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Dietary factors and MRI biomarkers of brain ageing in general populations: a comprehensive systematic review

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Review Article

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Abstract

This systematic review examined the associations of dietary factors such as nutrients, food intake, dietary patterns and dietary biomarkers with structural and functional brain MRI biomarkers, focusing on macrostructural, microstructural, lesion and perfusion measures, and functional activity/connectivity. Articles published in English were systematically searched in PubMed, Embase and PsycInfo up to 19 July 2024. A total of thirty-eight prospective cohort studies (twenty-three cross-sectional and fifteen longitudinal analyses) and thirteen intervention studies were included. Cross-sectional analyses revealed heterogenous associations: baked fish correlated with larger hippocampal volumes ($\beta = 0{\cdot}21$), while oily fish, dairy products and tofu adversely related to ventricle grade. Pro-inflammatory dietary patterns were positively associated with silent infarct risk (DII Q4 *v.* Q1, OR = 1·77), whereas anti-inflammatory patterns tended to favour brain preservation. Longitudinal studies demonstrated more consistent protective associations: green tea consumption (+100 mL/d) reduced hippocampal atrophy by 0·024%/year, prudent dietary patterns preserved +203 mm^3 left hippocampal volume over 4 years and higher plasma carotenoids decreased medial temporal lobe loss by 0·02 cm^3/year. However, null findings were common across multiple dietary factors. Interventions showed limited structural benefits (effective in only two of six studies), while polyphenol-rich supplements more consistently improved cerebral perfusion and functional connectivity. Longitudinal and intervention studies demonstrated more consistent patterns than cross-sectional analyses; however, current evidence remains limited for clinical translation. Findings from cross-sectional analyses, despite being from prospective cohorts, require careful interpretation. Further replication across diverse populations and standardised long-term studies are needed before translating these associations into clinical practice.

Introduction

Dementia is a collective term for various diseases that impair cognitive function and the ability to perform daily activities, and has profound physical, psychological, social and economic impacts on patients, their families and society on multiple levels[1]. Ageing is a major risk factor for dementia. As of 2024, the global population aged 65 years and over is estimated to exceed 760 million, with projections suggesting it could reach 2·2 billion by 2080[2]. Currently, more than 55 million people worldwide are living with dementia, and nearly 10 million new cases are diagnosed annually[1]. By 2050, the number of people with dementia among those aged 60 years or older is projected to increase to 130 million[3]. Current treatments can temporarily alleviate symptoms or slow the progression of dementia but cannot reverse existing brain damage[4]. Furthermore, given that the trajectory of dementia progression exhibits substantial variation among individuals[5], identifying effective preventive factors to mitigate the risk of dementia can be a successful strategy to promote healthy brain ageing[6,7].

The World Health Organization (WHO) guidelines (2019)[6,8] and the *Lancet* Commission (2020) have emphasised several modifiable risk factors such as smoking, drinking, physical inactivity, obesity, hypertension and diabetes, which collectively account for approximately 40% of dementia risk globally[6,9]. Among these, dietary factors can be broadly categorised as (1) nutrients and other bioactive food components, (2) specific foods or food groups, (3) dietary patterns reflecting habitual dietary quality – collectively considered as dietary intake factors – and (4) objective biomarkers that reflect dietary exposure. These dietary factors – including specific nutrients (*e.g.* vitamin E, flavonols, B-vitamins and n-3 fatty acids) and nutrient-rich foods such as vegetables, berries and seafood[10–13]; dietary patterns such as Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets[12,13]; and dietary biomarkers (*e.g.* plasma fatty acids,

carotenoids, vitamin E and choline)[14] – have been recognised for their potential cognitive benefits. However, findings have not been entirely consistent. While observational studies, including those on the MIND diet, have suggested protective associations with cognitive decline and dementia[12,13], randomised controlled trials (RCTs) targeting older adults, including interventions focusing on the Mediterranean diet[15], exercise[16] and hypertension reduction[17], have shown limited efficacy in mitigating cognitive decline. This may be because of the irreversible nature of sub-clinical organ damage accumulated over the lifespan[18,19]. Therefore, it is increasingly important to identify markers that can capture early-stage brain alterations before the onset of overt cognitive symptoms when preventive interventions are likely to be more effective.

Cognitive impairment is commonly assessed using short neuropsychological tools, such as the Mini-Mental State Examination (MMSE), which classify individuals by applying a numerical threshold for dementia diagnosis[20]. However, these conventional assessments tend to cognitive decline only after functional deficits have emerged, making them insufficient for capturing early, pre-clinical brain changes[21]. Consequently, novel biomarkers that capture sub-clinical changes in biology and cognition have been explored[22]. Magnetic resonance imaging (MRI)-based biomarkers, which directly measure degradation of the brain, the only organ responsible for cognition, memory and intellectual function, are proposed as sensitive indicators of accelerated brain aging during midlife (defined as 40–64 years) and subtle changes that may not be detectable through cognitive tests alone[21,23]. However, previous systematic reviews investigating the associations between dietary factors and MRI biomarkers have been limited[23–25]. Two focused exclusively on dietary and nutrient patterns[23,24]. The other review summarised evidence on the associations between comprehensive dietary factors and MRI-based brain outcomes[25]. However, it categorised some cross-sectional analyses, where MRI biomarkers were measured only once at the follow-up visit after dietary assessments, as longitudinal studies. In addition, it used blood lipid profiles (*e.g.* HDL cholesterol and triacylglycerols), rather than nutrient biomarkers (*e.g.* folate and carotenoids), as dietary biomarkers[25].

This systematic review aims to comprehensively summarise the relationships between dietary factors – including nutrients and other bioactive food components, foods, dietary patterns and nutrient biomarkers – and MRI-based structural and non-structural biomarkers in general populations. The review included findings from intervention studies and prospective cohort studies, including both longitudinal analyses and cross-sectional analyses derived from cohorts in which dietary assessments were conducted prior to MRI measurements. To reduce the risk of reverse causation, cross-sectional studies that collected dietary and MRI data at the same visit were excluded.

Methods

This systematic review adhered to international guidelines, specifically the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement[26] (Supplementary Tables S1 and S2).

Eligibility criteria

The inclusion criteria were as follows: (1) original, peer-reviewed articles, including short communications with original data; (2) studies involving human participants from general, middle-aged and older adult populations (typically ≥40 years); (3) studies assessing dietary factors as the primary exposure and MRI-based brain biomarkers as the primary outcome; and (4) studies using either longitudinal designs or cross-sectional analyses derived from cohort studies (*i.e.* dietary assessments conducted at an earlier visit, with MRI measurements obtained during a subsequent follow-up). These designs allowed for a temporal ordering from exposure to outcome, even though the analyses were cross-sectional and MRI biomarkers at the time of dietary assessment were not available. The exclusion criteria were as follows: non-original articles or short communications without original data involving humans; grey literature not subjected to peer-review; studies conducted exclusively in populations with specific medical or cognitive conditions (*e.g.* mild cognitive impairment, hypertension or stroke); cross-sectional studies that collected dietary data and MRI measurements at the same visit, which were excluded to minimise the risk of reverse causation; studies including only young adults aged 20–40 years; and articles not published in English. For studies generating multiple publications, all articles were included if they assessed different dietary factors or MRI biomarkers. If identical exposures and outcomes were reported across publications, only the most recent or most comprehensive article was retained. Studies were excluded if dietary factors were not the primary exposure, MRI biomarkers were not the outcome or if dietary factors were part of a broader exposure without independent results.

Data sources and search strategy

Original articles published up to 19 July 2024 were identified using a comprehensive search strategy in three databases: PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Ovid-Embase (https://ovidsp.tx.ovid.com) and PsycInfo (https://www.proquest.com/psycinfo). Detailed search index terms are listed in Supplementary Table S3. Study design filters were provided by the University of Texas (https://libguides.sph.uth.tmc.edu/search_filters). Among observational studies, cross-sectional studies using dietary data and MRI biomarkers measured at the same visit were excluded after reviewing the full text.

Study selection and data extraction

Two researchers independently performed a blinded screening of titles and abstracts using the Rayyan platform. Rayyan is a free, web-based tool developed by the Qatar Computing Research Institute (https://www.rayyan.ai/) to facilitate systematic review screening and study selection through semi-automatic duplicate detection, keyword highlighting and blinded collaboration among multiple reviewers. When consensus on eligibility could not be reached, a third investigator determined relevance. The extracted data were general characteristics (author, year and country), study design (type of study and duration/follow-up period), population characteristics (sample size, age or age range and sex and race distributions), dietary factors (dietary intake and biomarkers, assessment methods), MRI biomarkers and covariates. In addition, we extracted the direction of associations or effects – depending on study design – from the most fully adjusted models and summarised the findings narratively, owing to substantial heterogeneity in exposures, outcomes and analytical methods. Given the large number of associations examined across studies, effect size estimates (r, β and OR) were reported only for statistically significant findings, when such estimates were explicitly reported (*e.g.* as many voxel-based analyses do not

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report explicit effect size maps). Results were synthesised on the basis of four dietary factors across cross-sectional and longitudinal analyses from prospective cohort studies: nutrients, foods, dietary patterns (including quality indices) and blood biomarkers from specimens. For intervention studies, only the first three of the above dietary factors were analysed.

The five MRI biomarkers (categorised into structural and functional measures) were as follows for structural MRI biomarkers: (1) macrostructural measures, such as whole and regional brain volumes and cortical thickness; (2) microstructural measures, such as white matter integrity (WMI); (3) lesion measures, such as white matter hyperintensity (WMH) and infarcts. For functional MRI biomarkers: (1) perfusion measures such as cerebral blood flow (CBF) and cerebral blood volume (CBV) and (2) functional measures, such as functional activity and connectivity. The following methods were used to measure MRI biomarkers[25]: First, macrostructural measures, including total brain volume (TBV), grey matter volume (GMV) and white matter volume (WMV), regional volumes and cortical thickness were measured using T1-weighted MRI scans. Second, microstructural measures, including diffusion tensor imaging (DTI) was utilised to examine WMI by detecting the directional diffusion of water in the brain, and by quantifying its anisotropic diffusion. Key metrics of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were used. Brain regions with high FA and low MD were assumed to have well organised axon arrays and better myelin integrity[27,28]. Third, lesion measures, such as WMH, which reflect pathophysiological structural changes, were assessed using T2-weighted (T2) and fluid attenuated inversion recovery (FLAIR) MRI sequences. WMHs represent altered interstitial fluid mobility and increased water. Fourth, perfusion measures were evaluated using perfusion imaging. CBF, measured by arterial spin labelling (ASL), typically decreases with age and reflects cerebral perfusion status. Fifth, functional connectivity was mainly assessed using resting-state functional MRI (rs-fMRI), which measures the temporal correlation of blood oxygenation level-dependent (BOLD) signals between brain regions. In addition, brain activation was investigated with task-based fMRI (t-fMRI), which identifies brain regions that show a significant change in BOLD signal during a specific task. Owing to the limited number of articles addressing identical dietary factors and MRI biomarkers, a meta-analysis was not feasible.

Quality assessment

Study quality was assessed using the Newcastle–Ottawa scale (NOS) for non-randomised studies[29] and the Cochrane Risk-of-Bias (RoB2) tool, version 2.0, for parallel and cross-over randomised trials[30]. The NOS evaluated selection, comparability and outcome domains through nine specific questions, while the RoB 2 tool examined the five domains of randomisation, intervention, missing outcome, measurement of outcome and result selection. Two investigators independently rated study quality ('good', 'fair' or 'poor' for cross-sectional analyses and longitudinal analyses) and risk of bias ('low', 'some concerns' or 'high' for randomised trials), resolving any discrepancies through discussion.

Results

Study selection

A total of 4523 articles (1992 from PubMed, 1803 from Embase and 728 from PsycInfo) were initially identified (Supplementary Fig. S1). After removing 904 duplicates, 3619 articles were screened on the basis of the titles and abstracts. From these, 3456 articles were excluded on the basis of title and abstract screening for irrelevance or ineligible design. However, cross-sectional studies were not excluded at this stage to distinguish cohort-based cross-sectional analyses from conventional cross-sectional studies during full-text screening, on the basis of the timing of dietary assessment and MRI measurement. Full-text screening was conducted on 163 articles, comprising 122 observational studies and 41 intervention studies. Of these, 112 were excluded owing to various reasons, such as not being peer-reviewed (*e.g.* conference abstracts), focusing on participants younger than 40 years, involving non-general populations or not including MRI biomarkers. During this process, thirty-one cross-sectional studies and two articles on altered mineral content were excluded because they were outside the review scope. Ultimately, thirty-eight observational studies (twenty-three cross-sectional and fifteen longitudinal analyses) and thirteen interventional studies were included in the systematic review.

