahexaenoic acid and Alzheimer's disease. Prog. Lipid Res. 48, 239–256. https://doi.org/10.1016/j.plipres.2009.04.001.

Cunnane, S., Nugent, S., Roy, M., Courchesne-Loyer, A., Croteau, E., Tremblay, S., Castellano, A., Pifferi, F., Bocti, C., Paquet, N., Begdouri, H., Bentourkia, M.'h., Turcotte, E., Allard, M., Barberger-Gateau, P., Fulop, T., Rapoport, S.I., 2011. Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition 27, 3–20. https://doi.org/10.1016/j.nut.2010.07.021.

Defrancesco, M., Egger, K., Marksteiner, J., Esterhammer, R., Hinterhuber, H., Deisenhammer, E.A., Schocke, M., 2014. Changes in white matter integrity before conversion from mild cognitive impairment to Alzheimer's disease. PLoS One 9, e106062. https://doi.org/10.1371/journal.pone.0106062.

Freedman, L.S., Kipnis, V., Schatzkin, A., Tasevska, N., Potischman, N., 2010. Can we use biomarkers in combination with self-reports to strengthen the analysis of nutritional

epidemiologic studies? Epidemiol. Perspect. Innov. 7, 2. https://doi.org/10.1186/1742-5573-7-2.
Gu, Y., Brickman, A.M., Stern, Y., Habeck, C.G., Razlighi, Q.R., Luchsinger, J.A., Manly, J.J., Schupf, N., Mayeux, R., Scarmeas, N., 2015. Mediterranean diet and brain structure in a multiethnic elderly cohort. Neurology 85, 1744–1751. https://doi.org/10.1212/WNL.0000000000002121.
Gu, Y., Vorburger, R.S., Gazes, Y., Habeck, C.G., Stern, Y., Luchsinger, J.A., Manly, J.J., Schupf, N., Mayeux, R., Brickman, A.M., 2016. White matter integrity as a mediator in the relationship between dietary nutrients and cognition in the elderly. Ann. Neurol. 79, 1014–1025. https://doi.org/10.1002/ana.24674.
Gu, Y., Manly, J.J., Mayeux, R.P., Brickman, A.M., 2018. An inflammation-related nutrient pattern is associated with both brain and cognitive measures in a multiethnic elderly population. Curr. Alzheimer Res. 15, 493–501. https://doi.org/10.2174/1567205015666180101145619.
Hu, F.B., 2002. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr. Opin. Lipidol. 13, 3–9. https://doi.org/10.1097/00041433-200202000-00002.
Hu, F.B., Willett, W.C., 2018. Current and future landscape of nutritional epidemiologic research. JAMA 320, 2073–2074. https://doi.org/10.1001/jama.2018.16166.
Jacobs, D.R., Tapsell, L.C., 2013. Food synergy: the key to a healthy diet. Proc. Nutr. Soc. 72, 200–206. https://doi.org/10.1017/S0029665112003011.
Karstens, A.J., Tussing-Humphreys, L., Zhan, L., Rajendran, N., Cohen, J., Dion, C., Zhou, X.J., Lamar, M., 2019. Associations of the Mediterranean diet with cognitive and neuroimaging phenotypes of dementia in healthy older adults. Am. J. Clin. Nutr. 109, 361–368. https://doi.org/10.1093/ajcn/nqy275.
Kitaura, H., Uozumi, N., Tohmi, M., Yamazaki, M., Sakimura, K., Kudoh, M., Shimizu, T., Shibuki, K., 2007. Roles of nitric oxide as a vasodilator in neurovascular coupling of mouse somatosensory cortex. Neurosci. Res. 59, 160–171. https://doi.org/10.1016/j.neures.2007.06.1469.
Knight, A., Bryan, J., Wilson, C., Hodgson, J.M., Davis, C.R., Murphy, K.J., 2016. The mediterranean diet and cognitive function among healthy older adults in a 6-Month randomised controlled trial: the MedLey study. Nutrients 8. https://doi.org/10.3390/nu8090579.
