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Mediterranean diet and dementia: MRI marker evidence from meta-analysis

Xiaojie Wang[4†], Zhiyao Xin[1,2,3†], Xiuwen Li[1,2,3], Keying Wu[1,2,3], Wanxin Wang[1,2,3], Lan Guo[1,2,3], Li Wang[4], Xin Mo[5], Xinjian Liu[4], Zhihui Guo[4], Jing Wang[5*] and Ciyong Lu[1,2,3*]

Abstract

Background Dementia is a growing public health concern with limited effective treatments. Diet may be a modifiable factor that significantly impacts brain health. Mediterranean diet (MeDi) has been suggested to be associated with brain Magnetic Resonance Imaging (MRI) markers related to dementia, but the existing evidence is inconsistent.

Objectives This systematic review and meta-analysis aimed to quantify the association between MeDi and dementia-related MRI markers.

Methods A systematic search was conducted on PubMed, Embase, and Web of Science up to September 2024. Two reviewers worked in parallel to select studies and extract data. We considered epidemiologic studies that reported beta coefficients (β) with 95% confidence intervals (*CI*s) for MRI markers related to MeDi. Separate meta-analyses were performed for cross-sectional and longitudinal studies.

Results A total of 20 relevant studies involving 44,893 individuals were included in the analysis. Thirteen cross-sectional studies included a total of 42,955 participants. A meta-analysis of cross-sectional studies revealed significant associations between MeDi and white matter hyperintensity (WMH) ($\beta = -0.03$, 95% $CI = -0.05 - -0.01$, $P = 0.02$). However, there were no significant associations found between MeDi and total brain volume (TBV) ($\beta = -0.03$, 95% $CI = -0.20–0.13$, $P = 0.71$), gray matter volume (GMV) ($\beta = 0.26$, 95% $CI = -0.19–0.71$, $P = 0.26$), white matter volume (WMV) ($\beta = -0.09$, 95% $CI = -0.40–0.22$, $P = 0.58$), or hippocampal volume (HCV) ($\beta = -1.02$, 95% $CI = -7.74–9.79$, $P = 0.82$). In the longitudinal analysis, seven prospective studies with an average follow-up period ranging from 1.5 to 9 years and involving 1,938 participants. The combined effect size of MeDi showed no significant association with TBV or GMV.

Conclusion Adherence to MeDi may be associated with reduced WMH in older adults. This suggests that MeDi may affect brain health and highlights the need for further research into its role as a modifiable lifestyle factor that might potentially modify the risk of dementia.

Keywords Mediterranean diet, Dementia, Magnetic resonance imaging markers, Meta-analysis

†Xiaojie Wang and Zhiyao Xin contributed equally to this article.

*Correspondence:
Jing Wang
wjing7997@163.com
Ciyong Lu
luciyong@mail.sysu.edu.cn
Full list of author information is available at the end of the article

Introduction

Dementia has become a growing public health concern due to the aging population [1]. Considering the limited effectiveness of current dementia treatments, prevention efforts can prove to be more viable by prioritizing modifiable lifestyle factors, such as diet [2]. Depending on the food combinations, dietary patterns can exert varying effects on brain structure, potentially influencing the risk of developing dementia [3, 4]. The Mediterranean diet (MeDi) is widely recognized as one of the most beneficial dietary patterns globally, which is characterized by a high intake of fruits, vegetables, cereals, legumes, nuts, fish, and olive oil and a low to moderate intake of dairy products, red or processed meats, and wine [5]. Additionally, the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean-DASH diet Intervention for Neurodegeneration Delay (MIND) are also popular dietary patterns. The DASH encourages the consumption of low-sodium foods, fruits, vegetables, low-fat dairy products, and whole grains. It also emphasizes limiting the intake of saturated fat, cholesterol, and refined sugars. The primary goal of the DASH is to lower blood pressure, which is a risk factor for dementia [6]. The MIND is a hybrid of the MeDi and DASH. It encourages the consumption of foods associated with MeDi and DASH, with a particular emphasis on the intake of berries and leafy greens. However, it does not emphasize high fruit intake or recommend eating fish more than once a week, unlike the MeDi [7]. All three diets promote brain health [8], but the MeDi may have a more distinct and comprehensive effect on MRI markers and dementia risk because of its richness in neuroprotective compounds and its emphasis on healthy fats, such as olive oil and fish. In addition, the MeDi is suitable for long-term adherence due to its flexible, unrestricted eating style. Therefore, this study focused on the MeDi pattern.

Evidence from studies suggests that MeDi may be associated with a reduced risk of dementia [8–10]. Several mechanisms may explain the positive effects of the MeDi on dementia. First, it may exert protective benefits through the reduction of oxidative stress. The MeDi is rich in antioxidants, such as vitamin E and folic acid, which can enhance antioxidant capacity and improve mitochondrial function [11]. Second, it could lower inflammation in the brain [12]. The MeDi can lower inflammatory markers, such as C-reactive protein, potentially providing protective effects for the nervous system [13]. Lastly, the diet may reduce vascular risk factors by lowering LDL cholesterol levels, which can improve blood flow to the brain and ensure it receives adequate nutrients [14]. Dementia-related neurodegeneration and vascular brain pathology can be detected by brain magnetic resonance imaging (MRI) even before the appearance of clinical symptoms of dementia. The decrease in total brain volume (TBV) was associated with brain atrophy, which is sensitive to AD-related neurodegeneration [15, 16]. In addition, the loss of gray matter volume (GMV) was associated with neuron loss and was also considered to be the marker of neurodegeneration [17]. Furthermore, White matter is where nerve fibers aggregate in the brain, and a decrease in white matter volume (WMV) may be associated with the injury and demyelination of these fibers, which affects nerve conduction [18]. White matter hyperintensity (WMH) refers to the damage of myelin surrounding nerve cells in the white matter of the central nervous system [19], and the hippocampal volume (HCV) is associated with memory function [20]. Changes in WMH [21, 22] and HCV [23, 24]are well-recognized neuroimaging markers associated with dementia. However, results from the existing studies investigating associations between MeDi and MRI markers are inconclusive. Previous studies have indicated that higher adherence to the MeDi was correlated with larger TBV and GMV, and smaller WMH volumes [25, 26]. For example, a study of older adults aged 65 and older in the WHICAP cohort found that following the MeDi was associated with larger TBV [27]. Zhang et al. [28]found that higher adherence to the MeDi was associated with a greater volume of GMV, but no significant associations with TBV, WMV, or HCV were observed. Gregory et al. [29] analyzed baseline data from a pan-European cohort and reported a negative association between MeDi adherence and WMH. In contrast, a study of older adults in Scotland did not find an association between MeDi and WMH, nor with TBV or GMV [30].

Given the inconsistency of results from individual studies, only narrative reviews have been conducted so far [15, 31, 32]. The extent of the relationship between MeDi and MRI markers of dementia remains unquantified. Therefore, we performed the current systematic review and meta-analysis of population-based studies to assess the cross-sectional and longitudinal associations between the MeDi and MRI markers, including TBV, GMV, WMV, WMH, and HCV among elderly adults.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), the PRISMA-S extension checklist, and the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines were followed in the conduct of this meta-analysis [33, 34]. This systematic review and meta-analysis was registered on PROSPERO (CRD42023417116).

Inclusion and exclusion criteria

The PICOS framework (Patient, Intervention, Comparator, Outcome, Study design) was utilized to establish the following eligibility criteria: (1) participants were to be 18 years of age or older; (2) adherence to MeDi was assessed using a validated score; (3) there were no restrictions on the comparative analysis; (4) neuroimaging outcomes needed to be reported; (5) only population-based observational studies (e.g., cross-sectional, case–control, or cohort studies) were included; (6) studies should provide beta (β) values or the mean and standard deviation (SD) for cases (i.e., high MeDi) and controls (i.e., low MeDi). We excluded case studies, systematic reviews, meta-analyses, comments, opinion pieces, and any definitions of MeDi that were unclear or non-compliant. We also excluded studies published in languages other than English.

Search strategy and article selection

Two researchers independently performed a literature search of the EMBASE, PubMed, and Web of Science from database inception through September 2024. Based on the keywords, MeSH terms, and requirements of the database, a Boolean search strategy was carried out using the general following logic: ("Mediterranean diet" OR "Mediterranean diets" OR "MeDi" OR "MIND diet" OR "Mediterranean-DASH Intervention for Neurodegenerative Delay") AND ("magnetic resonance imaging" OR "MRI" OR "diffusion magnetic resonance imaging" OR "diffusion tensor imaging" OR "DTI" OR "DWI" OR "diffusion MRI" OR "brain connectivity" OR "neuroimaging" OR "white matter" OR "white matters" OR "brain volume"). Supplementary data (Table S1) contains the full search strategy.

