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

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## 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 found associations between a wide range of 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.

## Keywords

Ageing, diet, MRI, brain volume, brain connectivity

# 1 Introduction

Obesity and type 2 diabetes are risk factors for dementia (Beydoun and Beydoun, 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 et al. 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, Cryan, and Nolan 2017). In research studies, diet patterns are often indirectly inferred from metabolic variables, such as cholesterol levels (Meusel et al. 2017; Spielberg et al. 2017), fatty acid profiles (Talukdar et al. 2019; Zwilling et al. 2019), or specific diets, such as the Mediterranean diet (MeDi; Luciano et al. 2017; Petersson and Philippou 2016; Titova et al. 2013b), caloric restriction (defined as limiting caloric intake without loss of nutrient content; Prehn et al. 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 et al. 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. Further, several studies implicate poor dietary health in a number of neurological and psychiatric disorders including depression (Molendijk et al. 2018; Quirk et al. 2013), stroke (Psaltopoulou et al. 2013; Román et al. 2019), sleep problems (Castro-Diehl et al. 2018; insomnia: Gangwisch et al. 2020), Alzheimer dementia, (Román et al. 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 et al. 2015; Mosconi et al. 2014; Staubo et al. 2017), lower WM hyperintensity (WMH) burden (Gardener et al. 2012), and preserved WM microstructure (Pelletier et al. 2015). Particularly relevant are connections between areas of the default mode network (DMN), a network which is first affected in dementia (see Hafkemeijer, van der Grond, and Rombouts 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 et al. 2000, 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, GM functional activation, WM microstructure (e.g., FA, diffusivity), network connections (e.g. resting-state functional connectivity, WM fibre tracts connection), WMH lesion load, CBF, infarcts and ventricular volume.
9) Studies which report p-values for all significant effects.

#### 2.2.2 Excluded studies

10) Non-human studies
11) Studies on unhealthy adults
12) Case studies
13) 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, 2014). This tool assesses several potential sources of bias in a study by covering different areas in fourteen questions. These areas include the assessment of study design to address a given research question, eligibility of the study population, sample size justification, and validity and reliability of the 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) vascular markers (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 (Sexton et al. 2014) is observed in normal ageing (Burzynska et al. 2010; Head et al. 2004; Yap et al. 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 decreases in cortical and limbic regions

during ageing, and this is linked with cognitive decline (e.g. Kullmann et al. 2016). In patients with Alzheimer's disease, lower GM functional connectivity of the DMN is widely reported (Douaud et al. 2014; see Hafkemeijer, van der Grond, and Rombouts 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 et al. 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 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 Figure A2). 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. Dietary factors were measured by intervention, observation, 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 (Figure 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 6.4) directly assessed complete dietary patterns using self-administered questionnaires.

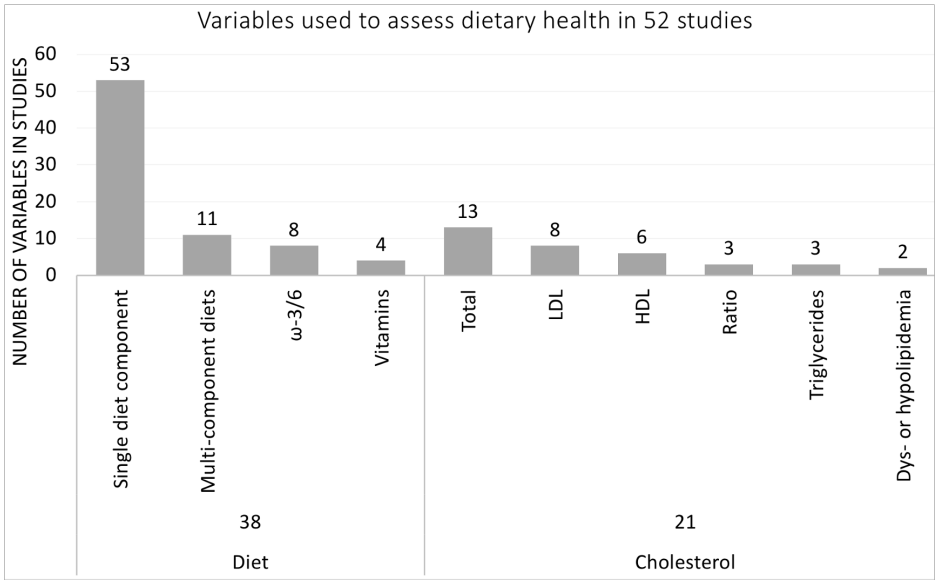


Figure 1: Variables used to assess dietary health in a total of 52 articles. Some studies assessed multiple dietary markers.

