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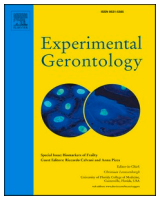

Review

Mediterranean diet and structural neuroimaging biomarkers of Alzheimer's and cerebrovascular disease: A systematic review

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ABSTRACT

Previous studies have demonstrated an association between adherence to the Mediterranean diet (MedDiet) and better cognitive performance, lower incidence of dementia and lower Alzheimer's disease biomarker burden. The aim of this systematic review was to evaluate the evidence base for MedDiet associations with hippocampal volume and white matter hyperintensity volume (WMHV). We searched systematically for studies reporting on MedDiet and hippocampal volume or WMHV in MedLine, EMBASE, CINAHL and PsycInfo. Searches were initially carried out on 21st July 2021 with final searches run on 23rd November 2022. Risk of bias was assessed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Of an initial 112 papers identified, seven papers were eligible for inclusion in the review reporting on 21,933 participants. Four studies reported on hippocampal volume, with inconclusive or no associations seen with MedDiet adherence. Two studies found a significant association between higher MedDiet adherence and lower WMHV, while two other studies found no significant associations. Overall these results highlight a gap in our knowledge about the associations between the MedDiet and AD and cerebrovascular related structural neuroimaging findings.

1. Introduction

Optimisation of brain health, with the aim of stroke and dementia prevention, is a public health priority (Frankish and Horton, 2017; Pandian et al., 2018; Livingston et al., 2020). Delaying dementia onset by even two years would result in a 19 % reduction in prevalence by 2050 in the UK (Lewis et al., 2014). Lifestyle modification may result in a reduction of half a million strokes a year (Feigin and Brainin, 2019). Nutrition is a tractable lifestyle factor associated with healthy brain aging (Livingston et al., 2020; O'Donnell et al., 2016). Specific dietary patterns, such as the Mediterranean diet (MedDiet), are particularly effective at maintaining brain health (SACN, 2018; Scarmeas et al., 2018). The MedDiet is a plant-based eating pattern, characterised by high consumption of fruit, vegetables, olive oil, legumes, nuts, and fish; a moderate consumption of red wine; and a low consumption of red meat, processed foods, and sugar-sweetened products (Trichopoulou et al., 2015). High adherence to a MedDiet has consistently been associated with a lower incidence of dementia (3, 4, 7–14). High adherence to a MedDiet has also been consistently associated with reduced risk for stroke, particularly for men (Psaltopoulou et al., 2013).

Longitudinal analysis of a two cohort studies within the Mediterranean region reported associations between higher adherence to the MedDiet and reduced risks or incidence for all-cause dementia (72 % lower risk and 20 % lower incidence respectively) (Charisis et al., 2021; Andreu-Reinón et al., 2021). Sub-group analysis conducted in one of the studies suggested adherence to the MedDiet was particularly beneficial for women with non-AD dementia and in those with a lower education (Andreu-Reinón et al., 2021). There are fewer studies investigating similar questions outside of the Mediterranean region; these studies do suggest a similar pattern in dementia incidence reduction by adhering to this diet. For example, analysis of the WHICAP cohorts, based in the United States of America, reported that higher adherence to the MedDiet was associated with reduced AD dementia incidence (Scarmeas et al., 2006), reduced mild cognitive impairment (MCI) incidence and reduced

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risk of MCI conversation to AD dementia (Scarmeas et al., 2009).

A recent review identified a reduced AD biomarker burden (measured by amyloid and tau) in those who followed a MedDiet in three of the four studies included that reported on the MedDiet, supporting the hypothesis of a pathophysiological process underpinning the relationship between diet and AD dementia incidence (Hill et al., 2019). Of these studies three were cross-sectional and one was longitudinal, with no associations seen between MedDiet and amyloid deposition in female participants in Australia (Hill et al., 2018). Conversely an autopsy study of the MIND diet, a combination of the Mediterranean diet and the Dietary Approach to Stop Hypertension (DASH), found no association between MIND diet adherence and brain pathology (Dhana et al., 2021).

A number of studies have identified significant associations between MedDiet adherence and cerebrovascular disease (Misirli et al., 2012). In particular, higher MedDiet adherence or components of the MedDiet have been associated with lower incidence of stroke in a number of cohort studies and one RCT (Estruch et al., 2013; Larsson et al., 2011; He et al., 2006; He et al., 2004). At a dietary component level processed meat has been associated with a higher risk of stroke in the Cohort of Swedish Men study (Larsson et al., 2011) while consumption of fruit, vegetables and fish have been all been associated with lower risk of stroke (He et al., 2006; He et al., 2004).

Changes in hippocampal volume (Broadhouse et al., 2019; Zhao et al., 2019; Wisse et al., 2017) and white matter lesions or hyperintensities (Bilello et al., 2015; Salvadó et al., 2019; Chutinet and Rost, 2014) are well recognised structural neuroimaging markers of Alzheimer's disease (AD) and cerebrovascular disease respectively. Structural neuroimaging plays an important role in the both the diagnosis and research of AD and cerebrovascular disease (Ledig et al., 2018; Vemuri and Jack, 2010; National Institute for Health and Care Excellence, 2019; DeLaPaz et al., 2011). The European Medicine Agency (EMA) has qualified low hippocampal volume as a qualification for enrolment into clinical trials at the pre-dementia stages (Pini et al., 2016). Hippocampal volume is also a key component of the ATN criteria, a method to biologically categorise participants on the AD spectrum, where it is used to determine neurodegeneration (N) positivity (Jack et al., 2018). As previous studies have shown reductions in diseases associated with poor brain health, it seems prudent to investigate associations with underlying brain pathologies. A fuller understanding of the mechanisms linking diet to brain health and disease would provide the basis for credible communications on the potential benefits, limitations and recommendations for adherence to dietary patterns, particularly considering intervention timing.

The objective of this systematic review is to evaluate the MedDiet in relation to hippocampal volume and white matter hyperintensities. To our knowledge, this is the first review to focus in this specific area within the broader topic linking diet and nutrition to biomarkers of neurodegenerative and cerebrovascular disease.

2. Methods

The Preferred Reporting for Systematic Reviews and Meta-Analysis (PRISMA) statement was used in the development of this systematic review. It is registered in PROSPERO (registration number: CRD42021269620).

2.1. Search strategy, study selection and data extraction

Search terms were identified by authors SG, HP and GMT guided by existing literature reviews and pilot tested for accuracy. Piloting suggested that including brain health related search terms limited the number of papers identified and these were removed. Following this initial searches were completed across all databases on 21st July 2021 with update searches run on 19th August 2021. A final search was conducted on 23rd November 2022. Included in the search were studies that evaluated the MedDiet (as defined by authors of papers identified, calculated through any form of dietary data collection and scoring), hippocampal volume or white matter hyperintensities (WMH). The search terms used for MedLine are available in Appendix One. Studies were included if they enrolled adults aged 18 and above, had a measure of self-reported or clinician/research administered MedDiet patterns, and were cross-sectional, longitudinal, case-control, cohort, or RCTs. Studies were excluded if they exclusively enrolled children or adolescents (age 0 to 17 years, inclusive), reported only on alcohol consumption outside of a wider dietary pattern, were non-human studies, case reports, systematic reviews, or meta-analyses. There were no restrictions placed on setting, timeframe or language. The search was performed in MedLine, EMBASE, CINAHL and PsycInfo with reference lists of included papers manually searched. The grey literature was searched on the same dates through thesis databases and Google Scholar in order to minimise risk of publication bias.

