Ageing Research Reviews 70 (2021) 101360

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Associations of dietary markers with brain volume and connectivity: A systematic review of MRI studies

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ARTICLE INFO

Keywords:
Ageing
Diet
MRI
Brain volume
Brain connectivity

ABSTRACT

The high prevalence of unhealthy dietary patterns and related brain disorders, such as dementia, emphasizes the importance of research that examines the effect of dietary factors on brain health. Identifying markers of brain health, such as volume and connectivity, that relate to diet is an important first step towards understanding the lifestyle determinants of healthy brain ageing. We conducted a systematic review of 52 studies (total n = 21,221 healthy participants aged 26–80 years, 55 % female) that assessed with a range of MRI measurements, which brain areas, connections, and cerebrovascular factors were associated with dietary markers.

We report associations between regional brain measures and dietary health.

Collectively, lower diet quality was related to reduced brain volume and connectivity, especially in white and grey matter of the frontal, temporal and parietal lobe, cingulate, entorhinal cortex and the hippocampus. Associations were also observed in connecting fibre pathways and in particular the default-mode, sensorimotor and attention networks.

However, there were also some inconsistencies in research methods and findings. We recommend that future research use more comprehensive and consistent dietary measures, more representative samples, and examine the role of key subcortical regions previously highlighted in relevant animal work.

1. Introduction

Obesity and type 2 diabetes are risk factors for dementia (Beydoun et al., 2008), including Alzheimer's dementia (Kivipelto et al., 2005; Vagelatos and Eslick, 2013; Walker and Harrison, 2015), but the effects of diet on the brain are not fully understood. There is evidence that diets high in fat, especially saturated fat as well as refined carbohydrates increase the risk of developing dementia (Gentreau, 2020; Luchsinger et al., 2002; Kalmijn et al., 1997a), whereas a diet high in ω-3 long-chain fatty acids, polyunsaturated fats (Barberger-Gateau et al., 2002) and certain antioxidants (Devore et al., 2010; Engelhart et al., 2002; Kalmijn et al., 1997b) are associated with decreased risk. With the growing ageing population and increased frequency of obesity (23 % in Europe, WHO Europe, 2016), it is critical to identify how modifiable dietary factors may influence the ageing brain in order to promote healthy ageing (Petersson and Philippou, 2016).

A balanced diet, facilitated by a combination of macronutrients, fatty acids and vitamins, is important for maintaining brain health (Hueston et al., 2017). In research studies, diet patterns are often indirectly inferred from metabolic variables, such as cholesterol levels (Meusel, 2017; Spielberg, 2017), fatty acid profiles (Talukdar et al., 2019; Zwilling et al., 2019), or specific diets, such as the Mediterranean diet (MeDi; Luciano, 2017; Petersson and Philippou, 2016; Titova et al., 2013b), caloric restriction (defined as limiting caloric intake without loss of nutrient content; Prehn, 2016), a health-aware diet (defined as a consumption of more fruits and less meat, eggs and spirits; Booth et al., 2014; Jacka et al., 2015) or food consumption assessed through questionnaires (Gu, 2015). As most dietary studies vary in their methods, study designs and samples, we lack an overall understanding of the specific microstructural, vascular and functional brain correlates of dietary health. These brain markers would have promising applications as intermediary outcomes in dietary clinical trials or intervention studies.

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https://doi.org/10.1016/j.arr.2021.101360
Received 27 November 2020; Received in revised form 22 April 2021; Accepted 8 May 2021
Available online 13 May 2021

Further, several studies implicate poor dietary health in a number of neurological and psychiatric disorders including depression (Molendijk et al., 2018; Quirk, 2013), stroke (Psaltopoulou, 2013; Román, 2019), sleep problems (Castro-Diehl et al., 2018; insomnia: Gangwisch, 2020), Alzheimer dementia, (Román, 2019), multiple sclerosis (Francis and Stevenson, 2018), and epilepsy (Fan et al., 2019; Huffman and Kossoff, 2006), however there is little clarity on how diet affects the brain in healthy ageing.

MRI can provide useful biomarkers for diet correlates of brain ageing. Few studies have examined specific brain areas in relation to diet markers in nonclinical populations. Some studies show associations of a healthier diet (i.e. higher scores for the MeDi diet) with larger cortical thickness (Gu, 2015; Mosconi, 2014; Staubo, 2017), lower WM hyperintensity (WMH) burden (Gardener, 2012), and preserved WM microstructure (Pelletier, 2015). Particularly relevant are connections between areas of the default mode network (DMN), a network which is first affected in dementia (see Hafkemeijer et al., 2012 for a review). Describing the role of these brain connections in relation to diet may be critical for our understanding of why unhealthy diets relate to an increased risk for dementia.

In this systematic review, we summarise the existing literature examining the influence of diet on the ageing brain. We focus on brain MRI-based studies examining (1) white matter (WM) connectivity, (2) grey matter (GM) functional connectivity, (3) WM and GM volumes and (4) cerebrovascular physiology. In the following sections we outline these diet-brain associations and assess whether these associations are persistent over the lifespan. We outline inconsistencies in the direction or strength of associations reported across studies and offer suggestions to overcome these inconsistencies.

2. Methods

This review was written in accordance with international guidelines, such as the PRISMA and MOOSE statements for reporting systematic reviews (Shamseer et al., 2015; Stroup, 2000) and the protocol was preregistered on the PROSPERO international database (protocol number: CRD42019123013).

2.1. Data sources

Studies examining the associations between DM markers and brain health across the lifespan were identified using MEDLINE and Ovidsp (Embase and PsycINFO) in January 2019. Search terms used for MEDLINE are shown in A1. These terms were adapted for the other databases used. The reference lists of retrieved studies were also screened for additional studies.

2.2. Inclusion criteria and data extraction

The inclusion and exclusion criteria are outlined below, and two authors (Daria E. A. Jensen, DEAJ and Virginia Leoni, VL) independently reviewed the retrieved articles to assess eligibility:

2.2.1. Included studies

1) Published as a journal article or letter.
2) Cross-sectional studies.
3) Longitudinal studies.
4) Only studies conducted on human participants.
5) Observational studies: i.e. studies which have assessed diet intake by self-report (e.g. Food Frequency Questionnaire, intake of ω-3 fatty acid) or cholesterol level
6) Interventional studies: i.e. studies which have performed a diet intervention (e.g. caloric restriction, randomised controlled trials).
7) Only studies which report participants' age.
8) Studies which examine any association between diet/metabolism and at least one of the following brain measures as an outcome variable: grey matter (GM) or white matter (WM) volume, WM microstructure (e.g., FA, diffusivity), network connections (e.g. resting-state functional connectivity, WM fibre tracts), WMH lesion load, CBF, infarcts and ventricular volume.
9) Studies which report p-values for all significant effects

2.2.2. Excluded studies

1) Non-human studies
2) Studies on unhealthy adults
3) Case studies
4) Non-English language articles

The list of shortlisted papers was then compared between the two authors, and any differences were resolved by discussion. When agreement was not obtained (n = 3 papers), a third analyst (SS) decided the relevance of the papers. Relevant papers were then independently assessed for quality, duplicates were removed, and the data was extracted for summary tables. Data extraction was carried out by using identical structured forms, which were subsequently compared to ensure consistency and accuracy in the information collected. Extracted data included study characteristics (e.g. first author, year of publication, study design, country of study), sample characteristics (e.g. sample size, participant's age and sex), diet intake assessment, brain imaging characteristics (e.g. neuroimaging technique and analysis, brain measure) and the reported findings (statistically significant results as indicated by $p < 0.05$, confound variables).

2.3. Quality assessment

Risk of bias was assessed by DEAJ and VL, using the Quality Assessment Tool for Observational Cohort and Cross-sectional Studies (NIH, 2008). This tool assesses several potential sources of bias in a study via 14 questions which assess the study design, eligibility of the study population, justification of the sample size, and validity and reliability of the study measures.Both researchers rated each included study to be of "good", "fair", or "poor" quality. Any discrepancies on the quality ratings of a study was resolved by discussions. Summary tables provide quality assessments and descriptive and inferential statistics from the research data.

2.4. Data synthesis

Results are summarised in four tables: (1) WM connectivity, (2) GM functional connectivity, (3) WM and GM volumes and (4) cerebrovascular physiology (WMH, ventricular volume, CBF, brain infarcts). Within each modality, studies are grouped according to the age category of participants, classed as young (20–35 years), middle-aged (36–55 years) and older adults (56 years and older).

2.5. MRI modalities

We examined MRI measurements of (1) WM connectivity, (2) GM functional connectivity, (3) WM and GM volume and (4) cerebrovascular physiology (WMH, ventricular volume, CBF and brain infarcts).

(1) WM connectivity: We focused on studies using DTI, which detects the directional diffusion of water in the brain. If the diffusion in a voxel is anisotropic, it follows more easily along the axons than perpendicular to them. The degree of anisotropy (FA), together with the magnitude of diffusion (MD), axial (AD) and radial diffusivity (RD) are used to estimate the microstructural integrity of fibre tracts. Brain regions showing high FA and low MD are assumed to contain well organized axon arrays and better myelin integrity. A decrease in FA along with an increase in diffusivity

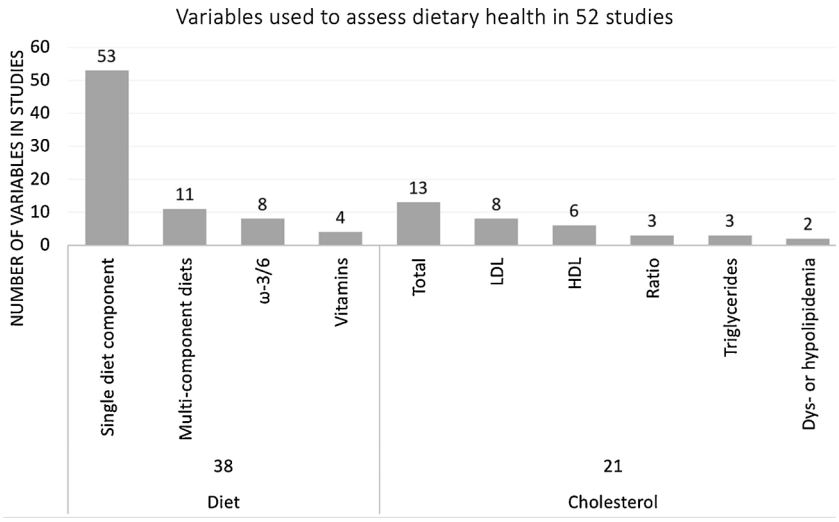

Fig. 1. Variables used to assess dietary health in a total of 52 articles. Some studies assessed multiple dietary markers.

(Sexton, 2014) is observed in normal ageing (Burzynska et al., 2010; Head, 2004; Yap, 2013) and to a greater extent in dementia (Suri et al., 2014). It can reflect dysfunctional properties of connecting axonal fibres and is related to disadvantages of cognitive processing (Johansen-Berg and Behrens, 2006).

(2) GM functional connectivity: We examined studies using resting-state-fMRI to probe GM functional connectivity. Functional connectivity generally decreases in cortical and limbic regions during ageing, and this is linked with cognitive decline (e.g. Kullmann, 2016). In patients with Alzheimer's disease, lower GM functional connectivity of the DMN is widely reported (Douaud et al., 2014; see Hafkemeijer et al., 2012 for a review).

(3) WM and GM volume: We examined studies using T1 MRI scans for assessing global and regional GM and WM volumes.

(4) Cerebrovascular physiology: Cerebrovascular correlates of DM markers were examined in studies using a range of MRI sequences: e.g. T2-weighted (T2) and fluid attenuated inversion recovery (FLAIR) scans for white matter hyperintensities (WMH), and arterial spin labelling (ASL) for cerebral blood flow. WMHs are indicators for altered interstitial fluid mobility and water content in the brain. WMHs usually increase with age (see Morris, 2009 for a review) and CBF declines with age (Arbab-Zadeh et al., 2004; Chen et al., 2001; Fujimoto et al., 2012). Both changes are also associated with cognitive impairments, increased risk of

Table 1
DM markers - white matter connectivity.

Study (Cohort if specified)	Sample size (% female)	Age, years (mean±SD)	Dietary marker	total WM	Brain WM Fibre Tracts: SLF	IFOF	ILF	UF	Cingulum bundle	CC + surrounding	splenium CC	genu CC	Forceps minor	Int./ext. capsule	Fornix	ATR	ACR	corona radiata	WM areas: frontal	temporal	parietal	occipital	subcortical areas	WM next to hippo	Follow-up (years)	Covariates *adjusted for other models
Cross-sectional studies																										
Mueller et al. 2011	49 (46.94%)	26.4±5.0	Leptin								↓AD ↓FA ↑RD	↓AD ↓FA ↑RD													-	Age
Booth et al. 2014 (Lothian Birth Cohort)	529 (47.9%)	72.7±0.7	Health-aware diet	↑FA																					-	Age, sex
Witte et al. 2014	65 (46.15%)	63.9±6.55	ω-3 (EPA and DHA)	↑FA ↓MD ↓RD	↑FA ↓MD ↓RD	↑FA ↓MD ↓RD		↑FA ↓MD ↓RD		↑FA ↓MD ↓RD						↑FA ↓MD ↓RD					↑FA ↓MD ↓RD				-	-
Williams et al. 2013 (BUADC)	125 (60.8%)	68.04±9.41	Chol.											↓FA				↓FA					↓FA		-	Age, sex
			Chol. HDL											↑FA		↓FA	↓FA			↓FA	↑FA	↑FA				
			Chol. LDL	↑AD ↑RD	↓FA	-	-	-	-	↓FA				↓FA	↓FA		↓FA	↓FA	↓FA	↓FA			↓FA			
			Chol. triglyceride									↓FA					↑FA	↑FA			↑FA		↓FA			
Longitudinal studies																										
Huhn et al. 2018	53 (52.85%)	68.08±4.99	Resveratrol (200 mg/day)																					MD-	0.5	Age, sex, Education
Witte et al. 2014	65 (46.15%)	63.9±6.55	ω-3 (EPA and DHA)		↑FA ↓RD	↑FA ↓MD ↓RD	↓RD	↑FA ↓RD				↓MD ↓RD													0.5	-
Mueller et al. 2015* (LIFE - overweight/obese)	16 (56%)	27.2±6.7	Chol. HDL							↑FA ↓RD													↑FA ↓RD	↑FA	0.25	-

Abbreviations: WM - white matter, SLF - superior longitudinal fasciculus, ILF - inferior-longitudinal fasciculus, IFOF - inferior-frontal occipital fasciculus, UF - uncinate fasciculus, CC - corpus callosum; ATR - anterior-temporal radiation; ACR - anterior corona radiata; hippo - hippocampus; FA - fractional anisotropy, MD - mean diffusivity, AD - axial diffusivity; RD - radial diffusivity, Chol. - cholesterol level; LDL - low-density lipoprotein, HDL - high-density lipoprotein, EPA - eicosapentaenoic acid, DHA - docosahexaenoic acid, BUADC - Boston University Alzheimer's Disease Center, LIFE - Leipzig Research Centre for Civilization Diseases.
Red text - interventional studies, black text - observational studies.
*intervention was not diet related.

	association not examined
	no significant association
	negative association of FA and/or positive association of diffusivity parameters
	positive association of FA and/or negative association of diffusivity parameters

Table 2
DM markers - functional connectivity.