Study characteristics

The twenty-three cross-sectional analyses were derived from fifteen specific cohorts (Table 1). Dietary factors investigated in these studies were nutrients ($n = 3$), foods ($n = 4$), dietary and nutrient patterns ($n = 12$) and dietary biomarkers ($n = 4$ using biomarkers only). Two studies assessed both dietary intake and circulating biomarkers[31,32]; only one of these reported an association with MRI biomarkers[32]. The most common dietary assessment method was a food frequency questionnaire ($n = 22$), followed by multiple food diary or recall method ($n = 8$). Most studies ($n = 15$) were conducted in the USA, with sample sizes ranging from fewer than 500 participants ($n = 12$) to more than 10 000 participants ($n = 3$). The time interval between dietary assessments and MRI measurements varied significantly, ranging from 1·8 years to more than 20 years. Fifteen longitudinal studies were derived from ten unique cohorts, including the National Institute for Longevity Sciences–Longitudinal Study of Aging (NILS-LSA), which reported results from four individual studies (Table 2). These studies assessed dietary factors of nutrients ($n = 1$), foods ($n = 4$), dietary patterns ($n = 6$) and dietary biomarkers measured in serum, plasma or erythrocytes ($n = 4$). The populations varied geographically, including studies from Japan ($n = 4$), the USA ($n = 2$), Australia ($n = 2$), the UK ($n = 2$), France ($n = 2$), Sweden ($n = 2$) and Korea ($n = 1$). Six studies had fewer than 500 participants, while one study included more than 10 000 participants. The average follow-up interval for MRI scans ranged from 2 to 10·5 years. Table 3 shows thirteen interventional studies that assessed nutrients ($n = 7$), foods ($n = 4$) and dietary patterns ($n = 2$). Eight of these studies were conducted in the USA, with intervention durations varying between 26 d to 3 years. The most common duration was 12 weeks, observed in five studies.

Dietary factors and MRI measurements

Tables 4, 5 and 6 summarise dietary factors and MRI biomarkers. Regardless of study design, dietary factors examined in this review encompassed eleven nutrients, twelve foods, twenty dietary patterns and nine dietary biomarkers. Frequently studied dietary patterns included the MedDiet and the MIND diet. Common nutrients investigated were omega-3 fatty acids, antioxidant vitamins and flavonoids, while foods such as soya nuts, nuts, dairy, fish, tea, coffee and berries were also studied. Dietary

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Table 1. Study characteristics: cross-sectional analyses in the prospective cohort studies

Authors, year (reference)	Country	Study name	Sample size (males/ females)	Race or ethnicity	Mean age, years or range (min–max)	Year(s) of data collection		Time duration of MRI after dietary assessment, years
						Dietary data	MRI data	
Nutrients								
Titova *et al.* (2013)[31]	Sweden	PIVUS cohort	198 (102/96)	Not specified	70 (SD = 0·0) at dietary data collection	2001–3 at 70 years old	At 75 years old	5
Shishtar *et al.* (2020)[51]	USA	FHS Offspring cohort	2086 (978/ 1108))	White and of European origin	60·6	1991–5 (exam 5), 1995–8 (exam 6), 1998–2001 (exam 7)	1999–2001 (exam)	
Tsiknia *et al.* (2023)[49]	USA	RBS	128 (41/87)	Non-Hispanic white predominantly	76·6 (SD = 7·9)	1984–1996	2014–16	22·8 (18·1–30·4)
Foods								
White *et al.* (2000)[47]	USA	HAAS	574 men	Asians (Japanese)	Mean for all: not specified, but 50s at baseline and 80s at MRI scan	1965–7, 1971–4	1994–6	At least 20
Raji *et al.* (2014)[36]	USA	CHS-CS	260 (104/156)	95% white	78·3 (SD = 3·54) in daily/ weekly fish consumption 78·4 (SD = 3·31) in infrequent fish consumption	1989–90	1998–9	9
del C, Valdes *et al.* (2017)[37]	UK	LBC 1936	189 (87 /102)	Not specified	72·7 (SD = 0·8)	2004–7	About 3 years later	3
Pellay *et al.* (2024)[48]	France	3C study	343 (135/208) for 3 year follow-up 195 (83/117) for 9 year follow-up	Not specified	For 3 year follow-up: 74·1 (SD = 3·8) at baseline For 9 year follow-up: 73·4 (SD = 3·7) at baseline	2001–2	2004–6 and 2010–11	3 and 9
Dietary patterns								
Gardener *et al.* (2012)[52]	USA	NOMAS	966 (570/396)	65% Hispanic, 16% non-Hispanic white, 17% Black, 2% other	72	Average 7·2 years before MRI (2–14 years prior)	Around 2003	7·2
Titova *et al.* (2013)[38]	Sweden	PIVUS cohort	194 (101 /93)	Not specified	70·1 (SD = 0·01) at 70 years of age, 75·3 (SD = 0·01) at 75 years of age	2001–3 at 70 years old	At 75 years old	5
Pelletier *et al.* (2015)[39]	France	3C study	146 (58 /88)	Not specified	73·0 (range = 67·7–83·2)	2001–2	2010–11	8·9
Gu *et al.* (2016)[50]	USA	WHICAP	239 (72/ 167)	29 % white, 35% African American, 35% Hispanic, 1% other	84·1 (SD = 5·1)	1992 or 1999–2001	2004 (starting year)	At least 3
Gu *et al.* (2018)[44]	USA	WHICAP	330 (118/212)	33% white, 32% Black, 33% Hispanic, 3% other	79·0 (SD = 5·76)	~5·3 years before the MRI scan	2004 (starting year)	Approximately 5·3
Akbaraly *et al.* (2018)[43]	UK		459 (371 /88)	94·1% white		1991–3 and 2002–4	2015–16	At least 13

Table 1. (*Continued*)

		Whitehall II Imaging Sub-study			59·6 (SD = 5·3) (during the 2002–04 phase of data collection)			
Chen, *et al.* (2021)[42]	USA	WHIMS-MRI	1302 women	91·6% Non-Hispanic white	69·7 (SD = 3·6) at baseline (65–79)	1996–98	2005–6	At least 7
Melo van Lent *et al.* (2021)[41]	USA	FHS Offspring cohort	2092 (956 /1136)	Primarily European ancestry	61 (SD = 9)	1991–5 (exam 5), 1995–8 (exam 6), 1998–2001 (exam 7)	1999–2001 (exam)	At least 8
Macpherson *et al.* (2021)[40]	UK	UK biobank	19 184 (9927 /9257)	98.0% white	53·8 (SD = 6·9)	2009–12	2014–19	At least 2
Guan *et al.* (2023)[32]	USA	BPRHS and ADNI for validation	157 (52/105)	Not specified	68 (SD = 6·7) at MRI scanning	2004	2016	12·7
Mulugeta *et al.* (2022)[114]	UK	UK biobank	25 894 (12 170 /13 724)	White, British ancestry	30–60	2006–10	2014–20	8·8
Melo van Lent *et al.* (2023)[35]	USA	FHS Offspring cohort	1897 (866 /1031)	White, European ancestry	62 (SD = 9)	1991–5 (exam 5), 1995–8 (exam 6), 1998–2001 (exam 7)	1999–2001 (exam)	At least 7
Dietary biomarkers only								
Tangney, *et al.* (2011)[53]	USA	CHAP	121 (59/62)	55% Black, 45% white	78·7 (SD = 5·7)	Biomarkers: 1997–2000	Average of 4·6 years after blood collection	4·6
Karakis *et al.* (2016)[105]	USA	FHS Offspring cohort	1291 (588 /703)	Almost all Caucasian	59·5 (SD = 9·1)	Biomarkers: 1995–2001 (cycles 6, 7)	Average 1·8 years after vitamin D measurement	1·8
Beydoun *et al.* (2020)[46]	USA	HANDLS study	240 (105 /135)	58·8% white, 41·2% African American	47·7 (SD = 8·9, range = 30–64)	Biomarkers: 2004–9	2011–15	5·7
Chen *et al.* (2020)[45]	USA	WHIMS-MRI	1315 women	91% Non-Hispanic white, 4·6% Black, 1·6% Hispanic white, 3·0% others or missing	70 at baseline (65–80)	Biomarkers: 1996–9	2005–6	At least 6

PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; SD, standard deviation; FHS, Framingham Heart Study; RBS, Rancho Bernardo Study of Healthy Aging; HAAS, Honolulu-Asia Aging Study; CHS-CS, Cardiovascular Health Study Cognition Study; LBC, Lothian Birth Cohort; 3C, Three-City; NOMAS, Northern Manhattan Study; WHICAP, Washington Heights/Hamilton Heights Inwood Columbia Aging Project; WHIMS-MRI, Women's Health Initiative Memory Study-MRI sub-study; BPRHS, Boston Puerto Rican Health Study; ADNI, Alzheimer's Disease Neuroimaging Initiative; CHAP, Chicago Health and Aging Project; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span.

Table 2. Study characteristics: longitudinal analyses in the prospective cohort studies

Authors, year (reference)	Country	Study name	Sample size (males/ females)	Race or ethnicity	Mean age, years or range (min–max)	Year(s) of data collection		Time duration between MRI scans, years	Number of MRI scans
						Dietary intake (bio-markers) data	MRI data		
Nutrients									
Tokuda *et al.* (2022)[54]	Japan	NILS-LSA	810 (418/392)	Asians (Japanese)	70·1 (SD = 6·9)	2008–10 (6th wave)	2008–10 (6th wave) and 2010–12 (7th wave)	2	2
Foods									
Virtanen *et al.* (2008)[33]	USA	CHS	4128 for sub-clinical infarct analyses 1124 for longitudinal analyses	White >90%	Not specified (inferred ~75)	1989–90 and 1995–6	1992–4 and 1997–9	Approximately 4–5	2
Lee *et al.* (2019)[55]	Korea, South	KoGES-Ansan	848 (397/451)	Asians (Koreans)	53·53 (SD = 6·60)	2005–6	2011–14 and 2015–17	4·13	2
Zhang *et al.* (2021)[57]	Japan	NILS-LSA	1693 (862/831)	Asians (Japanese)	59·9 (SD = 11·9)	2008–10 (6th wave)	2008–10 and 2010–12	2	2
Gardener *et al.* (2021)[64]	Australia	AIBL study	51 (22/29)	Not specified	69·92 (SD = 5·2)	Not specified (average of 3·38 years (SD = 0·9) after the baseline assessment	At baseline and on up to seven additional occasions, with each scan occurring 18 months apart	126 months (10·5 years)	8
Dietary patterns								4	
Jacka *et al.* (2015)[58]	Australia	PATH	255 (137 /118)	Not specified	62·6 (SD = 1·42)	2001	1st wave and 2nd wave (4 years later)		2
Otsuka *et al.* (2021)[59]	Japan	NILS-LSA	1636 (815 /821)	Asians (Japanese)	40–89	2008–10 (6th wave)	2008–10 and 2010–12	2	2
Luciano, *et al.* (2022)[65]	UK	LBC 1936	298 (162 /136)	Not specified	70 years at dietary data collection	2004–7 (around 70 years of age)	At ages 73, 76 and 79	3, 6 and 9	3
Song *et al.* (2022)[56]	USA	CR study and RANN study	183 (89 /94)	65·6% Non-Hispanic white and other, 21·9% Non-Hispanic Black, 12·6% Hispanic	53·19 (SD = 16·52, range = 20–80)	Unclear (~2015)	At a follow-up visit after an average of 5 years (until Jan 2020)	5	2
Chen *et al.* (2024)[66]	UK	UK biobank	26 466 (12 314 /14 152)	97·0% white	55·1 (SD = 7·5, range = 37–73)	2009–12	2014–20 and 2018–22	2·2	2
Zhang *et al.* (2024)[60]	Japan	NILS-LSA	1636 (815 /821)	Asians (Japanese)	60·8 (SD = 11·7) for men and 59·8 (SD = 11·9) for females at baseline survey	2008–10 (6th wave)	2008–10 and 2010–12	2	2

Table 2. (*Continued*)