Study selection was performed by two independent investigators (SG and HP) in two stages. Initially titles and abstracts were reviewed for suitability, followed by full text review against the inclusion and exclusion criteria. Conflicts were resolved by discussion and a third reviewer (GMT) was available if needed. Study selection was performed using the Covidence cloud platform. Data was extracted by one reviewer (SG) using a standardised form to gather the following information: paper, country, cohort, age, gender, ethnicity/race, education, diagnosis, MedDiet adherence measure, MedDiet adherence scoring methodology, MedDiet adherence, covariates and interactions, hippocampal volume outcome, and WMH outcome. Data extraction was checked for accuracy by a second reviewer (HP) and any disagreements were resolved through discussion. The NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to assess risk of bias (NIH-NIoH, 2014). Quality assessment was completed by one reviewer (SG) and checked for accuracy by HP. Data was narratively synthesised from the data extraction tool by SG and checked by all authors. Due to a small number of papers identified with moderate to high heterogeneity a meta-analysis was deemed unsuitable and instead narrative synthesis was selected to present the results. There was no patient and public involvement in this systematic review.

2.2. Role of funding source

This systematic review was funded by the MRC (MRC UK Nutrition Research Partnership (NRP) Collaboration Award) (MR/T001852/1). The funder had no involvement in the protocol design, data collection, analysis or manuscript preparation.

3. Results

We identified a total of 118 papers through database review, of which 67 were screened after duplicates were removed. 52 papers were excluded during the title and abstract screening stage. Eight papers were excluded during the full text review, leaving seven papers for inclusion in this review. Full details on each stage and reasons for study exclusion are presented in the PRISMA diagram (Fig. 1). No papers were identified during manual search of reference lists or the grey literature. The studies included in total reported on data from 21,933 participants. The mean age of participants in studies ranged from 53.19 years to 80.3 years and participants were typically healthy volunteers or had subjective cognitive decline, with a small number ($n = 46$) with dementia. Six of the seven papers reported data from cross-sectional analysis, with one reporting on a longitudinal analysis. Of the seven papers included four reported on hippocampal volume and four on WMH volume (WMHV). The results presented below are organised by outcome measure. Study characteristics are fully described in Table 1.

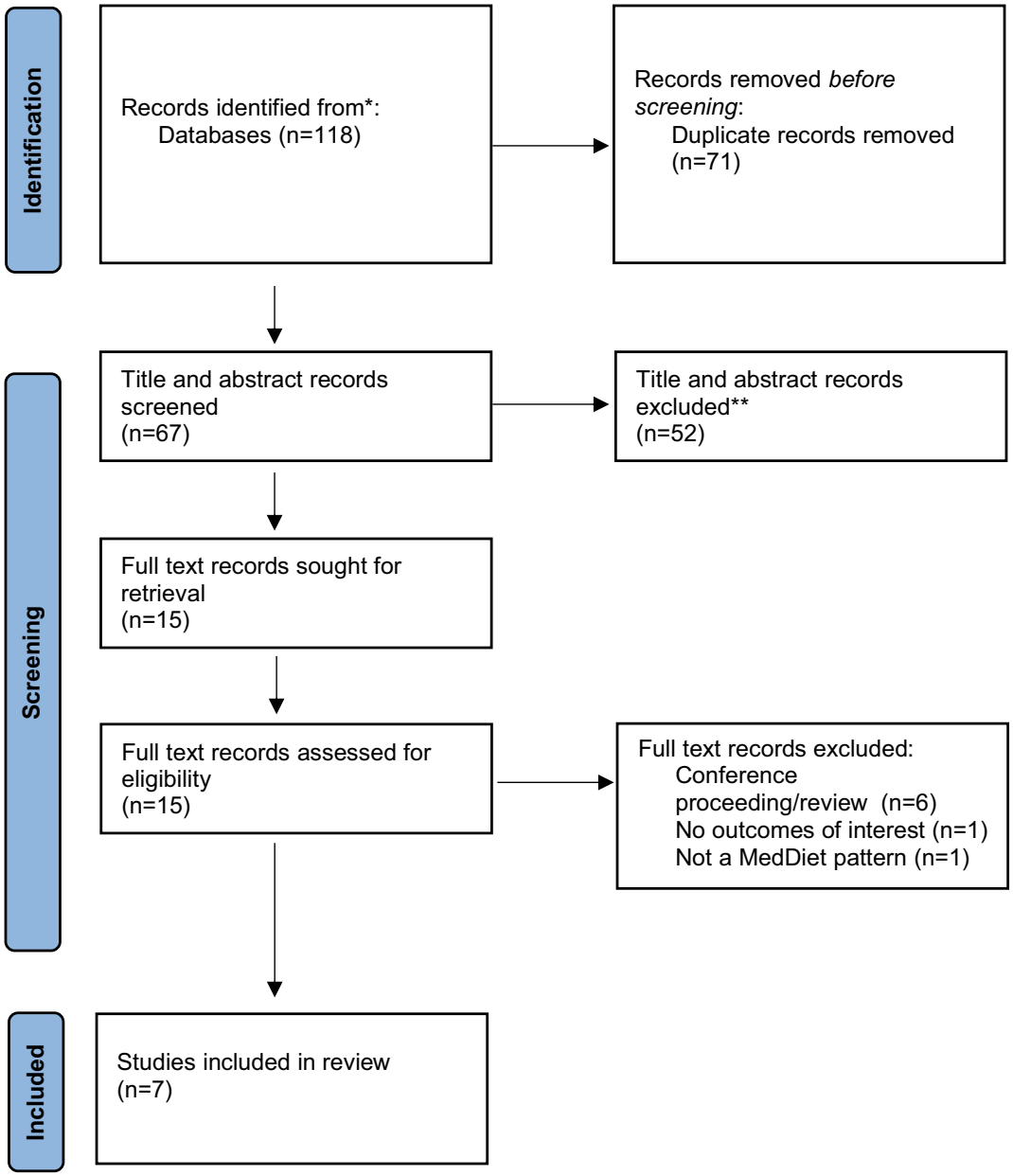

Fig. 1. PRISMA flow diagram.

3.1. Hippocampal volume

Four studies including a total of 20,077 participants investigated MedDiet adherence and hippocampal volume. There was no conclusive pattern of results seen from these studies which are further described below. Full extracted results from studies with hippocampal volume outcomes can be seen in Table 2.