We also manually examined reference lists of relevant reviews for additional articles that were not captured in the original literature.

Data extraction

Two researchers independently extracted data from each included study. Any inconsistencies were resolved by a third author. The data collected included the following elements: author name, publication year, country, study design, sample size, age, gender, diet assessment scale, MeDi assessment cut-off score, MeDi adherence, duration of MeDi exposure, MRI markers, and variables adjusted in the multivariable-adjusted model.

Quality assessment

The quality of the included studies was estimated independently by two researchers, using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institutes of Health (NIH) [35, 36]. This tool contains 14 questions that assess several aspects associated with the risk of bias, as well as type I and type II errors, transparency, and confounding factors. Each study was assigned a score based on the following scale: 0–6 indicates poor quality, 7–10 indicates fair quality, and 11–14 indicates good quality. The agreement rate between the reviewers for the quality assessment was 99%.

Data analysis

The beta coefficient (β) with a 95% confidence interval (*CI*) was calculated to evaluate the associations between adherence to MeDi and MRI markers. The I^2 and Cochran's Q test statistics were used to investigate heterogeneity among the studies. The I^2 test categorized the degree of heterogeneity as low (25%), moderate (50%), or high (75%). Given the statistical heterogeneity observed ($I^2 > 50\%$ and $P < 0.05$), we applied a random effects model. Meta-regression analyses were conducted to identify potential sources of heterogeneity based on age (i.e., years), geographical location (i.e., Europe and US), MeDi assessment cut-off scores (i.e., s 9-point MeDi diet score, PREDIMED diet score, Pyramid based Mediterranean diet score, 55-point MeDi diet score, Principal component analysis, and MeDi-style) and sample size (i.e., number of participants). To assess the robustness of the findings, we conducted a remove-one sensitivity analysis to evaluate the effect of each study on the overall estimate. If the pooled effect size changes significantly after removing a study, it may indicate that the study influenced the overall results, suggesting potential publication bias. A funnel plot and Beggar's test would be used to explore publication bias if 10 or above studies were included. Statistical analyses were carried out using R version 4.4.1. *P*-values less than 0.05 were considered statistically significant.

Results

Literature search

We conducted a comprehensive search across various databases and identified 2,032 publications. After removing duplicates and excluding irrelevant papers by screening the titles and abstracts, we narrowed it down to 69 articles. We then closely assessed the full texts of these remaining articles. Further, 49 articles were excluded for reviews (n = 19), irrelevant outcomes (n = 4), not a Mediterranean diet (n = 10), comment (n = 4), Conference (n = 8), book chapter (n = 1), study design (n = 1), letter (n = 1), and supplementary issue (n = 1). Finally, 20 studies were included in the qualitative analysis, and 14 studies provided data to be included in the pooled analysis.

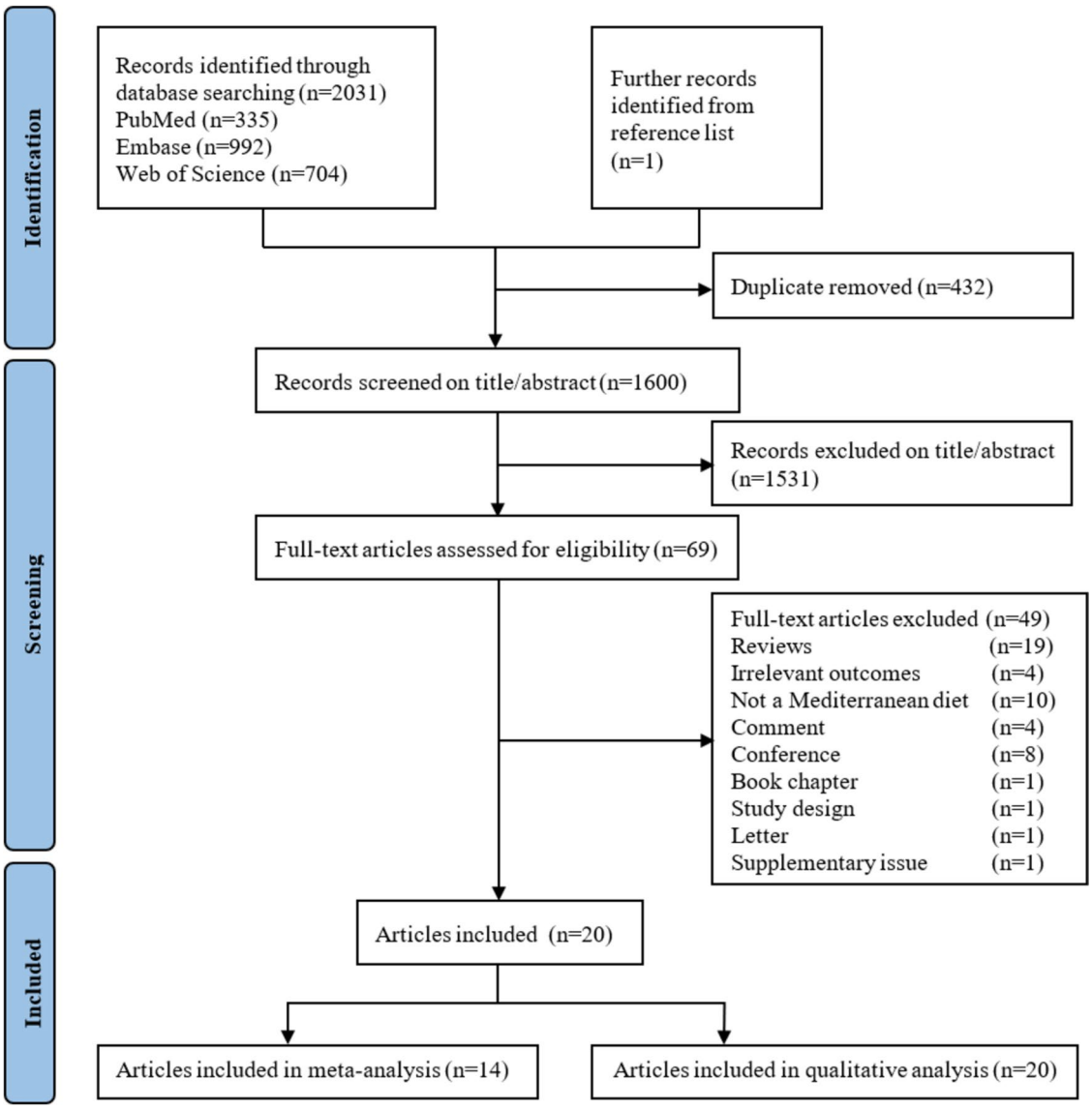

Fig. 1 PRISMA diagram of the study selection process

Figure 1 illustrates the detailed flow diagram of our search strategy and the study selection process.

Study characteristics

Tables 1 and 2 present a description of the included cross-sectional and prospective studies, respectively. Fig. S3 describes the regional distribution of the included cross-sectional and longitudinal studies. Fig. S4 describes the MeDi assessment cut-off score of the included cross-sectional and prospective studies.

Thirteen cross-sectional studies [26–30, 37–44] published between 2012 and 2024 included a total of 42,955 participants. Geographically, 9 studies were conducted in Europe (four in the UK, one covering both the UK and Ireland, two in Germany, one in Sweden, and one pan-European study), while 4 studies took place in North America (all in the USA). The prevalence of participants with high adherence to MeDi diet varied from 24.1% to 52.4%. In the majority of these publications (53.8%), a food frequency questionnaire (FFQ) was used to assess dietary intakes, including one SCG FFQ, four Willett FFQs, and two Block FFQs. Other dietary assessment tools included 24-h Dietary Recall (23.1%), the Mediterranean Diet Adherence Screening (MEDAS) (15.4%), and the DH method (7.7%). Regarding the assessment of MeDi, six articles utilized a 9-point MeDi diet score (46.1%), three used a PREDIMED diet score (23.1%), one used a 55-point MeDi diet score (7.7%), one used a