Study (Cohort if specified)	Sample size (% female)	Age, years (mean±SD)	Dietary marker		networks	Follow-up (weeks)	Covariates *adjusted for other models
Observational cross-sectional studies							
Zwilling et al. 2019 (Illinois Brain Aging Study cohort)	116 (63%)	69±3.3	MUFA:SFA ratio & low Vit. E	↓	ventral attention	-	Age, sex, Education, BMI *
			Vit. B6	-	n.s.		
			Vit. A1 &B2	-	n.s.		
			Carotenoid	-	n.s.		
			Vit. B (riboflavin, folate, B12) & D	↓	DMN & frontal-parietal network		
			Carotene	↑	limbic network		
			Lycopene	↑	dorsal & executive function network		
			Lycopene x dorsal	↑	dorsal & executive function network		
Talukdar et al. 2018 (Illinois Brain Aging Study cohort)	96 (61%)	69±3	ω-3 PUFAs	↑	connected cluster peaks at: cingulate, precuneus, lateral occipital, primary visual cortex, amygdala, frontal pole, hippocampus.	-	Age, SES, Education, income, BMI, depressive symptoms
Zwilling et al. 2019 (Illinois Brain Aging Study cohort)	116 (63%)	69±3.2	ω-3 PUFAs	↑	visual network	-	Age, sex, Education, SES, BMI *
			ω-6 PUFAs	↑	motor & ventral network		
			ω-3/ω-6 mix	-	n.s.		
			ω-3 x frontal	↑	Fronto - parietal network		
			ω-6 x dorsal	↑	dorsal attention network		
Kharabian Masouleh et al. 2018 (LIFE-Adult-Study cohort)	616 (42%)	69±5	Chol.	-	n.s. of ICs	-	Age, sex, hypertension, diabetes, WMH, Education, depressive symptoms
			Chol. HDL	-	n.s. of ICs		
Spielberg et al. 2017	206 (10%)	32±8.7	Chol. LDL	↓	superior temporal sulcus	-	Age, sex, DSM-IV, alcohol intake, BMI, weight, BP, cardiometabolic syndrome, diabetes, smoking status, medication prescription, motion
Meusel et al. 2017	30 (53%)	72.2±5.7	Chol. LDL	↓	DMN	-	Age
			Framingham Offspring cohort risk score*	-	DMN		
Interventional longitudinal studies							
Prehn et al. 2016	37 (100%)	61±5	Caloric restriction	↓	hippocampal to parietal areas	16	-
Huhn et al. 2018	53 (52.85%)	68.08±4.99	Resveratrol (200 mg/day)	-	n.s.	26	Age, sex, Education
Witte et al. 2014	46 (39%)	64.25±6.05	Leptin (resveratrol intervention)	↓	hippocampal FC	26	Age, sex, BMI
Petrie et al. 2017	26 (51.85%)	65.42±5.3	Beetroot juice	↑	FC from somatosensory to insula & motor regions	6	Sex

Abbreviations: GM - grey matter, WM - white matter, DMN - default mode network, IC - intrinsic connectivity, FC - functional connectivity, MUFA - ratio of mono-unsaturated fatty acids, SFA - saturated fatty acids, PUFAs - Polyunsaturated fatty acids, Vit. - vitamin, BMI - body mass index, BP - blood pressure, Chol. - cholesterol level, LDL - low-density lipoprotein, HDL - high-density lipoprotein, HbA1c - glycated haemoglobin, ICN, intrinsic connectivity networks, VMHC, Voxel-mirrored Homotopic Connectivity, MDMR, multivariate distance-based matrix regression, BMI - body mass index, BP - blood pressure (systolic, diastolic), ICV - intracranial volume.
*cardiovascular risk profile, with total and HDL-Chol.

	no significant association
	negative association
	positive association

having a stroke and developing dementia (see Debette and Markus, 2010; Douaud et al., 2014; Ogoh, 2017).

3. Results

3.1. Study selection and dietary variables

Initial database searches revealed 2632 articles, and after reviewing the titles and abstracts a total of 52 studies met the inclusion criteria for this review (see Fig. A1). Results from 52 studies comprised 21,221 participants (54,74 % female). The risk of bias assessment revealed no quality risk of the 52 studies in the review; only twelve out of 52 studies had a 'fair' risk and no study met the criteria for 'poor', and therefore no study was rejected (see A3). The studies varied in their use of dietary markers, study designs, samples and analysis methodology. Some studies assessed multiple dietary markers. Dietary markers were measured by interventional, observational, cross-sectional, and longitudinal studies. From the total of 52 reviewed studies, only nine studies were interventional, focussing mainly on the effect of dietary supplements (Fig. 1). Other studies assessed single diet components (n = 53), ω-3 or 6 fatty acid (n = 8) or vitamins (n = 4), or dietary markers such as blood cholesterol (n = 21) but only a few studies (n = 11, see overview in Appendix 5.4) directly assessed complete dietary patterns using self-administered questionnaires.

3.2. White matter connectivity

Results from six studies including 837 participants (52 % female) addressed the relationship between dietary factors and WM connectivity. Four of those studies were cross-sectional and two were longitudinal studies with mean follow-up of 26 weeks. Most studies used region of interest or whole-brain regression analyses, including atlas-based and tract-based spatial statistics (Table 1).

Booth et al. (2014) showed that a health-aware diet (defined as a consumption of more fruits and less meat, eggs and spirits) was associated with improved global WM connectivity, i.e. higher FA. Further, higher serum leptin was associated with worse WM connectivity (Mueller, 2011). Witte et al. (2014a) reported higher global WM FA and lower diffusivity after higher intake of ω-3 fatty acid, including in tracts such as the superior longitudinal fasciculus (SLF), inferior-frontal occipital fasciculus (IFOF) and uncinate fasciculus (UF), corpus callosum (CC), anterior-temporal radiation (ATR) and parietal WM. In the longitudinal trial of the same study, a 26 week intervention of fish-oil (rich in ω-3 fatty acid, 4 capsules each contain 1320 mg eicosapentaenoic acid (EPA) and 880 mg docosahexaenoic acid (DHA)) intake was associated with increased WM connectivity in the SLF, IFOF and UF, and the inferior-longitudinal fasciculus (ILF) and forceps minor (Witte et al., 2014a). Although resveratrol intake was shown by Huhn et al., 2018 to be associated with various vascular health benefits, they found limited interventional evidence to link it to improvements in WM connectivity.

Two studies examined the association between cholesterol (total, HDL and LDL cholesterol, triglyceride) and different tracts in young (Mueller, 2015) and older adults (Williams, 2013). Williams, 2013 reported that higher total cholesterol, LDL cholesterol level and triglycerides were related to lower FA in various fibre tracts (see Table 1). Higher HDL cholesterol was also related to higher FA in the CC (Mueller,

Table 3
DM markers - WM volume.

Study (Cohort if specified)	Sample size (% female)	Age, years (mean±SD)	Dietary marker	TBV	WMV	WM areas: frontal lobe	WM areas: temporal lobe	WM areas: parietal lobe	WM areas: occipital lobe	Follow-up (years)	Covariates *adjusted for other models
Observational cross-sectional studies											
Chee et al. 2009 (Singapore Longitudinal Aging Brain Study)	284 (52.8%)	65.8±6.53	HCy		↓					-	Head-size
Gu et al. 2015 (WHICAP)	674 (67%)	80.1±5.6	MeDi (FFQ)		↑					-	Age, sex, Eth, Ed, BMI, diabetes, cognition *
Observational longitudinal studies											
Devore et al. 2013 (Rotterdam study cohort)	5395	66.2±7.3	Dietary FRAP score	↑	-					13.8	Age, Ed, ApoE4, total energy, smoking status, BMI, supplement use
Titova et al. 2013a (PIVUS cohort)	252 (48.41%)	70.1±0.1	ω-3 (EPA and DHA, FFQ)	-	-					5	Age, total energy, Ed, serum LDL, BMI, sys BP, homa-IR *
Haller et al. 2018 (sCON group)	52 (63.5%)	73.6±3.4	Caffeine		-	↓	-	↓	-	1.5	Age, sex, Ed, MMSE
			Chocolate		-	-	-	-	-		
			Wine		-	-	-	↑	-		
(Geneva and Lausanne)	145 (55.9%)	73.8±3.5	Wine (white)		↓	-	-	-	-		

	association not examined
	no significant association
	negative association
	positive association

Abbreviations: WMV - white matter volume, TBV - total brain volume, ATR - anterior thalamic radiation, HCy - homocysteine level; MeDi - Mediterranean diet; FFQ - Food Frequency questionnaire, EPA - eicosapentaenoic acid, DHA - docosahexaenoic acid, FRAP - ferric-reducing antioxidant power, BMI - body mass index, Eth - Ethnicity, Ed - Education, BMI - body mass index, WHICAP -Washington Heights/Hamilton Heights Inwood Columbia Aging Project, PIVUS - Prospective Investigation of the Vasculature in Uppsala Seniors, sCON - stable cognition.

2015), the internal/external capsule and parietal and occipital WM, but paradoxically lower FA in ACR, ATR and temporal WM (Williams, 2013). Williams, 2013 attributed this unexpected direction of FA to differences in the damaging effect of higher HDL cholesterol of anterior-temporal to parietal-occipital WM. Somewhat in agreement with Williams, 2013; Mueller, 2015 showed that participants with higher (good) HDL cholesterol show altered trans-callosal diffusivity of water molecules with lower RD in the CC (Mueller, 2015), whereas participants with higher (bad) LDL cholesterol show dysfunctional axonal properties with higher RD and AD in the total WM (Williams, 2013).

3.3. Grey matter functional connectivity

Results from nine studies comprising 1,226 participants (53 % female) addressed the relationship between dietary markers and grey matter functional connectivity (Table 2). Five studies were cross-sectional and four longitudinal, with a mean follow-up of 18.5 weeks. Most studies used independent component analyses or similar intrinsic connectivity network analyses; and we also describe studies using seed-based functional connectivity, node-based approaches, such as graph theory and network modularity, multivariate distance-based matrix regression and voxel-mirrored homotopic connectivity.

Studies on older adults showed an enhanced effect on the functional brain network organisation across different regions with beetroot juice intake (Petrie, 2017), higher lycopene (Zwilling et al., 2019), ω-3 (Talukdar et al., 2018; Zwilling et al., 2019) and ω-6 (Zwilling et al., 2019) level. Moreover, intervention with caloric-restricted diets (Prehn, 2016) and resveratrol supplementation (Huhn et al., 2018; Witte et al., 2014b) was associated with higher functional connectivity between the hippocampal subnuclei and the hippocampus and parietal areas. Further, a higher ratio of monounsaturated fatty acids to saturated fatty acids and higher levels of vitamin E and B was associated with lower functional connectivity in the DMN and attention networks (Zwilling et al., 2019). This indicates that lower concentration of these vitamins is associated with higher functional efficiency (Zwilling et al., 2019).

Higher LDL cholesterol was associated with lower functional connectivity in the DMN in old adults (Meusel, 2017) and in the superior temporal sulcus in young adults (Spielberg, 2017). Conversely, some studies have reported no associations between functional connectivity and the Framingham risk score (tracks the cardiovascular risk profile with total and HDL-cholesterol; Meusel, 2017) and with total or HDL-cholesterol (Kharabian Masouleh et al., 2018). The authors argue that this highlights the deleterious effect of LDL-cholesterol on brain health and the development of Alzheimer's disease pathology (discussed in Meusel, 2017; Reed, 2014), especially in areas which are also affected by cognitive decline during ageing (e.g. Douaud et al., 2014; Kharabian Masouleh et al., 2018). However, as only three studies examined cholesterol and brain connectivity, further work is warranted.

3.4. Volume

All examined studies used T1 MRI scans to assess brain volumes, however they used a variety of techniques: voxel-based morphometry (VBM), GM volumes (atrophy), region of interest analyses) including manual segmentation, FreeSurfer-based parcellations and tensor-based morphometry or whole-brain analyses. Nonetheless, the direction of the association between dietary markers and brain volumes appeared largely consistent across techniques (compare with Tables 3 and 4).

3.4.1. White matter volume

Results from five studies with 6,750 participants (56 % female) addressed the relationship between dietary markers and WM volume (Table 3). Two studies were cross-sectional and three were longitudinal with a mean follow-up time of 5.5 years across studies.

Gu, 2015 assessed the effect of the MeDi diet studied by using Food-Frequency questionnaires and showed that a healthier diet was related to larger WM volume. Further, Haller, 2018 reported that a higher intake of caffeine and white wine was associated with smaller total, frontal and parietal WM volumes, but paradoxically that higher total wine intake was associated with larger parietal WM volume (Haller, 2018). The positive impact of total wine intake compared to white wine suggests the positive antioxidant impact of red wine onto the brain, however further studies are needed to confirm this (see discussion 4.2 for details). Although the effect directions varied between these diet markers, the reduced total WM volume with higher white wine (and not total wine) intake is likely to be the more statistically robust association due to the larger sample size (n = 145 vs n = 52 in the subgroups; Haller, 2018, Table 3). Other studies have reported no associations between WM volume and ω-3 fatty acid or chocolate intake (Titova et al., 2013a) or the antioxidant-rich food intake (measured using the dietary ferric-reducing antioxidant power score; Devore, 2013).

Table 4
DM markers - grey matter volume.

Cross-sectional studies

Study (Cohort if specified)	Sample size (% female)	Age, years (mean±SD)	Dietary marker	GMV	TBV	Cortical: frontal lobe	Cortical: temporal lobe	Cortical: parietal lobe	Cortical: occipital lobe	Cortical: insular	Cortical: cingulate	Cortical: suppl. motor area	Cortical: Precuneus	Cortical: caudate gyrus	Subcortical: hippocampus / parahippocampus	Subcortical: Entorhinal cortex	Subcortical: thalamus	Subcortical: other subcortical regions	cerebellum	Covariates *adjusted for additional models
Mosconi et al. 2018	116 (62%)	50±6	MeDi			↑	↑				↑					↑		↑		Age, sex, ApoE
Booth et al. 2014 (Lothian Birth Cohort)	565 (47.9%)	72.7±0.7	Health-aware diet		↑															Age, sex
Luciano et al. 2017 (Lothian Birth Cohort)	562 (47.9%)	72.65±0.72	MeDi	-	-															Age, sex, Ed, BMI, diabetes, cognitive ability & MMSE
Gu et al. 2015 (WHICAP)	674 (67%)	80.1±5.6	MeDi (FFQ)	↑		↑	↑	↑			↑				↑					Age, sex, Ed, Eth, BMI, diabetes, mean cognition
Bowtell et al. 2017	26 (50%)	68.3±0.9	Blueberry supplementation (baseline)			↑	↑			↑	↑		↑				↑	↑		-
Gu et al. 2015 (WHICAP)	674 (67%)	80.1±5.6	Fish	↑											-					Age, sex, Ed, Eth, BMI, diabetes, mean cognition
Erickson et al. 2008	32 (59.37%)	68±6	Folate		-															-
Hooshmand et al. 2016	501 (59.88%)	70.9±9.1	Folate (baseline)		-															Age, sex*
Pase et al. 2017 (Framingham Offspring cohort)	4276 (54%)	54±11	Soft drink with sugar (0-3/week; >1/week)		-										-					Age, sex, Head-size, diabetes, energy intake, PA
			Sugary beverages (1-2/day or >2/day)		-		-								-					
			Fruit Juice (>_1/day)		↓										↓					
Gu et al. 2015 (WHICAP)	674 (67%)	80.1±5.6	Fruit	-		-	↓	-			-				↓					Age, sex, Ed, Eth, BMI, diabetes, mean cognition
Mosconi et al. 2018	116 (62%)	50±6	Insulin sensitivity			↑	↑				↑					↑				Age, sex, ApoE
			HCy			-	-				-					-				Age, sex, ApoE
Hooshmand et al. 2016	501 (59.88%)	70.9±9.1	HCy (baseline)		↓															Age, sex*
			Holotranscobalamin (baseline)		-															Age, sex*
Narita et al. 2009	34(44%)	64.5±4.8	Leptin plasma level				↑								↑ ↑*				↑	Age, sex, BMI, WMH, ICV, plasma leptin
Zamroziewicz et al. 2016	76 (67%)	69±3	Lutein				↑								↑*					sex, Ed, income, depressive symptoms, BMI
Hooshmand et al. 2016	501 (59.88%)	70.9±9.1	Sulphur amino acids (baseline)		-															Age, sex*
Gu et al. 2015 (WHICAP)	674 (67%)	80.1±5.6	Meat	↓	↓	↓	-	-			-				-					Age, sex, Ed, Eth, BMI, diabetes, mean cognition *
Berti et al. 2015	52 (71%)	54±11	Sat., trans-sat fats, Chol. & sodium	↓		↓					↓									Age, sex, Eth, Ed, total energy, BMI, alcohol, family history & APOE status *
			Vit. A, C, antioxidants & fibres	-																
			Vit. B & minerals	↑		↑														
			Vit. B12, D & zinc	↑		↑	↑													
Erickson et al. 2008	32 (59.37%)	68±6	Vit. B12					↑												-
			Vit. B6			↑	↑	↑			↑	↑						↑		Age, BMI, sex, total energy, Ed
Hooshmand et al. 2016	501 (59.88%)	70.9±9.1	Vit. B12 (baseline)		-															Age, sex*
Berti et al. 2015	52 (71%)	54±11	Vit. E and PUFA (monosat/polysat. fats, ω-3 & ω-6)	-																Age, sex, Eth, Ed, total energy, BMI, alcohol, family history & APOE status *
Zamroziewicz et al. 2016	100 (62%)	69±3	NBP 1 (product n-3 PUFAs)			-		-					-	-				-		Age, sex, Ed, BMI
			NBP 2 (precursors n-3 PUFAs)			-		↑ /-						-						
Koschack et al. 2009	69 (53.6%)	50±13	Chol -OH												↑					TBV, total Chol
			Chol.												-					TBV
			Chol. 24S-OH												↑					Age, TBV, ApoEe4
			Chol. 27-OH												-					
Gonzales et al. 2011	40 (43%)	50.7±6.3	Chol. /HDL ratio			↓		↓												Age, sex, cardiovascular risk
Ward et al. 2005 (WRAP)	114 (62.28%)	54.2±6.6	Chol.		-															A
Leritz et al. 2011 (HCPA)	115 (60.87%)	68.34±9.56	Chol.			↓	↓	↓			↓								↓	A
Hoogendam et al. 2012 (Rotterdam study cohort)	3962 (54.42%)	60.1±8.50	Chol.																↑	Age, sex, ICV
Mosconi et al. 2018	116 (62%)	50±6	Chol. HDL			-	-				-					-				Age, sex, ApoE
Hoogendam et al. 2012 (Rotterdam study cohort)	3962 (54.42%)	60.1±8.50	Chol. HDL																↑	Age, sex, ICV
Leritz et al. 2011 (HCPA)	115 (60.87%)	68.34±9.56	Chol. LDL			↓	↓	↓			↓								↓	A
Raz et al. 2012	144 (68%)	58.89±9.09	Chol. LDL																	Age, sex
Chung et al. 2018	802 (56%)	59.2±5.7	Chol. LDL (low)			↓					↓								↓	Age, sex, ICV, vas, lipids, med
			Chol. LDL x Hypertension								↓								↓	
Ottino-González et al. 2017	63 (57%)	31±6.15	Allostatic load: 15 biomarkers			↓	↓	↓	↓				↓							Age, Ed