Using a subset of the WHICAP cohort (USA), Gu et al investigated the association between MedDiet adherence and hippocampal volume. This study included 674 older participants with a mean age of 80.1 (±5·6) years, mainly female (67 %) and 10.7 (±4·8) years of education. Participants represented a diverse ethnic group with 27 % of participants identifying as white, 35 % as black, 36 % as Hispanic and 2 % as another ethnicity. All were cognitively healthy. In the WHICAP cohort, participants completed Willett's semi-structured food frequency questionnaire (FFQ) in either English or Spanish. The dietary questionnaire was completed at one time point and asked participants to provide information about their average diet over the previous year. One point was assigned for each beneficial element (vegetables, legumes, cereals, fish, fruits/nuts, and monounsaturated fats to saturated fats ratio) with a caloric-adjusted intake equal or greater than the sex-specific population median. One point was awarded to each detrimental element (meat and dairy) for caloric-adjusted intake below the sex-specific population median. Finally one point was awarded for mild to moderate alcohol intake (>0 to <30 g/day). MedDiet scores were calculated from 0 to 9 and used as both a continuous measure and categorised into low (0–4) and high (5–9) groups for analysis. MRI scans were undertaken using a 1.5 T scanner and hippocampal volumes were derived using FreeSurfer v5.1, adjusted for total intracranial volume. In unadjusted and partially adjusted (age) models there was a significant association between higher MedDiet score and higher hippocampal volume (unadjusted model-b: 0·14, $p = 0·03$; partially adjusted model-b: 0·14, $p = 0·02$) however this association was attenuated in the fully adjusted model (b: 0·11, $p = 0·08$, model adjusted for age, sex, education, ethnicity, body mass index (BMI), diabetes and mean cognition) (Gu et al., 2015).

A second smaller study ($n = 82$) based in the USA recruited a younger

Table 1
Table of study characteristics for the papers included in the systematic review. Data extracted from studies included in the final narrative synthesis. HC: healthy control; MedDiet: Mediterranean diet; MRI: magnetic resonance imaging; SCD: subjective cognitive decline.

First author, year	Country, cohort and study design	Participant details	MedDiet adherence measure	MedDiet adherence scoring method	MedDiet adherence
Gardener et al., 2012a	USA; The Northern Manhattan Study (NOMAS). Cross-sectional.	Mean age: 71·6 (±8·3) years; Age at MRI, diet data ~7 years prior Sex: 573 Female (59·3 %) Ethnicity: 151 White (15·6 %); 169 Black (17·5 %); 624 Hispanic (59·8 %); 22 Other (2·3 %) Education: 439 high school completers (45·4 %) Diagnosis: None *N* = 966	Block National Cancer Institute Food Frequency Questionnaire (English or Spanish) over last year including Hispanic dietary items	Scale used: Trichopoulou MedDiet Score (Trichopoulou et al., 2003) Methodology: Regression of calorific intake and calculated derived residual daily gram intake for dairy, meat, fruits, vegetables, legumes, cereals and fish. 1 point for the beneficial items (fruits, vegetables, legumes, cereals, fish), and 1 for detrimental components (dairy, meat) below median and 1 for ratio of monounsaturated fats to saturated fats above medium and 1 for mild to moderate alcohol consumption (>0 to ≤2 drinks per day). Dimensions: MedDiet score (0–9). Categorised into 0–2, 3, 4, 5, 6–9	MedDiet category 0–2: 112 participants (11·6 %) MedDiet category 3: 153 participants (15·8 %) MedDiet category 4: 222 participants (23·0 %) MedDiet category 5: 227 participants (23·5 %) MedDiet category 6–9: 252 participants (26·1 %)
Schwarz et al., 2020	Germany, SmartAge, Cross-sectional.	Mean age: 69 (±6·0) years Sex: 70 Female (51·1 %) Ethnicity: Not provided Education: 17 (±3·0) years Diagnosis: SCD or HC *N* = 137 (90 SCD, 47 HC)	89-item food frequency questionnaire based on gold standard Food Frequency Questionnaire of Willett et al. (1985)	Scale used: Mediterranean Diet Adherence Screener (MEDAS) questionnaire adapted to remove Sofrito consumption (Schröder et al., 2011) Methodology: One point was assigned for the following; using olive oil as main cooking fat and one point for preferring white meat to red meat. One point was assigned for consuming beneficial foods (olive oil (tablespoons per day), vegetables, fruit, red wine, pulses, fish, nuts) above pre-specified limits, eating 4 or more tablespoons of olive oil a day. One point was assigned for consumption for assigning detrimental components (red meat or sausages, animal fat, sugar-sweetened beverages, commercial pastries) at lower than the prespecified limits. If the condition was not met for a category, 0 points were awarded. Dimensions: total score from 0 to 13	Mean MedDiet score: 4·1 (±1·7) (Range 1–10) *By participant type* Healthy controls mean MedDiet score: 3·7 (±1·7) (Range 1–8) Subjective cognitive decline mean MedDiet score: 4·3 (±1·8) (Range 1–10)
Gu et al., 2015	USA, WHICAP. Cross-sectional.	Mean age: 80·1 (±5·6) years Sex: 454 Female (67 %) Ethnicity: 187 White (27 %); 235 Black (35 %); 239 Hispanic (36 %); 13 Other (2 %) Education: 10·7 (±4·8) years Diagnosis: None *N* = 674	Willett's semi-quantitative Food Frequency Questionnaire in English or Spanish	Scale used: Trichopoulou MedDiet Score (Trichopoulou et al., 2003) Methodology: Assigned 1 point for each beneficial good (vegetables, legumes, cereals, fish, fruits/nuts and monounsaturated fats to saturated fats) if the participants caloric-adjusted food was equal to or greater than sex-specific population median; 1 point for each detrimental component (meat and dairy) if caloric adjusted consumption below the mean; 1 point for mild to moderated alcohol consumption (>0 to <30 g/day). Dimensions: MedDiet score (0–4 Lower MedDiet, 5–9 Higher MedDiet)	Lower MedDiet category: 370 (54·9 %) Higher MedDiet category: 304 (45·1 %)
Scarmeas et al., 2011	USA, WHICAP. Cross-sectional.	Mean age: 80·3 (±5·7) years Sex: 468 Female (66 %) Ethnicity: 192 White (27 %); 250 Black (35 %); 251 Hispanic (36 %); 14 Other (2 %) Education: 10·6 (±4·8) years Diagnosis: 46 dementia (latterly excluded from analysis) *N* = 707	Willett's semi-quantitative Food Frequency Questionnaire in English or Spanish	Scale Used: Trichopoulou MedDiet Score (Trichopoulou et al., 2003) Methodology: Assigned 1 point for each beneficial good (vegetables, legumes, cereals, fish, fruits/nuts and monounsaturated fats to saturated fats) if the participants caloric-adjusted food was equal to or greater than sex-specific population median; 1 point for each detrimental component (meat and dairy) if caloric adjusted consumption below the mean; 1 point for mild to moderated alcohol consumption (>0 to <30 g/day). Dimensions: MedDiet score split into tertiles (low 0–3, middle 4–5, high 6–9)	MedDiet mean score: 4·4 (±1·7) Low tertile: 221 participants (31 %) Middle tertile: 298 participants (42 %) High tertile: 188 participants (27 %)

(*continued on next page*)

Table 1 (*continued*)