Krikorian, R., Boespflug, E.L., Fleck, D.E., Stein, A.L., Wightman, J.D., Shidler, M.D., Sadat-Hossieny, S., 2012. Concord grape juice supplementation and neurocognitive function in human aging. J. Agric. Food Chem. 60, 5736–5742. https://doi.org/10.1021/jf300277g.
Luciano, M., Corley, J., Cox, S.R., Valdés Hernández, M.C., Craig, L.C.A., Dickie, D.A., Karama, S., McNeill, G.M., Bastin, M.E., Wardlaw, J.M., Deary, I.J., 2017. Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. Neurology 88, 449–455. https://doi.org/10.1212/WNL.0000000000003559.
Lundberg, J.O., Weitzberg, E., Gladwin, M.T., 2008. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. Nat. Rev. Drug Discov. 7, 156–167. https://doi.org/10.1038/nrd2466.
Ly, M., Canu, E., Xu, G., Oh, J., McLaren, D.G., Dowling, N.M., Alexander, A.L., Sager, M. A., Johnson, S.C., Bendlin, B.B., 2014. Midlife measurements of white matter microstructure predict subsequent regional white matter atrophy in healthy adults. Hum. Brain Mapp. 35, 2044–2054. https://doi.org/10.1002/hbm.22311.
Marseglia, A., Xu, W., Fratiglioni, L., Fabbri, C., Berendsen, A.A.M., Bialecka-Debek, A., Jennings, A., Gillings, R., Meunier, N., Caumon, E., Fairweather-Tait, S., Pietruszka, B., de Groot, L.C.P.G.M., Santoro, A., Franceschi, C., 2018. Effect of the NU-AGE diet on cognitive functioning in older adults: a randomized controlled trial. Front. Physiol. 9, 349. https://doi.org/10.3389/fphys.2018.00349.
Marstaller, L., Williams, M., Rich, A., Savage, G., Burianová, H., 2015. Aging and large-scale functional networks: white matter integrity, gray matter volume, and functional connectivity in the resting state. Neuroscience 290, 369–378. https://doi.org/10.1016/j.neuroscience.2015.01.049.
Michels, K.B., Schulze, M.B., 2005. Can dietary patterns help us detect diet-disease associations? Nutr. Res. Rev. 18, 241–248. https://doi.org/10.1079/NRR2005107.
Monti, J.M., Moulton, C.J., Cohen, N.J., 2015. The role of nutrition on cognition and brain health in ageing: a targeted approach. Nutr. Res. Rev. 28, 167–180. https://doi.org/10.1017/S0954422415000141.
Morris, M.C., Tangney, C.C., Wang, Y., Sacks, F.M., Barnes, L.L., Bennett, D.A., Aggarwal, N.T., 2015. MIND diet slows cognitive decline with aging. Alzheimers Dement. 11, 1015–1022. https://doi.org/10.1016/j.jalz.2015.04.011.
Mosconi, L., Murray, J., Tsui, W.H., Li, Y., Davies, M., Williams, S., Pirraglia, E., Spector, N., Osorio, R.S., Glodzik, L., McHugh, P., de Leon, M.J., 2014. Mediterranean diet and magnetic resonance imaging-assessed brain atrophy in cognitively normal individuals at risk for Alzheimer's disease. J. Prev. Alzheimers Dis. 1, 23–32.
Mosconi, L., Walters, M., Sterling, J., Quinn, C., McHugh, P., Andrews, R.E., Matthews, D.C., Ganzer, C., Osorio, R.S., Isaacson, R.S., de Leon, M.J., Convit, A., 2018. Lifestyle and vascular risk effects on MRI-based biomarkers of Alzheimer's disease: a cross-sectional study of middle-aged adults from the broader New York City area. BMJ Open 8, e019362. https://doi.org/10.1136/bmjopen-2017-019362.
National Institute of Health National Heart, 2019. Study Quality Assessment Tools | National Heart, Lung, and Blood Institute (NHLBI) accessed 16 December. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.