Dietary biomarkers only								
Samieri *et al.* (2012)[61]	France	3C-Bordeaux study	281 (119 /162)	Not specified	72·3 (SD = 3·8)	Biomarkers: 1999–2000	At baseline and 4 years later	4	2
Hooshmand *et al.* (2016)[62]	Sweden	SNAC-K	501 (201 /300)	Not specified	70·9 (SD = 9·1)	Biomarkers: 2001–4	2001–9 (repeated MRI at intervals of 3–6 years)	Up to 6	2
Hooshmand *et al.* (2019)[67]	Sweden	SNAC-K	501 (201 /300)	Not specified	70·9 (SD = 9·1)	Biomarkers: 2001–4	2001–9 (repeated MRI at intervals of 3–6 years)	Up to 6	2
Thomas *et al.* (2021)[63]	France	3C-Bordeaux study	461 (192 /269)	Not specified	72·5 (SD = 3·9)	Biomarkers: 2000–1	2000–1, 2004–6, 2010–11	Up to 11·8 with a median follow-up time of 5·1	3

NILS-LSA, National Institute for Longevity Sciences-Longitudinal Study of Aging; SD, standard deviation; CHS, Cardiovascular Health Study; KoGES-Ansan, the Korean Genomic and Epidemiology Study-Ansan cohort; AIBL, Australian Imaging, Biomarkers, and Lifestyle; PATH, Personality and Total Health Through Life Study; LBC, Lothian Birth Cohort; CR study, Cognitive Reserve study; RANN, Reference Ability Neural Network; 3C, Three-city; SNAC-K, Swedish National Study on Aging and Care in Kungsholmen.

biomarkers comprised carotenoids, vitamin B and D levels and omega-3 fatty acid profiles. Most studies used validated dietary assessment methods, including 24-h dietary recalls and food frequency questionnaire (FFQ). MRI scans were predominantly conducted at field strengths of 1·5T or 3T. Observational studies primarily used T1-weighted sequences to measure macrostructural measures such as brain volume and cortical thickness, including regions such as the hippocampus (Supplementary Table S4). Additional imaging sequences included DTI for evaluating white matter integrity (WMI) and FLAIR for assessing white matter hyperintensity (WMH). Abnormal signal intensity (≥3 mm)[33] or Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria[34,35] were used to define subclinical brain infarcts. In contrast, intervention studies utilised a broader array of imaging techniques including functional imaging methods (rest-state and task-based fMRI) (Table 6). Cerebrovascular markers, including cerebral blood flow (CBF), were frequently assessed in these trials using ASL.

Associations between dietary factors and MRI biomarkers

Across cross-sectional analyses, several dietary factors showed beneficial associations with MRI biomarkers; however, findings were inconsistent across studies or biomarkers, with some reporting opposite-direction associations (Table 7). Fish consumption showed mixed results for macrostructural measures: baked or broiled fish consumption (≥1–4 times/week *v.* <1/week) was beneficially associated with GMVs in regions such as hippocampus volume (standardised $\beta = 0{\cdot}21$)[36], while oily fish was positively associated with lateral ventricular volume (LVV)[37]. Dietary patterns demonstrated variable associations with macrostructural measures. Within the MedDiet, higher consumption of meat and meat products was inversely associated with total brain volume (TBV)[38], yet overall MedDiet scores showed no significant associations in some studies[39,40]. The MIND diet study showed positive associations [*e.g.* per 1-unit increase, TBV % intracranial volume (ICV), $\beta = 0{\cdot}02$][41], though another MIND-like score yielded non-significant outcomes for white matter measures (total white matter, $\beta = 0{\cdot}74$; temporal WM, $\beta = 0{\cdot}19$) after Benjamini–Hochberg correction[42]. The alternative Healthy Eating Index (AHEI)-2010 correlated positively with hippocampal volume (HV)[43], whereas inflammatory patterns (inflammation-related nutrient pattern (INP)[44] and dietary inflammatory index (DII)[35]) were inversely associated with brain volumes. Blood biomarkers showed selective associations: omega-3 fatty acid levels correlated positively with white matter volume (WMV)[45], homocysteine (Hcy) negatively with TBV, while vitamin B_{12} showed no associations[46]. Unexpectedly, tofu consumption correlated with increased ventricular enlargement[47], and dairy products with larger LVV[37] and smaller medial temporal lobe volume (MTLV)[48]. For microstructural measures, omega-3 fatty acids intake enhanced total restricted diffusion[49] and MedDiet score[39], while PUFA and vitamin E pattern[50] and HEI-2005[32] similarly improved white matter integrity (WMI). Blood vitamin D[46] and folate[46] were also beneficially associated with WMI. Lesion measures revealed mixed patterns: flavonoids[51] and MediDiet reduced lesions[52], whereas homocysteine (Hcy)[53] and fish products[37] were associated with increased white matter hyperintensity volume (WMHV). The MIND diet showed no significant associations[41], while DII was positively associated with silent infarcts (OR = 1·77, 95% CI 1·05–3·00 in Q4 *v.* Q1)[35].

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Table 3. Characteristics of the intervention studies included in the systematic review

Authors, year (reference)	Country	Study design	Parallel/ cross-over	Numbers of analysed treatment /control groups	Number allo-cated	Percentage of women in treatment /control groups	Mean age, year (SD, min–max) treatment /control	Duration	Wash-out period (cross-over)
Nutrients									
Brickman *et al.* (2014)[74]	USA	Double-blind, RCT	Parallel	19/18	21/20	68/78	57 (5, 50–69)	12 weeks	–
Witte *et al.* (2014)[68]	Germany	Double-blind, RCT	Parallel	32/33	40/40	47/45	65 (6·3, 51–75) /62·9 (6·8, 50–75)	26 weeks	–
Carmichael *et al.* (2018)[78]	USA	Double-blind, placebo-controlled trial	Cross-over	10	11	40	67·3 (2·01)	26 d	30 d
Lindbergh *et al.* (2018)[79]	USA	Double-blind, RCT	Parallel	30/14	Not specified	53/71	72·43 (6·48) /70·43 (5·43)	12 months	–
Mewborn *et al.* (2019)[70]	USA	Double-blind, RCT	Parallel	33/14	43/17	52/71	72·4 (6·27) /70·4 (5·43)	12 months	–
Lindbergh *et al.* (2020)[80]	USA	Double-blind, RCT	Parallel	34/14	Not specified	53/71	73·06 (6·48) /70·43 (5·43)	12 months	–
Sloan *et al.* (2021)[75]	USA	Double-blind, RCT	Parallel	10:13:12/14 (low:med: high/control)	53:53:52/53 (low:med:high/ control)	(57:57:56/59 in the original study)	61·99 (6·44, 50–75)	12 weeks	–
Foods									
Bowtell *et al.* (2017)[76]	UK	Double-blind, RCT	Parallel	12/14	Not reported	42/57	67·5 (0·9) /69·0 (0·9)	12 weeks	–
Sala-Vila *et al.* (2020)[72]	Spain	Observer-blind, RCT	Parallel	58/50 (in subset of Barcelona centre for MRI study)	362/346	(69 in total set of Barcelona centre)	69·4 (69·0–69·8)/ 68·9 (68·5–69·3)	2 years	–
Kleinloog *et al.* (2021)[77]	Netherlands	Researchers-blind, RCT	Cross-over	11/12	12/13	– (52% overall)	64 (3)	16 weeks	6–12 weeks (median 8 weeks)
Flanagan *et al.* (2022)[71]	UK	Double-blind, RCT	Parallel	19/13	29/30	(59/58 in the original study)	65·86 (5·51)/ 65·32 (4·91)	12 weeks	–
DIETARY PATTERNS									
Kaplan *et al.* (2022)[69]	Israel	Open-label, RCT	Parallel	72:71:81 (Green-Med: Med: HDG)	98:98:98 (Green-Med: Med: HDG)	(10·8:11·6:12·5) (Green-Med: Med: HDG in the original study)	51·1 (10·6)	18 months	–
Barnes *et al.* (2023)[73]	USA	Open-label, RCT	Parallel	101/100	134/133	(65/65 in the original study	70·4 (4·2)	3 years	–

RCT, randomised clinical trial; Med, Mediterranean diet; HDG, healthy dietary guidelines.

Table 4. Dietary factors and MRI biomarkers in the cross-sectional analyses from the prospective cohort studies

Authors, year (reference)	Dietary factors		Dietary assessment	Structural biomarkers		
	Intake	Biomarkers		Macrostructural measures	Microstructural measures	Lesion measures
Nutrients						
Titova *et al.* (2013)[31]	Dietary EPA and DHA intake	Proportions of DHA and EPA	Food diary: 7-d food diary Serum (phospholipids)	GMV, WMV, brain tissue volume (% TICV) at 75 years		
Shishtar *et al.* (2020)[51]	Total and six classes of flavonoid intake	–	FFQ: 126-items semi-quantitative	TBV, HV		WMHV
Tsiknia *et al.* (2023)[49]	Omega-3 fatty acid during midlife	–	FFQ: Willett's FFQ		WMI (total restricted diffusion in ILF, IFOF, and SCSF)	
Foods						
White *et al.* (2000)[47]	Tofu	–	FFQ: 26 specific food and drink items	Ventricular enlargement: ventricular grade (continuous variable); ventricular enlargement (grade <6 *v.* 6+)		
Raji *et al.* (2014)[36]	Fish consumption	–	FFQ: National Cancer Institute's	GMVs of regions (hippocampus, precuneus, posterior cingulate, orbital frontal cortex, *etc.*)		
del C. Valdes *et al.* (2017)[37]	Iodine-rich foods (dairy and fish) and iodine intake	–	FFQ: 175-items (foods and drinks) Scottish Collaborative Group FFQ-FFQ)	HV (right HV, left HV), cerebellar volume (WM right, cortex right, WM left, cortex left) All measures: % volume in ICV . Brain ventricular volume (right, left, third, fourth LVV), subarachnoid space value		WMHV
Pellay *et al.* (2024)[48]	Total dairy products, milk, fresh dairy products, and cheese (frequency)	–	FFQ: 148-items (foods and beverages)	GMV, medial temporal lobe volume, mean CT in Alzheimer' disease-vulnerable regions		
Dietary patterns						
Gardener *et al.* (2012)[52]	MedDiet and its components	–	FFQ: a Modified Block National Cancer Institute's			WMHV (relative to TICV)
Titova *et al.* (2013)[38]	MedDiet score and its components	–	7-d food diary	TBV, GMV and WMV (relative to ICV)		
Pelletier *et al.* (2015)[39]	MedDiet adherence (three groups: 0–3 for low; 4–5 for medium; 6–8 for high)	–	FFQ: 148-items 24-h recall: for total energy intake and monounsaturated to saturated fatty acids	GMV, WMV,	WMI (FA, MD)	
Gu *et al.* (2016)[50]	Nutrient patterns using 24 nutrients	–	FFQ: 61-item Willett's semi-quantitative	TBV, TGMV, TWMV	WMI (FA)	
Gu *et al.* (2018)[44]	INP	–	FFQ: 61-item Willett's semi-quantitative	TBV, TGMV, TWMV, Mean CT		WMHV (used Log_{10} (WMHV/ICV)

(*Continued*)

Table 4. (*Continued*)

Authors, year (reference)	Dietary factors			Structural biomarkers		
	Intake	Biomarkers	Dietary assessment	Macrostructural measures	Microstructural measures	Lesion measures
Akbaraly *et al.* (2018)[43]	AHEI-2010	–	FFQ: 217 items semi-quantitative	TICV, HV		
Chen, *et al.* (2021)[42]	MIND-like diet adherence	–	FFQ: National Cancer Institute and Block's	TBV, normal brain, TWMV and regional WMV (frontal lobe, parietal lobe, temporal, corpus callosum), HV		
Melo van Lent *et al.* (2021)[41]	MIND diet score	–	FFQ: 126-item Harvard semi-quantitative	TBV (% ICV), HV (% ICV), LVV (% ICV),		WMHV (log transformed, % ICV), Silent brain infarcts
Macpherson *et al.* (2021)[40]	Diet quality score: MedDiet, HDS, RFS		WebQ	TBV, GMV, WMV, left and right HGMV		
Guan *et al.* (2023)[32]	HEI-2005	Vitamin B_6, B_{12}, 26 long chain fatty acids	FFQ Blood samples	HV	Medial temporal lobe tracts (left/right IFOF, ILF, SLFT) WMI (FA)	
Mulugeta *et al.* (2022)[114]	Healthy Diet Score: based on the American Heart Association guidelines	–	Food frequency questionnaire	TBV, GMV, WMV, HV,		WMH
Melo van Lent *et al.* (2023)[35]	DII	–	FFQ: 126-item Harvard semi-quantitative	TBV, HV, TGMV LVV		WMHV, silent infarcts, cerebral microbleeds
Dietary biomarkers only						
Tangney, *et al.* (2011)[53]	–	Vitamin B_{12} status: tHcy, methylmalonic acid, cystathionine, and 2-methylcitric acid	Serum	TBV		WMHV, cerebral infarcts (yes/no)
Karakis *et al.* (2016)[105]	–	Vitamin D status (25(OH)D)	Serum	TBV, HV		WMHV, WMH (extensive), brain infarcts (yes/no)
Beydoun *et al.* (2020)[46]	–	Vitamin D (25(OH)D), folate, cobalamin	Serum	TBV, GMV, WMV, regions	WHI (FA, MD)	
Chen *et al.* (2020)[45]	–	RBC omega-3 index, EPA, DHA	RBC	WMV, GMV, HV		