Longitudinal cross-sectional studies

Study (Cohort if specified)	Sample size (% female)	Age, years (mean±SD)	Dietary marker	GMV	TBV	Cortical: frontal lobe	Cortical: temporal lobe	Cortical: parietal lobe	Cortical: occipital lobe	Cortical: insular	Cortical: cingulate	Cortical: Precuneus	Cortical: fusiform	Cortical: caudate gyrus	Subcortical: hippocampus / parahippocampus	Subcortical: other subcortical regions	cerebellum	Follow-up (years)	Covariates *adjusted for additional models
Akbaraly et al. 2018 (WHII)	459 (19.2%)	59.6±5.3	AHEI												↑			11	M1+ occupational grade, Eth, smo, PA, vas, BMI, antecedent of coronary heart diseases, hypertension, diabetes, dyslipidaemia
Boraxbekk et al. 2015	20 (100%)	61.3±1.6	Paleolithic diet												↓			0.5	-
Prehn et al. 2016	37 (100%)	61±5	Caloric restriction			↑									↑			0.29	-
Jacka et al. 2015 (PATH)	255 (46%)	62.6 ±1.42	FFQ: healthy 'prudent' dietary pattern												↑			4	Age, sex, Ed, SES, depressive symptoms, med, PA, smo, hypertension, diabetes
			FFQ: unhealthy "Western" dietary pattern												↓				
Devore et al. 2013 (Rotterdam study cohort)	5395	66.2±7.3	FRAP score	-	↑													13.8	Age, Ed, ApoE4, total energy, smo, BMI, supplements
Titova et al. 2013b (Uppsala Seniors cohort)	194 (48%)	70.1±0.01	MeDi (7-day)	-														5	sex, total energy, Ed, PA, LDL Chol, BMI, sys BP, HOMA-IR
Luciano et al. 2017 (Lothian Birth Cohort)	401 (47.9%)	72.65±0.72	MeDi	-	↑													3	Age, sex, other models: Ed, BMI, diabetes, cognitive ability, MMSE *
Del C Valdes Hernandez et al. 2017 (Lothian Birth Cohort)	189 (53.97%)	72±0.8	energy (KJ/day)												-		-	3	Age
Walhovd et al. 2014	92 (58.70%)	63.3±8.7	ω-3 DHA	-			↑											3.6±0.5	Age, sex
			ω-3 EPA	-			-												
Witte et al. 2014	65 (46.15%)	63.9±6.55	ω-3 (EPA and DHA)			↑	↑	↑							↑			0.5	-
Titova et al. 2013a (PIVUS cohort)	252 (48.41%)	70.1±0.1	ω-3 EPA-DHA	↑ /-	-													5	Age, total energy, Ed, serum LDL, BMI, sys BP, homa-IR *
Pottala et al. 2014 (Women's Health Initiative Memory Study cohort)	1111 (100%)	79.5±3.7	ω-3		↑										↑			8	Ed, environmental factors (i.e. smo, PA, alcohol, BMI), disease comorbidities (i.e., prior vas, diabetes, treated & untreated hypertension).
			ω-3 EPA		-														Age, ICV, Eth, Ed, med, time to MRI scan, clinical sites *
Mueller et al. 2015* (LIFE - overweight/obese)	16 (56%)	27.2±6.7	BDNF							↓					↓		↓	0.25	-
Bowtell et al. 2017	26 (50%)	68.3±0.9	Blueberry supplementation		-			↑	↑									0.25	-
Del C Valdes Hernandez et al. 2017 (Lothian Birth Cohort study)	700 (47.43%)	72±0.8	Dairy intake low												-		-	3	Age
	189 (53.97%)	72±0.8	Fat high												-		-		
			Sat. fats high												-		-		
			Proteins high												-		-		
Boraxbekk et al. 2015	20 (100%)	61.3±1.6	Fat low			↑	↓		↑	↓			↓		↓			0.5	-
Titova et al. 2013b (Uppsala Seniors cohort)	194 (48%)	70.1±0.01	Meat				↓	↓			↓	↓		↓	↓*	↓		5	Sex, total energy, Ed, PA, LDL Chol., BMI, sys BP, HOMA-IR
			Meat		↓*/ -													5	Age, sex, total energy, Ed, PA, LDL Chol., BMI, sys BP, HOMA-IR
Del C Valdes Hernandez et al. 2017 (Lothian Birth Cohort)	700 (47.43%)	72±0.8	Fish low												-		-	3	Age
Luciano et al. 2017 (Lothian Birth Cohort)	401 (47.9%)	72.65±0.72	Meat & fish	-	-													3	Age, sex, Ed, BMI, diabetes, cognitive ability, MMSE
Brickman et al. 2014	37 (58%)	57.72	Flavanol												↑			0.25	Sex
	19 (68%)	57	Flavanol-in high												↑				
	18 (78%)	58.5	Flavanol-in low												-				
Hooshmand et al. 2016	299 (59.9%)	70±8.6	Folate		-													6	Age, sex*
			HCy		↓														
			Holotranscobalamin		↓														
Del C Valdes Hernandez et al. 2017 (Lothian Birth Cohort)	700 (47.43%)	72±0.8	Iodine intake low												-		-	3	Age
Lindbergh et al. 2018	30 (53%)	72.43±6.48	Lutein & zeaxanthin supplement			↑					↑				-			1	Age *
Huhn et al. 2018	53 (52.85%)	68.08±4.99	Resveratrol (200 mg/day)												-			0.5	Age, sex, Ed
Del C Valdes Hernandez et al. 2017 (Lothian Birth Cohort)	189 (53.97%)	72±0.8	Sodium high												-		-	3	Age
Hooshmand et al. 2016	299 (59.9%)	70±8.6	Sulphur amino acids		-													6	Age, sex*
			Vit. B12		↓														
Mueller et al. 2015* (LIFE - overweight/obese)	16 (56%)	27.2±6.7	Chol. HDL							↓					↓		↓	0.25	-
Walhovd et al. 2014	92 (58.70%)	63.3±8.7	Chol.	↓														3.6±0.5	Age, sex
Del C Valdes Hernandez et al. 2017 (Lothian Birth Cohort)	189 (53.97%)	72±0.8	Chol.												-		-	3	Age
den Heijer et al. 2012	518 (50%)	73.5±7.9	Chol.												↓/*	↓/*		10.4±0.4	Age, sex*

Abbreviations: GMV - grey matter volume, TBV - total brain volume; str - structural, func - functional, func* - functional task fMRI, MeDi - Mediterranean diet, FFQ - Food Frequency questionnaire, AHEI - alternative health eating index, EPA - eicosapentaenoic acid, DHA - docosahexaenoic acid, HCy - homocysteine level, Vit. - vitamin, NBP - nutrient biomarker patterns, BMI - body mass index, BP - blood pressure, Chol. - cholesterol level, LDL - low-density lipoprotein, HDL - high-density lipoprotein; HbA1c - glycated haemoglobin, SES - sociodemographic, Eth - ethnicity, Ed - Education, H - health-related variables, Chol - Cholesterol level, smo -

smoking status, BMI - body mass index, BP - blood pressure (systolic, diastolic), ICV - intracranial volume, med - medications, PA - physical exercise, vas - cardiovascular disease.
red - interventional studies, black - observational studies.
*intervention was not diet related.

	association not examined
	no significant association
	negative association
	positive association

Table 5
DM markers - Cardiovascular markers.

Observational cross-sectional studies:

Study (Cohort if specified)	Sample size (% female)	Age, years (mean±SD)	Dietary marker	WMH	Ventricular	CBF	Brain Infarcts	Covariates: *adjusted for other models
Booth et al. 2014 (Lothian Birth Cohort)	565 (47.9%)	72.7±0.7	Health-aware diet	-				Age, sex
King et al. 2014	2011 (58.3%)	67.94±10.44	Sum of BMI, diabetes, BP & glucose	↑				Sex, Ethnicity, ICV
Pase et al. 2017 (Framingham Offspring Cohort)	4276 (54%)	54±11	Fruit Juice (>_1/day)	-			-	Age, sex, Head-size *
			Soft drink with sugar (0-3/week)	-			↑*	Age, sex, Head-size, systolic BP, treatment for hypertension, smo, vas, atrial fibrillation, left ventricular hypertrophy, Chol, HDL Chol, diabetes, CESD scores ≥16 & WHR) *
			Soft drink with sugar (>3/week)	↑*			-	
			Sugary beverages (1-2/day)	-			-	
			Sugary beverages (>2/day)	↑/-*			-	
Raz et al. 2012	144 (68%)	58.89±9.09	HCy x age	↑				Age, sex
Chee et al. 2009 (Singapore Longitudinal Aging Brain Study)	284 (52.8%)	65.8±6.53	HCy		↑			Head-size
Hooshmand et al. 2016	501 (59.88%)	70.9±9.1	HCy	-				Age, sex*
Suwa et al. 2015	286 (43.71%)	68.12±5.52	ω-3 to 6 ratio (DHA/AA<0.84)	-				-
			low ω-3 to 6 ratio (EPA/AA<0.38)	↑				
Hooshmand et al. 2016	501 (59.88%)	70.9±9.1	Vit. B12	-				Age, sex*
			Folate	-				
			Sulphur amino acids	-				
			Holotranscobalamin	-				
Raz et al. 2012	144 (68%)	58.89±9.09	Chol. triglyceride			↓		Age, sex
Chung et al. 2018	802 (56%)	59.2±5.7	Chol. LDL x Hypertension	↑				Age, sex, ICV, vas, level of other circulatory lipids & hypertensive/lipid lower. med
Birdsill et al. 2013 (WRAP)	29 (55.2%)	62.6±5.8	Chol. LDL low			-		Age
Chee et al. 2009 (Singapore Longitudinal Aging Brain Study)	284 (52.8%)	65.8 ±6.53	Chol.		-			Head-size
Suwa et al. 2015	286 (43.71%)	68.12±5.52	Dyslipidaemia	-				-

Observational longitudinal studies:

Study (Cohort if specified)	Sample size (% female)	Age, years (mean±SD)	Dietary marker	WMH	Ventricular volume	Brain Infarcts	Follow-up (years)	Covariates: *adjusted for other models
Del C Valdes Hernandez et al. 2017 (Lothian Birth Cohort)	700 (47.43%)	72±0.8	Low Oily fish	-	↑		3	Age
			Low Iodine intake	-	↑			
			Iodine intake & supplements	-	↑			
			Low All dairy	-	↑			
			Low fish products	↑	-			
(Lothian Birth Cohort - extreme/middle iodine intake/ avoidance)	189 (53.97%)	72±0.8	Energy (KJ/day)	-	↑			
			High fat	↑	↑			
			High proteins	↑	↑			
			High saturated fats	↑	↑			
			High sodium	↑	↑			
Hooshmand et al. 2016	299 (59.9%)	70±8.6	Vit. B12	-			6	Age, sex*
			Folate	-				
			Sulphur amino acids	-				
			HCy	-				
			Holotranscobalamin	-				
Willey et al. 2014	1282 (61%)	64.0±8.4	Chol. (Baseline)	-		-	6.2	Age, time from baseline to MRI, sex, Ethnicity, Education, smoking status, hypertension, diabetes, BMI, alcohol intake, PE, eGFR, apoE, Chol, drugs *
			Chol. HDL (Baseline)	-		-		
			Chol. HDL higher risk	↑		-		
			Chol. LDL (Baseline)	-		-		
			Chol. total higher risk	↑		-		
			Chol. triglycerides (Baseline)	-		-		
Del C Valdes Hernandez et al. 2017 (Lothian Birth Cohort - extreme/middle iodine intake/ avoidance)	189 (53.97%)	72±0.8	Chol.	-	↑		3	Age
Dickie et al. 2016 (Lothian Birth Cohort)	439 (45%)	76.4±0.64	Chol. (Baseline)	-			3	Sex, vas, BMI
			Chol. / HDL ratio low	↑				
			Hyperlipidaemia	-				

	association not examined
	no significant association
	negative association
	positive association

Abbreviations: WMH - white matter hyperintensity, CBF - cerebral blood flow, HCy - homocysteine level; Vit. - vitamin, Chol. - cholesterol level, LDL - low-density lipoprotein, HDL - high-density lipoprotein, EPA - eicosapentaenoic acid, DHA - docosahexaenoic acid, AA – arachidonic acid, SES - sociodemographic, BMI - body mass index, BP - blood pressure (systolic, diastolic), vas - vascular risk factors/disease history.

No associations were found between cholesterol and WM volume.

3.4.2. Grey matter volume

Results from 36 studies comprising 15,874 participants (58.79 % female) addressed the relationship between dietary markers and GM volume (Table 4). 17 of those studies were cross-sectional and 19 were longitudinal with a mean follow-up time of 4,23 years across studies, whereas seven were diet interventional studies.

In older (Boraxbekk et al., 2015; Gu, 2015; Luciano, 2017; Prehn, 2016) and middle-age adults (Mosconi, 2018), a 'healthier' diet was consistently related to higher GM volume. Several composite dietary scores were associated with higher total brain volume, total GM volume, and the volumes of hippocampus, cingulate gyrus, entorhinal cortex, frontal, temporal and parietal lobe. This includes a higher score on the MeDi scale (Gu, 2015; Luciano, 2017; Mosconi, 2018; Titova et al., 2013b), the Alternative Health Eating Index-2010 (AHEI-2010; Akbaraly et al., 2018), higher scores in the healthy 'prudent' diet and lower scores in the unhealthy 'Western' diet scales (Jacka et al., 2015), lower scores in the Palaeolithic diet (Boraxbekk et al., 2015), as well as caloric restriction scales (Prehn, 2016).