Nystad, A.E., Torkildsen, Ø., Wergeland, S., 2018. Effects of vitamin D on axonal damage during de- and remyelination in the cuprizone model. J. Neuroimmunol. 321, 61–65. https://doi.org/10.1016/j.jneuroim.2018.05.016.
O'Brien, J.T., Erkinjuntti, T., Reisberg, B., Roman, G., Sawada, T., Pantoni, L., Bowler, J. V., Ballard, C., DeCarli, C., Gorelick, P.B., Rockwood, K., Burns, A., Gauthier, S., DeKosky, S.T., 2003. Vascular cognitive impairment. Lancet Neurol. 2, 89–98. https://doi.org/10.1016/S1474-4422(03)00305-3.
Pelletier, A., Barul, C., Féart, C., Helmer, C., Bernard, C., Periot, O., Dilharreguy, B., Dartigues, J.-F., Allard, M., Barberger-Gateau, P., Catheline, G., Samieri, C., 2015. Mediterranean diet and preserved brain structural connectivity in older subjects. Alzheimers Dement. 11, 1023–1031. https://doi.org/10.1016/j.jalz.2015.06.1888.
Potischman, N., 2003. Biologic and methodologic issues for nutritional biomarkers. J. Nutr. 133, 875S–880S. https://doi.org/10.1093/jn/133.3.875S.
Presley, T.D., Morgan, A.R., Bechtold, E., Clodfelter, W., Dove, R.W., Jennings, J.M., Kraft, R.A., King, S.B., Laurienti, P.J., Rejeski, W.J., Burdette, J.H., Kim-Shapiro, D. B., Miller, G.D., 2011. Acute effect of a high nitrate diet on brain perfusion in older adults. Nitric Oxide 24, 34–42. https://doi.org/10.1016/j.niox.2010.10.002.
Prins, N.D., Scheltens, P., 2015. White matter hyperintensities, cognitive impairment and dementia: an update. Nat. Rev. Neurol. 11, 157–165. https://doi.org/10.1038/nrneurol.2015.10.
Qin, B., Adair, L.S., Plassman, B.L., Batis, C., Edwards, L.J., Popkin, B.M., Mendez, M.A., 2015. Dietary patterns and cognitive decline among Chinese older adults. Epidemiology 26, 758–768. https://doi.org/10.1097/EDE.0000000000000338.
Reddan, J.M., Macpherson, H., White, D.J., Scholey, A., Pipingas, A., 2018. Examining the relationship between nutrition and cerebral structural integrity in older adults without dementia. Nutr. Res. Rev. 1–20. https://doi.org/10.1017/S0954422418000185.
Reijmer, Y.D., Schultz, A.P., Leemans, A., O'Sullivan, M.J., Gurol, M.E., Sperling, R., Greenberg, S.M., Viswanathan, A., Hedden, T., 2015. Decoupling of structural and functional brain connectivity in older adults with white matter hyperintensities. Neuroimage 117, 222–229. https://doi.org/10.1016/j.neuroimage.2015.05.054.
Richardson, W.S., Wilson, M.C., Nishikawa, J., Hayward, R.S., 1995. The well-built clinical question: a key to evidence-based decisions. ACP J. Club 123, A12–3. https://doi.org/10.7326/ACPJC-1995-123-3-A12.
Samieri, C., Perier, M.-C., Gaye, B., Proust-Lima, C., Helmer, C., Dartigues, J.-F., Berr, C., Tzourio, C., Empana, J.-P., 2018. Association of cardiovascular health level in older age with cognitive decline and incident dementia. JAMA 320, 657–664. https://doi.org/10.1001/jama.2018.11499.
Scarmeas, N., Stern, Y., 2003. Cognitive reserve and lifestyle. J. Clin. Exp. Neuropsychol. 25, 625–633. https://doi.org/10.1076/jcen.25.5.625.14576.