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; GM(V), grey matter (volume); WM(V), white matter (volume); (T)ICV, total intracranial volume; FFQ, food frequency questionnaire; TBV, total brain volume; HV, hippocampal volume; WMH(V), white matter hyperintensity (volume); WMI, white matter integrity; ILF, inferior longitudinal fasciculus; IFOF, inferior frontal occipital fasciculus; SCSF, superior cortico-striatal fasciculus; LVV, lateral ventricular volume; CT, cortical thickness; MedDiet, Mediterranean diet; FA, fractional anisotropy; MD, mean diffusivity; INP, inflammation-related nutrient pattern; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; HDS, Healthy Diet Score; RFS, Recommended Food Score; WebQ, validated web-based 24-h dietary recall questionnaire; HGMV, hippocampal grey matter volume; HEI, Healthy Eating Index; SLFT, superior longitudinal fasciculus; DII, Dietary Inflammatory Index; tHcy, total homocysteine; 25(OH)D, 25-hydroxyvitamin D; WHI, white matter integrity; LC, long-chain; RBC, erythrocytes.

Table 5. Dietary factors and change of MRI biomarkers in the longitudinal analyses from the prospective cohort studies

Authors, year (reference)	Dietary factors		Diet collection method (intake/biomarker)	Structural biomarkers	
	Intake	Biomarkers		Macrostructural measures	Lesion measures
Nutrients					
Tokuda *et al.* (2022)[54]	ALA, EPA, DHA, LA, ARA, n-3/n-6 LC-PUFA	–	3-d dietary record (2 weekdays, 1 weekend day)	TGMV, regional GMV (frontal, temporal cortex and hippocampus)	
Foods					
Virtanen *et al.* (2008)[33]	Tuna or other fish, Fried fish	–	FFQ: National Cancer Institute's		Sub-clinical infarcts
Lee *et al.* (2019)[55]	18 food groups	–	FFQ: 106-items	GMV, WMV, HV, frontal, parietal, occipital, temporal volume	
Zhang *et al.* (2021)[57]	Green tea consumption (mL/d)	–	3-d dietary record	GM, WM, HV (relative to TICV)	
Gardener *et al.* (2021)[64]	Habitual coffee intake	–	FFQ: CSIRO's	Cortical GMV, WMV, HV	
Dietary patterns					
Jacka *et al.* (2015)[58]	Dietary quality based on 'prudent diet' and 'Western diet' patterns	–	FFQ: CSIRO's	HV, amygdala V, ICV	
Otsuka *et al.* (2021)[59]	QUANTIDD	–	3-d dietary record	TGMV, HV	
Luciano, *et al.* (2022)[65]	MedDiet adherence	–	FFQ: 168 items Scottish Collaborative Group (SCG) version 7	TBV (relative to ICV)	
Song *et al.* (2022)[56]	MedDiet score (0–55) and its components (10 food groups and alcohol)	–	FFQ: Willett's 61-items		WMH (burden, log)
Chen *et al.* (2024)[66]	MIND diet adherence to 10 healthy food groups and 5 unhealthy food groups	–	24-h recall using WebQ (mean frequency = 2·5)	Global measures (TBV, WMV, GMV), subcortical volumes (thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens), and regional GMV (thalamus, caudate, putamen, pallidum, hippocampus, and amygdala)	WMH
Zhang *et al.* (2024)[60]	Three dietary patterns: the Western diet, vegetable-fruit-dairy (men) or grain-vegetable-fruit (women) diet, and traditional Japanese diet	–	3-d dietary record	GMV, WMV, volume of lobes (frontal, parietal, occipital, temporal and insular)	
Dietary biomarkers only					
Samieri *et al.* (2012)[61]	–	Fatty acids (EPA and DHA)	Plasma	GMV and regional volume (HV, para-HV, amygdala)	
Hooshmand *et al.* (2016)[62]	–	RBC folate, vitamin B_{12}, 5 sulfur amino acids	Plasma, RBC	TBV, GMV, WMV, HV	WMHV
Hooshmand *et al.* (2019)[67]	–	Methionine, homocystein, vitamin B_{12}, RBC folate	Serum, RBC	TB tissue V, GMV, WMV	WMHV
Thomas *et al.* (2021)[63]	–	Carotenoids: α-carotene, β-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin	Plasma	MTLV	

ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linoleic acid; ARA, arachidonic acid; LC-PUFA, long-chain polyunsaturated fatty acid; (T)GM(V), total grey matter volume; FFQ, food frequency questionnaire; WM(V), white matter (volume); HV, hippocampal volume; (T)ICV, (total) intracranial volume; CSIRO, Commonwealth Scientific and Industrial Research Organisation; QUANTIDD, Quantitative Index for Dietary Diversity including 13 food groups; MedDiet, Mediterranean diet; WMH(V), white matter hyperintensity (volume); MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; WebQ, validated web-based 24-h dietary recall questionnaire; RBC, erythrocyte; TBV, total brain volume; MTLV, medial temporal lobe volume.

Table 6. Dietary factors and MRI biomarkers in the interventional studies included in the systematic review

Author, year (reference)	Intervention factors		Structural biomarkers			Functional measurement	
	Treatment group	Control group	Macrostructural measures	Microstructural measures	Lesion measures	Perfusion measures	Functional activity/connectivity
Nutrients and bioactive food components							
Brickman *et al.* (2014)[74]	High-flavanol cocoa powder: 900 mg/d cocoa flavanol and 138 mg/d (−)-epicatechin	Low-flavanol cocoa powder: Placebo (low flavanol): 10 mg/d cocoa flavanol and <2 mg/d (−)-epicatechin	–			CBV in the DG of the hippocampus	
Witte *et al.* (2014)[68]	Supplement capsule: 2·2 g/d LC-n3-FA	Placebo: capsule with sunflower oil in identical shape and colour	GMV	WM integrity (FA, MD, RD)			–
Carmichael *et al.* (2018)[78]	Daily supplement: EPA (960 mg) + DHA (624 mg) + total ginsenosides (16 mg) + catechins (26 mg)	Placebo: a corn oil emulsion matched to the active product in taste, colour, odour, and texture	–				t-fMRI: activation in the ACC and PCC t- and rs-fMRI functional connectivity: ROIs – left medial frontal gyrus, left middle frontal gyrus, left and right precentral gyri, left and right anterior dorsal premotor cortex, and left superior parietal lobule
Lindbergh *et al.* (2018)[79]	Daily supplement: lutein (10 mg) + zeaxanthin (2 mg)	Placebo: identical appearance to the supplement	–				t-fMRI during a verbal learning and recall trial task: increased or decreased BOLD signal in ROI. During learning task: medial temporal lobe, supramarginal and angular gyri, percuneus, dorsolateral and ventrolateral prefrontal cortex, anterior and posterior cingulate gyrus, Broca's area, cerebellum, and premotor areas. During recall trials: addition of anterior prefrontal cortex, retrosplenial cortex and cuneus
Mewborn *et al.* (2019)[70]	Daily supplement: lutein (10 mg) + zeaxanthin (2 mg)	Placebo: identical appearance to the supplement	Global and regional GMV, WMV	WM integrity (FA, MD, RD and AD)			
Lindbergh *et al.* (2020)[80]	Daily supplement: lutein (10 mg) + zeaxanthin (2 mg)	Placebo: identical appearance to the supplement	–				rs-fMRI functional connectivity measures within and between brain networks Within-network connectivity: DMN overlap rate similarity Between-network connectivity: inter-network connectivity (connection between the DMN and other brain networks)

Table 6. (*Continued*)

Sloan *et al.* (2021)[75]	Supplement (cocoa flavanol capsules): 260 mg/d for low intake group, 510 mg/d for medium intake group and 770 mg/d for high intake group	Placebo: capsule without flavanols	–			CBV in the DG of the hippocampus	
Foods							
Bowtell *et al.* (2017)[76]	Blueberry concentrate: 30 mL/d (387 mg anthocyanidins)	Placebo: a synthetic blackcurrant and apple cordial with added sugar to match energy content of the blueberry concentrate	–			Cerebral perfusion of GM in frontal, parietal and occipital lobes	t-fMRI: brain activation during cognitive tasks
Sala-Vila *et al.* (2020)[72]	Walnuts at approximately 15% of daily energy intake (30–60 g/d)	Abstained from walnuts and avoided consuming other nuts at doses greater than 2 servings per week	Cortical thickness		WMHV	CBF	t-fMRI maps during N-back task
Kleinloog *et al.* (2021)[77]	Soya nuts: 67 g/d (approximately 25·5 g soya protein and 174 mg isoflavones)	No nuts; normal diet as per Dutch guidelines	–			CBF in the left and right hemispheres; regional blood flow, particularly in the occipital, temporal, parietal and frontal lobes	
Flanagan *et al.* (2022)[71]	Freeze-dried cranberry powder: equivalent to 100 g/d of fresh cranberries	Placebo powder	GM		WMH	Regional brain perfusion in areas such as hippocampus and ROI	
Patterns							
Kaplan *et al.* (2022)[69]	Green-MED group: individualised dietary counselling - Followed a Mediterranean diet with high polyphenols, reduced red/processed meat, green tea (3–4 cups daily), walnuts (28 g daily) and Mankai plant-based shakes (100 g daily). For MED group: individualised dietary counselling - Followed a Mediterranean diet rich in vegetables, poultry, fish and walnuts (28 g daily), with a moderate amount of red meat. No green tea or Mankai supplementation	For HDG group: - individualised dietary counselling for the general healthy dietary guidelines with a focus on balanced nutrition, whole grains, fruits, vegetables and legumes, without emphasis on polyphenols or reduced meat intake	HOC, LVV	WM tract integrity (FA)			

(*Continued*)

Table 6. (*Continued*)

Author, year (reference)	Intervention factors		Structural biomarkers			Functional measurement	
	Treatment group	Control group	Macrostructural measures	Microstructural measures	Lesion measures	Perfusion measures	Functional activity/connectivity
Barnes *et al.* (2023)[73]	MIND-diet group with mild caloric restriction: individualised dietary counselling - Followed the MIND diet with mild caloric restriction, focusing on green leafy vegetables, nuts, berries, fish and olive oil; received monthly supplies of blueberries, mixed nuts and olive oil	Usual diet with mild caloric restriction: individualised dietary counselling - Focused on portion control, calorie tracking and behavioural strategies for weight management	HV, GMV, WMV		WMH		

CBV, cerebral blood volume; DG, dentate gyrus; LC-n3-FA, long chain-n3-fatty acid; GMV, grey matter volume; WM, white matter; FA, fractional aniosotropy; MD, mean diffusivity; RD, radial diffusivity; PCC, posterior cingulate cortex; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; BOLD, blood oxygenation level-dependent; ROIs, regions of interest; WMV, white matter volume; AD, axial diffusivity; DMN, Default Mode Network; CBF, cerebral blood flow; WMHV, white matter hyperintensity volume; MeD, Mediterranean diet; HDG, healthy dietary guidelines; HOC, hippocampal occupancy score; LVV, lateral ventricular volume; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; HV, hippocampal volume.