Other individual diet markers, such as higher fish intake (Gu, 2015), vitamins (vitamin B, E, A, C, antioxidants and fibres; Berti et al., 2015; Devore, 2013; Erickson et al., 2008; blueberry supplementation: Bowtell et al., 2017), ω-3 or 6 fatty acids (Berti et al., 2015; Pottala, 2014; Walhovd, 2014; Witte et al., 2014a; Titova et al., 2013a), folate (Erickson et al., 2008), leptin (Narita, 2009), flavanol (Brickman et al., 2014) and lutein intake (Lindbergh, 2018; Zamroziewicz, 2016) were associated with larger GM volume across the brain, but primarily in the hippocampus and often also including the temporal lobe (in 10 out of 14 studies).

In contrast, higher intake of some individual diet markers, such as fruit (Gu, 2015), fruit juice (Pase, 2017), saturated fats, trans-sat fats and sodium (Berti et al., 2015), fat fatty acids (Boraxbekk et al., 2015), meat (Gu, 2015; Titova et al., 2013b), higher homocysteine level (Hooshmand, 2016) and brain-derived neurotrophic factor (Mueller, 2015) have been associated with smaller GM volume. While it was surprising that higher fruit consumption was associated with lower GM volume, it can be argued that this might be driven by the high fruit sugar (fructose)

Table 6
General trends observed in the diet-brain relationship. We have discussed the few inconsistencies for each of these relationships, however these are the overall directions of associations across the 52 reviewed studies.

Main Exposures:	**GM volume** *(Main ROIs: temporal, frontal and parietal lobe, cingulate and entorhinal cortex, hippocampus)*	**WM volume** *Main ROIs: temporal and frontal WM*	**GM functional connectivity** *Main ROIs: DMN, sensorimotor and attention network*	**WM connectivity** *Main ROIs: SLF, ILF, CC and IFOF*	**Cerebro-vascular markers** *Main ROIS: WMH, ventricular volume, CBF, infarcts*
Caloric restriction or low energy intake					
Health-aware, AHEI or MeDi diet					
Western or paleo diet					
High ω□3 polyunsaturated fatty acid level					
High fruit juice consumption					
Antioxidant-rich food					
High meat, saturated fat, sugar, caffeine or alcohol consumption (except red wine)					
High total or LDL or low HDL cholesterol level					

Correlations:

Poor MRI indicators of brain health (lower brain volume, lower functional connectivity, higher FA and/or lower RD, higher ventricular volume, WMH and infarcts and lower CBF)

Healthier brain MRI outcomes (opposite pattern to above)

not significant

not tested

Abbreviations: GM - grey matter, WM - white matter, WMH - white matter hyperintensity, CBF - cerebral blood flow, DMN - default mode network, SLF - superior longitudinal fasciculus, ILF - inferior-longitudinal fasciculus, IFOF - inferior-frontal occipital fasciculus, FA - fractional anisotropy, RD - radial diffusivity, AHEI - alternative health eating index, MeDi - Mediterranean diet, LDL - low-density lipoprotein, HDL - high-density lipoprotein.

intake. However, the result of Gu, 2015 is contradictory to other studies on multi-dimensional diets which showed that higher fruit intake is associated with larger GM volume (Akbaraly et al., 2018; Mosconi, 2018; Luciano, 2017; Jacka et al., 2015; Booth et al., 2014, see detailed information in Appendix 5.4).

Notably, the FFQ in Pase, 2017 did not account for added sugar in fruit juice, though regardless of added sugar all juice contains high amounts of fructose, which is on average more than the daily recommended allowance per 200 mL serving (Boulton et al., 2016). To exacerbate this fruit juices contain negligible levels of fibre, which is suggested to be beneficial for brain function (Martin, 2000). Studies have also reported no significant associations of GM volume with sugary beverages, resveratrol intake (Huhn et al., 2018) and combined meat and fish (Luciano, 2017).

Moreover, in young (Mueller, 2015), middle-aged (Gonzales, 2011; Koschack et al., 2009) and older adults (Chung et al., 2018; den Heijer et al., 2012; Hoogendam, 2012; Leritz, 2011; Walhovd, 2014), lower total cholesterol (Hoogendam, 2012; Koschack et al., 2009; Leritz, 2011), higher LDL cholesterol (Chung et al., 2018; Leritz, 2011) or lower HDL cholesterol level (Mueller, 2015; Hoogendam, 2012) and lower total to HDL cholesterol ratio (Gonzales, 2011) were associated with smaller total GM volume (Walhovd, 2014), larger volumes in the frontal (Chung et al., 2018; Gonzales, 2011; Leritz, 2011), parietal (Chung et al., 2018; Gonzales, 2011; Leritz, 2011) and temporal lobe (Leritz, 2011), the hippocampus (den Heijer et al., 2012; Koschack et al., 2009; Mueller, 2015), other subcortical areas (Chung et al., 2018; den Heijer et al., 2012; Leritz, 2011), the cerebellum (Hoogendam, 2012; Mueller, 2015), insula (Mueller, 2015) and cingulate gyrus (Chung et al., 2018; Leritz, 2011). However, the directions of associations observed in the cerebellum shown in Mueller, 2015 and Hoogendam, 2012 were inconsistent, which could be due to their discrepant methodologies. MRI analyses were conducted using VBM (Mueller, 2015) and FreeSurfer (Hoogendam, 2012), but only the latter study used covariates such as age, sex and ICV in their statistical analyses.

Taken together, while these studies varied in how they assessed diet (e.g. composite scores or individual dietary components) and regional GM volume, a traditionally 'healthier' diet rich in vegetables, vitamins, antioxidants, ω-3 polyunsaturated fatty acids or fish intake, was most consistently linked to larger GM volumes across ages, whereas diets high in saturated and trans fats, proteins and meat were associated with smaller GM volumes. Moreover, while a few studies have reported no significant association between GM volume and total cholesterol (Del C Valdes Hernandez et al., 2017; Ward, 2005), LDL cholesterol (Raz et al., 2012) or HDL cholesterol level (Mosconi, 2018), the majority of the evidence (5 out of 9 cross-sectional and 2 out of 3 longitudinal studies) suggested that higher levels of "bad" cholesterol (total and LDL) relate to smaller total and regional GM volumes.

3.5. Cerebrovascular markers

Twelve cross-sectional and four longitudinal studies with a mean follow-up time of 5 years across studies assessed cerebrovascular correlates of diet markers, with a combined sample of 10,315 participants (56 % female). Overall, worse dietary health in most (but not all) studies were generally associated with poor measures of cerebrovascular health such as higher occurrence of white matter hyperintensities and infarcts, larger ventricular volume and hypoperfusion (Table 5).

In six cross-sectional studies, higher WMH was correlated with markers of poor DM health, such as high LDL cholesterol, high beverage (>2/day) or sugary soft drinks intake (>3/day) and low ω-3 to ω-6 ratio (Chung et al., 2018; Debette et al., 2010, Debette, 2014; King et al., 2014; Pase, 2017; Suwa, 2015). A similar trend was shown in three longitudinal studies, where higher WMH was associated with lower fish intake, more fats, proteins, saturated fats and sodium (Del C Valdes Hernandez et al., 2017), higher homocysteine level (Raz et al., 2012), higher total and HDL cholesterol (Willey et al., 2014), lower total to HDL cholesterol ratio (Dickie et al., 2016). Sugary soft drink consumption was also linked to a higher percentage of brain infarcts (Pase, 2017), whereas Willey et al. (2014) found no longitudinal association between cholesterol level and brain infarcts.

Some dietary patterns (higher homocysteine level, low dairy consumption, oily fish and iodine, higher total caloric intake (kcal/day), fats, proteins, sodium and total cholesterol) were also linked with larger ventricular volumes in one cross-sectional (Chee et al., 2009) and one longitudinal study (Del C Valdes Hernandez et al., 2017). Although relationships with CBF have been far less studied, higher triglyceride cholesterol level (Raz et al., 2012) and lower metabolic syndrome (Birdsill et al., 2013) were associated with lower CBF, measured using arterial spin labelling.

However, some studies also found no association between WMH and intake of fruit juice (Pase, 2017), different vitamins and micronutrients (Hooshmand, 2016), a health-aware diet (Booth et al., 2014), intake of iodine or the total caloric intake (in kcal/day; Del C Valdes Hernandez et al., 2017), and cholesterol level at baseline (total, HDL and LDL cholesterol level, dys- and hyperlipidaemia; Del C Valdes Hernandez et al., 2017; Dickie et al., 2016; Suwa, 2015; Willey et al., 2014). Similarly, studies also report no associations between CBF and LDL cholesterol (Birdsill et al., 2013). Despite these discrepancies, the majority of reviewed studies have linked cerebrovascular abnormalities with at least one 'unhealthy' dietary marker.

4. Discussion

4.1. Diet, metabolism and brain atrophy

Most of the articles discussed in this review suggest that diets high in meat, refined carbohydrates (including sugary beverages), saturated fats, processed foods, protein, caffeine and alcohol (as well as wine intake) such as the Western and the Paleo diet are related to poorer indicators of brain structure. Higher total and LDL cholesterol levels, but lower HDL cholesterol levels are also related to worse brain health. On the other hand, caloric restriction, diets such as a health-aware diet or the MeDi, diets rich in fruits and vegetables, ω-3 fatty acids and antioxidants, and low in meat, eggs and spirits are related to better brain health indicated by larger brain volumes, more efficient connectivity and better cerebrovascular health, although there are contrasting trends for each of these associations (Table 6).

In the following sections, we discuss the physiological mechanisms that may underpin the diet-brain relationship and delve into the inconsistencies between study methodologies and findings. We conclude with a recommendation for dietary choices and discuss future research.

4.2. Physiological mechanisms underlying the association of poor DM markers with worse brain health outcomes

Our review observes that poor dietary markers were largely associated with measures of poor cerebral health. While the specific physiological mechanism for this link is not well understood, evidence suggests that cholesterol impairs the supply of oxygen-rich blood in the brain via the accumulation of plaques in arteries. This can lead to neuronal health deficits such as cerebral hypoperfusion, damage to the blood brain barrier, oxidative stress, and the occurrence of ischemic insults (see Schmahmann, 2003 for more information). Unhealthy dietary markers can also produce a loss of neuronal homeostasis (Shalev and Arbuckle, 2017), an increase in neuroinflammation (Swarbrick, 2014), and can ultimately lead to neuronal dysfunction or death. Neuroinflammation has a negative influence on axonal health and myelination and can be indirectly gauged by lower FA and higher radial diffusivity in WM. We observed this association between lower FA and higher LDL and lower HDL across several studies in this review.

On the other hand, we also observed that caloric restriction, a health-aware diet, higher score of the AHEI-2010 and the MeDi were related to

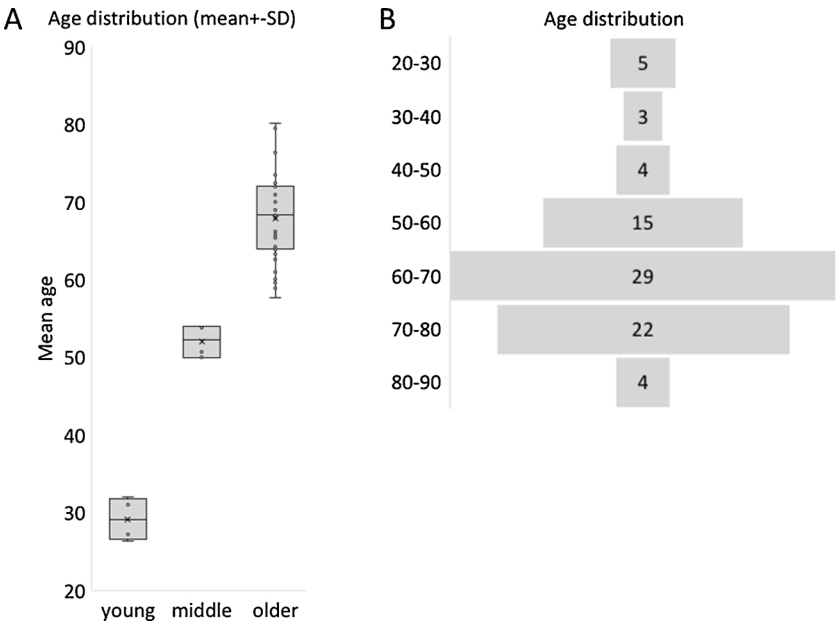

Fig. 2. Age distribution in the reviewed samples of 52 articles. **A** shows the mean age and standard deviation (SD) of young (20–35 years), middle (36–55 years) and older adults (56 years and older). **B** shows the age distribution in quantiles considering the age range of each study. Some studies assessed multiple age quantiles.

lower levels of brain atrophy. Lower caloric intake (kcal), higher ω-3 fatty acid and antioxidant-rich food showed a relationship with better fibre integrity and functional connectivity, suggesting that ω-3 fatty acids might buffer age-related declines in these brain markers. Further support for nutritional interventions comes from the studies which investigated antioxidant nutrients such as lycopene, lutein and polyphenol (e.g. included in red wine and blueberries), vitamin E and C and the dietary ferric-reducing antioxidant power score (Devore, 2013), all of which had a positive impact on brain health. Those antioxidative nutrients act protectively against free radicals, thereby protecting the brain from oxidative damage.

Ultimately, the diet-brain relationship can impact cognition and memory. For example, unhealthy diets (Boraxbekk et al., 2015), and higher LDL cholesterol level (Meusel, 2017) have been related to deficits in cognitive performance (Kharabian Masouleh et al., 2018; Zamroziewicz, 2016) such as working memory performance (Boraxbekk et al., 2015; Meusel, 2017; Witte et al., 2014b), attention (Kohn, 2016), and episodic memory performance (Boraxbekk et al., 2015; Kharabian Masouleh et al., 2018; Prehn, 2016). Conversely, in the reviewed studies, the beneficial effects of polyunsaturated fatty acids were observed in regions that support executive function (prefrontal cortex), memory (hippocampus), and emotion (amygdala; Talukdar et al., 2018). Previous research also confirms the relationship between antioxidant nutrient intake and better attention and executive function (Vauzour, 2017; Zwilling et al., 2019), improved cognition (e.g. Bajerska et al., 2014; Martínez-Lapiscina, 2013; Wengreen, 2013; Ye, 2013) and decreased risk for mild cognitive impairment (MCI) and dementia (Galbete, 2015; Morris, 2015; Psaltopoulou, 2013; Scarmeas et al., 2006a, b; Trichopoulou, 2015), and progressing from MCI to Alzheimer's dementia (Singh, 2014).

Thus, given the negative effects of inflammation and oxidative stress on brain health, preventing these responses through a healthy diet rich in antioxidant, anti-inflammatory factors could conceivably be a preventive nutritional strategy for healthy brain and cognitive ageing. Moreover, this review suggests that even though high LDL cholesterol is discussed as the main risk factor for heart disease and stroke (American Heart Association), both high LDL and low HDL cholesterol could be used as proxy markers for an unhealthy diet-brain relationship.

In summary, we observed support for the following dietary health recommendations in order to maintain brain connectivity:

- maintain healthy total and LDL cholesterol
- follow certain diets such as a 'health-aware' (Booth et al., 2014; Jacka et al., 2015) or a MeDi diet
- include a balanced intake of different vitamins and micronutrients with the higher consumption of fruit and vegetables (each four-five servings per day), fish, antioxidative nutrients such as lycopene, lutein and polyphenol (e.g. included in red wine and blueberries), seeds, nuts, whole grains and vitamin E and C, adequate vitamin B, B12 and minerals levels and the low consumption of meat, refined carbohydrates/sugar (including sugary beverages), saturated and trans fats, processed foods, and alcohol, reducing the total caloric intake (kcal/day), increase ω-3 fatty acids and have a lower ω-3 to ω-6 ratio.

This recommendation is in accordance with the Memory Nutrition Program in the USA (Emerson-Lombardo et al., 2006; Wolf, 2012) and the American Heart Association, but in this review, we have summarised additional evidence for their beneficial effects on brain structure, connectivity and function.