Scarmeas, N., Anastasiou, C.A., Yannakoulia, M., 2018. Nutrition and prevention of cognitive impairment. Lancet Neurol. 17, 1006–1015. https://doi.org/10.1016/S1474-4422(18)30338-7.
Shim, J.-S., Oh, K., Kim, H.C., 2014. Dietary assessment methods in epidemiologic studies. Epidemiol. Health 36. https://doi.org/10.4178/epih/e2014009 e2014009.
Sizonenko, S.V., Babiloni, C., de Bruin, E.A., Isaacs, E.B., Jönsson, L.S., Kennedy, D.O., Latulippe, M.E., Mohajeri, M.H., Moreines, J., Pietrini, P., Walhovd, K.B., Winwood, R.J., Sijben, J.W., 2013. Brain imaging and human nutrition: which measures to use in intervention studies? Br. J. Nutr. 110, S1–30. https://doi.org/10.1017/S0007114513001384.
Smith, C.D., Chebrolu, H., Wekstein, D.R., Schmitt, F.A., Jicha, G.A., Cooper, G., Markesbery, W.R., 2007. Brain structural alterations before mild cognitive impairment. Neurology 68, 1268–1273. https://doi.org/10.1212/01.wnl.0000259542.54830.34.
Stern, Y., 2002. What is cognitive reserve? Theory and research application of the reserve concept. J. Int. Neuropsychol. Soc. 8, 448–460.
Talukdar, T., Zamroziewicz, M.K., Zwilling, C.E., Barbey, A.K., 2019. Nutrient biomarkers shape individual differences in functional brain connectivity: evidence from omega-3 PUFAs. Hum. Brain Mapp. 40, 1887–1897. https://doi.org/10.1002/hbm.24498.
Tan, Z.S., Harris, W.S., Beiser, A.S., Au, R., Himali, J.J., Debette, S., Pikula, A., Decarli, C., Wolf, P.A., Vasan, R.S., Robins, S.J., Seshadri, S., 2012. Red blood cell ω-3 fatty acid levels and markers of accelerated brain aging. Neurology 78, 658–664. https://doi.org/10.1212/WNL.0b013e318249f6a9.
Tangney, C.C., Kwasny, M.J., Li, H., Wilson, R.S., Evans, D.A., Morris, M.C., 2011. Adherence to a Mediterranean-type dietary pattern and cognitive decline in a community population. Am. J. Clin. Nutr. 93, 601–607. https://doi.org/10.3945/ajcn.110.007369.
Titova, O.E., Ax, E., Brooks, S.J., Sjogren, P., Cederholm, T., Kilander, L., Kullberg, J., Larsson, E.M., Johansson, L., Ahlstrom, H., Lind, L., Schioth, H.B., Benedict, C., 2013. Mediterranean diet habits in older individuals: associations with cognitive functioning and brain volumes. Exp. Gerontol. 48, 1443–1448. https://doi.org/10.1016/j.exger.2013.10.002.
Tondelli, M., Wilcock, G.K., Nichelli, P., De Jager, C.A., Jenkinson, M., Zamboni, G., 2012. Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. Neurobiol. Aging 33 (825), e25–825. https://doi.org/10.1016/j.neurobiolaging.2011.05.018 e36.
Trichopoulou, A., Costacou, T., Bamia, C., Trichopoulos, D., 2003. Adherence to a Mediterranean diet and survival in a Greek population. N. Engl. J. Med. 348, 2599–2608. https://doi.org/10.1056/NEJMoa025039.
Valls-Pedret, C., Sala-Vila, A., Serra-Mir, M., Corella, D., de La Torre, R., Martínez-González, M.Á., Martínez-Lapiscina, E.H., Fitó, M., Pérez-Heras, A., Salas-Salvadó, J., Estruch, R., Ros, E., 2015. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern. Med. 175, 1094–1103. https://doi.org/10.1001/jamainternmed.2015.1668.
van Leijsen, E.M.C., Bergkamp, M.I., van Uden, I.W.M., Ghafoorian, M., van der Holst, H. M., Norris, D.G., Platel, B., Tuladhar, A.M., de Leeuw, F.-E., 2018. Progression of white matter hyperintensities preceded by heterogeneous decline of microstructural integrity. Stroke 49, 1386–1393. https://doi.org/10.1161/STROKEAHA.118.020980.