First author, year	Country, cohort and study design	Participant details	MedDiet adherence measure	MedDiet adherence scoring method	MedDiet adherence
Karstens et al., 2019	USA. Cross-sectional.	Mean age: 68·8 (±6·88) years Sex: 42 Female (50 %) Ethnicity: 41 White (50 %); 39 Black (48 %); 2 Latino (2 %) Education: 15·4 (±2·63) years Diagnosis: None *N* = 82	Block 2005 Food Frequency Questionnaire in English or Spanish	Scale used: Adapted Panagiotakos score (Tangney et al., 2011; Panagiotakos et al., 2007) Methodology: 7 components (non-refined grains, fruits, vegetables, potatoes, fish, legumes, nuts) scored on a Likert scale (0: never, 1: rare, 2: frequent, 3: very frequent, 4: weekly, 5: daily). Reverse scored for 3 components (red and processed meats, poultry, full-fat dairy). Alcohol: higher scores given for moderate daily alcohol consumption. Dimensions: MedDiet. Scores 0–55, higher score relates to more MedDiet compliance, split into high and low around the median.	Low MedDiet score: 39 participants (47·6 %) (Range 25–33) High MedDiet score: 43 participants (52·4 %) (Range 34–43)
Macpherson et al., 2021	UK, UK Biobank.	Mean age: 63·19 (±53·8) years Sex: 9257 Female (48·3 %) Ethnicity: 18,800 White (98 %), 91 Mixed (0·5 %), 187 Asian/Asian British (1·0), Black/Black British (0·6 %) Education: 10,255 college/ university degree (53·3 %), 1688 vocational qualification (8·8 %), 2646 A levels (13·8 %), 3950 O levels/GCSEs/CSEs (20·6 %), 675 none of the above (3·5 %) Diagnosis: None *N* = 19,184	Oxford WebQ	Scale Used: Trichopoulou MedDiet Score (Trichopoulou et al., 2003) Methodology: Assigned 1 point for each beneficial good (vegetables, legumes, cereals, fish, fruits/nuts and monounsaturated fats to saturated fats) if the participants caloric-adjusted food was equal to or greater than sex-specific population median; 1 point for each detrimental component (meat and dairy) if caloric adjusted consumption below the mean; 1 point for mild to moderated alcohol consumption (>0 to <30 g/day). Dimensions: MedDiet score 0–9, higher score related to higher MedDiet adherence.	MedDiet mean score: 4·3 (1·7)
Song et al., 2022	USA, Cognitive Reserve & Reference Ability Neural Network. Longitudinal	Mean age: 63·19 (±16·52) years Sex: 94 Female (51·37 %) Ethnicity: 120 Non-Hispanic white or other (65·57 %), 40 Non-Hispanic black (21·86 %), 23 Hispanic (12·57 %) Education: 16·33 (2·37) years Diagnosis: None *N* = 183	Willett's semi-quantitative Food Frequency Questionnaire in English	Scale used: Adapted Panagiotakos score (Tangney et al., 2011; Panagiotakos et al., 2007) Methodology: 7 components (non-refined grains, fruits, vegetables, potatoes, fish, legumes, nuts) scored on a Likert scale (0: never, 1: rare, 2: frequent, 3: very frequent, 4: weekly, 5: daily). Reverse scored for 3 components (red and processed meats, poultry, full-fat dairy). Alcohol: higher scores given for moderate daily alcohol consumption. Dimensions: MedDiet score − 055 split into tertiles of low, middle and high.	MedDiet mean score: 28·20 (5·54) Low tertile: 67 participants (36·7 %) Middle tertile: 50 participants (27·3 %) High tertile: 66 participants (36 %)

cohort (68.8 (±6·9) years) with 50 % female participants and a higher average education of 15.4 (±5·6) years. Again, the study had some ethnic diversity with 50 % identifying as white, 48 % as black and 2 % as Latino. In this study the Block 2005 FFQ in English or Spanish was used to create MedDiet scores. The questionnaire was completed once and participants asked to report their average diet from the previous year. Seven beneficial components (non-refined grains, fruits, vegetables, potatoes, fish, legumes, nuts) were scored on a six-point Likert scale ranging from 0 (never) to 5 (daily). Three detrimental components (red and processed meats, poultry, full-fat dairy) were reverse scored on this same Likert scale. Higher scores were given for moderate daily alcohol consumption. The MedDiet scores ranged from 0 to 55 and due to a lack of variability were split into low and high groups around the median for the analysis. Hippocampal volume was derived from 3 T MRI scan images using FreeSurfer v6.0 with automated subfield segregation, all adjusted for total intracranial volume. There was no significant difference in hippocampal volume between the two MedDiet groups (b: 0·18, $p = 0{\cdot}07$) although it should be noted this analysis may have been underpowered due to the small sample size (Karstens et al., 2019).

The final study reporting on hippocampal volume took place in Germany and recruited 137 older adults from the SmartAge study who were classified either as healthy controls ($n = 47$) or having subjective cognitive decline ($n = 90$). The mean age of the participant group was 69 (±6·0) years, roughly half were female (51·1 %), and were highly educated (17 (±3·0) years). No ethnicity information was provided. Similar to the first study described here a FFQ based on Willett's was utilised and the MedDiet calculated using the Mediterranean Diet Adherence Screener (MEDAS) questionnaire (excluding Sofrito consumption) giving a total score from 0 to 13 (Schröder et al., 2011). Participants completed the FFQ once and provided data about their diet over the last year. The positive components in this screener include olive oil, vegetables, fruit, wine, pulses, fish or seafood, nuts, and a preference for poultry over red meat. The detrimental components are red and processed meats, butter, margarine and cream, carbonated drinks, and pastries. Hippocampal volume was derived from scans acquired on a 3 T scanner using FreeSurfer v6.0 software and adjusted for intracranial volume. A path analysis was used to assess the association and possible mediation between MedDiet, spermidine (a polyamine associated with healthy aging (Wirth et al., 2019)) and hippocampal volume. While the overall model had a number of significant paths (MedDiet → spermidine, b: 0·068, $p \leq 0{\cdot}001$; spermidine → hippocampal volume, b: 0·069, $p = 0{\cdot}002$; indirect, b: 0·005, 95 % CI: 0·0016, 0·0079) the path between MedDiet and hippocampal volume was not significant (b: −0·001, p = 0·64) suggesting that in this study the association between MedDiet and

Table 2
Table of data extracted from studies reporting hippocampal volume outcomes included in the final narrative synthesis. BMI: body mass index; HCV: hippocampal volume; MedDiet: Mediterranean diet.