4.3. *Inconsistencies/bias in findings related to methodology*

We identified variations in measurement techniques, MRI analysis methods, and confounding covariates which may have influenced study outcomes.

4.3.1. *MRI analysis and acquisition bias*

Although the reviewed results from volume and connectivity analyses are mostly consistent across techniques (see e.g. 3.4), it is important to note that different analysis techniques can introduce substantial bias. Several of our reviewed studies only used region of interest or cluster peak region analyses which can underestimate the influence of other brain regions or networks. This is not the case for VBM or whole-brain network studies, which examine global effects and their interactions. MRI studies also generally suffer from a 'healthy participant' bias, such that participants in this study were not at the extremes of the health spectrum (e.g. all reviewed studies excluded extremely obese participants due to the bore size of the MRI scanner). This may have influenced the true scale of the effect of dietary health on brain ageing.

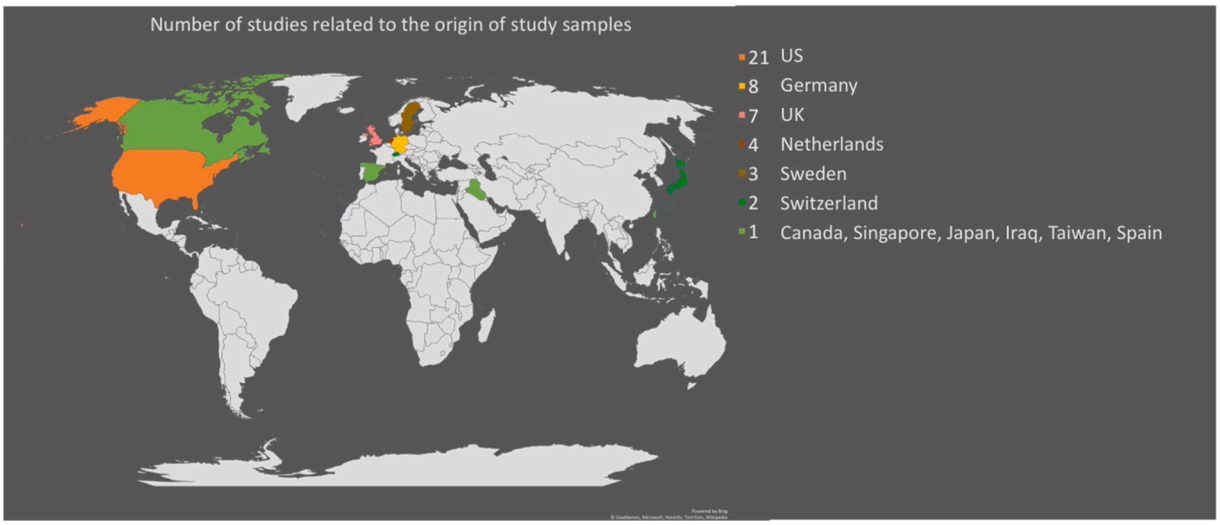

Fig. 3. Origin of samples in the studies examined in this review and covered samples sizes. The figure shows the number of studies in each country/region in the world. The sample size of each country in percent in relation to the whole reviewed sample is for the US - 52.6%, Germany: 4.5 %, UK: 5.7 %, Netherlands: 25.4 %, Sweden: 3 %, Switzerland: 1.5 %, Canada: 0.1 %, Singapore: 1.3 %, Japan: 1.5 %, Iraq: 1 %, Taiwan: 3.8 % and Spain: 0.3 %.

4.3.2. The role of age and sex: Findings from young, middle- and older aged adults

Across all reviewed studies, most findings about the relationship between DM and brain markers were consistent across age groups, but the majority of studies investigated associations only in older adults (see Fig. 2, 45 studies). Thus, conclusions about middle-aged (six studies) or young adults (four studies) have to be drawn with caution. We therefore recommend that future studies focus on younger age ranges, as early dietary interventions may stand to offer long-term benefits on brain and cognitive health. Some studies have shown an interaction of age with a higher summary score of unhealthy DM markers including higher BMI, BP, glucose and diabetes; King et al., 2014) and total plasma homocysteine (Raz et al., 2012) which was associated with more WMH. No reviewed study assessed the interaction between age and unhealthy diet markers on brain volumes and connections.

The evidence suggests that anatomical or hormonal differences between men and women may influence the effect of obesity on brain volume and connectivity (Mueller, 2011, discussed by Boccardi et al., 2006; den Heijer et al., 2003). In this review, some studies failed to report the sex distribution of the sample, and a few studies on caloric restriction (Prehn, 2016) and palaeolithic diet (Boraxbekk et al., 2015) were conducted only on a female sample, thus, results cannot necessarily be generalized to the entire population without further research on gender balanced samples. Nonetheless, some of the reviewed studies which were conducted on solely female samples (Boraxbekk et al., 2015; Pottala, 2014; Prehn, 2016) showed similar diet - brain associations as studies on mixed sex samples. Moreover, while most studies used sex as a covariate in their analyses (see Willette and Kapogiannis, 2015 for a review), only one study performed a sex stratified analysis (Kohn, 2016). Thus, additional studies are needed to elucidate potential sex differences in the diet - brain relationship.

4.3.3. Sociodemographic and socioeconomic bias

Environmental factors such as food availability and quality differ across countries and could affect the brain ageing process (in Bamshad, 2005; Chee et al., 2009; Kirkwood, 2005). In this review, 49.3 % of individuals from 44 studies were from North America, of which the large majority was from the US. 40.5 % of participants came from Europe and only 9.8 % from Asia (Fig. 3). Three studies controlled their analyses for the ethnicity of the participants (Akbaraly et al., 2018; Berti et al., 2015; Gu, 2015), but only two of these studies examined the diet - brain relationship in multiple (more than two) ethnic groups, including White, African American and Hispanic participants (Berti et al., 2015; Gu, 2015). No reviewed sample was acquired in South America, Africa or Australia which could bias the conclusions from this review (Fig. 3). In general, there was insufficient data to estimate differences between countries in terms of existing diet - brain associations. For instance, the same diet marker such as the MeDi diet could be assessed differently across the world due to different dietary habits: lower intake of legumes in the Swedish population (Titova et al., 2013b) compared to the US population may explain the significant result of Gu, 2015 compared to Titova et al. (2013a). Future research on brain health should especially be acquired in Asian countries, as the most rapidly growing ageing population in the world (Chee et al., 2009).

The literature suggests that socioeconomic and lifestyle factors such as income (Sattler et al., 2012), education (Stern et al., 1992), and exercise (Radak, 2010; Scarmeas, 2009) covary with obesity, and are risk factors for cognitive decline or neurodegeneration (discussed in Ronan, 2016). Although some studies in this review used participants' socioeconomic status (e.g. status in society, income, socio-demographic information) as covariates (Berti et al., 2015; Gu, 2015; Haller, 2018; Jacka et al., 2015, 2015; Luciano, 2017; Pottala, 2014), most studies failed to include socioeconomic variables. Thus, it is difficult to draw conclusions about whether the diet - brain associations described here were driven, at least in part, by socioeconomic status and geography.

4.3.4. Other relevant brain areas

We noticed a relative lack of studies reporting relationships with diet in subcortical regions of the brain. This is surprising given the large body of animal work highlighting the importance of subcortical structures, such as the hypothalamus, in relation to feeding behaviour (Kolber et al., 2008; Ongur and Price, 2000). In humans, the hypothalamus coordinates the activity in the gut and integrates visceral functions through the hypothalamic-pituitary axis and is connected with limbic-system structures such as the hippocampus, the amygdala and the cerebral cortex. Investigating subcortical rather than cortical brain regions is often hindered by a lower signal-to-noise ratio and the need for a higher spatial resolution. However, these challenges can be overcome with optimized pulse MRI sequence and appropriate preprocessing steps. Future studies should consider the importance of subcortical structures in association with diet markers.

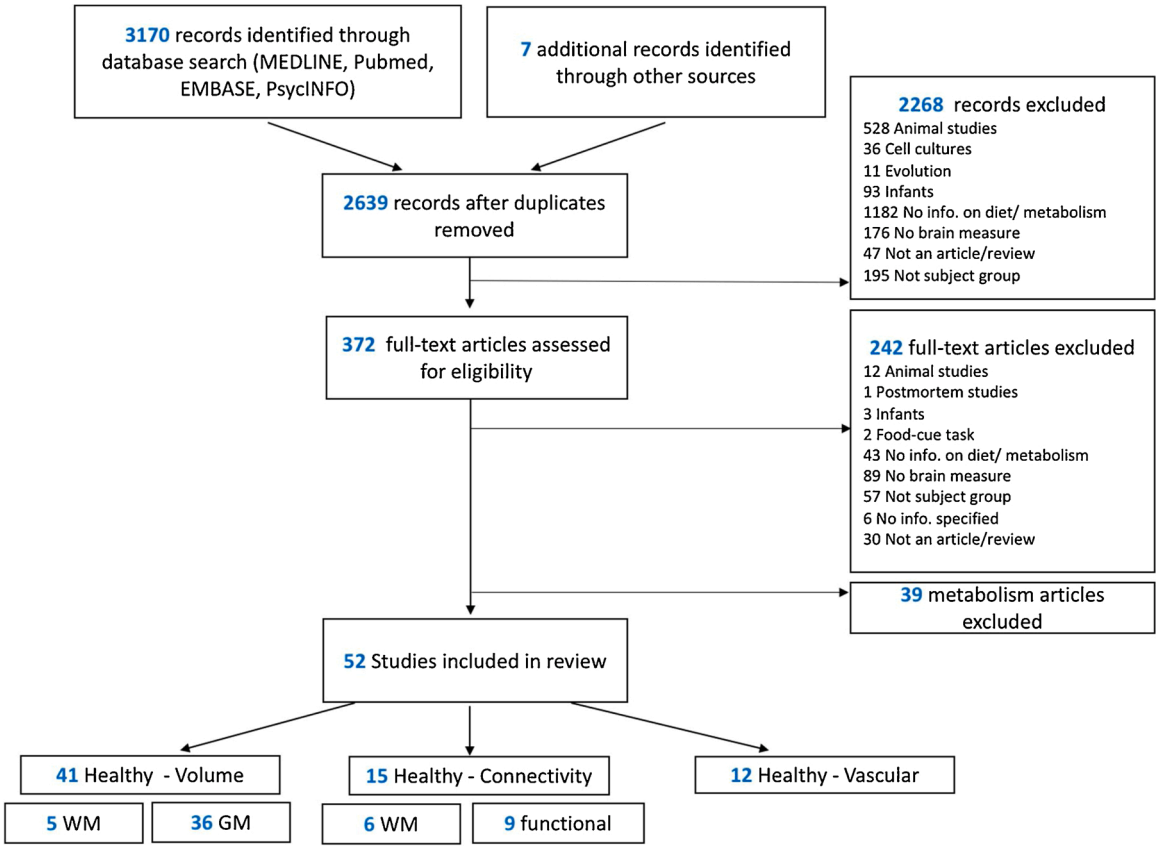

Fig. A1. Study identification and selection process.

5. Conclusion

We reviewed studies investigating a range of dietary markers such as vitamins, ω-3, ω-6, intake of fruits, proteins, Mediterranean diet etc. and metabolic markers, such as cholesterol, glucose and blood pressure. The review offers support for an association between lower dietary quality and reduced brain volume and connectivity, especially of the default-mode network and the frontal and temporal lobes. Specifically, associations between 'healthy' diet markers and larger GM volume were found in the frontal, temporal, parietal, cingulate and entorhinal cortex and the hippocampus. Other studies found a relationship between frontal and temporal WM volume and 'healthy' diets. The influence of diet markers on functional connectivity was especially pronounced in the DMN and the sensorimotor and attention networks. WM connectivity was only examined by a few studies, but consistent associations were shown for the SLF and ILF, the CC and IFOF. Further, there was comparatively little research on subcortical structures, despite their importance in relevant animal work (e.g. hippocampus: information processing, memory; hypothalamus: homeostasis, feeding behaviour).

This systematic review concludes that a wide range of regional brain measures are associated with diet markers, however there are inconsistencies in research methods and results on how specific diets affect brain connectivity and volume. Future studies establishing the effect of complete diet measures for the brain are needed. We also discussed the importance of considering the relationship between age, sex and socioeconomic and demographic markers and diet factors and the need for longitudinal and more interventional studies to assess the influence of confounding variables on the diet - brain associations.

Funding

DEAJ is supported by HDH Wills 1965 Charitable Trust (1117747). SS is supported by an Alzheimer's Society Research Fellowship (Grant Ref: 441) and the Academy of Medical Sciences/the Wellcome Trust/the Government Department of Business, Energy and Industrial Strategy/ the British Heart Foundation/Diabetes UK Springboard Award (Grant Ref: SBF006\1078). Work on this study was supported by the UK National Institute of Health Research (NIHR)Oxford Health Biomedical Research Centre (BRC). The Wellcome Centre for Integrative Neuroimaging (WIN) is supported by core funding from the Wellcome Trust (203139/Z/16/Z). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. KPE was supported by UK Medical Research Council Grants G1001354 and MR/K013351/1, the HDH Wills 1965 Charitable Trust (1117747), and the EU Horizon 2020 Programme "Lifebrain" (Grant No. 732592).

Declaration of Competing Interest

The authors declare no competing financial interests.

Acknowledgments

DEAJ conducted the meta-analysis and wrote the manuscript. SS supervised the work and reviewed the manuscript. DEAJ and VL independently scored the study quality. All authors edited the manuscript. We would like to thank the study authors who kindly provided additional information about their studies.

Appendicx A

A1 : Search terms for MEDLINE and Ovidsp (Embase and PsycINFO)

1) diet*.mp OR food.mp OR nutritio*.mp OR cholesterol.nm OR lipid.nm OR vitamin*.nm OR carbohydrate.nm OR amino acids.mp
2) ageing.mp OR aging.mp
3) 1 and 2
4) exp magnetic resonance imaging/ OR exp brain/ OR brain connectivity.mp OR brain network.mp OR functional connectivity.mp OR structural connectivity.mp OR diffusion tensor imaging.mp OR resting state fMRI.mp
5) 3 and 4
6) limit 5 to (english language and humans and (journal article or letter))
7) NOT review articles

A2 : Study identification and selection process

A3 : Results of the quality assessment in 52 studies

Study/Authors	Risk of bias (DEAJ and VL)
Akbaraly et al. (2018)	good
Berti et al. (2015)	good
Birdsill et al. (2013)	good
Booth et al. (2014)	fair
Boraxbekk et al. (2015)	good
Bowtell et al. (2017)	good
Brickman et al. (2014)	good
Chee et al., 2009	good
Chung et al., 2018	good
den Heijer et al., 2012	good
Devore, 2013	good
Dickie et al. (2016)	good
Erickson et al. (2008)	good
Gonzales, 2011	fair
Gu, 2015	good
Haller, 2018	fair
Del C Valdes Hernandez et al. (2017)	fair
Hoogendam, 2012	good
Hooshmand, 2016	good
Huhn et al., 2018	good
Jacka et al. (2015)	good
Kharabian Masouleh et al. (2018)	good
King et al. (2014)	good
Koschack et al. (2009)	good
Leritz, 2011	fair
Lindbergh, 2018	good
Luciano, 2017	good
Meusel, 2017	fair
Mosconi, 2018	fair
Mueller, 2011	good
Mueller, 2015	good
Narita, 2009	fair
Ottino-González, 2017	fair
Pase, 2017	good
Petrie, 2017	good
Pottala, 2014	good
Prehn, 2016	fair
Raz et al. (2012)	good
Spielberg, 2017	good
Suwa, 2015	fair
Talukdar et al. (2018)	good
Titova et al. (2013a)	good
Titova et al. (2013b)	good
Walhovd, 2014	good
Ward, 2005	fair
Willey et al. (2014)	good
Williams, 2013	good
Witte et al. (2014b)	good
Witte et al. (2014a)	good
Zamroziewicz, 2016	good
Zamroziewicz et al. (2018)	good
Zwilling et al. (2019)	good

A4 : Assessed multi-component diets (11 diets in n = 10 studies)

Mediterranean diet (MeDi) score was studied in four articles (Gu, 2015; Luciano, 2017; Mosconi, 2014; Titova et al., 2013b) by obtaining dietary information of each individual using FFQs. In all reviewed studies, the MeDi score was calculated for each participant by summing the scores of different food components. An assigned value of 0 or 1 was used for each component, using caloric-adjusted sex-specific medians as cut-offs. Further, exclusions were made for incomplete data and extreme energy intakes. Thus, for beneficial components, scores at or above the median were assigned a value of 1, whereas for detrimental components, scores at or above the median were given a value of 0. A higher MeDi score indicated closer adherence to the MeDi. In all of those studies, a higher MeDi score indicated a diet rich in fruits and vegetables, legumes, cereals, fish and higher ratio of monounsaturated fats to saturated fats, and low in meat and dairy products. Notably, while a moderate amount of alcohol intake is a characteristic component of the MeDi, the threshold for moderate alcohol intake varied across studies slightly. Further, the food components, the number of items in the FFQ and length of the acquisition period differed across the four studies in this review (Gu, 2015; Luciano, 2017; Mosconi, 2014; Titova et al., 2013b).