Vernooij, M.W., Ikram, M.A., Vrooman, H.A., Wielopolski, P.A., Krestin, G.P., Hofman, A., Niessen, W.J., van der Lugt, A., Breteler, M.M.B., 2009. White matter microstructural integrity and cognitive function in a general elderly population.

Arch. Gen. Psychiatry 66, 545–553. https://doi.org/10.1001/archgenpsychiatry.2009.5.
Walters, M.J., Sterling, J., Quinn, C., Ganzer, C., Osorio, R.S., Andrews, R.D., Matthews, D.C., Vallabhajosula, S., de Leon, M.J., Isaacson, R.S., Mosconi, L., 2018. Associations of lifestyle and vascular risk factors with Alzheimer's brain biomarker changes during middle age: a 3-year longitudinal study in the broader New York City area. BMJ Open 8, e023664. https://doi.org/10.1136/bmjopen-2018-023664.
Wang, Y., West, J.D., Flashman, L.A., Wishart, H.A., Santulli, R.B., Rabin, L.A., Pare, N., Arfanakis, K., Saykin, A.J., 2012. Selective changes in White Matter Integrity in MCI and older adults with cognitive complaints. Biochim. Biophys. Acta 1822, 423–430. https://doi.org/10.1016/j.bbadis.2011.08.002.
Wengreen, H., Munger, R.G., Cutler, A., Quach, A., Bowles, A., Corcoran, C., Tschanz, J. T., Norton, M.C., Welsh-Bohmer, K.A., 2013. Prospective study of dietary approaches to stop hypertension- and mediterranean-style dietary patterns and age-related cognitive change: the cache county study on memory, health and aging. Am. J. Clin. Nutr. 98, 1263–1271. https://doi.org/10.3945/ajcn.112.051276.
Wightman, E.L., Haskell-Ramsay, C.F., Thompson, K.G., Blackwell, J.R., Winyard, P.G., Forster, J., Jones, A.M., Kennedy, D.O., 2015. Dietary nitrate modulates cerebral blood flow parameters and cognitive performance in humans: a double-blind, placebo-controlled, crossover investigation. Physiol. Behav. 149, 149–158. https://doi.org/10.1016/j.physbeh.2015.05.035.
Willett, W.C., Howe, G.R., Kushi, L.H., 1997. Adjustment for total energy intake in epidemiologic studies. Am. J. Clin. Nutr. 65, 1220S–1228S. https://doi.org/10.1093/ajcn/65.4.1220S.
Witte, A.V., Kerti, L., Hermannstädter, H.M., Fiebach, J.B., Schreiber, S.J., Schuchardt, J. P., Hahn, A., Flöel, A., 2014. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cereb. Cortex 24, 3059–3068. https://doi.org/10.1093/cercor/bht163.
Zamroziewicz, M.K., Barbey, A.K., 2016. Nutritional cognitive neuroscience: innovations for healthy brain aging. Front. Neurosci. 10, 240. https://doi.org/10.3389/fnins.2016.00240.
Zamroziewicz, M.K., Paul, E.J., Rubin, R.D., Barbey, A.K., 2015. Anterior cingulate cortex mediates the relationship between O3PUFAs and executive functions in APOE e4 carriers. Front. Aging Neurosci. 7, 87. https://doi.org/10.3389/fnagi.2015.00087.
Zwilling, C.E., Talukdar, T., Zamroziewicz, M.K., Barbey, A.K., 2019. Nutrient biomarker patterns, cognitive function, and fMRI measures of network efficiency in the aging brain. Neuroimage. 188, 239–251. https://doi.org/10.1016/j.neuroimage.2018.12.007.