Paper	Covariates & interactions	Hippocampal volume measurement	Hippocampal volume outcome
Schwarz et al., 2020	Age, sex, education, diagnostic group; spermidine (mediator)	MRI Scanner: 3 T MRI scanner (Siemens Magnetom Trio/PrismaFit, Erlangen, Germany). Analysis package: FreeSurfer v6.0 Methodology: Hippocampal volume derived using FreeSurfer. Left and right hemispheres summed and adjusted for differences in head size by dividing raw volumes by total intracranial volume.	Path A (MedDiet → spermidine): β: 0·068, $p < 0·001$ Path B (spermidine → HCV): β:0·069, $p = 0·002$ Path C (MedDiet → HCV): β: −0·001, p = 0·636 Path AB (indirect): β: 0·005, CI: 0·0016, 0·0079
Gu et al., 2015	Model One: unadjusted Model Two: age Model Three: age, sex, education, ethnicity, BMI, diabetes, mean cognition	MRI Scanner: 1.5 T MRI scanner (Philips Medical Systems, Best, The Netherlands). Analysis package: FreeSurfer v5.1 Methodology: Hippocampal volume derived using FreeSurfer. Left and right hemispheres summed and adjusted for differences in head size by dividing raw volumes by total intracranial volume.	Model One Per MedDiet unit: β: 0·03, p = 0·08 MedDiet high vs low: β: 0·14, $p = 0·03$ Model Two Per MedDiet unit: β: 0·04, p = 0·03 MedDiet high vs low: β: 0·14, p = 0·02 Model Three Per MedDiet unit: β: 0·03, p = 0·10 MedDiet high vs low: β: 0·11, p = 0·08
Karstens et al., 2019	Age, sex, education, BMI, estimated daily calorie intake	MRI Scanner: 3 T MRI scanner (MR 750 Discovery; General Electric Health Care). Analysis package: FreeSurfer v6.0 Methodology: Hippocampal volume derived using FreeSurfer with automating subfield segregation and adjusted for total intracranial volume.	No significant difference in hippocampal volume between high and low MedDiet groups (β: 0·18, $p = 0·07$)
Macpherson et al., 2021	Model one: Brain volume Model two: age, sex, education, income, energy intake and ethnic background Model three: age, sex, education, income, ethnic background, heart conditions, depression, physical activity, BMI, smoking	MRI Scanner: 3 T MRI scanner (Siemens Skyra, Erlangen, Germany). Analysis package: FMRIB's Integrated Registration and Segmentation Tool (FIRST) Methodology: Hippocampal volume derived using FIRST and normalised using head size scaling factor.	Left hippocampal grey matter volume Model one: β: −3·89, $p = 0·12$ Model two: β: 3·08, p = 0·19 Model three: β: 0·91, p = 0·70 Right hippocampal grey matter volume Model one: β: −6·87 p = 0·008 Model two: β: 0·46, p = 0·85 Model three: β: −1·37, p = 0·58

hippocampal volume is mediated via spermidine levels (Schwarz et al., 2020).

The largest of the included studies used the UK Biobank to investigate several dietary patterns, including the MedDiet, and hippocampal volume among other imaging variables. This study used a subset of the UK Biobank who had imaging, dietary and covariate data, and focused on those in midlife, defined as aged 65 years or below. Using this criteria, the analysed sample included 19,184 of the over 500,000 participants in UK Biobank. The included sample had a mean age of 53·8 (±6·9) years, nearly equal numbers of male and female participants (48·3 % female) and over half had a college or university degree (n = 10,225, 53·3 %). The participants were mainly of white ethnicity (98·0 %), with small numbers of Asian (1.0 %), Black (0.6 %) and mixed (0.5 %) ethnicity participants. Dietary intake was assessed using a web-based self-administered questionnaire, the Oxford WebQ, which asked participants to complete data at four time points over a 12-month period. A mean across all time points was used to generate the dietary scores. To calculate the MedDiet a score of one was assigned to beneficial elements (vegetables, fruits, legumes, unsalted nuts, cereals, fish and monounsaturated to saturated fats ratio above the median), a score of one was assigned to a consumption below the median of detrimental components (dairy, meat) and a score of one was assigned for low to moderate alcohol intake (considered up to two drinks a day). The scores were summed for a total of 0 to nine and the scores were used continuous in the analysis. MRI scans were conducted using 3 T scanners, and the hippocampal volumes were modelled using the FIRST tool (Fisher et al., 2018) and then normalised using head size scaling factor. There was no significant association between adherence to the MedDiet and hippocampal volume when the full sample was analysed (left hippocampus fully adjusted model β: 0·91, 95 % CI: −3·71, 5·53, p: 0.70; right hippocampus fully adjusted model β: −1·37, 95 % CI: −6·19, 3·45, p: 0.58). The authors investigated any sex-diet interactions, and again no significant associations were seen between diet, sex and hippocampal volume (left hippocampus fully adjusted model β: 7·26, 95 % CI: −1·85, 16·37, p: 0.12; right hippocampus fully adjusted model β: 4·00, 95 % CI: −5·49, 13·49, p: 0.41) (Macpherson et al., 2021).

3.2. White matter hyperintensity volumes

Four studies including a total of 1938 participants analysed associations between MedDiet adherence and WMHV. Two studies found a significant negative association between MedDiet and WMHV, whereby higher Mediterranean Scores were associated with lower level of WHMV. The two other studies found no significant associations. Full extracted results from studies with WMHV outcomes can be seen in Table 3.

A study utilising the magnetic resonance imaging (MRI) sub-cohort of the Northern Manhattan study included 966 participants with a mean age of 71·6 (±8·3) years, majority of females (59·3 %), and moderate levels of education (45·4 % high school completers). The cohort was biased towards recruitment of Hispanic participants (59·8 %) compared to white (15·6 %), black (17·5 %) and other (2·3 %) participants. As with paper (Karstens et al., 2019) the Block FFQ was used in English or Spanish but with an adaptation to include Hispanic dietary items. The FFQ was completed once to include average diet as reported by participants over the previous year. The scoring of the MedDiet was similar to the previously described study. One point was awarded for each beneficial component (fruits, vegetables, legumes, cereals, fish)

Table 3
Table of data extracted from studies reporting white matter hyperintensity volume outcomes included in the final narrative synthesis. APOE: apolipoprotein E; BMI: body mass index; DBP: diastolic blood pressure; HDL: high density lipoprotein cholesterol; LDL cholesterol: low density lipoprotein cholesterol; MedDiet: Mediterranean diet; MRI: magnetic resonance imaging; NARTIQ: National Adult Reading Test-assessed Intelligence Quotient; SBP: systolic blood pressure; WMHL white matter hyperintensity; WMHV: white matter hyperintensity volume.