Table 8 presents findings from longitudinal studies between dietary factors and MRI biomarkers, including macrostructural and lesion measures. Protective dietary factors demonstrated consistent associations with brain preservation. Fatty acids (arachidonic acid, DHA and EPA)[54], vegetables[55,56], green tea[57], prudent (healthy) dietary patterns[58], dietary diversity[59] and healthy dietary patterns[60] all correlated with structural preservation across TBV, GMV and HV. Blood biomarkers similarly showed protective effects: EPA and DHA[61], vitamins B_{12} and E[62], and carotenoids[63] were associated with reduced atrophy rates in TBV, GMV, amygdala and MTLV. Notably, green tea consumption (+100 mL/d) showed slower hippocampal atrophy (annual percentage change in hippocampal volume ratio, $\beta = -0{\cdot}024$)[57], while healthier dietary patterns ('prudent') preserved left hippocampal volume ($\beta = 45{\cdot}7$ mm^3), with good *v.* poor diet showing +203 mm^3 difference over 4 years – equivalent to 62% of the average decline[58]. Higher plasma carotenoids and β-carotene (per one standard deviation (SD) increase) reduced the rate of medial temporal lobe volume (MTLV) loss by 0·02 cm^3/year[63]. For lesion measures, vegetables reduced WMH progression[56], while elevated Hcy was associated with increased lesion burden among hypertensive participants[62]. Conversely, dairy products were positively associated with WMHV[56]. However, several longitudinal studies reported null findings: tuna or fish[33], coffee[64], MedDiet[65], MIND diet[66], blood folate[62] and vitamin B_{12}[67], consistent with cross-sectional study heterogeneity.

Table 9 demonstrates the effects of dietary interventions on structural MRI biomarkers. For macrostructural measures, only two of six studies showed beneficial associations: omega-3 fatty acids supplementation enhanced regional GMV[68], while the Green-MedDiet and pooled MedDiet improved hippocampal occupancy scores and reduced LVV expansion[69]. Similarly, omega-3 supplementation was the sole intervention benefiting WMI among omega-3 and carotenoid studies[68,70]. No dietary interventions affected lesion measures[71–73]. Cerebral perfusion showed more consistent improvements. High-flavanol cocoa enhanced hippocampal cerebral blood volume, particularly in the dentate gyrus (DG)[74,75]. Blueberry[76], cranberry powder[71] and soya nut[77] supplementation enhanced regional blood flow. However, the MIND diet showed no significant effects on either CBV or structural measures[73]. Functional connectivity demonstrated selective improvements. EPA/DHA/ginsenoside/green tea catechin supplementation increased activation in the anterior and posterior cingulate cortices and enhanced functional connectivity in the medial frontal gyrus (MFG) and anterior cingulate cortex during tasks[78], while lutein and zeaxanthin supplementation enhanced BOLD signals in the left dorsolateral prefrontal cortex and anterior cingulate cortex, as viewed on t-fMRI scans[79], and increased inter-network connectivity between DMN and other resting state networks on rs-fMRI scans[80] Similarly, blueberry and walnut supplementation enhanced functional activation in task-associated regions[72,76].

Risk of bias

Most observational studies scored 'good' ($n = 19$ cross-sectional and $n = 14$ longitudinal analyses) or 'fair' ($n = 3$ cross-sectional) on quality assessment scales. A common limitation was not explicitly reporting the exclusion of critical conditions related to outcomes, such as stroke. Among intervention trials, even in double-blinded RCTs[68,71,74–76,78], all but three[70,79,80] raised

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Table 7. Associations between dietary factors and MRI biomarkers in the cross-sectional analyses from the prospective cohort studies

Authors, year (reference)	Dietary factors	Structural biomarkers			Confounders	Quality score
		Macrostructural measures	Microstructural measures	Lesion measures		
Nutrients						
Titova *et al.* (2013)[31]	EPA and DHA (g/d)	NS			Age, gender, energy intake, education, self-reported physical activity and cardiometabolic risk factors (serum LDL cholesterol, BMI, systolic blood pressure, HOMA-IR)	Good
Shishtar *et al.* (2020)[51]	Total flavonoids (mg/d) Flavan-3-ols (mg/d) Flavonoid polymers (mg/d)	NS		↓WMHV (cm^3): quartiles of total flavonoids, p trend = 0·03; flavan-3-ols, p trend = 0·01; and flavonoid polymers, p trend = 0·03	Age, sex, education, total energy intake, APOE4 genotype, total intracranial vault volume (model 1) + BMI, physical activity index, smoking status, prevalent diabetes, prevalent hypertension, prevalent hypercholesterolemia (model 2) + overall dietary quality, vitamin and mineral supplement use, dietary intakes of alcohol, n3 fatty acids EPA and DHA, lutein, zeaxanthin (model 3 for 1976 observations)	Good
Tsiknia *et al.* (2023)[49]	Omega-3-FA intake (mg/d)		↑ Restricted diffusion: SCSF (r = 0·20), Cingulum >80y (r = 0·47); APOE4 carriers: ILF (r = 0·50), IFOF (r = 0·46)		Age, time between dietary assessment and MRI, and sex	Good
FOODS						
White *et al.* (2000)[47]	Frequency of tofu intake in two different time periods (high–high *v.* low–low)	↑ Ventricle grade (0–9): high–high group, β = 0·62			Age, Cognitive Abilities Screening Instrument score, internal skull diameter, apolipoprotein E4 zygosity, large infarcts (≥1 cm), small infarcts (<1 cm)	Good
Raji *et al.* (2014)[36]	Baked or broiled fish (≥1–4 times/week *v.* <1/week)	↑ GMV: Orbital frontal cortex (β = 0·29); posterior cingulate/hippocampus (β = 0·21); significant clusters (hippocampus, precuneus, posterior cingulate, orbital frontal cortex)			TICV, age, gender, race, education, WML, type 2 diabetes mellitus, MRI-identified infarcts, waist/hip ratio, physical activity	Good
del C, Valdes *et al.* (2017)[37]	Iodine-rich foods (g/d) and iodine intake (μg/d, dietary and total)	↑ LVV (% volume in ICV): All dairy products R + L LVV (β = 0·21); iodine R LVV (β = 0.24), L (β = 0·29); iodine and supplements R (β = 0·24) and L (β = 0·30); oily fish L LVV (β = 0·20) for oily fish		↑WMH (% volume in ICV): Fish products, β = 0·28	Age and gender	Fair
Pellay *et al.* (2024)[48]	Consumption frequency of total dairy products, milk, fresh dairy products and cheese (frequency)	↓ MTLV (cm^3): Fresh dairy products, high *v.* low, 9 year follow-up, β = –0·99			Age, sex, education level, APOE4 carrier status, TICV, diabetes, history of stroke, number of medications taken per d, stoutness, total energy intake, frequencies of consumption of charcuterie, meat and alcohol	Good

(*Continued*)

Table 7. (*Continued*)

Authors, year (reference)	Dietary factors	Structural biomarkers			Confounders	Quality score
		Macrostructural measures	Microstructural measures	Lesion measures		
Dietary patterns						
Gardener *et al.* (2012)[52]	MediDiet score and its nine components			↓WMHV (% total cranial volume): Per 1-point increase of MedDiet, $\beta = -0{\cdot}04$; monounsaturated: saturated fat ratio > median, $\beta = -0{\cdot}20$	Age at MRI, sex, race/ethnicity, high school education completion, moderate to heavy physical activity, and total caloric intake (for MedDiet model 2 and its components) and smoking status, LDLc, HLDc, systolic blood pressure, diastolic blood pressure, interaction between diastolic blood pressure and antihypertensive medication use, diabetes and history of cardiac disease (for MediDiet model 3)	Good
Titova *et al.* (2013)[38]	MedDiet score and its components	↓TBV (mL): Meat and meat products component, > sex-specific median value, $\beta = -0{\cdot}16$			Gender, energy intake, education, self-reported physical activity, LDLc, BMI, systolic blood pressure and HOMA-IR	Good
Pelletier *et al.* (2015)[39]	MedDiet adherence (MedDiet score: 0–8)	NS	↓ MD, AD, RD: Per 1 point increment of MedDiet score, whole corpus callosum, anterior/posterior thalamic radiations, paracingulate gyrus, parahippocampal fornix (all $p < 0{\cdot}05$) ↑ FA: Per 1 point increment of MedDiet score, corpus callosum, anterior/posterior thalamic radiations, inferior fronto-occipital fasciculus (all $p < 0{\cdot}05$)		Age, gender, education, APOE4 allele status	Good
Gu *et al.* (2016)[50]	Nutrient patterns (24 nutrients)	NS	↑ WMI (mean FA cross 26 tracts): PUFA and vitamin E pattern, per 1-point increase in score, $\beta = 0{\cdot}0045$; T3 (*v.* T1), $\beta = 0{\cdot}010$		Age, sex, education, ethnicity, APOE, caloric intake, TBV, BMI, hypertension, stroke, diabetes and heart disease	Good
Gu *et al.* (2018)[44]	INP	↓ TBV (cm^3): Per 1 unit increment of INP $\beta = -22{\cdot}90$ ↓ TGMV (cm^3): $\beta = -36{\cdot}79$ ↓ TWMV (cm^3): $\beta = -22{\cdot}76$		NS	Age, sex, education, ethnicity, caloric intake, APOEe4, vascular burden, BMI and ICV	Good
Akbaraly *et al.* (2018)[43]	AHEI-2010	↑HV (mm^3): Per 1 SD increment of AHEI-2010 score, R + L HV ($\beta = 0{\cdot}11$); L ($\beta = 0{\cdot}12$) A component (alcohol), no or light alcohol consumption, R + L HV ($\beta = 0{\cdot}15$)			Age, sex, total energy intake, physical activity, smoking status, cardiometabolic health factors, cognitive impairment and depressive symptoms	Fair

Table 7. (*Continued*)

Chen, *et al.* (2021)[42]	MIND-like diet adherence score (10 brain-healthy food groups and 5 brain-unhealthy food groups)	Per 0·5 point increment in the MIND score ↑WM (cm^3): TWM ($\beta = 0{\cdot}74$); temporal lobe WM ($\beta = 0{\cdot}19$) But NS at Benjamini–Hochberg *p*-value			Age, race/ethnicity, US region, education level, employment, smoking status, alcohol consumption, BMI, physical activity, medical histories of hypertension, diabetes, hypercholesterolemia, cardiovascular diseases, WHI-HRT treatment assignment, total energy intake and intracranial volume	Fair
Melo van Lent *et al.* (2021)[41]	MIND diet score	↑TBV (% ICV): 1 unit increment of the MIND diet score, $\beta = 0{\cdot}02$		NS	Age at MRI, age squared at MRI, sex, apolipoprotein 4 status, average daily calorie intake, and time from exam 7 to MRI imaging, BMI, physical activity index, smoking status, diabetes status, prevalent cardiovascular disease, depression status, anti-hypertensive medication usage, systolic blood pressure and total to HDL cholesterol ratio	Good
Macpherson *et al.* (2021)[40]	MedDiet; HDS; RFS	NS			Age, sex, education, income, ethnicity, energy intake, heart conditions, depression, physical activity, BMI and smoking status	Good
Guan *et al.* (2023)[32]	HEI-2005, blood Vitamin B_6, B_{12}, 26 LC-FA	Not specified	↑WMI: only among APOE4 carriers: R_ILF: blood B_{12}, $r = 0{\cdot}375$; blood total n3 FA, $r = 0{\cdot}353$; L_ IFOF: blood DHA, $r = 0{\cdot}342$		Age, sex in partial correlation	Good
Mulugeta *et al.* (2022)[114]	HDS based on the American Heart Association guidelines	NS		NS	Age, sex, assessment centre, duration until imaging (in year), education, Townsend deprivation index, employment, alcohol consumption and longstanding illness	Good
Melo van Lent *et al.* (2023)[35]	DII	↓TBV (% ICV): Per 1-unit increment of DII, $\beta = -0{\cdot}16$; Q4 *v.* Q1, $\beta = -0{\cdot}64$ ↑ LVV (% ICV): Per 1-unit increment, $\beta = 0{\cdot}04$ ↓TGMV (% ICV): Per 1-unit increment, $\beta = -0{\cdot}08$; Q4 *v.* Q1, $\beta = -0{\cdot}30$		↑Silent infarcts: Q4 *v.* Q1, OR = 1·77 (95% CI 1·05–3·00)	Age at MRI, age-squared at MRI exam, sex, time from exam to MRI, education, APOE4 status, BMI, smoking status, physical activity index score, total energy intake, total cholesterol to HDLc ratio, use of anti-cholesterol medication	Good
Dietary biomarkers only						
Tangney, *et al.* (2011)[53]	Vitamin B_{12} status (pg/mL): Hcy (µmol/L), methylmalonic acid (nmol/L), cystathionine (nmol/L), and 2-methylcitric acid (nmol/L)	↓TBV (% ICV): Per 1 unit increment of Hcy, $\beta = -0{\cdot}34$; methylmalonic acid, cystathione, and 2-methylcitric acid, $\beta = -0{\cdot}01$		↑WMHV (% ICV): Per 1 unit increment of Hcy (µmol/L), $\beta = 10{\cdot}27$	Age, sex, education, race, serum creatinine levels, and time elapsed between blood sampling, MRI evaluation and serum creatinine concentrations	Good