Table 1 Characteristics of the included cross-sectional studies

Author	Year	Region	Study design/ duration of follow-up(y)	Sample size	Age / mean ± SD (y)	Female (%)	Diet assessment	MeDi assessment	MeDi adherence	Duration of MeDi exposure	MRI markers	Variables adjusted in the multivariable-adjusted model
Gregory et al.	2024	UK, Ireland	Cross-sectional	516	51.2 ± 5.4	310 (60.1)	SCG FFQ	Pyramid-based MeDi score	MeDi mean score: 8.09 ± 1.55	preceding 2 ~ 3 months	WMH, HCV	age, sex, years of education, parental history of dementia, APOEε4 carrier status, socioeconomic status, physical activity, TIV, total kilocalories, Western diet score
Hepsomali et al.	2024	UK	Cross-sectional	32	25.6 ± 7.5	23 (71.9)	MEDAS	PREDIMED diet score	Low tertile: 50.0% High tertile: 50.0%	preceding 1 month	GMV	BMI, TIV
Gregory et al.	2023	pan-European countries	Cross-sectional	1625	65.5 ± 7.4	908 (55.9)	MEDAS	PREDIMED diet score	MeDi mean score: 6.92 ± 1.55	preceding 1 month	WMH, HCV	age, sex, education, family history, APOEε4, CAIDE, smoking, BMI, hypertension, hypercholesterolemia, hyperglycemia, diabetes, stroke, antihypertensive medication use, diabetic medication use, living in the Mediterranean, MeDi score, TIV
Samuelsson et al.	2023	Sweden	Cross-sectional	610	70.0	328 (53.8)	DH method	PCA	MeDi component score: 0.054 ± 1.001	preceding 3 months	HCV	sex, energy intake, BMI, physical activity level, education, and smoking

Table 1 (continued)

Author	Year	Region	Study design/ duration of follow-up(y)	Sample size	Age / mean ± SD (y)	Female (%)	Diet assessment	MeDi assessment	MeDi adherence	Duration of MeDi exposure	MRI markers	Variables adjusted in the multivariable-adjusted model
Zhang et al.	2023	UK	Cross-sectional	18,214	55.9 ± 7.5	9,670(53.1)	24-Hour Day Recall	9-point MeDi diet score	MeDi mean score: 5.47 ± 1.0 Low tertile: 39.2% Middle tertile: 36.7% High tertile: 24.1%	preceding 24 h	TBV, WMV, GMV, HCV	age, sex, educational level, APOE, BMI, smoking status, alcohol consumption, regular physical activity, time on watching TV, sleep duration, Townsend deprivation index, family history of dementia, primary diseases at baseline (i.e., cancer, cardiovascular disease and diabetes)
Corley et al.	2020	UK	Cross-sectional	358	79.3 ± 0.6	168 (46.9)	Willett FFQ	MeDi-style Diet	Low tertile: 33.4% Middle tertile: 27.3% High tertile: 33.4%	preceding 1 year	TBV, WMH, GMV	age, sex, physical activity, alcohol intake, smoking, diabetes, stroke, hypertension, hypercholesterolemia, APOE e4 carrier status, Age 11 IQ
MacPherson et al.	2021	UK	Cross-sectional	19,184	53.8 ± 6.9	9,257 (48.3)	24-Hour Day Recall	9-point MeDi diet score	MeDi mean score: 4.3 ± 1.7	preceding 24 h	TBV, WMV, GMV	age, sex, education, income, ethnicity, energy intake, heart conditions, depression, physical activity, BMI, smoking status

Table 1 (continued)

Author	Year	Region	Study design/ duration of follow-up(y)	Sample size	Age / mean ± SD (y)	Female (%)	Diet assessment	MeDi assessment	MeDi adherence	Duration of MeDi exposure	MRI markers	Variables adjusted in the multivariable-adjusted model
Ballarini et al.	2021	Germany	Cross-sectional	512	69.5 ± 5.9	279 (52.7)	24-Hour Day Recall	9-point MeDi diet score	MeDi mean score: 4.5 ± 1.6	preceding 24 h	GMV	age, sex, caloric intake, BMI, physical activity, APOE e4, TIV
Schwarz et al.	2020	Germany	Cross-sectional	137	69.0 ± 6.0	70 (51.1)	Willett FFQ	PREDIMED diet score (remove Sofrito)	MeDi mean score: 4.1 ± 1.7	preceding 1 month	TBV, WMV, GMV, HCV	age, sex, years of education, diagnostic group (healthy controls and subjective cognitive decline)
Karstens et al.	2019	USA	Cross-sectional	82	68.8 ± 6.88	42 (50.0)	Block FFQ	55-point MeDi diet score	MeDi mean score: 33.31 ± 4.42 Low tertile: 47.6% High tertile: 52.4%	preceding 1 year	WMH, WMV, HCV	age, sex, education, BMI, estimated kilocalories
Gu et al.	2015	USA	Cross-sectional	674	80.1 ± 5.6	454 (67.0)	Willett FFQ	9-point MeDi diet score	Lower tertile: 54.9% High tertile: 45.1%	preceding 1 year	TBV, WMV, GMV	age, sex, education, ethnicity, BMI, diabetes, mean cognition
Matthews et al.	2014	USA	Cross-sectional	45	54 ± 11	32 (71.0)	Willett FFQ	9-point MeDi diet score	Lower tertile: 60.0% High tertile: 40.0%	preceding 1 year	GMV	age, sex

Table 1 (continued)

Author	Year	Region	Study design/ duration of follow-up(y)	Sample size	Age / mean ± SD (y)	Female (%)	Diet assessment	MeDi assessment	MeDi adherence	Duration of MeDi exposure	MRI markers	Variables adjusted in the multivariable-adjusted model
Gardener et al.	2012	USA	Cross-sectional	966	71.6 ± 8.3	573 (59.3)	Block FFQ	9-point MeDi diet score	MeDi score 0–2: 11.6% MeDi score 3: 15.8% MeDi score 4: 23.0% MeDi score 5: 23.5% MeDi score 6–9: 26.1%	preceding 1 year	WMH	age at MRI, sex, race/ethnicity, high school education completion, moderate to heavy physical activity, Kcal, smoking, LDL, HDL, systolic blood pressure, diastolic blood pressure, the interaction between diastolic blood pressure and antihypertensive medication use, diabetes, cardiac disease history

USA: United States of America, UK: United Kingdom, y: Year, SD: Standard Deviation, FFQ: Food Frequency Questionnaire, MEDAS: Mediterranean Diet Adherence Screener, SCG: Scottish Collaborative Group, DH: The diet history, MeDi: Mediterranean diet, WMH: White Matter Hyperintensities, TBV: Total brain volume, WMV: Total white matte, GMV: Gray matter volume, HCV: hippocampal volume, TIV: Total Intracranial Volume, BMI: Body Mass Index, CAIDE: cardiovascular risk factors, aging and dementia

Table 2 Characteristics of the included longitudinal studies

Author	Year	Region	Study design/ duration of follow-up (y)	Sample size	Age / mean ± SD (y)	Female (%)	Diet assessment	MeDi assessment	MeDi adherence	Duration of MeDi exposure	MRI markers	Variables adjusted in the multivariable-adjusted model
Song et al.	2022	USA	Cohort (5y)	183	53.2 ± 16.5	94 (51.4)	Willett FFQ	55-point MeDi diet score	MeDi mean score: 28.2 ± 5.5 Low tertile: 36.7% Middle tertile: 27.3% High tertile: 36.0%	preceding 1 year	WMH	age, gender, education, National Adult Reading Test-assessed Intelligence Quotient, race/ethnicity, total daily energy intake, baseline WMH, baseline gray matter volume residual, baseline mean thickness, and follow-up interval
Rodrigues et al.	2020	Portugal	Cohort (1.5y)	76	66.4 ± 7.8	37 (49.3)	MEDAS	PREDIMED diet score	Low tertile: 72.4% High tertile: 27.6%	preceding 1 month	WMV, GMV	age, sex, years of education, TIV, BMI, time between assessments
Berti et al.	2018	USA	Cohort (3y)	70	49.5 ± 9	47 (67.0)	Willett FFQ	9-point MeDi diet score	Low tertile: 51.1% High tertile: 48.9%	preceding 1 year	GMV	age, sex, education, BMI, diabetes, cognitive ability, Mini-Mental State Examination
Luciano et al.	2017	Scotland	Cohort (6y)	562	72.7 ± 0.7	269 (47.9)	SCG FFQ	9-point MeDi diet score	Low tertile: 51.1% High tertile: 48.9%	preceding 2 ~ 3 months	TBV, GMV	age, sex, education, BMI, diabetes, cognitive ability, Mini-Mental State Examination
Pelletier et al.	2015	France	Cohort (9y)	146	73.0 ± 3.7	88 (60.3)	FFQ	9-point MeDi diet score	Low tertile: 26.0% Middle tertile: 47.0% High tertile: 27.0%	preceding 1 year	WMV, GMV	age, sex, education, APOE ε4 carrier status, history of cardiovascular diseases, hypertension, hypercholesterolemia