Paper	Covariates & interactions	White matter hyperintensity volume measurement	White matter hyperintensity outcome
Gardener et al., 2012a	Model One: age at MRI Model Two: age at MRI, sex, race/ethnicity, high school education completion, moderated to heavy physical activity, smoking, caloric intake Model Three: age at MRI, sex, race/ethnicity, high school education completion, moderated to heavy physical activity, smoking, caloric intake, LDL cholesterol, HDL cholesterol, SBP, DBP, diabetes, cardiac disease history. Interaction between DBP and antihypertensive medication use. Model Four: age at MRI, sex, race/ethnicity, high school education completion, moderated to heavy physical activity, smoking, caloric intake, LDL cholesterol, HDL cholesterol, SBP, DBP, diabetes, cardiac disease history, BMI. Interaction between DBP and antihypertensive medication use.	MRI Scanner: 1.5 T MRI scanner (Philips Intera, Columbia University Medical Centre). Analysis package: QUANTA 6.2 Methodology: Semi-automated measurement of pixel distributions to distinguish cerebral spinal fluid from brain matter. WMHV expressed as a proportion of total cranial volume, corrected for head size and log transformed for a normal distribution.	A 1 point increase in MedDiet score was associated with significantly lower log WMHV. Model one (adjusted for age at MRI): 3 vs 0–2 β: −0·221 (0·04) 4 vs 0–2 β: −0·156 (0·11) 5 vs 0–2 β: −0·358 (<0·01) 6–9 vs 0–2 β: −0·248 (0·01) Trend *p* value: 0·02 Continuous 1 point increase in score β: −0·40 (0·02) Remains significant in all models Ratio of monounsaturated fats to saturated fat was the only independent predictor of WMHV Model four covariates of significance: age at MRI (β = 0·047, *p* < 0·001), black race (vs white, β = 0·355, p < 0·001), Hispanic ethnicity (vs white, β = 0·208, *p* = 0·02), DBP (β = 0·01, p = 0·01), interaction of DBP and antihypertensive use (β = 0·002, p = 0·02) and BMI (β = −0·14, p = 0·01)
Song et al., 2022	Model 1: age, follow up interval Model 2: age, follow up interval, gender, education, NARTIQ, race/ethnicity, total daily energy intake, baseline WMH Model 3: age, follow up interval, gender, education, NARTIQ, race/ethnicity, total daily energy intake, baseline WMH, baseline grey matter volume residual, baseline men thickness	MRI Scanner: 3 T MRI scanner (Philips Achieva) Analysis package: Not provided Analysis: Fully automatic supervised machine learning Methodology: Randomized decision trees machine algorithm to segment WMH to generate a probability map with 0 indicating not likely that a voxel is hyperintense and 1 indicat8ing that a voxel is likely to be hyperintense. Images visually checked and corrected if erroneously identified as WMH.	Higher MedDiet score associated with lower increases in WMH burden (β: −0.014, p: 0.034). Significant moderation by age, young (<45 years) as reference group: Middle aged X MedDiet, p: 0.075 Older X MedDiet, p: 0.037
Scarmeas et al., 2011	Model One: unadjusted Model Two: age, sex, ethnicity, education, APOE, caloric intake, BMI, duration between diet evaluation and MRI Model Three: age, sex, ethnicity, education, APOE, caloric intake, BMI, duration between diet evaluation and MRI, smoking, diabetes, hypertension, heart disease Model Four: age, sex, ethnicity, education, APOE, caloric intake, BMI, duration between diet evaluation and MRI, smoking, diabetes, hypertension, heart disease, plasma total cholesterol, high density lipoprotein cholesterol, triglycerides, low density lipoprotein cholesterol	MRI Scanner: 1.5 T MRI scanner (Philips Medical Systems, Best, The Netherlands). Analysis package: Not provided Methodology: Brain matter isolated using manually tracing of dura mater. Single Gaussian distribution fitted to the image data with a threshold set for WMH of 3.5 SD in pixel intensity above the mean. WMHV calculated as sum of voxels greater than or equal to 3.5SD above the mean. Adjusted for intracranial volume and log transformed.	Low tertile (mean (SD)): −4·8 (0·91); Middle tertile −4·8 (0·86), High tertile: −4·7 (0·86), *p* = 0·70 Continuous: β = 0·008, p = 0·070 No changes when models were adjusted.
Karstens et al., 2019	Age, sex, education, BMI, estimated daily calorie intake	MRI Scanner: 3 T MRI scanner (MR 750 Discovery; General Electric Health Care). Analysis package: White Matter Lesion Segmentation, Section for Biomedical Image Analysis: University of Pennsylvania; FreeSurfer v6.0 Methodology: Co-registration of T1-BRAVO and T2-FLAIR data. Brain images extracted and automated WMH segmentation using support vector machine classifier. Adjusted for intracranial volume and log transformed.	No significant effect of MedDiet group on log-transformed WMHV (β:-0·04, p = 0·70)

above the median, one point for each detrimental component (dairy, meat) below the median, one point for the ratio of monounsaturated fats to saturated fats above the median and one point for mild to moderate alcohol consumption (>0 to ≤2 drinks per day). Participants were scanned using a 1.5 T MRI scanner and WMHV was calculated using semi-automated measurements and expressed as a proportion of total cranial volume. WMHV was corrected for head size and log transformed prior to analysis. In this cohort, a one point increase in MedDiet score was associated with a significantly lower log WMHV (continuous MedDiet score- b: −0·40, $p = 0·02$; 3 points vs 0–2 points- b:-0·22, p = 0·04; 4 points vs 0–2 points- b: −0·16, p = 0·11; 5 points vs 0–2 points- b: −0·36, $p < 0·01$; 6–9 points vs 0–2 points - b: −0·25, p = 0·01). This association remained significant in all models (see Table 1 for full details of models and covariates). A component level analysis identified the ratio of monounsaturated fats to saturated fats as the only item that was an independent predictor of WMHV (Gardener et al., 2012a).

Cognitively healthy participants from the Cognitive Reserve and Reference Ability Neural Network studies, both enrolling in Columbia, USA, were included in a longitudinal analysis to investigate the association between baseline MedDiet adherence and five year change in WHM burden. This study includes 183 participants, with a mean age of 51·9 (±16.52) years, a majority of female participants (51.37 %) and majority non-Hispanic white (65.57 %). Participants completed Willet's semi-structured FFQ. Each food category of the MedDiet was assigned a score from 0 to 5, with higher scores reflecting higher portions consumed per month for foods characteristics of a MedDiet (non-refined cereals, potatoes, fruits, vegetables, legumes, nuts, fruits and olive oil) and higher scores reflecting lower portions consumed per month for foods less characteristic of a MedDiet (poultry, red meat and full fat dairy products). Five points was awarded for alcohol consumptions between 1 and 2 servings a month, zero points for no servings or >60 servings a month and scores of one to four were assigned for consumption of 3–4, 5–14, 15–30 and 31–60 servings a month. The scores for each food component were summed to give a total score of 0–55 with higher scores indicating greater MedDiet adherence. The scores were then split into tertiles to represent low, middle and high adherence. Participants were scanned using a 3 T MRI and WMH calculated from fluid attenuated inversion recovery (FLAIR) scans processed using a fully automatic supervised machine learning technique, with values log transformed and then change scores calculated between baseline and follow up. The majority of participants had a maintenance or increase in WMH between baseline and follow up. A higher MedDiet score was associated with a lower increased in WMH burden, an association which remained significantly after adjusting for sociodemographic data, calorie intake, brain markers and follow up interval. This associated was moderated by age, where the younger participants (<45 years of age) showed less increased in WMH burden for each MedDiet point increase compared to participants in later life. In particularly higher intake of vegetables and lower intake of dairy was associated with lower increased in WMH burden (Song et al., 2022).