## 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 et al. 2011). Witte, Kerti, Hermannstädter et al. (2014) 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, Kerti, Hermannstädter et al. 2014). 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 et al. 2015) and older adults (Williams et al. 2013). Williams et al. (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 et al. 2015), the internal/external capsule and parietal and occipital WM, but paradoxically lower FA in ACR, ATR and temporal

WM (Williams et al. 2013). Williams et al (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 et al (2013), Mueller et al. (2015) showed that participants with higher (good) HDL cholesterol show altered trans-callosal diffusivity of water molecules with lower RD in the CC (Mueller et al. 2015), whereas participants with higher (bad) LDL cholesterol show dysfunctional axonal properties with higher RD and AD in the total WM (Williams et al. 2013).

Table 1: DM markers - white matter connectivity

| Study (Cohort if specified) | Sample size (% female) | Age, years (mean±SD) | Dietary marker | Brain WM Fibre Tracts | | | | | | | | | | | | | WM areas | | | | | | Follow-up (years) | Covariates *adjusted for other models |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | total WM | SLF | IFOF | ILF | UF | Cingulum bundle | CC + surrounding | splenium CC | genu CC | Forceps minor | Int./ext. capsule | Fornix | ATR | ACR | corona radiata | frontal | temporal | parietal | occipital | subcortical areas | WM next to hippo | | |
| **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 | | |
| | | | 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 | | ↑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 | - |

interventional 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 |

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.

## 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 et al. 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 et al. 2016), resveratrol supplementation (Huhn et al. 2018; Witte, Kerti, Margulies, et al. 2014) 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, 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 et al. 2017) and in the superior temporal sulcus in young adults (Spielberg et al. 2017). Conversely, studies reported no associations between functional connectivity and the Framingham risk score (tracks the cardiovascular risk profile with total and HDL-cholesterol; Meusel et al. 2017), nor 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 et al. 2017; Reed et al. 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.

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 |

interventional studies

*cardiovascular risk profile, with total and HDL-Chol.

| | |
|---|---|
| | no significant association |
| | negative association |
| | positive association |

Abbreviations: GM - grey matter, WM - white matter, DMN - default mode network, IC - intrinsic connectivity, FC - functional connectivity, MUFA - ratio of monounsaturated 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.

## 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 Table 3 and Table 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 et al. (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 et al. (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 et al. 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 et al. 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 et al. 2013).

No associations were found between cholesterol and WM volume.

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

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### 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 et al. 2015; Luciano et al. 2017; Prehn et al. 2016) and middle-age adults (Mosconi et al. 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 et al. 2015; Luciano et al. 2017; Mosconi et al. 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 et al. 2016).

Other individual diet markers, such as higher fish intake (Gu et al. 2015), vitamins (vitamin B, E, A, C, antioxidants and fibres; Berti et al. 2015; Devore et al. 2013; Erickson et al. 2008; blueberry supplementation: Bowtell et al. 2017), ω-3 or 6 fatty acids (Berti et al. 2015; Pottala et al. 2014; Walhovd et al. 2014; Witte et al. 2014; Titova et al. 2013a), folate (Erickson et al. 2008), leptin (Narita et al. 2009), flavanol (Brickman et al. 2014) and lutein intake (Lindbergh et al. 2018; Zamroziewicz et al. 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 et al. 2015), fruit juice (Pase et al. 2017), saturated fats, trans-sat fats and sodium (Berti et al. 2015), fat fatty acids (Boraxbekk et al. 2015), meat (Gu et al. 2015; Titova et al. 2013b), higher homocysteine level (Hooshmand et al. 2016) and brain-derived neurotrophic factor (Mueller et al. 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) intake. However, the result of Gu et al. (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 et al. 2018; Luciano et al. 2017; Jacka et al. 2015; Booth et al. 2014, see detailed information in Appendix 6.4).
Notably, the FFQ in Pase et al. (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 et al. 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 et al. 2017).