Table 2 (continued)

Author	Year	Region	Study design/ duration of follow-up (y)	Sample size	Age / mean ± SD (y)	Female (%)	Diet assessment	MeDi assessment	MeDi adherence	Duration of MeDi exposure	MRI markers	Variables adjusted in the multivariable-adjusted model
Titova et al.	2013	Sweden	Cohort (5y)	194	70.1 ± 0.01	93(47.9)	7-Day Dietary registration	9-point MeDi diet score	–	preceding 1 week	TBV, GMV	gender, energy intake, education, self-reported physical activity, serum concentration of low-density cholesterol, BMI, systolic blood pressure, homeostasis model assessment of insulin resistance
Scarmeas et al.	2011	USA	Cohort (5.8y)	707	80.4 ± 5.5	147 (30.0)	Willett FFQ	9-point MeDi diet score	MeDi mean score: 4.4 ± 1.7 Low tertile: 31.0% Middle tertile: 42.0% High tertile: 27.0%	preceding 1 year	WMH	age, sex, ethnicity, education, smoking, APOE genotype, caloric intake, BMI, diabetes, hypertension, heart disease, duration between diet evaluation and MRI

USA: United States of America, y: Year, SD: Standard Deviation, FFQ: Food Frequency Questionnaire, MEDAS: Mediterranean Diet Adherence Screener, SCG: Scottish Collaborative Group, MeDi: Mediterranean diet, PREDIMED: PREvención con Dieta MEDiterránea, PCA: Principal component analysis, WMH: White Matter Hyperintensities, TBV: Total brain volume, WMV: Total white matte, GMV: Gray matter volume, TIV: Total Intracranial Volume, BMI: Body Mass Index

principal component analysis (PCA) (7.7%), one applied a MeDi-Style diet (7.7%), and one used a Pyramid based Mediterranean diet score (7.7%). Moreover, the duration over which the Mediterranean diet was evaluated was most commonly assessed for the preceding year (38.4%), followed by the preceding month (23.1%), the preceding 24 h (23.1%), 2–3 months (7.7%), and 3 months (7.7%). Five studies assessed total brain volume (TBV), eight studies assessed gray matter volume (GMV), five studies assessed white matter hyperintensity (WMH), five studies assessed white matter volume (WMV), and six studies assessed hippocampal volume (HCV).

The seven longitudinal studies [25, 45–50], published between 2011 and 2022, investigated 1,938 participants. The duration of follow-up for these cohort studies varied from 1.5 years to 9 years. Geographically, four studies were conducted in Europe (Portugal, Scotland, France, and Sweden), while 3 studies took place in North America (all in the USA). The rate of high adherence to MeDi ranged from 27.0% to 48.9%. Diet assessment tools included FFQ (71.4%), 7-Day Dietary Registration (14.3%), and MEDAS (14.3%). MeDi diet assessment was generally calculated using the 9-point MeDi diet score (71.4%), 55-point MeDi diet score (14.3%), and PREDIMED (14.3%). The duration of dietary exposure ranged from the past week to the past year. Two studies assessed total brain volume (TBV), five studies assessed gray matter volume (GMV), two studies assessed white matter hyperintensity (WMH), and two studies assessed white matter volume (WMV).

Quality assessment

The overall quality assessment of cross-sectional and prospective studies is shown in Table S2. Generally, the cross-sectional studies were assessed to be at a low risk of bias, as they provided comprehensive details about the research question (Q1), and participant group (Q2), and recruited participants in the same or similar population (Q4). Additionally, they included information on exposure (Q9), and outcome variables (Q11). Almost all articles adjusted for confounding variables, but two articles did not sufficiently adjust for key potentially confounding variables (Q14). Eight studies examined different levels of MeDi scores (Q8). Furthermore, two studies provided a power calculation to justify the sample size (Q5), and two assessed diet more than once (Q10). Seven studies reported a participation rate of at least 50% among the invited individuals (Q3). No studies reported if assessors were blinded to outcome measures (Q12).

The quality of prospective studies ranged from fair to good. All studies clearly defined the research question (Q1) and identified the study population (Q2). Participants were recruited from the same or similar populations (Q4), and the exposure of interest was measured prior to assessing the outcomes (Q6). Each study provided a sufficient timeframe (Q7) and specified both independent (Q9) and dependent variables (Q11). Only one article did not sufficiently adjust for key potentially confounding variables (Q14).

Two studies had a follow-up rate of 20% or lower after the baseline (Q13). Six studies examined different levels of MeDi scores (Q8). Additionally, four studies noted that at least 50% of the invited individuals accepted to participate in the research (Q3), and two studies assessed diet more than once (Q10). One prospective investigation reported whether assessors were blinded to the outcome measures (Q12). Finally, none of the studies provided a justification for their sample sizes (Q5).

Cross-sectional associations between MeDi and MRI markers

The cross-sectional association between adherence to MeDi and MRI markers is shown in Fig. 2. The studies by Zhang [28] and MacPherson [41] measured the volume of MRI markers in mm^3, while the other 12 studies reported measurements in ml. To ensure consistency in our analysis, we adjusted the effect sizes from the Zhang [28] and MacPherson [41] studies by dividing them by 1000.

Four studies involving 38,430 participants investigated the association between MeDi and TBV (Fig. 2A). No significant association between MeDi and TBV was observed among studies ($\beta = -0.03$, 95% $CI = -0.20$–0.13, $P = 0.71$). The I^2 index was 55%, which indicates a moderate level of heterogeneity among the studies ($Q = 6.69$, $df = 3$, $P = 0.08$).

Four studies (including 38,430 participants) investigated the association between MeDi and GMV (Fig. 2B). The pooled analysis indicated no significant association ($\beta = 0.26$, 95% $CI = -0.19$–0.71, $P = 0.26$) between MeDi and GMV. An I^2 index of 69% was observed among studies and classified as representing substantial heterogeneity ($Q = 9.65$, $df = 3$, $P = 0.02$).

Four studies (including 38,154 participants) investigated the association between MeDi and WMV (Fig. 2C). No significant association between MeDi and WMV ($\beta = -0.09$, 95% $CI = -0.40$–0.22, $P = 0.58$) was observed. Heterogeneity was classified as might not be important ($Q = 3.11$, $df = 3$, $P = 0.37$).

Five studies (including 3,547 participants) investigated the association between MeDi and WMH (Fig. 2D). The pooled analysis indicated a significant association ($\beta = -0.03$, 95% $CI = -0.05$– -0.01, $P = 0.02$), the I^2 index was 80%, indicating significant heterogeneity ($Q = 19.54$, $df = 4$, $P < 0.001$).