A second study also used a subset of the WHICAP cohort (as (Gu et al., 2015)), including 707 participants with a mean age of 80·3 (±5·7) years, a majority of female participants (66 %), and average education (10·6 (±4·8) years). As in the previously reported WHICAP study, participants represented a diverse ethnic group with 27 % identifying as white, 35 % as black, 36 % as Hispanic and 2 % as another ethnicity. Participants completed Willett's semi-structured FFQ in either English or Spanish and MedDiet scores were calculated from 0 to 9 with identical data collection and scoring as previously described by Gu et al. (2015), however unlike the previously reported study these scores were separated into tertiles (0–3, 4–5, 6–9) in addition to use of MedDiet as a continuous measure. Participants were scanned using a 1.5 T MRI scanner and WMHV were identified manually as the sum of voxels with pixel intensity of greater than or equal to 3.5 standard deviations above the mean. WMHV was adjusted for intracranial volume and log transformed prior to analysis. There was no significant association according to commonly accepted significance thresholds between continuous MedDiet score and WMHV (b: 0·008, $p = 0·07$) and no significant differences between the tertiles (Scarmeas et al., 2011).

The final study reported here is a second analysis included in the Karstens et al paper reported in the hippocampal volume section (Karstens et al., 2019). WMHV was calculated by extracting co-registered T1 and T2 data and running automated WMHV segmentation using a support vector machine classifier. WMHV was adjusted for intracranial volume and was log transformed prior to analysis. This analysis found no significant effect of MedDiet group on log transformed WMHV (b: −0·04, p = 0·70).

3.3. Quality assessment

We used the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies to assess risk of bias, see Table 4 for further details about the included studies. Generally, the studies were assessed to be at a low risk of bias with comprehensive details provided about the research question, participant group, exposure and outcome variables. Studies that selected sub-groups from larger cohorts typically excluded over 50 % of participants, however it should be noted that the papers often provided data on any demographic differences between the included and excluded participants. Few papers referred to statistical power, and those that had included it did not specifically provide the power of their study, simply discussing the potential for the analyses to be underpowered. With the exception of the UK Biobank study, papers only included one measurement of diet and future studies should consider repeated measurements. It was often difficult to ascertain if there was any or sufficient blinding to exposure status of participants in the outcome assessors (in this case those who rated the MRI scans).

4. Discussion

Overall these results highlight a gap in our knowledge about the associations between the MedDiet and AD and cerebrovascular related structural neuroimaging findings, with more larger studies required to truly understand the associations, or lack thereof, between MedDiet adherence and structural brain imaging.

There were no significant associations seen between MedDiet adherence and hippocampal volume in the four studies included in the review. This is an interesting finding given the frequently reported reduction in dementia incidence and benefits on cognitive function reported in multiple studies (SACN, 2018; Scarmeas et al., 2018; Scarmeas et al., 2006; Scarmeas et al., 2009; van de Rest et al., 2015; Anastasiou et al., 2017; Loughrey et al., 2017; Samieri et al., 2013a; Kesse-Guyot et al., 2013; Tangney et al., 2011). Some of these previous studies have looked at all-cause dementia, where hippocampal volume is not a hallmark pathology, however many of the studies have more specifically investigated AD where hippocampal volume is a core feature as outlined in the ATN criteria (Jack et al., 2018). It is important to note that all four studies were cross-sectional analyses from larger cohort studies. To establish causative associations longitudinal associations and RCT trials are needed. None of the studies included in the review reporting on hippocampal volume recruited participants in the Mediterranean region. There is inconsistent evidence from previous studies as to the benefits of the MedDiet on cognition and cognitive aging in studies recruiting outside the Mediterranean (Tangney et al., 2011; Chan et al., 2013; Samieri et al., 2013b; Vercambre et al., 2012; Roberts et al., 2010; Gu et al., 2010; Cherbuin and Anstey, 2012; Gardener et al., 2012b). It may be that for reductions in dementia incidence, lifelong adherence to the MedDiet achieved from living in a Mediterranean region is more beneficial than later life adoption. Studies are needed that investigate the association between the MedDiet and hippocampal volume within the Mediterranean region, to understand if the diet has an association with this brain imaging measure within this region before we are able to draw firm conclusion on this association. Given the lack of association

Table 4
NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies assessment for included studies. CD: cannot determine; NA: not applicable. Colouring of cells indicates quality assessment outcome. Green: meets critiera; Red: does not meet critiera; Peach: cannot determine if paper meets critiera; Grey: not applicable.

Criteria	Gardener et al, 2012 [43]	Schwarz et al, 2020 [40]	Gu et al, 2015 [36]	Scarmeas et al, 2011 [45]	Karstens et al, 2019 [37]	Macpherson et al, 2021 [42]	Song et al, 2022 [44]
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specific and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation of eligible persons at least 50%?	No	Yes	No	No	Yes	No	No
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description or variance and effect estimates provided?	No	No	No	No	Yes	No	No
6. For the analyses in the paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	CD	Yes	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. For exposures that can vary in amount of level, did the study examined different levels of exposure as related to the outcome (e.g. categories of exposure or exposure measured as continuous variable)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the exposure measures (independent variables) clearly defined, valid, reliable and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	No	No	No	No	No	Yes	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	Yes	CD	CD	CD
13. Was loss to follow up after baseline 20% or less?	NA	NA	NA	NA	NA	NA	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

between the MedDiet and hippocampal volume it is worth considering other potential mechanisms that may explain the associations between MedDiet adherence and lower dementia incidence. Some studies have found evidence of lower AD biomarker burden in those adhering to a MedDiet (Hill et al., 2019), however this is not a universal finding (Hill et al., 2018). Utilisation of amyloid and tau positron emission tomography (PET) brain scans to explore biomarker deposition and MedDiet adherence may be a sensible future research avenue given the CSF review findings.

Two of the studies included in the review reported significant associations between higher MedDiet adherence and lower WMH burden or volume, while two studies reported no significant associations. These findings are relevant for both AD and cerebrovascular disease. Previous studies have consistently identified associations between the MedDiet and lower incidence of stroke and cerebrovascular disease (Psaltopoulou et al., 2013; Misirli et al., 2012; Estruch et al., 2013; Larsson et al., 2011; He et al., 2006; He et al., 2004). These studies have been conducted globally, and unlike in cognitive aging we do not see a particular bias towards consistency only within the Mediterranean (Psaltopoulou et al., 2013; Paterson et al., 2018).

The systematic methodology of our review is a key strength, with a considered, appropriately piloted search strategy. Unfortunately, as we only identified a small number of studies, with heterogeneity of methodology, we were unable to perform a meta-analysis as planned in our a priori protocol. The systematic review may have been limited by restricting the brain imaging outcomes to hippocampal volume and WMHV rather than included a broad number of brain imaging outcomes.

This diversity in dietary analytical choice across the seven papers included is worth considering for future studies in this field to agree on a gold standard approach to the methodological considerations. Of the studies included four studies used a FFQ based on that of Willet et al. (Willett et al., 1985), two (Karstens et al., 2019; Gardener et al., 2012a), used the Block National Cancer Institute FFQ and one used the Oxford WebQ (Liu et al., 2011). Papers administered studies in German, English and Spanish where relevant, and two included Hispanic dietary items. Comparative analysis of the Willet and Block FFQs found that while the Block FFQ may perform better at absolute intake estimates, after energy adjustment the two are comparable (Collins et al., 2014; Subar et al., 2001). The Oxford WebQ has not been validated against the other FFQs discussed in this review.