In Gu, 2015 the MeDi score (ranging 0–9) was obtained using nine food components which were calculated for each participant based on a 61-item FFQ over a period of a year. A value of 1 was assigned for the six beneficial components (including fruits, vegetables, legumes, cereals, fish and the ratio of monounsaturated fats to saturated fats) and a value of 0 was assigned for the two components presumed to be detrimental (such as meat, dairy products). Further, mild to moderate alcohol consumption (0–30 g/day) was assigned a value of 1.

In Mosconi, 2014 the MeDi score (ranging 0–9) was obtained using a 61-item FFQ over a period of four months. The MeDi score was calculated equal to Gu, 2015, whereas the thresholds for mild to moderate alcohol consumption was specified with >0 drinks per week and <2 drinks per day in the previous year.

In Luciano, 2017 information from 168-item four-day weighted FFQ was used to obtain the MeDi score (ranging 0–9) in each individual based on components equal to (Gu, 2015). Moderate alcohol consumption was a positively scored component. It was defined as between 10 and 50 g alcohol per day for men and between 5 and 25 g per day for women.

In Titova et al. (2013b) the MeDi score (ranging 0–8) was obtained using a 7-day dietary registration containing about 1500 food items, drinks, and recipes. The score included beneficial (vegetables, legumes, fruits and **nuts**, cereal, fish and ratio of monounsaturated lipids to saturated lipids) and detrimental (meat, **poultry**, and dairy products) components and moderate alcohol intake with 10–50 g/day for males and 5–25 g/day for females, respectively. Because Titova et al. (2013b)'s study was in a Swedish population compared to the Greek population in Trichopoulou et al. (2003), some modification in the scores were made:

In this score, polyunsaturated fatty acids replaced monounsaturated fatty acids when estimating dietary fat quality since in a traditional Swedish diet saturated and monounsaturated fats have similar food origins. In addition, because of their very low intake, nuts and seeds were excluded, and dietary leguminous plants were pooled with vegetables in our score.

The reported intake of potatoes was added to cereals, because potato consumption contributes considerably to carbohydrate intake in the Swedish population of older adults.

The **AHEI-2010** in Akbaraly et al. (2018) was performed 3 times over 11 years of follow-up (1991–1993 and 2003–2004). AHEI-2010 assessment is based on 11 components, including six beneficial components (vegetables, fruit, whole grains, nuts and legumes, long chain omega-3 fats, and polyunsaturated fatty acids) and four components for which avoidance or lowest intake are supposed to be ideal (sugar-sweetened drinks and fruit juice, red and processed meat, trans fat, and sodium). In the original score in Chiuve et al., 2012, moderate alcohol intake was considered to be ideal (similar to the MeDi score); however, for brain related outcomes, the latest evidence supports to recommend avoidance or low consumption of alcohol rather than moderate consumption (Opie, 2017; Topiwala, 2015).

The **health-aware diet** in Booth et al. (2014) was defined as a consumption of more fruits and less meat, eggs and spirits. This was measured using a component score derived in Mõttus, 2013 based on responses to a 9-point FFQ (ranging from rarely or never to seven or more times per day) which contained a list of 168 foods and drinks, grouped under major food groups.

Jacka et al. (2015) distinguished between the **unhealthy "Western" dietary pattern and the healthy 'prudent' dietary** pattern. Both are orthogonal diet factors which were established from the FFQ. Higher scores represented greater levels of consumption. The "prudent" (healthy) diet was characterized by the consumption of fresh vegetables, salad, fruit and grilled fish. In contrast, the "Western" (unhealthy) diet was characterized by the consumption of roast meat, sausages, hamburgers, steak, chips, crisps and soft drinks.

The diet intervention of the paleolithic **diet with Nordic Nutrition Recommendations (PD + NNR)** in Boraxbekk et al. (2015) was assessed using four-day self-reported food records at baseline and at 6 months. The energy intake in PD consisted of 30 % protein, 40 % fat and 30 % carbohydrates. Recommended was a high intake of mono- and polyunsaturated fatty acids, lean meat, fish, fruit, vegetables, root vegetables, eggs, and nuts (see Mellberg, 2014). The NNR diet was aiming for an energy intake of 10 % protein, 25–30 % fat, and 55-60 % carbohydrates, mainly in low-fat dairy and high-fibre products. Different to other multi-components diet, Boraxbekk et al. (2015)'s study included an intervention with eight meetings between a dietician and the participants during the first six months of the study, where participants got information about dietary effects on health, how to change behaviour, and group discussions. Further, both diets were ad libitum without any restrictions in total calorie intake.

King et al. (2014) assessed diet as a **summary score** of different diet and metabolic variables. Those included BMI, diabetes mellitus, BP and serum glucose (fasting, or non-fasting glucose).

The **total caloric intake or energy intake** was measured in kcal/day in Del C Valdes Hernandez et al. (2017).

References

Akbaraly, T., Sexton, C., Zsoldos, E., Mahmood, A., Filippini, N., Kerleau, C., Michel Verdier, J., Virtanen, M., Gabelle, A., Ebmeier P., K., Kivimaki, Mika, 2018. Association of long-term diet quality with hippocampal volume: longitudinal cohort study. Am. J. Med. https://www.sciencedirect.com/science/article/pii/S0002934318306430.

Arbab-Zadeh, A., Dijk, E., Prasad, A., Fu, Q., Torres, P., Zhang, R., James D., T., Palmer, D., Levine D., B., 2004. Effect of aging and physical activity on left ventricular compliance. Circulation 110 (13), 1799–1805.

Bajerska, J., Woźniewicz, M., Suwalska, A., Jeszka, J., 2014. Eating patterns are associated with cognitive function in the elderly at risk of metabolic syndrome from rural areas. Eur. Rev. Med. Pharmacol. Sci. 18 (21), 3234–3245.

Bamshad, M., 2005. Genetic influences on health: does race matter? J. Am. Med. Assoc. 294 (8), 937–946.

Barberger-Gateau, P., Letenneur, L., Deschamps, V., Pérès, K., François Dartigues, J., Renaud, S., 2002. Fish, meat, and risk of dementia: cohort study. Br. Med. J. 325 (7370), 932–933.

Berti, V., Murray, J., Davis, M., Spector, N., Tsui, W.H., Li, Y., Williams, S., Pirraglia, E., Vallabhajosula, S., McHugh, P., Pupi, A., de Leon, M.J., Mosconi, L., 2015. Nutrient

patterns and brain biomarkers of Alzheimer's disease in cognitively normal individuals. J. Nutr. Health Aging 19 (4), 413–423.
Beydoun, M.A., Beydoun, H.A., Wang, Y., 2008. 9 Obesity Reviews *Obesity and Central Obesity as Risk Factors for Incident Dementia and Its Subtypes: a Systematic Review and Meta-analysis*. Obesity Reviews, pp. 204–218.
Birdsill, A.C., Carlsson, C.M., Willette, A.A., Okonkwo, O.C., Johnson, S.C., Xu, G., Oh, J. M., Gallagher, C.L., Koscik, R.L., Jonaitis, E.M., Hermann, B.P., LaRue, A., Rowley, H.A., Asthana, S., Sager, M.A., Bendlin, B.B., 2013. Low cerebral blood flow is associated with lower memory function in metabolic syndrome. Obesity (Silver Spring) 21 (7), 1313–1320.
Boccardi, M., Ghidoni, R., Govoni, S., Testa, C., Benussi, L., Bonetti, M., Binetti, G., Frisoni, G.B., 2006. Effects of hormone therapy on brain morphology of healthy postmenopausal women: A Voxel-based morphometry study. Menopause 13 (4), 584–591. https://doi.org/10.1097/01.gme.0000196811.88505.10, 10723714.
Booth, T., Möttus, R., Corley, J., Gow, A.J., Henderson, R.D., Maniega, S.M., Murray, C., Royle, N.A., Sprooten, E., Valdés Hernández, M.C., Bastin, M.E., Penke, L., Starr, J. M., Wardlaw, J.M., Deary, I.J., 2014. Personality, Health, and Brain Integrity: The Lothian Birth Cohort Study 1936. Health Psychol. 33 (12), 1477–1486.
Boraxbekk, C.-J., Stomby, A., Ryberg, M., Lindahl, B., Larsson, C., Nyberg, L., Olsson, T., 2015. Diet-induced weight loss alters functional brain responses during an episodic memory task. Obes. Facts 8 (4), 261–272.
Boulton, J., Hashem, K.M., Jenner, K.H., Lloyd-Williams, F., Bromley, H., Capewell, S., 2016. How much sugar is hidden in drinks marketed to children? A survey of fruit juices, juice drinks and smoothies. BMJ Open 6 (3), 1–5.
Bowtell, J.L., Aboo-Bakkar, Z., Conway, M.E., Adlam, A.-L.R., Fulford, J., 2017. Enhanced task-related brain activation and resting perfusion in healthy older adults after chronic blueberry supplementation. Appl. Physiol. Nutr. Metab. 42 (7), 773–779.
Brickman, A.M., Khan, U.A., Provenzano, F.A., Yeung, L.-K., Suzuki, W., Schroeter, H., Wall, M., Sloan, R.P., Small, S.A., 2014. Enhancing dentate Gyrus function with dietary flavanols improves cognition in older adults. Nat. Neurosci. 17 (12), 1798–1803.
Burzynska, A.Z.Z., Preuschhof, C., Bäckman, L., Nyberg, L., Li, S.-C.C., Lindenberger, U., Heekeren, H.R.R., 2010. Age-related differences in white matter microstructure: region-specific patterns of diffusivity. NeuroImage 49 (3), 2104–2112.
Castro-Diehl, C., Wood, A.C., Redline, S., Reid, M., Johnson, D.A., Maras, J.E., Jacobs, D. R., Shea, S., Crawford, A., St-Onge, M.P., 2018. Mediterranean diet pattern and sleep duration and insomnia symptoms in the multi-ethnic study of atherosclerosis. Sleep 41 (11). https://pubmed.ncbi.nlm.nih.gov/30137563/.
Chee, M.W.L., Chen, K.H.M., Zheng, H., Chan, K.P.L., Isaac, V., Sim, S.K.Y., Chuah, L.Y. M., Schuchinsky, M., Fischl, B., Ng, T.P., 2009. Cognitive function and brain structure correlations in healthy elderly east asians. NeuroImage 46 (1), 257–269.
Chen, C.H., Fetics, B., Nevo, E., Rochitte, C.E., Chiou, K.R., Ding, P.Y.A., Kawaguchi, M., Kass, D.A., 2001. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J. Am. Coll. Cardiol. 38 (7), 2028–2034.
Debette, S., et al., 2014. Abdominal obesity and lower gray matter volume: a Mendelian randomization study. Neurobiol. Aging 35 (2), 378–386.
Debette, S., Beiser, A., Hoffmann, U., DeCarli, C., O'Donnell, C.J., Massaro, J.M., Au, R., Himali, J.J., Wolf, P.A., Fox, C.S., Seshadri, S., 2010. Visceral fat is associated with lower brain volume in healthy middle-aged adults. Ann. Neurol. 68 (2) n/a-n/a.
Debette, S., Markus, H.S., 2010. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis, 341 BMJ (Online). BMJ. https://pubmed.ncbi.nlm.nih.gov/20660506/.
Chiuve, S.E., Fung, T.T., Rimm, E.B., Hu, F.B., McCullough, M.L., Wang, M., Stampfer, M. J., Willett, W.C., 2012. Alternative dietary indices both strongly predict risk of chronic disease. J. Nutr. 142 (6), 1009–1018.
Chung, C.-P., Chou, K.-H., Peng, L.-N., Liu, L.-K., Lee, W.-J., Chen, L.-K., Lin, C.-P., Wang, P.-N., 2018. Associations between low circulatory low-density lipoprotein cholesterol level and brain health in non-stroke non-demented subjects. NeuroImage 181, 627–634.
Del C Valdes Hernandez, M., Armitage, P.A., Thrippleton, M.J., Chappell, F., Sandeman, E., Munoz Maniega, S., Shuler, K., Wardlaw, J.M., 2017. Dietary iodine exposure and brain structures and cognition in older people. Exploratory analysis in the Lothian birth cohort 1936. J. Nutr. Health Aging 21 (9), 971–979.
den Heijer, T., Skoog, I., Oudkerk, M., de Leeuw, F.-E., de Groot, J.C., Hofman, A., Breteler, M., 2003. Association between blood pressure levels over time and brain atrophy in the elderly. MB Neurobiology of aging 24 (2), 307–313. https://doi.org/10.1001/archneur.60.2.213, 0197-4580.
den Heijer, T., van der Lijn, F., Ikram, A., Koudstaal, P.J., van der Lugt, A., Krestin, G.P., Vrooman, H.A., Hofman, A., Niessen, W.J., Breteler, M.M.B., 2012. Vascular risk factors, apolipoprotein E, and hippocampal decline on magnetic resonance imaging over a 10-year follow-up. Alzheimer's Dement. 8 (5), 417–425.
Devore, E.E., Feskens, E., Ikram, M.A., den Heijer, T., Vernooij, M., van der Lijn, F., Hofman, A., Niessen, W.J., 2013. Total Antioxidant Capacity of the Diet and Major Neurologic Outcomes in Older Adults. Neurology 80 (10), 904–910.
Devore, E.E., Grodstein, F., Van Rooij, F.J.A., Hofman, A., Stampfer, M.J., Witteman, J.C. M., Breteler, M.M.B., 2010. Dietary antioxidants and long-term risk of dementia. Arch. Neurol. 67 (7), 819–825.
Dickie, D.A., Ritchie, S.J., Cox, S.R., Sakka, E., Royle, N.A., Aribisala, B.S., del C. Valdés Hernández, M., Maniega, S.M., Pattie, A., Corley, J., Starr, J.M., Bastin, M.E., Deary, I.J., Wardlaw, J.M., 2016. Vascular risk factors and progression of white matter hyperintensities in the Lothian birth cohort 1936. Neurobiol. Aging 42, 116–123.
Douaud, G., Groves, A.R., Tamnes, C.K., Westlye, L.T., Duff, E.P., Engvig, A., Walhovd, K. B., James, A., Gass, A., Monsch, A.U., Matthews, P.M., Fjell, A.M., Smith, S.M., Johansen-Berg, H., 2014. A common brain network links development, aging, and vulnerability to disease. Proc. Natl. Acad. Sci. U. S. A. 111 (49), 17648–17653.
Emerson-Lombardo, N.B., Volicer, L., Martin, A., Wu, B., Zhang, X.W., 2006. Memory Preservation DietTM to Reduce Risk and Slow Progression of Alzheimer's Disease. Serdi Publishing Company. https://nyuscholars.nyu.edu/en/publications/memory-preservation-diettm-to-reduce-risk-and-slow-progression-of.
Engelhart, M.J., Geerlings, M.I., Ruitenberg, A., Van Swieten, J.C., Hofman, A., Witteman, J.C.M., Breteler, M.M.B., 2002. Dietary intake of antioxidants and risk of Alzheimer disease. J. Am. Med. Assoc. 287 (24), 3223–3229.
Erickson, K.I., Colcombe, S.J., Elavsky, S., McAuley, E., Korol, D.L., Scalf, P.E., Kramer, A.F., 2008. Greater intake of vitamins B6 and B12 spares gray matter in healthy elderly: a voxel-based morphometry study. Brain Res. 1199, 20–26.
Fan, Y., Wang, H., Liu, X., Zhang, J., L, G., 2019. Crosstalk Between the Ketogenic Diet and Epilepsy: From the Perspective of Gut Microbiota, 2019 Mediators of Inflammation. Hindawi Limited.
Francis M., H., Stevenson J., R., 2018. Potential for diet to prevent and remediate cognitive deficits in neurological disorders. Nutrition Reviews 76 (3), 204–217. https://doi.org/10.1093/nutrit/nux073.
Fujimoto, N., Hastings, J., Bhella, P., Shibata, S., Gandhi, N.K., Carrick-Ranson, G., Palmer, D., Levine, B.D., 2012. Effect of ageing on left ventricular compliance and distensibility in healthy sedentary humans. J. Physiol. 590 (8), 1871–1880.
Galbete, C., Toledo, E., Toledo, J.B., Bes-Rastrollo, M., Buil-Cosiales, P., Marti, A., Guillén-Grima, F., Martínez-González, M.A., 2015. Mediterranean diet and cognitive function: the sun project. J. Nutr. Health Aging 19 (3), 305–312.
Gangwisch, J.E., Hale, L., St-Onge, M.P., Choi, L., Leblanc, E.S., Malaspina, D., Opler, M. G., Shadyab, A.H., Shikany, J.M., Snetselaar, L., Zaslavsky, O., Lane, D., 2020. High glycemic index and glycemic load diets as risk factors for insomnia: analyses from the women's health initiative. Am. J. Clin. Nutr. 111 (2), 429–439.
Gardener, H., Scarmeas, N., Gu, Y., Boden-Albala, B., Elkind, M.S.V., Sacco, R.L., DeCarli, C., Wright, C.B., 2012. Mediterranean diet and white matter hyperintensity volume in the Northern Manhattan study. Arch. Neurol. 69 (2), 251–256.
Gentreau, M., Chuy, V., Féart, C., Samieri, C., Ritchie, K., Raymond, M., Berticat, C., Artero, S., 2020. Refined carbohydrate-rich diet is associated with long-term risk of dementia and Alzheimer's disease in apolipoprotein e E4 allele carriers. Alzheimer's Dement. 16 (7), 1043–1053.
Gonzales, M.M., Tarumi, T., Eagan, D.E., Tanaka, H., Biney, F.O., Haley, A.P., 2011. Current serum lipoprotein levels and FMRI response to working memory in Midlife. Dement. Geriatr. Cogn. Disord. 31 (4), 259–267.
Gu, Y., Brickman, A.M., Stern, Y., Habeck, C.G., Razlighi, Q.R., Luchsinger, J.A., Manly, J.J., Schupf, N., Mayeux, R., Scarmeas, N., 2015. 'Mediterranean Diet and Brain Structure in a Multiethnic Elderly Cohort' ed. Brickman Anastasiou Bowman Brickman, Dale, Dickerson, Dyall, Fischl, Fischl, Gardener, Gu, Gu, Jack, Luchsinger, Luchsinger, Manly, Mattsson, McKhann, Mosconi, Pacheco, Perrone, Petersen, Raji, Scarmeas, Segonne, Segonne, Sled, Smith, Sofi, Stern, Taka, Annweiler. Neurology 85 (20), 1744–1751.
Hafkemeijer, A., Grond, J., Rombouts, S.A.R.B., 2012. 1822 Biochimica et Biophysica Acta - Molecular Basis of Disease *Imaging the Default Mode Network in Aging and Dementia*. Biochim. Biophys. Acta. https://pubmed.ncbi.nlm.nih.gov/21807094/.
Haller, S., Montandon, M.-L., Rodriguez, C., Herrmann, F.R., Giannakopoulos, P., 2018. Impact of coffee, wine, and chocolate consumption on cognitive outcome and MRI parameters in old age. Nutrients 10 (10).
Head, D., Buckner, R.L., Shimony, J.S., Williams, L.E., Akbudak, E., Conturo, T.E., McAvoy, M., Morris, J.C., Snyder, A.Z., 2004. Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the alzheimer type: evidence from diffusion tensor imaging. Cerebral Cortex (New York, N.Y.: 1991) 14 (4), 410–423.
Hoogendam, Y.Y., van der Geest, J.N., van der Lijn, F., van der Lugt, A., Niessen, W.J., Krestin, G.P., Hofman, A., Vernooij, M.W., Breteler, M.M.B., Ikram, M.A., 2012. Determinants of cerebellar and cerebral volume in the general elderly population. Neurobiol. Aging 33 (12), 2774–2781.
Hooshmand, B., Mangialasche, F., Kalpouzos, G., Solomon, A., Kareholt, I., Smith, A.D., Refsum, H., Wang, R., Muhlmann, M., Ertl-Wagner, B., Laukka, E.J., Backman, L., Fratiglioni, L., Kivipelto, M., 2016. Association of vitamin B12, folate, and sulfur amino acids with brain magnetic resonance imaging measures in older adults: a longitudinal population-based study. JAMA Psychiatry 73 (6), 606–613.
Hueston, C.M., Cryan, J.F., Nolan, Y.M., 2017. Stress and adolescent hippocampal neurogenesis: diet and exercise as cognitive modulators. Transl. Psychiatry 7 (4), e1081–17.
Huffman, J., Kossoff, E.H., 2006. 6 Current Neurology and Neuroscience Reports *State of the Ketogenic Diet(s) in Epilepsy*. Springer. https://link.springer.com/article/10.1007/s11910-006-0027-6.
Huhn, S., Beyer, F., Zhang, R., Lampe, L., Grothe, J., Kratzsch, J., Willenberg, A., Breitfeld, J., Kovacs, P., Stumvoll, M., Trampel, R., Bazin, P.-L., Villringer, A., Witte, V.A., 2018. Effects of resveratrol on memory performance, hippocampus connectivity and microstructure in older adults – A randomized controlled trial. NeuroImage 174, 177–190.
Jacka, F.N., Cherbuin, N., Anstey, K.J., Sachdev, P., Butterworth, P., 2015. Western diet is associated with a smaller Hippocampus: a longitudinal investigation. BMC Med. 13 (1), 215.
Johansen-Berg, H., Behrens E. J., T., 2006. Just pretty pictures? What diffusion tractography can add in clinical neuroscience. Current Opinion in Neurology 19 (4), 379–385. https://doi.org/10.1097/01.wco.0000236618.82086.01, 1350-7540.
Kalmijn, S., Launer, L.J., Ott, A., Witteman, J.C.M., Hofman, A., Breteler, M.M.B., 1997a. Dietary fat intake and the risk of incident dementia in the Rotterdam study. Ann. Neurol. 42 (5), 776–782.