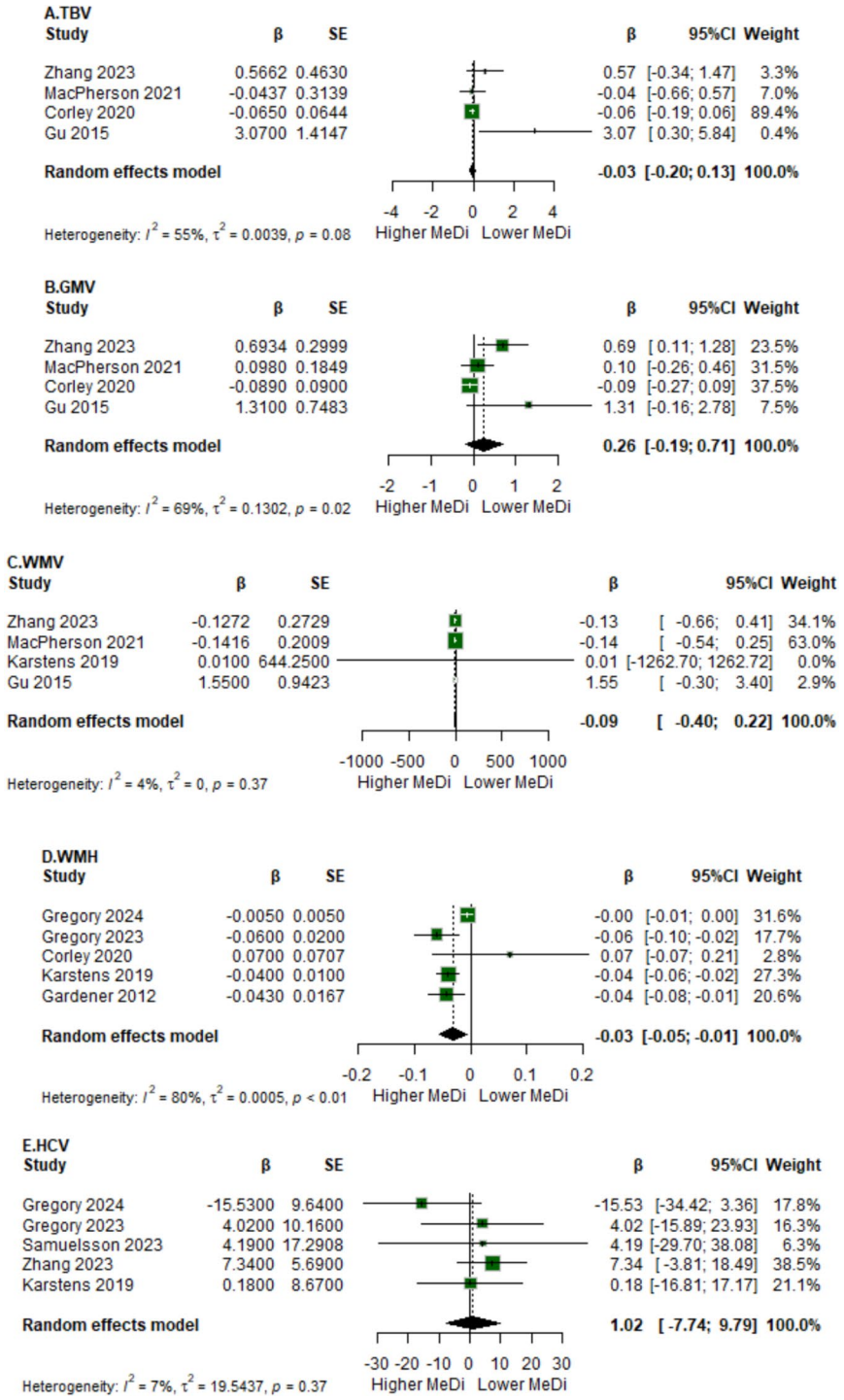

Fig. 2 Cross-sectional meta-analysis of MeDi and MRI markers. **A** Total brain volume (TBV). **B** Total gray matter volume (GMV). **C** Total white matter volume (WMV). **D** White matter hyperintensity volume (WMH). E. hippocampal volume (HCV). *SE* standard error, *CI* confidence interval, MeDi Mediterranean diet

Five studies examining 21,047 participants investigated the association between MeDi and HCV (Fig. 2E). The analysis found no significant association between MeDi and HCV ($\beta = -1.02$, 95% CI = − 7.74–9.79, $P = 0.82$). The heterogeneity among the studies was low ($Q = 4.28$, $df = 4$, $P = 0.37$), suggesting that the effects observed were relatively consistent across the studies.

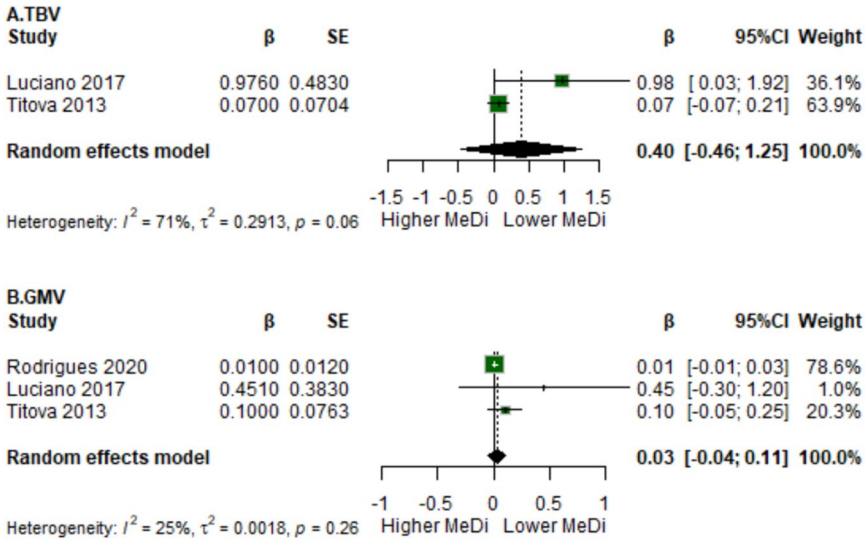

Fig. 3 Longitudinal meta-analysis of MeDi and MRI markers. **A** Total brain volume (TBV). **B** Total gray matter volume (GMV). *SE* standard error, *CI* confidence interval, MeDi Mediterranean diet

Longitudinal associations between MeDi and MRI markers

The longitudinal association between adherence to MeDi and MRI markers is shown in Fig. 3.

Combining 2 studies (including 756 participants) illustrated that there was no significant association between MeDi and TBV ($\beta = 0.40$, 95% $CI = -0.46$–1.25, $P = 0.36$; Fig. 3A), heterogeneity was moderate ($I^2 = 71\%$, $Q = 3.45$, $df = 1$, $P = 0.06$).

Three studies (including 832 participants) investigated the association between MeDi and GMV (Fig. 3B). The pooled analysis indicated no significant association ($\beta = 0.03$, 95% $CI = -0.04$–0.11, $P = 0.40$) between MeDi and GMV. An I^2 index of 25% was observed among studies and classified as representing substantial heterogeneity ($Q = 2.67$, $df = 2$, $P = 0.26$).

Two studies including a total of 222 participants analysed associations between MeDi and WMV. Both studies did not find an association between MeDi and WMV. Both studies were conducted in Europe. The study conducted by Rodrigues [49] indicated that no association was found between MeDi and WMV ($\beta = -0.019$, $P = 0.09$). This study included 76 older participants with a mean age of 66.4 (±7.8) years, and 49.3% were female. The dietary assessment questionnaire used in this study was MEDAS. Pelletier [47] et al. conducted MRI examinations 8.9 years on average after dietary assessment using FFQ, the result showed that MeDi was not associated with WMV. The average age of the participants was 73.0 (±3.7) years, and 60.3% were female.

Two studies (including 890 participants) investigated the association between MeDi and WMH. The result of Song et al. [50] suggests that greater adherence to MeDi was associated with a lesser increase in WMH over time ($\beta = -0.014$, 95% $CI = -0.026$– -0.001, $P = 0.034$). The result of Scarmeas et al. [45], however, suggests that WMH was not related to MeDi ($\beta = -0.0004$, $P = 0.99$). Song et al. included 183 participants aged 53.19 ± 16.52 years, and 51.4% were female. The questionnaire used was Willett FFQ and the cut-off score of the MeDi assessment was a 55-point MeDi diet score. Scarmeas et al. included 707 participants aged 80.4 ± 5.5 years, 30% of whom were female. The questionnaire used was Willett FFQ and the cut-off score for MeDi assessment was a 9-point MeDi diet score. The Standard error of the study conducted by Scarmeas could not be calculated, and there were differences in the age and sex ratio of the participants in the two studies, thus, the effect sizes of the two studies could not be combined.

Meta-regression and publication bias

Significant heterogeneity was observed in the pooled analysis of the longitudinal studies examining TBV and GMV. However, due to the limited number of studies available, we were unable to perform a meta-regression to identify potential sources of this heterogeneity. Potential reasons for the observed heterogeneity may include differences in MeDi assessment cut-off score or geographic variations. The two studies on TBV, from Scotland and Sweden, were geographically far apart, which may have contributed to differences in eating habits. Additionally, the three studies on GMV originated from geographically distant locations, and they used two different cut-off scores (PREDIMED and 9-point MeDi diet score), which may lead to differences in MeDi adherence.

A meta-regression was conducted on cross-sectional studies that investigated MRI markers. In these studies, the age of participants had a significant impact on the outcomes of the meta-analysis for WMH ($\beta = -0.0374$, 95% $CI = -0.0563 - -0.0186$, $P < 0.001$), indicating a meaningful impact of age on the heterogeneity. Additionally, the geographical location had a significant effect on the heterogeneity of the meta-analysis for TBV ($\beta = 3.1227$, 95% $CI = 0.3472 - 5.8981$, $P = 0.0274$). These findings suggest that cut-off scores for the MeDi assessment or the the geographical location may significantly contribute to the heterogeneity observed in the meta-analysis of TBV results.

Due to the reduced number of studies included in this meta-analysis, publication bias via funnel plots could not be performed (i.e. < 10).