(*Continued*)

Table 7. (*Continued*)

Authors, year (reference)	Dietary factors	Structural biomarkers			Confounders	Quality score
		Macrostructural measures	Microstructural measures	Lesion measures		
Karakis *et al.* (2016)[105]	Vitamin D deficiency (25(OH)D <10 ng/mL)	↓ HV (% ICV): $\beta = -0{\cdot}01$		NS	Age, gender, time from vitamin D measurement to MRI, vascular risk factors (smoking, hypertension, diabetes, prevalent cardiovascular disease and Hcy)	Good
Beydoun *et al.* (2020)[46]	Vitamin D (25(OH)D ng/mL), folate (ng/mL), cobalamin (pg/mL)	↑ WMV (mm^3): 25(OH)D level (standardised β): TWMV ($\beta = 0{\cdot}19$; $\beta = 0{\cdot}18$ in the additional covariates adjusted model) Occipital WMV ($\beta = 0{\cdot}25$; $\beta = 0{\cdot}24$); parietal WMV ($\beta = 0{\cdot}23$; $\beta = 0{\cdot}22$); left occipital pole ($\beta = 0{\cdot}31$; $\beta = 0{\cdot}27$)	↑FA, bilateral mean: Cingulum (cingulate Glyrus), 25(OH)D, $\beta = 0{\cdot}31$ ($\beta = 0{\cdot}28$: additional covariates adjusted model) ↓MD (mm^2/s), bilateral mean: Anterior limb of the internal capsule, folate, $\beta = -0{\cdot}23$ ($\beta = -0{\cdot}26$)		Age, sex, race, poverty status, time between visits (+additional covariates including lifestyle (smoking and drug use, adiposity, HEI 2010, dietary approaches to stop hypertension, mean adequacy ratio, depressive symptoms), health-related factors (self-reported medical history of cardiometabolic diseases etc), other biomarkers (serum cholesterol and altherogenic indices, serum uric acid, albumin and CRP, *etc.*))	Good
Chen *et al.* (2020)[45]	RBC omega-3 index (%), DHA (%), EPA (%)	↑ WMV (cm^3): Total: omega-3 index, $\beta = 5{\cdot}03$; RBC DHA, $\beta = 4{\cdot}69$; RBC EPA, $\beta = 3{\cdot}74$ Hippocampus: omega-3 index, $\beta = 0{\cdot}08$; RBC DHA, $\beta = 0{\cdot}09$ Frontal lobe: RBC DHA, $\beta = 2{\cdot}02$; RBC EPA, $\beta = 1{\cdot}59$ Parietal lobe: RBC DHA, $\beta = 1{\cdot}14$; RBC EPA, $\beta = 0{\cdot}79$ Temporal lobe: RBC DHA, $\beta = 1{\cdot}25$; RBC EPA, $\beta = 1{\cdot}03$ Corpus callosum: RBC DHA, $\beta = 0{\cdot}11$; RBC EPA, $\beta = 0{\cdot}07$			Age, race/ethnicity, region, education, family income, intracranial volume, smoking status, alcohol consumption, BMI, physical activity, hormone therapy and medical history	Good

↑ indicates positive association (greater volume, higher integrity or lower lesion burden); ↓ indicates negative association (smaller volume, lower integrity or greater lesion burden). Effect sizes are presented as standardised regression coefficients (β), correlation coefficients (r), odd ratios (OR) or p for trend values, as reported in each study.

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; NS, not significant; LDL(c), low density lipoprotein (cholesterol); BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; HV, hippocampal volume; WMH(V), white matter hyperintensity (volume); APOE4, apolipoprotein E4; omega-3-FA, omega-3 fatty acid; SCSF, superior cortico-striatal fasciculus; ILF, inferior longitudinal fasciculus; IFOF, inferior frontal occipital fasciculus; (T)GM(V), (total) grey matter (volume); (T)ICV, (total) intracranial volume; WMLs, white matter lesions; LVV, lateral ventricular volume; R, right; L, left; MTLV, medial temporal lobe volume; MedDiet, Mediterranean diet; HDL(c), high density lipoprotein (cholesterol); TBV, total brain volume; (T)WM(V), (total) white matter (volume); MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; FA, fractional anisotrophy; PUFA, polyunsaturated fatty acid; INP, inflammation-related nutrient pattern; (A)HEI, Alternative Healthy Eating Index; WHI-HRT, Women's Health Initiative Hormone Replacement Therapy trial; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; HDS, healthy diet score; RFS, recommended food score; SLFT, superior longitudinal fasciculus; ILF, inferior longitudinal fasciculus; DII, Dietary Inflammatory Index; Q, quartile; Hcy, homocysteine; 25(OH)D, 25-hydroxy vitamin D; LC, long chain; RBC, erythrocytes.

Table 8. Associations between dietary factors and MRI biomarkers in the longitudinal analyses from the prospective cohort studies

Authors, year (reference)	Dietary factors	Structural biomarkers		Confounders	Quality score
		Macrostructural measures	Lesion measures		
Nutrients					
Tokuda *et al.* (2022)[54]	FA: ALA (g/d), EPA (mg/d), DHA (mg/d), LA (g/d), ARA (mg/d), n-3/n-6 LC-PUFA	(Mean *GMV* volume change (mm^3) for 2 years) TGMV: arachidonic acid (mg/d), −5091 in T3 *v.* −7383 in T1 Frontal cortex volume: DHA (mg/d), −332 in T3 *v.* −103 in T1; EPA, −174 in T3 *v.* −37 in T1		Age, sex, education, and medical history (stroke, heart disease, hypertension, dyslipidaemia and diabetes), body mass index, smoking status, alcohol consumption, physical activity, depressive symptoms and baseline value of each MRI biomarker	Good
Foods					
Virtanen *et al.* (2008)[33]	Tuna or other fish, fried fish (servings)		NS (in the longitudinal analysis)	Age, sex, race, enrolment centre (four sites), diabetes, education, smoking status, smoking history (pack-years), BMI, CHD at the time of MRI, alcohol use, physical activity, total energy intake, meat consumption and vegetable consumption, and tuna/other fish intake for fried fish intake analysis (fried fish for tuna/other fish intake analysis)	Good
Lee *et al.* (2019)[55]	18 food groups	(Volume change* over 4-year follow-up) GMV: vegetables, $\beta = -2{\cdot}28$ (smaller decrease) Temporal region: vegetables, $\beta = -0{\cdot}63$ (smaller decrease) at Bonferroni-corrected significance level ($0{\cdot}05/7 = 0{\cdot}007$)		Age, sex, BMI, education, total caloric intake, smoking status, drinking status, regular exercise, CRP, hypertension, DM, total cholesterol, depression, intracranial volume size, years of MRI follow-up	Good
Zhang *et al.* (2021)[57]	Green tea consumption (mL/d)	(Annual change (%)† between baseline and follow up) Hippocampal ratio: per 100 mL/d increment of green tea, $\beta = -0{\cdot}024$		Age, gender, APOE genotype, history of disease (stroke, hypertension, heart disease, dyslipidaemia, diabetes), smoking status, alcohol intake, total physical activity, education level, depressive symptoms, fish consumption, vegetable and fruit consumption, energy intake	Good
Gardener *et al.* (2021)[64]	Coffee (g/d, tertiles)	NS		Age, APOE4 carrier status, sex, education level, energy intake, time from baseline to FFQ completion	Good
Dietary patterns					
Jacka *et al.* (2015)[58]	Prudent (healthy) pattern *v.* western (unhealthy) pattern Good diet *v.* poor diet‡	(Longitudinal repeated-measures analysis) Left HV (mm^3): prudent pattern, $\beta = 45{\cdot}7$ Good (*v.* poor diet), the predicted difference over 4 years, 203 mm^3 larger (corresponding to 62% of the average decline)		Age, gender, education, employment status, depressive symptoms and medication, physical activity, smoking, hypertension, diabetes and elapsed time	Good
Otsuka *et al.* (2021)[59]	Dietary diversity scores	(Decrease %§ for 2 years) Across quintiles of dietary diversity scores TGMV: 0·69% in Q5 *v.* 1·02% in Q1, *p*-trend = 0·017 HV: 0·85% in Q5 *v.* 1·31% in Q1, *p*-trend = 0·003		Age, sex, education, smoking status, alcohol intake, physical activity, and history of stroke, dyslipidaemia, diabetes, hypertension and heart disease	Good

(*Continued*)

Table 8. (*Continued*)

Authors, year (reference)	Dietary factors	Structural biomarkers		Confounders	Quality score
		Macrostructural measures	Lesion measures		
Luciano, *et al.* (2022)[65]	MedDiet score	NS		Age, sex, education, baseline general cognitive ability (time invariant), BMI, diabetes and MMSE as a possible cognitive impairment indicator (time varying)	Good
Song *et al.* (2022)[56]	MedDiet and its individual component scores		(Change over 5 years) ($\log_{10}$(WMH + 1) transformed WMHV) WMHV (= follow-up log scores-baseline log scores): MedDiet score, $\beta = -0{\cdot}014$; components: higher intake of vegetables, $\beta = -0{\cdot}095$; less intake of dairy, $\beta = -0{\cdot}045$	Age, follow-up interval, gender, years of education, National Adult Reading Test assessed Intelligence Quotient, race/ethnicity, total daily energy intake, baseline WMH volume, baseline TGMV residuals and baseline mean cortical thickness	Good
Chen *et al.* (2024)[66]	MIND diet adherence	NS	NS	Age, age squared, sex, time interval from recruitment to MRI, ethnicity, Townsend deprivation index, education level, physical activity, smoking and total energy intake	Good
Zhang *et al.* (2024)[60]	Healthy or traditional diet *v.* Western diet	(Annual change (%)† between baseline and follow-up) Traditional Japanese diet (*v.* Western): TGMV: $\beta = -0{\cdot}145$ in women (smaller decrease) Parietal lobe: $\beta = -0{\cdot}214$ in women (smaller decrease)		Age, APOE genotype, education level, smoking status, total physical activity, energy intake, BMI, depressive symptoms, medical history (*e.g.* stroke, hypertension, heart disease, dyslipidaemia, diabetes)	Good
Dietary biomarkers only					
Samieri *et al.* (2012)[61]	Plasma fatty acids: EPA (%) and DHA (%)	(Volume change (mm^3/year) over 4 years) Right amygdala: per 1 SD higher EPA (%) at baseline, $\beta = 1{\cdot}3$ mm^3 (smaller decrease)		Age, education, gender, APOE4 carrier status, baseline TICV and their interactions with time (model 1), and depressive symptoms, BMI, tobacco use, alcohol consumption, history of cardiovascular and cerebrovascular disease, hypertension, hypercholesterolemia, diabetes, hypertriglyceridemia, and their interactions with time (model 2) and TGMV change × time (model 3)	Good
Hooshmand *et al.* (2016)[62]	RBC folate (ng/mL), vitamin B_{12} (pmol/L), holotranscobalamin (pmol/L) Sulfur amino acid: Hcy (μmol/L), methionine (mg/dL), cystathione (nmol/L), cysteine (μmol/L)	(Volume change over 6 years) Total brain tissue volume: per 1 SD increase of vitamin B_{12} (pmol/L), $\beta = 0{\cdot}048$; holotranscobalamin (pmol/L), $\beta = 0{\cdot}040$; Hcy (μmol/L), $\beta = -0{\cdot}035$ (faster loss rate)	Per 1 SD increase in Hcy levels: associated with progression of WMH among participants with high systolic blood pressure	Age, sex, education, APOE4 status, systolic blood pressure, creatinine, use of vitamin supplements, smoking, treatment of hypertension, plasma total cholesterol level, obesity, history of cardiovascular conditions, their interactions with time	Good
Hooshmand *et al.* (2019)[67]	Serum vitamin B_{12} (pg/mL), methionine (mg/dL), Hcy (μmol/L), RBC folate (ng/mL)	(Volume change over 6 years) Total brain tissue volume: methionine to homocysteine ratio, $\beta = 0{\cdot}038$ GMV: methionine to homocysteine ratio, $\beta = 0{\cdot}034$	NS	Age, sex, education level, creatinine level, systolic blood pressure, use of vitamins, albumin level, smoking status, history of cardiovascular conditions and APOE4 status	Good