Kalmijn, S., Feskens, E.J.M., Launer, L.J., Kromhout, D., 1997b. Polyunsaturated Fatty Acids, Antioxidants, and Cognitive Function in Very Old Men. American Journal of Epidemiology 145 (1), 33–41.
Kharabian Masouleh, S., Beyer, F., Lampe, L., Loeffler, M., Luck, T., Riedel-Heller, S.G., Schroeter, M.L., Stumvoll, M., Villringer, A., Witte, V.A., 2018. Gray matter structural networks are associated with cardiovascular risk factors in healthy older adults. J. Cerebral Blood Flow Metab. 38 (2), 360–372.
King, K.S., Peshock, R.M., Rossetti, H.C., McColl, R.W., Ayers, C.R., Hulsey, K.M., Das, S. R., 2014. Effect of normal aging versus hypertension, abnormal body mass index, and diabetes mellitus on white matter hyperintensity volume. Stroke 45 (1), 255–257.
Kirkwood, T.B.L., 2005. 120 Cell *Understanding the Odd Science of Aging*. Cell Press. https://pubmed.ncbi.nlm.nih.gov/15734677/.
Kivipelto, M., Ngandu, T., Fratiglioni, L., Viitanen, M., Kaareholt, I., Winblad, B., Helkala, E.L., Tuomilehto, J., Soininen, H., Nissinen, A., 2005. Obesity and vascular risk factors at Midlife and the risk of dementia and Alzheimer disease. Archives of Neurology 62 (10), 1556–1560.
Kohn, N., Wassenberg, A., Toygar, T., Kellermann, T., Weidenfeld, C., Berthold-Losleben, M., Chechko, N., Orfanos, S., Vocke, S., Laoutidis, Z.G., Schneider, F., Karges, W., Habel, U., 2016. Prolonged fasting impairs neural reactivity to visual stimulation. Brain Struct. Funct. 221 (1), 147–158.
Kolber, B.J., Wieczorek, L., Muglia, L.J., 2008. Hypothalamic-pituitary-Adrenal Axis dysregulation and behavioral analysis of mouse mutants with altered glucocorticoid or mineralocorticoid receptor function. Stress (Amsterdam, Netherlands) 11 (5), 321–338.
Koschack, J., Lütjohann, D., Schmidt-Samoa, C., Irle, E., 2009. Serum 24S-Hydroxycholesterol and hippocampal size in middle-aged normal individuals. Neurobiol. Aging 30 (6), 898–902.
Kullmann, S., Callaghan, M.F., Heni, M., Weiskopf, N., Scheffler, K., Häring, H.-U., Fritsche, A., Veit, R., Preissl, H., 2016. Specific white matter tissue microstructure changes associated with obesity. NeuroImage 125, 36–44.
Leritz, E.C., Salat, D.H., Williams, V.J., Schnyer, D.M., Rudolph, J.L., Lipsitz, L., Fischl, B., McGlinchey, R.E., Milberg, W.P., 2011. Thickness of the human cerebral cortex is associated with metrics of cerebrovascular health in a normative sample of community dwelling older adults. NeuroImage 54 (4), 2659–2671.
Lindbergh, C.A., Renzi-Hammond, L.M., Hammond, B.R., Terry, D.P., Mewborn, C.M., Puente, A.N., Miller, L.S., 2018. Lutein and Zeaxanthin Influence Brain Function in Older Adults: A Randomized Controlled Trial. J. Int. Neuropsychol. Soc. 24 (1), 77–90.
Luchsinger, J.A., Tang, M.X., Shea, S., Mayeux, R., 2002. Caloric intake and the risk of alzheimer disease. Archiv. Neurol. 59 (8), 1258–1263.
Luciano, M., Corley, J., Cox, S.R., Valdes Hernandez, M.C., Craig, L.C.A., Dickie, D.A., Karama, S., McNeill, G.M., Bastin, M.E., Wardlaw, J.M., Deary, I.J., 2017. Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish Cohort. Neurology 88 (5), 449–455.
Martin, A., Prior, R., Shukitt-Hale, B., Cao, G., Joseph, J.A., 2000. Effect of fruits, vegetables, or vitamin E-rich diet on vitamins E and C distribution in peripheral and brain tissues: implications for brain function. J. Gerontol.: Ser. A: Biol. Sci. Med. Sci. 55 (3), B144–51.
Martínez-Lapiscina, E.H., Clavero, P., Toledo, E., Estruch, R., Salas-Salvadó, J., San Julián, B., Sanchez-Tainta, A., Ros, E., Valls-Pedret, C., Martinez-Gonzalez Á, M., 2013. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. J. Neurol. Neurosurg. Psychiatry 84 (12), 1318–1325.
Mellberg, C., Sandberg, S., Ryberg, M., Eriksson, M., Brage, S., Larsson, C., Olsson, T., Lindahl, B., 2014. Long-term effects of a palaeolithic-type diet in obese postmenopausal women: a 2-year randomized trial. Eur. J. Clin. Nutr. 68 (3), 350–357.
Meusel, L.-A.C., Anderson, N.D., Parrott, M.D., Yuen, W., Tchistiakova, E., MacIntosh, B. J., Feldman, S., Greenwood, C.E., 2017. Brain function is linked to LDL cholesterol in older adults with cardiovascular risk. J. Am. Geriatrics Soc. 65 (2), e51–55.
Molendijk, M., Molero, P., Ortuño Sánchez-Pedreño, F., Van der Does, W., Angel Martínez-González, M., 2018. Diet Quality and Depression Risk: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Elsevier B.V., 226.
Morris, Z., Whiteley, W.N., Longstreth, W.T., Weber, F., Lee, Y.C., Tsushima, Y., Alphs, H., Ladd, S.C., Warlow, C., Wardlaw, J.M., Al-Shahi Salman, R., 2009. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ (Online) 339 (7720), 547–550.
Morris, M.C., Tangney, C.C., Wang, Y., Sacks, F.M., Barnes, L.L., Bennett, D.A., Aggarwal, N.T., 2015. MIND diet slows cognitive decline with aging. Alzheimer's Dementia 11 (9), 1015–1022.
Mosconi, L., Murray, J., Tsui, W.H., Li, Y., Davies, M., Williams, S., Pirraglia, E., Spector, N., Osorio, R.S., Glodzik, L., McHugh, P., de Leon, M.J., 2014. Mediterranean diet and magnetic resonance imaging-assessed brain atrophy in cognitively normal individuals at risk for Alzheimer's disease. J. Prev. Alzheimer's Dis. 1 (1), 23–32.
Mosconi, L., Walters, M., Sterling, J., Quinn, C., McHugh, P., Andrews, R.E., Matthews, D.C., Ganzer, C., Osorio, R.S., Isaacson, R.S., De Leon, M.J., Convit, A., 2018. Lifestyle and vascular risk effects on MRI-based biomarkers of Alzheimer's disease: a cross-sectional study of middle-aged adults from the broader New York City area. BMJ Open 8 (3), e019362.
Mõttus, R., McNeill, G., Jia, X., Craig, L.C.A., Starr, J.M., Deary, I.J., 2013. The associations between personality, diet and body mass index in older people. Health Psychol. 32 (4), 353–360.
Mueller, K., Anwander, A., Moller, H.E., Horstmann, A., Lepsien, J., Busse, F., Mohammadi, S., Schroeter, M.L., Stumvoll, M., Villringer, A., Pleger, B., 2011. Sex-dependent influences of obesity on cerebral white matter investigated by diffusion-tensor imaging. PloS One 6 (4), e18544.
Mueller, K., Moller, H.E., Horstmann, A., Busse, F., Lepsien, J., Bluher, M., Stumvoll, M., Villringer, A., Pleger, B., 2015. Physical Exercise in Overweight to Obese Individuals Induces Metabolic- and Neurotrophic-Related Structural Brain Plasticity. Front. Hum. Neurosci. 9. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc12&NEWS=N&AN=2015-34383-001.
Narita, K., Kosaka, H., Okazawa, H., Murata, T., Wada, Y., 2009. Relationship between plasma leptin level and brain structure in elderly: a voxel-based morphometric study. Biol. Psychiatry 65 (11), 992–994.
NIH, 2008. NIH Public Access. Bone 23 (1), 1–7. https://doi.org/10.1038/jid.2014.371.
Ogoh, Shigehiko, 2017. Relationship Between Cognitive Function and Regulation of Cerebral Blood Flow. Springer, Tokyo, 67. https://link.springer.com/articles/10.1007/s12576-017-0525-0.
Ongur, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex (New York, N.Y. : 1991) 10 (3), 206–219.
Opie, R.S., Itsiopoulos, C., Parletta, N., Sanchez-Villegas, A., Akbaraly, T.N., Ruusunen, A., Jacka, F.N., 2017. Dietary recommendations for the prevention of depression. Nutr. Neurosci. 20 (3), 161–171.
Ottino-González, J., Jurado, M.A., García-García, I., Segura, B., Marqués-Iturria, I., Sender-Palacios, M.J., Tor, E., Prats-Soteras, X., Caldú, X., Junqué, C., Garolera, M., 2017. Allostatic load is linked to cortical thickness changes depending on body-weight status. Front. Hum. Neurosci. 11 (December), 1–11.
Pase, M.P., Himali, J.J., Jacques, P.F., DeCarli, C., Satizabal, C.L., Aparicio, H., Vasan, R. S., Beiser, A.S., Seshadri, S., 2017. Sugary beverage intake and preclinical Alzheimer's disease in the community. Alzheimer's Dementia 13 (9), 955–964.
Pelletier, A., Barul, C., Féart, C., Helmer, C., Bernard, C., Periot, O., Dilharreguy, B., Dartigues, J.F., Allard, M., Barberger-Gateau, P., Catheline, G., Samieri, C., 2015. Mediterranean diet and preserved brain structural connectivity in older subjects. Alzheimer's Dementia 11 (9), 1023–1031.
Petersson, S.D., Philippou, E., 2016. Mediterranean diet, cognitive function, and dementia: a systematic review of the evidence. Adv. Nutr. (Bethesda, Md.) 7 (5), 889–904.
Petrie, M., Rejeski, W.J., Basu, S., Laurienti, P.J., Marsh, A.P., Norris, J.L., Kim-Shapiro, D.B., Burdette, J.H., 2017. Beet Root Juice: An Ergogenic Aid for Exercise and the Aging Brain. J. Gerontol.: Ser. A: Biol. Sci. Med. Sci. 72 (9), 1284–1289.
Pottala, J.V., Yaffe, K., Robinson, J.G., Espeland, M.A., Wallace, R., Harris, W.S., 2014. Higher RBC EPA + DHA corresponds with larger total brain and hippocampal volumes: WHIMS-MRI study. Neurology 82 (5), 435–442.
Prehn, K., Jumpertz von Schwartzenberg, R., Mai, K., Zeitz, U., Witte, A.V., Hampel, D., Szela, A.-M., Fabian, S., Grittner, U., Spranger, J., Flöel, A., 2016. Caloric restriction in older adults—differential effects of weight loss and reduced weight on brain structure and function. Cereb. Cortex bhw008.
Psaltopoulou, T., Sergentanis, T.N., Panagiotakos, D.B., Sergentanis, I.N., Kosti, R., Scarmeas, N., 2013. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. Ann. Neurol. 74 (4), 580–591.
Quirk, S.E., Williams, L.J., O'Neil, A., Pasco, J.A., Jacka, F.N., Housden, S., Berk, M., Brennan, S.L., 2013. The association between diet quality, dietary patterns and depression in adults: a systematic review. BMC Psychiatry 13. https://pubmed.ncbi.nlm.nih.gov/23802679/.
Radak, Z., Hart, N., Sarga, L., Koltai, E., Atalay, M., Ohno, H., Boldogh, I., 2010. 20 Journal of Alzheimer's Disease *Exercise Plays a Preventive Role Against Alzheimer's Disease*. IOS Press.
Raz, N., Yang, Y., Dahle, C.L., Land, S., 2012. Volume of white matter hyperintensities in healthy adults: contribution of age, vascular risk factors, and inflammation-related genetic variants. Biochimica et biophysica acta 1822 (3), 361–369.
Reed, B., Villeneuve, S., Mack, W., DeCarli, C., Chui, H.C., Jagust, W., 2014. Associations between serum cholesterol levels and cerebral amyloidosis. JAMA Neurol. 71 (2), 195–200.
Román, G.C., Jackson, R.E., Gadhia, R., Román, A.N., Reis, J., 2019. 175 Revue Neurologique *Mediterranean Diet: The Role of Long-Chain omega-3 Fatty Acids in Fish; Polyphenols in Fruits, Vegetables, Cereals, Coffee, Tea, Cacao and Wine; Probiotics and Vitamins in Prevention of Stroke, Age-Related Cognitive Decline, and Alzheimer Disease*. Elsevier Masson SAS.
Ronan, L., Alexander-Bloch, A.F., Wagstyl, K., Farooqi, S., Brayne, C., Tyler, L.K., Fletcher, P.C., 2016. Obesity associated with increased brain age from Midlife. Neurobiol. Aging 47, 63–70.
Sattler, C., Toro, P., Schönknecht, P., Schröder, J., 2012. Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease. Psychiatry Res. 196 (1), 90–95.
Scarmeas, N., Stern, Y., Tang, M.X., Mayeux, R., Luchsinger, J.A., 2006a. Mediterranean diet and risk for Alzheimer's disease. Ann. Neurol. 59 (6), 912–921.
Scarmeas, Nikolaos, Stern, Yaakov, Mayeux, Richard, Luchsinger, Jose A., 2006b. Mediterranean diet, Alzheimer disease, and vascular mediation. Archiv. Neurol. 63 (12), 1709.
Scarmeas, N., Luchsinger, J.A., Schupf, N., Brickman, A.M., Cosentino, S., Tang, M.X., Stern, Y., 2009. Physical activity, diet, and risk of Alzheimer disease. JAMA – J. Am. Med. Assoc. 302 (6), 627–637.
Schmahmann D, J., 2003. Vascular syndromes of the thalamus. AHA journals 34 (9), 2264–2278. https://doi.org/10.1161/01.STR.0000087786.38997.9E, 00392499.
Sexton, C.E., Walhovd, K.B., Storsve, A.B., Tamnes, C.K., Westlye, L.T., Johansen-Berg, H., Fjell, A.M., 2014. Accelerated changes in white matter microstructure during aging: a longitudinal diffusion tensor imaging study. J. Neurosci. 34 (46), 15425–15436.