Sensitivity analysis

In the cross-sectional studies, the sensitivity analysis indicated that no individual study significantly affected the pooled results when any single study was excluded. However, when Gregory's (2024) or Corley's studies were removed, the pooled effect size associated with MeDi and WMH changed (Fig. S1).

In the longitudinal studies, due to the limited number of studies on TBV, a sensitivity analysis was only conducted for GMV. The results showed that the removal of any article had no effect on the pooled results (Fig. S2).

Discussion

The main findings of the present systematic review and meta-analysis indicate that high adherence to MeDi might be associated with lower WMH among elderly adults, while the associations with MeDi of TBV, GMV, WMV, and HCV were not significant. This meta-analysis could inform future intervention studies and support dietary recommendations for the use of MeDi to maintain cognitive function in the elderly.

Our cross-sectional meta-analysis found a negative association between MeDi and WMH, this finding is supported by a longitudinal study assessed to be of good quality. The result of Song et al. [50] suggests that greater adherence to MeDi was associated with a lesser increase in WMH. While the result of Scarmeas et al. [45] suggests that WMH was not related to MeDi. The quality assessment of Scarmeas et al. is fair. This inconsistency may stem from a variety of factors such as age, sex ratio, and truncation scores on the MeDi assessment of the study population. Combined with the results of the cross-sectional meta-analysis, we concluded that there may be a negative association between MeDi and WMH. Sensitivity analysis found 2 cross-sectional studies that examined the association between MeDi and WMH significantly influenced the stability pool effect size. If these two studies are removed, the combined results of the meta-analysis tend to support the conclusion that there is an association between MeDi and WMH. The combined results of the meta-analysis were consistent with those of the other three papers. Although the two studies have a significant influence on the results, the comprehensive results are in line with other studies, so these results can be considered to be reliable, while more high-quality studies are needed to confirm the findings in the future. Two longitudinal studies examined the association between MeDi and WMH and found opposite results. We were unable to calculate a combined effect size because the standard error for one of the studies was unavailable. Additionally, the studies differed in participant age and sex ratio, which limits our understanding of the association between MeDi and WMH. Future studies should consider these factors and more high-quality research is needed to further validate the impact of the Mediterranean diet on elevated WMH. Previous narrative reviews concluded that no difference was detected between high and low adherence to the MeDi [31], however, the MeDi was associated with white matter integrity [51]. Impaired microstructural integrity has been shown to precede conversion into WMH [52]. WMH is a surrogate of small-vessel vascular disease that is predictive of cognitive performance and cognitive decline [53]. These findings support the idea that the MeDi may preserve brain function through its effects on vasculature.

There are several potential mechanisms that could explain the relationship between adherence to MeDi and WMH. Prolonged exposure to MeDi may enhance the protective effects of antioxidants, anti-inflammatory agents, vascular damage, and neuroprotective factors. These factors are linked to brain aging and the etiology of dementia [54, 55]. Aging of the brain is largely caused by oxidative stress. The brain has a high metabolic load, making it extremely vulnerable to oxidative injury [56]. It has been demonstrated that antioxidant-rich foods and dietary patterns shield the brain from oxidative damage. In fact, the current study discovered that following the MeDi was typically linked to the preservation of brain structure. Furthermore, reducing neuroinflammation might be another pathway to improved brain function. Unbalanced synthesis of pro- and anti-inflammatory cytokines and reactive oxygen species through glial cells can result in neurotoxicity and cell death when dietary n-6 and n-3 polyunsaturated fatty acids are not balanced [57]. In addition, low-density lipoprotein and cholesterol levels in the blood are decreased by healthy eating patterns like the MeDi, which lowers the risk of vascular comorbidities, dyslipidemia, hypertension, and coronary artery disease [58]. These are linked to fewer white

matter lesions in the brain through vascular pathways [59]. Hence, it's important to reduce inflammation, oxidative stress, and vascular damage by consuming nutritious foods and healthy eating habits [60–63]. This may also be a useful tactic to slow down age-related neurodegenerative processes.

The combined evidence suggests that MeDi is not associated with TBV, GMV, WMV, and HCV, which is consistent with an earlier narrative review [32].

Five cross-sectional and two longitudinal studies measured the association between MeDi and TBV, the results of the cross-sectional and longitudinal meta-analysis did not find an association between MeDi and TBV. Among these, a cross-section study [27] found that larger TBV, GMV, and WMV were associated with higher MeDi adherence. A longitudinal study [25] reported lower adherence to the MeDi was associated with a greater 3-year reduction in TBV, indicating that adherence to the MeDi affects the trajectory of brain changes in older adults.

Eight cross-sectional and five longitudinal studies measured the association between MeDi and GMV, the combined effect size of the cross-sectional and longitudinal studies showed that no association was found between MeDi and GMV. Among the articles included in the cross-sectional meta-analysis, only one study [28, 39] has found an association between MeDi and GMV. In the qualitative review, we summarized GMV studies of MeDi, which could not be included in the meta-analysis, but nonetheless deepened our understanding of the precise relationship. A total of six articles not included in the meta-analysis measured the association between MeDi and GMV, including four cross-sectional studies and two longitudinal studies. Three cross-sectional studies [38–40] reported lower adherence to MeDi was associated with lower GMV volume. Combined with the results of the longitudinal studies, we did not find an association between MeDi and GMV.

Five cross-sectional studies and two longitudinal studies measured the association between MeDi and WMV. A cross-sectional meta-analysis with low heterogeneity (4%) found no association between MeDi and WMV. In addition, combined with two longitudinal studies that reached similar conclusions, our study also found no significant association between MeDi and WMV. Notably, in the meta-analysis of the cross-sectional study of WMV, the standard error of the results of Karstens [26] was large, and the weight in the meta-analysis was 0%. However, in the sensitivity analysis, the removal of the study of Karstens had no significant impact on the results. Considering that the study quality was fair, we still included the study of Karstens in the meta-analysis. Six cross-sectional studies measured the association between MeDi and HCV. None of the six articles found an association between the MeDiand HCV.

For the result that WMH showed significant results compared to other markers, following are the possible explanations. The MeDi is rich in anti-inflammatory and vascular-protective ingredients, which may directly benefit vascular health. The effects of diet on improving blood flow and reducing inflammation are more easily observed in WMH compared to other measures of brain volume [59]. In addition, WMH often serves as an early and sensitive indicator of vascular-associated brain changes [64, 65]. It is likely more responsive to dietary interventions compared to other brain volume measures, which may take longer to show significant changes. Furthermore, the anti-inflammatory and antioxidant properties of the MeDi may help reduce neuroinflammation and oxidative stress associated with WMH [55]. However, these properties may not significantly influence TBV, GMV, and HCV during the study period. In conclusion, the association between MeDi and MRI markers may be influenced by a complex interplay of dietary factors, disease progression, and the varying sensitivity of different brain markers to dietary changes. Further research is needed with larger sample sizes, longer follow-up periods, and more uniform study populations to explore these associations fully.

Given the lack of association between MeDi adherence and TBV, GMV, WMV, and HCV, it is important to explore other potential mechanisms that may explain the links between MeDi adherence and reduced incidence of dementia. One possibility lies in the neuroprotective properties of specific nutrients abundant in MeDi, such as omega-3 fatty acids, antioxidants, and vitamins that combat oxidative stress and inflammation, both known contributors to neurodegeneration [66, 67]. Additionally, MeDi may positively influence the gut-brain axis, promoting a diverse microbiome that enhances cognitive function through the production of beneficial metabolites [68, 69]. Another important aspect is the idea of cognitive reserve, where lifestyle factors linked to adherence to MeDi, such as increased physical activity and social engagement, may enhance cognitive resilience against neurodegenerative changes [70]. Additionally, while the DASH and MIND diets were not evaluated, they may also influence MRI markers due to their vascular and anti-inflammatory effects. Gaining a better understanding of how these dietary patterns differ and complement each other could provide more effective dietary recommendations for preventing dementia and promoting brain health. Future studies should explore the comparative effects of the DASH and MIND diets on MRI markers to clarify their roles in preventing neurodegenerative diseases. Overall, a multifaceted approach is essential to

fully understand how MeDi may confer protective effects against dementia, warranting further investigation into these interrelated mechanisms. We performed a meta-regression analysis to explore the source of heterogeneity. Meta-regression analysis indicated that age significantly influenced the heterogeneity of WMH meta-analysis results. This could be because older individuals may be more responsive to the health benefits of MeDi. WMH increases with age, they are very common among older adults and are linked to poorer cognitive performance [71]. The MeDi, which is rich in antioxidants, healthy fats, and fiber, may help protect and improve cognitive function in older adults [67]. The geographical location has a significant effect on the heterogeneity of TBV. In countries around the Mediterranean, such as Spain and Italy, healthy eating like MeDi is more common. This indicates that we may need large sample size studies to be sufficient to find an association between MeDi and TBV and that further studies in other regions are needed. In addition, We cannot exclude the possibility that various confounding factors, which were not analyzed in the meta-regression. Specifically, we were not able to examine the impact of variables such as socioeconomic status and genetic predisposition on the results. Socioeconomic Status (SES) is a multidimensional measure that encompasses education level, occupational status, and economic resources [72]. SES is associated not only with health behaviors but also may impact susceptibility to dementia. Additionally, genetic predispositions significantly influence neurodegenerative diseases [73], for instance, the APOE ε4 gene may play a significant role in the development of Alzheimer's disease [74]. Besides, participation in physical exercise [75], and social support [73, 76] may have influenced the heterogeneity observed in the current study. In future studies, it is essential to consider and adjust for potential confounding factors.