Differences in scanning and outcome derivation methodologies may also be important to consider, particularly in the calculation of WMHV. Utilisation of a 3 T compared to a 1.5 T scanner gives a better signal to noise ratio compared to 1.5 T scanners, increasing power to identify between group differences (Chow et al., 2015; Di Perri et al., 2013). While manual segmentation remains the gold standard for WMHV derivation, there are a growing number of semi- and fully-automated programs able to detect these areas with growing accuracy rates (Heinen et al., 2019).

It is possible that we did not select brain pathologies most sensitive to MedDiet effects. For example cortical thinning has been associated with lower adherence to the MedDiet (Mosconi et al., 2014) and is also associated with Mild Cognitive Impairment (MCI) and AD dementia (Singh et al., 2006; Tosun et al., 2011; Abushakra et al., 2020). Hippocampal subfields, in particular the subiculum and CA1 hippocampal subfields may be suitable outcome measures, with a small study finding that higher levels of serum Docosahexaenoic acid, a nutrient common to the MedDiet, were associated with larger subiculum volume (Yassine et al., 2016). Evidence from animal studies also suggests amyloid beta accumulation and gliosis in the subiculum and CA1 subfields after high fat diet feeding (Moser and Pike, 2017; Christensen and Pike, 2019). Many other mechanisms to explain associations between MedDiet adherence and lower dementia and stroke incidence rates have been discussed in the literature (Frisardi et al., 2010), and include effects on blood pressure (Cowell et al., 2021), preservation of white matter microstructure (Pelletier et al., 2015; Rodrigues et al., 2020), induction

of cerebral blood flow (Farooqui and Farooqui, 2018) and beneficial impacts on mitochondrial structure and function (Shannon et al., 2021). Further exploration of these associations with MedDiet in AD and cerebrovascular studies is important to further define possible mechanisms of action.

Future analysis may also consider inclusion of additional relevant covariates to statistical models. Risk factors such as physical activity (Zhao et al., 2018; Serra et al., 2020), sleep (Zhao et al., 2018; Pistollato et al., 2016) and stress (Pistollato et al., 2016) may associate with dietary patterns to increase risk for AD. These risk factors have all been associated with both AD and diet quality. Higher physical activity levels have been associated with reduced risk for AD (Meng et al., 2020), with one systematic review suggesting this may be lowered by between 28 and 45 % (Hamer and Chida, 2009). Participants who adhere to a MedDiet are often more likely to be physically active (Alvarez-Alvarez et al., 2018; Bizzozero-Peroni, 2022). The interaction between MedDiet and physical activity has been highlighted as significant in reducing overall mortality (Alvarez-Alvarez et al., 2018; Hershey et al., 2022), suggesting it is important to look at interaction effects in outcomes such as AD and cerebrovascular disease. Poor sleep quality has been associated with higher risk for AD (Minakawa et al., 2019), with adherence to the MedDiet associated with better sleep quality (Zuraikat et al., 2020), suggesting a possible intervention opportunity to reduce AD risk. Finally stress has been associated with risk for AD in a number of studies, with higher cortisol (the stress hormone) associated with faster disease progression (Ouanes and Popp, 2019). The MedDiet was reported to be associated with reductions in cortisol responses to stress and increased in stress resilience in a preclinical study involving female cynomolgus macaques (Shively et al., 2020). Only one study included in our review controlled for physical activity (Gardener et al., 2012a), two controlled for smoking (Gardener et al., 2012a; Scarmeas et al., 2011), and none controlled for sleep or other behaviours such as substance use. Similarly diet is associated with a number of health conditions which confer additional risk for AD, such as obesity (Livingston et al., 2020; Estruch and Ros, 2020; Buckland et al., 2008; D'Innocenzo et al., 2019) and type 2 diabetes (Livingston et al., 2020; Esposito et al., 2015; Esposito and Giugliano, 2014; Salas-Salvadó et al., 2016). Expansion of selected covariates in dietary pattern analysis in brain health studies to include more lifestyle variables is critical to further exploring any mediating and moderating relationships.

In addition to including more lifestyle factors as covariates it is important to consider the impact of socio-economic status (SES) in dietary analyses. None of the studies included considered this, although all included education which may in part serve as a proxy. Previous studies have identified potentially higher costs of adhering to a MedDiet in the UK and Spain (Tong et al., 2018; Pastor et al., 2021). Higher income has been identified as one of the predictors of adherence to the MedDiet (Bonaccio et al., 2012). SES has also be associated with dementia and stroke, with those in lower SES groups more likely to receive a diagnosis of dementia after referral, as opposed to MCI (Petersen et al., 2021), and higher stroke incidence with lower chances of survival and greater stroke severity in lower SES groups (Cox et al., 2006).

We identified no evidence from low- and middle-income countries (LMIC). Nutritional anthropology tells us that there is a multitude of factors influencing food choice, including but not limited to social, cultural, and historical considerations (Waldstein, n.d.; Ulijaszek, n.d.; Wiley, n.d.). Given this we must be cautious when making generalisations about dietary patterns to different settings. Modelling studies suggest increasingly high estimations of dementia in LMIC (Cleret de Langavant et al., 2020) with a growing incidence rate (Livingston et al., 2020; Alzheimer's Disease International, 2015). Simply extrapolating knowledge and strategies from high income countries (HIC) is not the most appropriate, effective, or efficient approach to this global problem (Alladi and Hachinski, 2018; Parra et al., 2019; Walker and Paddick, 2019). LMIC led data collection and analysis will be essential to developing effective and appropriate dietary focussed interventions to prevent or delay dementia in each of these settings.

4.1. Unanswered questions and future research

Future studies should focus on replicating the reported analyses in larger cohorts, within the Mediterranean region and with repeated dietary measures. Focus should also be given to alternative appropriate imaging outcomes such as cortical thinning and PET amyloid and tau. Studies in LMIC are a priority for this field to better understand dietary patterns and neuroimaging findings.

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CRediT authorship contribution statement

SG designed the research question, systematic review protocol, performed the literature search, screened titles, abstracts and full texts and wrote the first draft of the article. SG acts as the guarantor for this work. HP was an independent second reviewer for titles, abstracts and full texts. SG extracted the data and performed the quality assessment, and this was reviewed and confirmed by HP. GM-T supervised the research question development, protocol design and resolved any conflicts between reviewers. All authors edited the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical approval

Not required for this systematic review.

Data sharing

Search terms are provided in the appendix. Data extraction templates can be requested from the corresponding author. All other data is in the public domain through publications.

Guarantor

The guarantor (SG) affirms that the manuscript is an accurate account of the study report, with no important aspects omitted and any changes from original methodologies clearly explained.

Declaration of competing interest

All authors have completed the ICMJE uniform disclosure form at

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Appendix. Supplementary data

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