Shalev, D., Arbuckle, M.R., 2017. Metabolism and memory: obesity, diabetes, and dementia. Biol. Psychiatry 82 (11), e81–e83.
Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., Altman, D.G., Booth, A., Chan, A.W., Chang, S., Clifford, T., Dickersin, K., Egger, M., Gøtzsche, P.C., Grimshaw, J.M., Groves, T., Helfand, M., Higgins, J., Lasserson, T., Lau, J., Lohr, K., McGowan, J., Mulrow, C., Norton, M., Page, M., Sampson, M., Schünemann, H., Simera, I., Summerskill, W., Tetzlaff, J., Trikalinos, T.A., Tovey, D., Turner, L., Whitlock, E., 2015. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (Prisma-p) : Elaboration and Explanation. BMJ Publishing Group, 349.
Singh, B., Parsaik, A.K., Mielke, M.M., Erwin, P.J., Knopman, D.S., Petersen, R.C., Roberts, R.O., 2014. 39 Journal of Alzheimer's Disease *Association of Mediterranean Diet With Mild Cognitive Impairment and Alzheimer's Disease: a Systematic Review and Meta-analysis*. IOS Press.
Spielberg, J.M., Sadeh, N., Leritz, E.C., McGlinchey, R.E., Milberg, W.P., Hayes, J.P., Salat, D.H., 2017. Higher serum cholesterol is associated with intensified age-related neural network decoupling and cognitive decline in early- to mid-life. Hum. Brain Mapp. 38 (6), 3249–3261.
Staubo, S.C., Aakre, J.A., Vemuri, P., Syrjanen, J.A., Mielke, M.M., Geda, Y.E., Kremers, W.K., Machulda, M.M., Knopman, D.S., Petersen, R.C., Jack, C.R., Roberts, R.O., 2017. Mediterranean diet, micronutrients and macronutrients, and MRI measures of cortical thickness. Alzheimer's Dementia 13 (2), 168–177.
Stern, Y., Alexander, G.E., Prohovnik, I., Mayeux, R., 1992. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. Ann. Neurol. 32 (3), 371–375.
Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., Thacker, S.B., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. J. Am. Med. Assoc. 283 (15), 2008–2012.
Suri, S., Machay E, C., Kelly E, M., Tunbridge M, E., Frisoni B, G., Matthews M, P., Ebmeier P, K., Bulte P, D., Filippini, N., 2014. Reduced cerebrovascular reactivity in young adults carrying the APOE ϵ4 allele. Alzheimer's & Dementia 11 (6), 648–657. e1. https://doi.org/10.1016/j.jalz.2014.05.1755.
Suwa, M., Yamaguchi, S., Komori, T., Kajimoto, S., Kino, M., 2015. The association between cerebral white matter lesions and plasma Omega-3 to Omega-6 polyunsaturated fatty acids ratio to cognitive impairment development. BioMed Res. Int. 2015, 1–7.
Swarbrick, M.M., 2014. 63 *A Lifetime on the Hips: Programming Lower-body Fat to Protect Against Metabolic Disease*. American Diabetes Association Inc.
Talukdar, M.T., Zamroziewicz, M., Zwilling, C., Barbey, A., 2018. Neurobiological markers of individual differences in Omega-3 fatty acids revealed by multivariate FMRI. Front. Hum. Neurosci. 12.
Talukdar, T., Zamroziewicz, M.K., Zwilling, C.E., Barbey, A.K., 2019. Nutrient Biomarkers Shape Individual Differences in Functional Brain Connectivity: Evidence from Omega-3 PUFAs. Hum. Brain Mapp. 40 (6), 1887–1897.
Titova, O.E., Sjogren, P., Brooks, S.J., Kullberg, J., Ax, E., Kilander, L., Riserus, U., Cederholm, T., Larsson, E.-M., Johansson, L., Ahlstrom, H., Lind, L., Schioth, H.B., Benedict, C., 2013a. Dietary intake of eicosapentaenoic and docosahexaenoic acids is linked to gray matter volume and cognitive function in elderly. Age (Dordrecht, Netherlands) 35 (4), 1495–1505.
Titova, O.E., Ax, E., Brooks, S.J., Sjögren, P., Cederholm, T., Kilander, L., Kullberg, J., Larsson, E.-M., Johansson, L., AAhlström, H., Lind, L., Schiöth, H.B., Benedict, C., 2013b. Mediterranean diet habits in older individuals: associations with cognitive functioning and brain volumes. Exp. Gerontol. 48 (12), 1443–1448.
Trichopoulou, A., Kyrozis, A., Rossi, M., Katsoulis, M., Trichopoulos, D., La Vecchia, C., Lagiou, P., 2015. Mediterranean diet and cognitive decline over time in an elderly Mediterranean population. Eur. J. Nutr. 54 (8), 1311–1321.
Trichopoulou, Antonia, Costacou, Tina, Bamia, Christina, Trichopoulos, Dimitrios, 2003. Adherence to a Mediterranean diet and survival in a Greek population. N. Engl. J. Med. 348 (26), 2599–2608.
Topiwala, A., Allan, C.L., Valkanova, V., Zsoldos, E., Filippini, N., Sexton, C.E., Mahmood, A., Singh-Manoux, A., Mackay, C.E., Kivimäki, M., Ebmeier, K.P., 2015. Resilience and MRI correlates of cognitive impairment in communitydwelling elders. Br. J. Psychiatry 207 (5), 435–439.
Vagelatos, N.T., Eslick, G.D., 2013. Type 2 diabetes as a risk factor for alzheimer's disease: the confounders, interactions, and neuropathology associated with this relationship. Epidemiol. Rev. 35 (1), 152–160.
Vauzour, D., Camprubi-Robles, M., Miquel-Kergoat, S., Andres-Lacueva, C., Bánáti, D., Barberger-Gateau, P., Bowman, G.L., Caberlotto, L., Clarke, R., Hogervorst, E., Kiliaan, A.J., Lucca, U., Manach, C., Minihane, A.M., Mitchell, E.S., Perneczky, R., Perry, H., Roussel, A.M., Schuermans, J., Sijben, J., Spencer, J.P.E., Thuret, S., van de Rest, O., Vandewoude, M., Wesnes, K., Williams, R.J., Williams, R.S.B., Ramirez, M., 2017. 35 Ageing Research Reviews *Nutrition for the Ageing Brain: Towards Evidence for an Optimal Diet*. Elsevier Ireland Ltd.
Walhovd, K.B., Storsve, A.B., Westlye, L.T., Drevon, C.A., Fjell, A.M., 2014. Blood markers of fatty acids and vitamin d, cardiovascular measures, body mass index, and physical activity relate to longitudinal cortical thinning in normal aging. Neurobiol. Aging 35 (5), 1055–1064.
Walker, J.M., Harrison, F.E., 2015. Shared Neuropathological Characteristics of Obesity, Type 2 Diabetes and Alzheimer's Disease: Impacts on Cognitive Decline. MDPI, AG, 7.
Ward, M.A., Carlsson, C.M., Trivedi, M.A., Sager, M.A., Johnson, S.C., 2005. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurol. 5, 23.
Wengreen, H., Munger, R.G., Cutler, A., Quach, A., Bowles, A., Corcoran, C., Tschanz, J. T., Norton, M.C., Welsh-Bohmer, K.A., 2013. Prospective study of dietary approaches to stop hypertension– and Mediterranean-style dietary patterns and age-related cognitive change: the cache county study on memory, health and aging. Am. J. Clin. Nutr. 98 (5), 1263–1271.
Willette, A.A., Kapogiannis, D., 2015. 20 *Does the Brain Shrink As the Waist Expands*? Elsevier Ireland Ltd.
Willey, J.Z., Gardener, H., Moon, Y.P., Yoshita, M., DeCarli, C., Cheung, Y.K., Sacco, R.L., Elkind, M.S.V., Wright, C.B., 2014. Lipid profile components and subclinical cerebrovascular disease in the Northern Manhattan study. Cerebrovascular Dis. 37 (6), 423–430.
Williams, V.J., Leritz, E.C., Shepel, J., McGlinchey, R.E., Milberg, W.P., Rudolph, J.L., Lipsitz, L.A., Salat, D.H., 2013. Interindividual variation in serum cholesterol is associated with regional white matter tissue integrity in older adults. Hum. Brain Mapp. 34 (8), 1826–1841.
Witte, A.V., Kerti, L., Hermannstädter, H.M., Fiebach, J.B., Schreiber, S.J., Schuchardt, J. P., Hahn, A., Flöel, A., 2014a. Long-chain Omega-3 fatty acids improve brain function and structure in older adults. Cereb. Cortex 24 (11), 3059–3068.
Witte, A.V., Kerti, L., Margulies, D.S., Floel, A., 2014b. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. J. Neurosci. 34 (23), 7862–7870.
Wolf, A.B., Braden, B.B., Bimonte-Nelson, H., Kusne, Y., Young, N., Engler-Chiurazzi, E., Garcia, A.N., Walker, D.G., Moses, G.S.D., Tran, H., Laferla, F., Lue, L., Emerson Lombardo, N., Valla, J., 2012. Broad-based nutritional supplementation in 3xTg mice corrects mitochondrial function and indicates sex-specificity in response to Alzheimer's disease intervention. J. Alzheimer's Dis. 32 (1), 217–232.
Yap, Q.J., Teh, I., Fusar-Poli, P., Sum, M.Y., Kuswanto, C., Sim, K., 2013. Tracking cerebral white matter changes across the lifespan: insights from diffusion tensor imaging studies. J. Neural Transm. 120 (9), 1369–1395.
Ye, X., Scott, T., Gao, X., Maras, J.E., Bakun, P.J., Tucker, K.L., 2013. Mediterranean diet, healthy eating index 2005, and cognitive function in middle-aged and older Puerto Rican adults. J. Acad. Nutr. Diet. 113 (2), 276–281 e3.
Zamroziewicz, M.K., Paul, E.J., Zwilling, C.E., Johnson, E.J., Kuchan, M.J., Cohen, N.J., Barbey, A.K., 2016. Parahippocampal Cortex Mediates the Relationship between Lutein and Crystallized Intelligence in Healthy, Older Adults. Front. Aging Neurosci. 8. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc13b&NEWS=N&AN=2016-59666-001.
Zamroziewicz, M.K., Paul, E.J., Zwilling, C.E., Barbey, A.K., 2018. Determinants of fluid intelligence in healthy aging: Omega-3 polyunsaturated fatty acid status and frontoparietal cortex structure. Nutr. Neurosci. 21 (8), 570–579.
Zwilling, C.E., Talukdar, T., Zamroziewicz, M.K., Barbey, A.K., 2019. Nutrient Biomarker Patterns, Cognitive Function, and FMRI Measures of Network Efficiency in the Aging Brain. NeuroImage 188, 239–251.