Table 8. (*Continued*)

Thomas *et al.* (2021)[63]	Plasma carotenoids (μg/L)	(Volume change over 10 years, cm^3/year) per 1-SD increase of plasma carotenoids MTLV: total carotenoids, 0·02 cm^3/year; β-carotene, 0·02 cm^3/year (smaller rate of loss)	Age, sex, educational level, APOE ε4 status, plasma triacylglycerols, total cholesterol, BMI, smoking status, alcohol consumption, physical activity, diabetes, history of cardiovascular and cerebral diseases, hypertension, hypercholesterolemia, depressive symptoms, total intracranial volume and their interactions with time	Good

*The volume changes were calculated from brain-region-specific volumes at baseline subtracted by that at follow-up.
†Annual change of region of interest (ROI) (%) $= \left(\left(\frac{\text{relative volume (or ratio) of ROI}_{\text{at follow-up}} - \text{relative volume (or ratio) of ROI}_{\text{at baseline}}}{\text{relative volume (or ratio) of ROI}_{\text{at baseline}}}\right) \div \left(\frac{\text{follow-up time (days)}}{365.25}\right)\right) \times 100\%$. Relative volume (or ratio) of ROI = ROI volume (mm^3)/total intracranial volume (mm^3).
‡Poor diet was defined as one SD below mean on prudent and 1 SD above mean on Western dietary factor scores. Good diet was defined as one SD above mean on prudent and one SD below on Western dietary factor scores.
§Decrease $\% = \frac{\text{Volume}_{\text{at baseline}} - \text{Volume}_{\text{at follow-up}}}{\text{Volume}_{\text{at baseline}}} \times 100\%$.
FA, fatty acid; ALA, alpha-linolenic acid; EPA, eicosapentaenoic acids; DHA, docosahexaenoic acid; LA, linoleic acid; ARA, arachidonic acid; LC-PUFA, long-chain polyunsaturated fatty acid; T, tertile; (T)GM(V), (total) grey matter (volume); NS, not significant; BMI, body mass index, CHD, coronary heart disease; HV, hippocampal volume; WM(V), white matter (volume); CRP, C-reactive protein; DM, diabetes mellitus; APOE, apolipoprotein E, FFQ, food frequency questionnaire; MedDiet, Mediterranean diet; MMSE, Mini-Mental State Examination; WMH(V), white matter hyperintensity (volume); MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; SD, standard deviation; TICV, total intracranial volume; RBC, erythrocyte; Hcy, homocysteine; MTLV, medial temporal lobe volume.

concerns owing to a lack of clear descriptions of random number generation and allocation concealment.

Discussion

In this systematic review evaluating thirty-eight prospective cohort studies (twenty-three cross-sectional and fifteen longitudinal analyses) and thirteen interventional studies investigating associations between dietary factors (including blood dietary biomarkers) and brain MRI biomarkers in general populations, diet–MRI associations were heterogeneous. Across cross-sectional analyses, several dietary factors showed beneficial associations with MRI biomarkers; however, results were inconsistent and some opposite-direction signals were observed – for example, baked/broiled fish aligned with larger GM volumes (*e.g.* in hippocampus, $\beta = 0{\cdot}21$), whereas oily fish/fish products were related to greater LVV and WMH, dairy products were linked to larger LVV and smaller MTLV, and tofu to higher ventricular grade. For dietary patterns, pro-inflammatory patterns were linked to smaller volumes and more silent infarcts (DII Q4 *v.* Q1, OR = 1·77), whereas diet-quality indices tended to favour larger volumes and lower lesion burden. However, the findings for MedDiet/MIND were mixed, circulating vitamin B_{12} showed no macrostructural associations, whereas homocysteine showed an adverse association. Longitudinal analyses demonstrated more consistent protective associations: though null results were common across multiple factors. Healthier patterns (*e.g.* vegetable-rich/prudent, greater diversity), green tea, specific fatty acids and higher plasma carotenoids/omega-3s were linked to structural preservation (slower atrophy): +100 mL/d green tea was related to a 0·024%/year slower decline in hippocampal volume ratio, a prudent pattern predicted a +203 mm^3 4-year advantage in left hippocampal volume, and per one SD higher plasma carotenoid level, MTLV loss was 0·02 cm^3/year smaller. Interventions showed limited structural benefits [in only two of six studies: long chain-n3-fatty acids (LC-n3); Green-Med/MedDiet], while polyphenol-rich supplements more often improved perfusion/functional metrics. Overall, clinically interpretable magnitudes centre on slower atrophy and fewer lesions with healthier diets/biomarkers, whereas cross-sectional signals require cautious interpretation given partial temporality.

Associations between dietary factors and MRI biomarkers

Overall, healthier exposures generally aligned with structural preservation, whereas pro-inflammatory profiles were associated with smaller brain volumes, greater ventricular enlargement and higher lesion burden, though directions varied by dietary factors and MRI biomarkers. For example, in the cross-sectional analyses, fish consumption showed contrasting results depending on type and preparation: baked/broiled fish was associated with larger GM volumes, including the hippocampus[36], whereas oily fish/fish products[37], dairy products[48] and tofu[47] were adversely associated with brain structural measures such as LVV, MTLV, ventricular grade and WMH. These findings from cross-sectional analyses of foods can be interpreted on the basis of the following possibilities: First, analyses focusing on individual foods may be problematic owing to the complexity of eating behaviours and inter-relationships among food items. Therefore, dietary pattern analysis has been suggested as a more appropriate approach to address these complexities[81]. Second, the differential associations observed between baked/broiled fish (beneficial)[36] and oily fish/

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Table 9. Effects of dietary factors on MRI biomarkers in the interventional studies included in the systematic review

Authors, year (reference)		Structural biomarkers			Functional biomarkers		Confounders examined	Risk of bias
		Macrostructural measures	Microstructural measures	Lesion measures	pMRI markers	Functional activity/connectivity		
Nutrients and bioactive food components								
Brickman *et al.* (2014)[74]	High-flavanol group *v.* low-flavanol group:				↑CBV % in DG/subiculum in H Group × time: $F_{1,33} = 27{\cdot}58$, $p < 0{\cdot}0001$, $\eta^2 = 0{\cdot}471$ High-flavanol: 2·9 at baseline *v.* 4·7 at follow-up Low-flavanol: 3·1 at baseline *v.* 2·8 at follow-up		Sex	Some concerns
Witte *et al.* (2014)[68]	LC-n3-FA supplementation *v.* placebo	↑ Regional GMV %: LC-n3-FA group: increases in the left H, precuneus, superior temporal, inferior parietal and postcentral gyri and in the right middle temporal gyrus ($p < 0{\cdot}001$)	↑ WMI LC-n3-FA group: voxel-wise increases in FA, decreases in MD and RD within selective WM tracts ($p < 0{\cdot}001$) (including CC (genu), UF, SLF, IFOF in Fr, temp, and limb areas of the left hemisphere; SLF and SFOF and IFOF within par., temp., limb., and Occ. areas of the right hemisphere)				Not specified	Some concerns
Carmichael *et al.* (2018)[78]	EPA, DHA and ginsenoside and green tea catechin supplement *v.* placebo					t-fMRI (switching task: colour–shape) (supplement): ↑ Activation (ACC, PCC) ↑ Functional connectivity (MFG–ACC) rs-fMRI (supplement): ↓ Functional connectivity (Precentral–MFG, Precuneus–MFG)	Not specified	High
Lindbergh *et al.* (2018)[79]	Lutein and zeaxanthin supplement *v.* placebo					t-fMRI (verbal learning task): Encoding: ↑ BOLD signal in left DLPFC and ACC (supplement only, $p < 0{\cdot}05$ FWE) Retrieval (exploratory): ↑ BOLD in left DLPFC and ACC (supplement only, $p < 0{\cdot}05$ FWE)	Age	Low

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Table 9. (*Continued*)

Mewborn *et al.* (2019)[70]	Lutein and zeaxanthin supplement *v.* placebo	NS	NS				Baseline age, CDR scores and MPOD	Low
Lindbergh *et al.* (2020)[80]	Lutein and zeaxanthin supplement *v.* placebo					rs-fMRI: ↑ DMN inter-network connectivity between DMN and nine other resting state networks (supplement only; $t = 2{\cdot}55$, $p = 0{\cdot}016$; d = 89; adj. MPOD $p < 0{\cdot}05$). (compensation of the aging brain's capacity)	MPOD	Some concerns
Sloan *et al.* (2021)[75]	Three levels of flavanol supplements *v.* placebo				Voxel-based: ↑ CBV (score) in anterior DG (DG head, outer ROI boundary, flavanol group only)		Age, sex and education	Some concerns
Foods								
Bowtell *et al.* (2017)[76]	Blueberry supplement *v.* placebo				ASL perfusion: ↑ GM Δperfusion (post–pre): blueberry *v.* placebo–parietal (+5·0% *v.* −2·9%, $p = 0{\cdot}013$); occipital (+8·0% *v.* −0·7%, $p = 0{\cdot}031$)	t-fMRI (numerical Stroop task): ↑ Activation (BA4/6/10/21/40/44/45*, precuneus, ACC, insula/thalamus; $p < 0{\cdot}001$)	Not specified	Some concerns
Sala-Vila *et al.* (2020)[72]	Walnuts *v.* control	NS		NS	NS	t-fMRI (N-back working-memory task: 3-back > 0-back contrast): Control only: ↑ activation *v.* baseline (right occipital/temporal; outside task-related regions)	Not specified (in the imaging data analysis)	Some concerns
Kleinloog *et al.* (2021)[77]	Soya nuts *v.* no nuts				ASL perfusion (soya nuts *v.* control): ↑ Regional CBF (mL 100 g/tissue/min): L occipital/temporal, +11·1 ($p < 0{\cdot}001$); bilateral occipital,+12·1 ($p = 0{\cdot}002$); R occipital/parietal, +12·7 ($p = 0{\cdot}005$); L frontal, +12·4 ($p = 0{\cdot}009$)		Period, gender and order (but in the final model)	

(*Continued*)

Table 9. (*Continued*)

Authors, year (reference)		Structural biomarkers			Functional biomarkers		Confounders examined	Risk of bias
		Macrostructural measures	Microstructural measures	Lesion measures	pMRI markers	Functional activity/connectivity		
Flanagan *et al.* (2022)[71]	Cranberry powder *v.* placebo	NS		NS	ASL perfusion (cranberry *v.* placebo): ↑CBF (mL·100 g/tissue/min) in R caudate (follow-up – baseline: +2·47 *v.* −2·29; $p = 0·049$), R NAc (+3·71 *v.* −3·37; $p = 0·034$), R entorhinal (+3·56 *v.* −2·42; $p = 0·030$) over 12 weeks		Age and education	Some concerns
Patterns								
Kaplan *et al.* (2022)[69]	Green-MED *v.* HDG; Med *v.* HDG	HOC and LVV: Green-MED *v.* HDG (≥50 years): lower decline in HOC (−0·78% *v.* −1·3%, $p = 0·042$); smaller increase in LVV (+2·3% *v.* +4·3%, $p = 0·021$) Green-MED *v.* HDG (entire cohort): LVV expansion attenuated (+1·2% *v.* +3·1%, $p = 0·04$) MEDs pooled *v.* HDG (≥50 years): HOC decline attenuated (−0·78% *v.* −1·3%, $p = 0·005$) LVV expansion attenuated (+2·4% *v.* +4·3%, $p = 0·003$)	NS				Age, sex and HOMA-IR	Some concerns
Barnes *et al.* (2023)[73]	MIND-diet *v.* usual diet	NS		NS			Clinical site	Some concerns

↑ indicates positive association; ↓ indicates negative association.