Several limitations should be considered while interpreting our findings. Firstly, studies were either cross-sectional which cannot exclude reverse causation, or observational longitudinal studies where residual confounding is inherent. The included cross-sectional studies were unable to establish causal associations, limiting the ability to draw conclusions about the long-term effects of the MeDi on brain structure and function and dementia risk. In the future, it is essential for the field to prioritize randomized controlled trials with long-term follow-up to explore the cause-and-effect relationship between MeDi and brain health. Secondly, the study only included populations in the United States and Europe and did not take into account populations in other regions, such as Asia. Future studies in more regions are needed to increase diverse geographic representation. A third potential limitation of this review is that studies reported the use of self-reported measures, such as FFQs. Self-reported measures are sensitive to social desirability bias such as the over-reporting of healthy foods and under-reporting of unhealthy foods [77]. Dietary patterns can be assessed in future studies using nutritional biomarkers. For example, a previous study used multivariate analysis to extract eight different nutrient biomarker patterns (NBPs) from the original 30 biomarkers (e.g., saturated fat pattern, carotenoid pattern, and so on) [78]. Fourth, we could not perform a meta-regression to investigate the source of heterogeneity in the longitudinal studies examining TBV and GMV due to the limited number of studies. The fifth limitation is due to the variability of included confounding covariates, while most studies controlled for the main potential confounders (age, sex, and body mass index), the variability of including confounders such as cardiovascular measures or socioeconomic variables may have influenced the study outcomes. Sixth, due to variability, longitudinal studies lacked a pooled estimate of WMH. Future research should focus on larger sample sizes, more consistent study populations, and improved methodologies to better validate the impact of MeDi on WMH. Finally, we only included studies published in English, which may exclude valuable data from studies conducted in other languages. Despite these limitations, to our knowledge, this is the first quantitative analysis of the association between MeDi and dementia-related MRI markers. These findings shed light on the pathophysiological processes that may underpin the association between MeDi and dementia in previous studies.

Conclusion

In conclusion, the findings from this meta-analysis indicate that higher adherence to MeDi may be associated with lower WMH among older adults. These findings support the notion that the MeDi displays potential for non-pharmacological prevention of dementia. However, it is important to note that current evidence is not sufficient to establish a definitive preventative effect on dementia. Future research should explore the role of MeD in non-Western populations or explore its synergistic effects with other lifestyle parameters. Additionally, large-scale randomized controlled trials will be necessary to investigate the causality between MeDi and structural changes related to dementia.

Supplementary Information

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Additional file 1

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Author contributions
Lu CY, Wang XJ, Xin ZY, and Wu KY conceived and designed the study. Xin ZY, Wu KY, Li XW, Wang J, and Liu XJ conducted the literature search and selection. Wang XJ, Xin ZY, Wu KY, Guo ZH, and Mo X extracted and analyzed the data. Xin ZY, Wu KY, Li XW, Wang WX, and Guo L all contributed to drafting and completing the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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Author details
[1]Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-Sen University, 74 Zhongshan Road 2, Guangzhou 510080, Guangdong, China. [2]Guangdong Provincial Key Laboratory of Food, Nutrition and Health, Sun Yat-Sen University, Guangzhou 510080, Guangdong, China. [3]Guangdong Engineering Technology Research Center of Nutrition Translation, Guangzhou 510080, Guangdong, China. [4]Department of Neurology, Shenzhen Qianhai Shekou Free Trade Zone Hospital, Shenzhen 518067, Guangdong, China. [5]Department of Radiology, Shenzhen Qianhai Shekou Free Trade Zone Hospital, 36 Industrial Road 7, Shenzhen 518067, Guangdong, China.

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References

1. Legdeur N, et al. Age dependency of risk factors for cognitive decline. BMC Geriatr. 2018;18(1):187.
2. Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. Lancet Neurol. 2018;17(11):1006–15.
3. Jacobs DJ, Gross MD, Tapsell LC. Food synergy: an operational concept for understanding nutrition. Am J Clin Nutr. 2009;89(5):1543S-1548S.
4. Solfrizzi V, et al. Relationships of dietary patterns, foods, and micro- and macronutrients with Alzheimer's disease and late-life cognitive disorders: a systematic review. J Alzheimers Dis. 2017;59(3):815–49.
5. Willett WC, et al. Mediterranean diet pyramid: a cultural model for healthy eating. Am J Clin Nutr. 1995;61(6 Suppl):1402S-1406S.
6. Appel LJ, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 1997;336(16):1117–24.
7. Morris MC, et al. MIND diet slows cognitive decline with aging. Alzheimers Dement. 2015;11(9):1015–22.
8. van den Brink AC, et al. The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets are associated with less cognitive decline and a lower risk of Alzheimer's Disease-a review. Adv Nutr. 2019;10(6):1040–65.
9. Valls-Pedret C, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern Med. 2015;175(7):1094–103.
10. Andreu-Reinon ME, et al. Mediterranean diet and risk of dementia and Alzheimer's disease in the EPIC-Spain dementia cohort study. Nutrients. 2021;13(2):700.
11. Navarro A, et al. Vitamin E at high doses improves survival, neurological performance, and brain mitochondrial function in aging male mice. Am J Physiol Regul Integr Comp Physiol. 2005;289(5):R1392–9.
12. McGrattan AM, et al. Diet and inflammation in cognitive ageing and Alzheimer's disease. Curr Nutr Rep. 2019;8(2):53–65.
13. Gu Y, et al. Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. J Alzheimers Dis. 2010;22(2):483–92.
14. Petersson SD, Philippou E. Mediterranean diet, cognitive function, and dementia: a systematic review of the evidence. Adv Nutr. 2016;7(5):889–904.
15. Gregory S, et al. Mediterranean diet and structural neuroimaging biomarkers of Alzheimer's and cerebrovascular disease: a systematic review. Exp Gerontol. 2023;172:112065.
16. Gupta M, et al. Association of 3.0-T brain magnetic resonance imaging biomarkers with cognitive function in the Dallas Heart Study. JAMA Neurol. 2015;72(2):170–5.
17. Dong C, et al. Cognitive correlates of white matter lesion load and brain atrophy: the Northern Manhattan Study. Neurology. 2015;85(5):441–9.
18. Persson N, et al. Regional brain shrinkage and change in cognitive performance over two years: the bidirectional influences of the brain and cognitive reserve factors. Neuroimage. 2016;126:15–26.
19. Ihara M, Yamamoto Y. Emerging evidence for pathogenesis of sporadic cerebral small vessel disease. Stroke. 2016;47(2):554–60.
20. Csukly G, et al. The differentiation of amnestic type MCI from the non-amnestic types by structural MRI. Front Aging Neurosci. 2016;8:52.
21. Salvado G, et al. Spatial patterns of white matter hyperintensities associated with Alzheimer's disease risk factors in a cognitively healthy middle-aged cohort. Alzheimers Res Ther. 2019;11(1):12.
22. Bilello M, et al. Correlating cognitive decline with white matter lesion and brain atrophy magnetic resonance imaging measurements in Alzheimer's disease. J Alzheimers Dis. 2015;48(4):987–94.
23. Broadhouse KM, et al. Memory performance correlates of hippocampal subfield volume in mild cognitive impairment subtype. Front Behav Neurosci. 2019;13:259.
24. Veitch DP, et al. Understanding disease progression and improving Alzheimer's disease clinical trials: recent highlights from the Alzheimer's disease Neuroimaging Initiative. Alzheimers Dement. 2019;15(1):106–52.
25. Luciano M, et al. Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. Neurology. 2017;88(5):449–55.
26. Karstens AJ, et al. Associations of the Mediterranean diet with cognitive and neuroimaging phenotypes of dementia in healthy older adults. Am J Clin Nutr. 2019;109(2):361–8.
27. Gu Y, et al. Mediterranean diet and brain structure in a multiethnic elderly cohort. Neurology. 2015;85(20):1744–51.
28. Zhang J, et al. Associations of midlife dietary patterns with incident dementia and brain structure: findings from the UK biobank study. Am J Clin Nutr. 2023;118(1):218–27.
29. Gregory S, et al. Mediterranean diet is associated with lower white matter lesion volume in Mediterranean cities and lower cerebrospinal fluid Aβ42 in non-Mediterranean cities in the EPAD LCS cohort. Neurobiol Aging. 2023;131:29–38.
30. Corley J, et al. Dietary patterns, cognitive function, and structural neuroimaging measures of brain aging. Exp Gerontol. 2020;142:111117.
31. Rodrigues B, et al. The association of dietary patterns with cognition through the lens of neuroimaging-a systematic review. Ageing Res Rev. 2020;63:101145.
32. Arnoldy L, et al. The association of dietary and nutrient patterns on neurocognitive decline: a systematic review of MRI and PET studies. Ageing Res Rev. 2023;87:101892.

33. Stroup DF, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008–12.
34. Page MJ, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. J Clin Epidemiol. 2021;134:103–12.
35. Kundaje A, et al. Integrative analysis of 111 reference human epigenomes. Nature. 2015;518(7539):317–30.
36. NIH, Study Quality Assessment Tools | NHLBI, NIH. 2024.
37. Gardener H, et al. Mediterranean diet and white matter hyperintensity volume in the Northern Manhattan study. Arch Neurol. 2012;69(2):251–6.
38. Matthews DC, et al. Physical activity, Mediterranean diet and biomarkers-assessed risk of Alzheimer's: a multi-modality brain imaging study. Adv Mol Imaging. 2014;4(4):43–57.
39. Schwarz C, et al. Spermidine intake is associated with cortical thickness and hippocampal volume in older adults. Neuroimage. 2020;221:117132.
40. Ballarini T, et al. Mediterranean diet, alzheimer disease biomarkers, and brain atrophy in old age. Neurology. 2021;96(24):E2920–32.
41. MacPherson H, et al. Associations of Diet quality with midlife brain volume: findings from the UK biobank cohort study. J Alzheimers Dis. 2021;84(1):79–90.
42. Samuelsson J, et al. Associations between dietary patterns and dementia-related neuroimaging markers. Alzheimers Dement. 2023;19(10):4629–40.
43. Gregory S, et al. The Mediterranean diet is not associated with neuroimaging or cognition in middle-aged adults: a cross-sectional analysis of the PREVENT dementia programme. Eur J Neurol. 2024; 31(8).
44. Hepsomali P, et al. Adherence to unhealthy diets is associated with altered frontal gamma-aminobutyric acid and glutamate concentrations and grey matter volume: preliminary findings. Nutr Neurosci. 2024.
45. Scarmeas N, et al. Mediterranean diet and magnetic resonance imaging-assessed cerebrovascular disease. Ann Neurol. 2011;69(2):257–68.
46. Titova OE, et al. Mediterranean diet habits in older individuals: associations with cognitive functioning and brain volumes. Exp Gerontol. 2013;48(12):1443–8.
47. Pelletier A, et al. Mediterranean diet and preserved brain structural connectivity in older subjects. Alzheimers Dement. 2015;11(9):1023–31.
48. Berti V, et al. Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. Neurology. 2018;90(20):E1789–98.
49. Rodrigues B, et al. Higher adherence to the Mediterranean diet is associated with preserved white matter integrity and altered structural connectivity. Front Neurosci. 2020; 14.
50. Song S, et al. Mediterranean diet and white matter hyperintensity change over time in cognitively intact adults. Nutrients. 2022;14(17):3664.
51. Trifan G, et al. Association of the Mediterranean diet with white matter integrity among hispanics/latinos. Results from the study of latinos-investigation of neurocognitive aging-MRI ancillary study. Stroke. 2024; 55.
52. van Leijsen E, et al. Progression of white matter hyperintensities preceded by heterogeneous decline of microstructural integrity. Stroke. 2018;49(6):1386–93.
53. Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. Nat Rev Neurol. 2015;11(3):157–65.
54. Esposito K, Giugliano D. Diet and inflammation: a link to metabolic and cardiovascular diseases. Eur Heart J. 2006;27(1):15–20.
55. Frisardi V, et al. Nutraceutical properties of Mediterranean diet and cognitive decline: possible underlying mechanisms. J Alzheimers Dis. 2010;22(3):715–40.
56. Esposito E, et al. A review of specific dietary antioxidants and the effects on biochemical mechanisms related to neurodegenerative processes. Neurobiol Aging. 2002;23(5):719–35.
57. Laye S, et al. Anti-inflammatory effects of omega-3 fatty acids in the brain: physiological mechanisms and relevance to pharmacology. Pharmacol Rev. 2018;70(1):12–38.
58. Hernaez A, et al. Mediterranean diet improves high-density lipoprotein function in high-cardiovascular-risk individuals: a randomized controlled trial. Circulation. 2017;135(7):633–43.
59. Smit RA, et al. Higher visit-to-visit low-density lipoprotein cholesterol variability is associated with lower cognitive performance, lower cerebral blood flow, and greater white matter hyperintensity load in older subjects. Circulation. 2016;134(3):212–21.
60. Miranda M, et al. Treatment of oral mucositis using platelet-rich-fibrin: a retrospective study on oncological patients. J Craniofac Surg. 2023;34(5):1527–9.
61. Rosa A, Pujia AM, Arcuri C. The protective role antioxidant of vitamin C in the prevention of oral disease: a scoping review of current literature. Eur J Dent. 2024;18(4):965–70.
62. Rosa A, Pujia AM, Arcuri C. Hyaluronic acid combined with ozone in dental practice. Biomedicines. 2024;12(11):2522.
63. Fiorillo L. Oral health: the first step to well-being. Medicina (Kaunas). 2019;55(10):676.
64. Panteleienko L, et al. Sulcal hyperintensity as an early imaging finding in cerebral amyloid angiopathy-related inflammation. Neurology. 2024;103(12): e210084.
65. Qiu W, et al. Total burden of cerebral small vessel disease predict subjective cognitive decline in patients with Parkinson's disease. Front Aging Neurosci. 2024;16:1476701.
66. Morrison CD, et al. High fat diet increases hippocampal oxidative stress and cognitive impairment in aged mice: implications for decreased Nrf2 signaling. J Neurochem. 2010;114(6):1581–9.
67. Trichopoulou A, et al. Mediterranean diet and cognitive decline over time in an elderly Mediterranean population. Eur J Nutr. 2015;54(8):1311–21.
68. Kesika P, et al. Role of gut-brain axis, gut microbial composition, and probiotic intervention in Alzheimer's disease. Life Sci. 2021;264: 118627.
69. Park G, et al. A modified Mediterranean-style diet enhances brain function via specific gut-microbiome-brain mechanisms. Gut Microbes. 2024;16(1):2323752.
70. Cheng ST. Cognitive reserve and the prevention of dementia: the role of physical and cognitive activities. Curr Psychiatry Rep. 2016;18(9):85.
71. Garnier-Crussard A, et al. White matter hyperintensities across the adult lifespan: relation to age, Abeta load, and cognition. Alzheimers Res Ther. 2020;12(1):127.
72. Bernini S, et al. Investigating the individual and joint effects of socioeconomic status and lifestyle factors on mild cognitive impairment in older Italians living independently in the community: results from the NutBrain study. J Nutr Health Aging. 2024;28(3): 100040.
73. Gaiteri C, et al. Genetic variants in Alzheimer disease—molecular and brain network approaches. Nat Rev Neurol. 2016;12(7):413–27.
74. Liu Y, et al. APOE genotype and neuroimaging markers of Alzheimer's disease: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2015;86(2):127–34.
75. Liu-Ambrose T, et al. Resistance training and executive functions: a 12-month randomized controlled trial. Arch Intern Med. 2010;170(2):170–8.
76. Shen C, et al. Associations of social isolation and loneliness with later dementia. Neurology. 2022;99(2):e164–75.
77. Hebert JR, et al. Social desirability bias in dietary self-report may compromise the validity of dietary intake measures. Int J Epidemiol. 1995;24(2):389–98.
78. Bowman GL, et al. Nutrient biomarker patterns, cognitive function, and MRI measures of brain aging. Neurology. 2012;78(4):241–9.

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