*BA stands for Brodmann area: BA4 (primary motor cortex), BA6 (premotor/supplementary motor area), BA10 (anterior prefrontal cortex), BA21 (middle temporal gyrus), BA40 (inferior parietal lobule) and BA44/45 (inferior frontal gyrus, Broca's area). pMRI, perfusion magnetic resonance imaging; fMRI, functional magnetic resonance imaging; CBV, cerebral blood volume; DG, dentate gyrus; H, hippocampus; LC-n3 FA, long chain-n3 fatty acid; GM(V), grey matter (volume); WM(I), white matter (integrity); FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; CC (genu), corpus callosum, genu (anterior corpus callosum); UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; SFOF, superior fronto-occipital fasciculus; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; Fr, frontal lobe; Temp, temporal lobe; Par, parietal lobe; Limb, limbic areas; Occ, occipital lobe; t-fMRI, task-based fMRI; rs-fMRI, resting state-fMRI; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; MFG, medial frontal gyrus; ROIs, regions of interest; DMN, default mode network; BOLD, blood oxygenation level-dependent; NS, not significant; DLPFC, dorsolateral prefrontal cortex; FWE, family-wise error rate; CDR, clinical dementia rating scale; MPOD, macular pigment optical density; WMH, white matter hyperintensity; CBF, cerebral blood flow; L, left; R, right; NAc, nucleus accumbens; MED, Mediterranean diet; HDG, healthy dietary guidelines; HOC, hippocampal occupancy score; LVV, lateral ventricular volume; HOMA-IR, homeostasis model assessment of insulin resistance; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay.

fish products (detrimental)[37] suggest that cooking methods and fish species variability may be more critical determinants than fish consumption per se. Third, the association between dairy products and greater LVV[37]/WMHV[56] and smaller MTLV[48] requires careful interpretation within the context of population-specific dietary patterns and dairy processing methods. The high fat and saturated fatty acid content of dairy has been suggested as a possible explanation[37,48], as these components are known to induce metabolic, inflammatory and microvascular changes[82,83]. However, beneficial effects of dairy in other regions (WMV and the occipital and temporal volume, all p-values <0.05, although not <0.007 of Bonferroni-corrected significance level)[55] indicates that the association of dairy with neural health cannot be conclusively attributed to the influence of fats. Notably, this beneficial association was observed only in Korean populations, whose traditional diet includes little dairy. Thus, the role of dairy products should be interpreted in the context of cultural dietary practices, particularly in populations with traditionally low dairy consumption[84]. Fourth, the association between tofu consumption and increased ventricular grade among Japanese men led authors to hypothesise soya isoflavone-mediated pathways involving tyrosine kinase inhibition or oestrogenic interference[47]. However, these proposed mechanisms remain speculative, as oestrogen-related pathways are poorly understood in men, and evidence linking endogenous oestrogen to cognitive function is inconsistent. Moreover, the hypothesis of soya-induced hippocampal tyrosine kinase inhibition and impaired long-term potentiation still requires further substantiation[85].

Key cognitive regions such the frontal, temporal, hippocampal and parietal cortices are central to executive function, episodic memory and attentional control, and their early vulnerability makes them critical indicators of brain ageing and dementia risk[86]. Evidence linking omega-3 fatty acids and their source foods such as fish, flavonoids and high-quality dietary patterns (*e.g.* MedDiet, prudent and AHEI) to greater preservation of these regions[36,45,52,54–56,59,61,68] suggests that diet may be directly associated with neural substrates of cognition. Longitudinal findings further highlight clinically meaningful magnitudes – slower hippocampal decline with green tea (~0·024%/year slower decline in HV ratio per +100 mL/d)[57], hippocampal volume preservation with prudent dietary patterns (+203 mm^3 over 4 years in left HV)[58] and reduced temporal lobe atrophy with higher plasma carotenoids (~0·02 cm^3/year less MTLV loss per one SD)[63].

Beyond global macrostructural indices, more sensitive MRI biomarkers provide additional insights into how diet influences brain ageing. Microstructural integrity, reflecting WM connectivity, underpins processing speed and executive function; its preservation with MedDiet[39], HEI[32], 'PUFA and vitamin E' pattern[50], and omega-3 fatty acid intake[49] and supplementation[68] indicated better WM connectivity (increased restricted diffusion: high FA and low MD)[27,28]. Serum vitamin D and folate levels with increased WHI[46] further suggest a protective role against demyelination[28]. Lesion measures, such as WMH and subclinical infarcts, were generally lower in individuals adhering to healthier dietary profiles closely tied to dietary factors. MedDiet and its component (vegetable)[52,56] flavonoids[51] were associated with WMH. However, it is noteworthy that no significant associations with structural measures or WMH were observed after a 3-year MIND diet intervention[73], despite the MIND diet being a hybrid of the DASH, and the MedDiet and incorporating components that are putatively protective against Alzheimer's disease[10]. Perfusion studies provide mechanistic clues: polyphenol-rich interventions (*e.g.* high-flavanol cocoa, blueberries and soya) enhanced hippocampal and cortical blood flow[74,76,77], supporting vascular pathways as a mediator of diet–brain links. While structural connectivity refers to the WM pathways between regions, functional connectivity refers to the node-to-node interactions between neurophysiologically active regions[87]. Functional MRI studies also revealed that dietary interventions with antioxidants could enhance functional connectivity[72,76,78,116]. In some fMRI biomarker studies, findings did not support the initial hypothesis that carotenoids (lutein and zeaxanthin) enhance neural efficiency, which refers to a more efficient allocation of neural resources[79,80]. Instead, these studies suggest that lutein and zeaxanthin support the ageing brain's compensatory mechanisms by enhancing integration between neural networks[80].

Possible mechanisms

Multiple plausible mechanisms may underlie the associations between dietary factors and MRI biomarkers, including oxidative stress, neuroinflammation, neurogenesis, synaptic plasticity and vascular integrity. The brain's high metabolic load and high content of polyunsaturated fatty acids in its cell membranes[88] make it particularly vulnerable to oxidative stress[89,90]. Oxidative stress contributes to cellular damage, but vitamins C and E, carotenoids, flavonoids (*e.g.* polyphenols and isoflavones), omega-3 fatty acids, and foods and dietary patterns, such as the MedDiet, with a high antioxidant capacity may neutralise these effects and protect the brain[91,92]. Neuroinflammation, often triggered by oxidative stress, promotes pathogenic brain changes, including reduced synaptic plasticity and neurogenesis[92–95]. Dietary factors may also modulate brain health by maintaining mitochondrial function, vascular integrity and membrane permeability.

Omega-3 fatty acids are involved in several neurological mechanisms. In addition to antioxidative effects, they play a critical role through pathways such as axonal myelination, synaptic transmission[96] and regulation of microglial function[97,98], which collectively enhance neurogenesis and hinder neuroinflammation. Moreover, omega-3 fatty acids optimise membrane fluidity and potentiate neurotrophic factors such as brain-derived neurotrophic factor (BDNF)[99], which promotes neuronal growth in key regions such as the hippocampus[100,101]. Polyphenols similarly enhance synaptic plasticity and hippocampal neurogenesis, protecting against cognitive decline[102]. The hippocampus, a critical centre for learning, memory and mood regulation, and is notably responsive to environmental factors such as diet[95]. Green tea rich in epigallo-catechin-3-gallate (a flavan-3-ol) may help suppress hippocampal atrophy, although the mechanisms remain unclear[57]. Neurovascular health is also impacted by diet; for instance, polyphenol-rich diets. High flavanol cocoa and blueberry supplementation improved perfusion in regions such as the occipital and parietal lobes, supporting visual and cognitive function[74,76]. This enhancement of brain perfusion is critical for sustaining cognitive performance in ageing populations as reduced cerebral blood flow (CBF) is an early marker of neurodegeneration[103]. Several vitamins contribute to brain health. Vitamin E attenuates axonal degeneration and promotes remyelination[39,104], while vitamin D influences cognitive function through its role in immune modulation and neuroinflammation[105]. Vitamin B_{12} and folate regulate homocysteine metabolism, and deficiencies in these vitamins are linked to WM damage and brain atrophy via impaired *S*-adenosymethione[106]. Conversely, elevated total homocysteine

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(tHcy) is associated with endothelial dysfunction and increased brain ageing[106]. High-fat diets rich in saturated and trans-fatty acids may adversely impact brain plasticity and neuroprotection, particularly in the hippocampus, by increasing inflammatory markers and tau phosphorylation[91,107]. Meat and meat products, major sources of these fatty acids, have been linked to negative effects on brain structure in experimental models[107]. These findings highlight the dual role of dietary factors in promoting or impeding brain health depending on the composition and quality of the diet.

Limitations and strengths

This systematic review has several limitations that should be acknowledged. First, most observational studies relied on self-reported dietary assessments, such as FFQs or 24-h recalls, which are inherently prone to recall bias. Error magnitude varies by method: single recalls inadequately capture habitual intake, whereas multiple recalls or validated tools better reflect usual diet[81]. To address these limitations, reducing dietary measurement error through calibration, repeated assessments and incorporation of objective biomarkers remains a key priority[81,108]. Second, substantial methodological heterogeneity was observed across studies, limiting comparability and clinical translation. This heterogeneity encompassed inconsistent ICV adjustment and unit reporting, divergent region of interest (ROI) definitions, non-standardised lesion metrics, variations in MRI field strengths and image-processing pipelines, and multi-site batch effects. Although residual ICV adjustment is generally recommended over raw or proportional methods[109,110], it can be less intuitive and model-dependent. In this review, most studies reported results as %ICV or in clinically interpretable units, such as −0·024%/year HV decline per 100 mL/d green tea[57], +203 mm^3 HV preservation over 4 years with a prudent diet[58], and −0·02 cm^3/year MTLV loss per one SD plasma carotenoids[63]. Standardised approaches are also needed for WMH quantification (*e.g.* STRIVE criteria[111]) and for reporting reproducibility indices such as test–retest reliability and minimal detectable change[112]. Third, we attempted to indirectly compare findings from relatively younger cohorts (mean age <60 years, $n = 10$) with those from older cohorts (≥60 years, $n = 41$); however, the small number of younger cohorts and substantial heterogeneity across studies limited the feasibility of direct comparisons. In addition, intervention studies were generally short in duration (often <1 year), which may not adequately capture the long-term effects of diet on brain health. Fourth, many studies also lacked transparency in reporting methodological details, such as randomisation procedures, allocation concealment and dropout rates, raising concerns about potential biases and result reliability. In addition, relatively small sample sizes and the absence of formal power calculations limited statistical power and increased the likelihood of type II errors, complicating the interpretation of null results.

Despite these limitations, this systematic review has several notable strengths such as a comprehensive synthesis across dietary factors, MRI biomarkers and study designs, offering a foundation for future standardised and adequately powered investigations.

Recommendations for future research

Future research should aim to address the identified limitations and build upon the findings of this review. First, longitudinal studies with extended follow-up periods and repeated assessments of dietary intake and MRI biomarkers are needed to better capture long-term effects and establish causal relationships. Cohort studies that integrate MRI, dietary patterns and cognitive outcomes over decades will provide a more robust understanding of the temporal dynamics of diet and brain health. Second, the standardisation of dietary assessment tools and MRI protocols is essential. Consistent use of validated dietary measures and harmonised imaging sequences across studies will enhance comparability and improve the reliability of findings. Furthermore, the integration of existing biomarkers – such as serum levels of omega-3 fatty acids, vitamins and flavonoids – can complement self-reported methods and help reduce measurement error[113], although the number of currently available dietary biomarkers is limited, and suitable objective markers do not exist for many dietary components. Therefore, continued efforts to identify and validate novel biomarkers are warranted to advance the field of nutritional neuroepidemiology. Third, future studies should prioritise diverse and under-represented populations to improve the generalisability of findings. As previously noted[25], studies have predominantly focused on the USA and European countries, highlighting the urgent need for research in Asia, where the elderly population is rapidly increasing. Genetic factors, such as the APOE genotype, were not the focus of this review; however, it is likely to modify the impact of dietary factors on brain structure and function. Therefore, gene–diet interactions will provide valuable insights into precision nutrition strategies for brain health. In addition, longer and more personalised intervention trials are needed to evaluate the cumulative effects of dietary changes, focusing on structural, functional and cerebrovascular outcomes.

Conclusions

This systematic review suggests that dietary factors with antioxidant and anti-inflammatory properties, such as omega-3 fatty acids and the Mediterranean diet, may be associated with beneficial brain health outcomes. Longitudinal and intervention studies showed more consistent patterns than cross-sectional analyses. Nevertheless, inconsistent findings highlight the need for further research to confirm these associations and inform preventive strategies for maintaining brain health. At present, the evidence remains insufficient for clinical translation, and findings from cross-sectional analyses – even when derived from prospective cohorts – should be interpreted with caution.

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