Moreover, in young (Mueller et al. 2015), middle-aged (Gonzales et al. 2011; Koschack et al. 2009) and older adults (Chung et al. 2018; den Heijer et al. 2012; Hoogendam et al. 2012; Leritz et al. 2011; Walhovd et al. 2014), lower total cholesterol (Hoogendam et al. 2012; Koschack et al. 2009; Leritz et al. 2011), higher LDL cholesterol (Chung et al. 2018; Leritz et al. 2011) or lower HDL cholesterol level (Mueller et al. 2015; Hoogendam et al. 2012) and lower total to HDL cholesterol ratio (Gonzales et al. 2011) were associated with smaller total

GM volume (Walhovd et al. 2014), larger volumes in the frontal (Chung et al. 2018; Gonzales et al. 2011; Leritz et al. 2011), parietal (Chung et al. 2018; Gonzales et al. 2011; Leritz et al. 2011) and temporal lobe (Leritz et al. 2011), the hippocampus (den Heijer et al. 2012; Koschack et al. 2009; Mueller et al. 2015), other subcortical areas (Chung et al. 2018; den Heijer et al. 2012; Leritz et al. 2011), the cerebellum (Hoogendam et al. 2012; Mueller et al. 2015), insula (Mueller et al. 2015) and cingulate gyrus (Chung et al. 2018; Leritz et al. 2011). However, the directions of associations observed in the cerebellum shown in Mueller et al. (2015) and Hoogendam et al. (2012) were inconsistent, which could be due to their discrepant methodologies. MRI analyses were conducted using VBM (Mueller et al. 2015) and FreeSurfer (Hoogendam et al. 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 et al. 2005), LDL cholesterol (Raz et al. 2012) or HDL cholesterol level (Mosconi et al. 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.

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 | | | | | | | | | Subcortical | | | | cerebellum | Covariates *adjusted for additional models |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | frontal lobe | temporal lobe | parietal lobe | occipital lobe | insular | cingulate | suppl. motor area | Precuneus | caudate gyrus | hippocampus *parahippocampus | Entorhinal cortex | thalamus | other subcortical regions | | |
| 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; >3/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<br>FFQ: unhealthy "Western" dietary pattern | | | | | | | | | | | | ↑<br>↓ | | | 4 | Age, sex, Ed, SES, depressive symptoms, med, PA, smo, hypertension, diabetes |
| 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<br>ω-3 EPA | -<br>- | | | ↑<br>- | | | | | | | | | | | 3.6±0.5 | Age, sex |
| 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<br>ω-3 EPA | | ↑<br>- | | | | | | | | | | ↑ | | | 8 | Ed, environmental factors (i.e. smo, PA, alcohol, BMI), disease comorbidities (i.e., prior vas, diabetes, treated & untreated hypertension).<br>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 | 700 (47.43%) | 72±0.8 | Dairy intake low<br>Fat high | | | | | | | | | | | | -<br>- | | -<br>- | 3 | Age |

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Lothian Birth Cohort study) | 189 (53.97%) | 72±0.8 | Sat. fats high<br>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%)<br>19 (68%)<br>18 (78%) | 57.72<br>57<br>58.5 | Flavanol<br>Flavanol-in high<br>Flavanol-in low | | | | | | | | | | | | ↑<br>↑<br>- | | | 0.25 | Sex |
| Hooshmand et al. 2016 | 299 (59.9%) | 70±8.6 | Folate<br>HCy<br>Holotranscobalamin | | -<br>↓<br>↓ | | | | | | | | | | | | | 6 | Age, sex* |
| 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<br>Vit. B12 | | -<br>↓ | | | | | | | | | | | | | 6 | Age, sex* |
| 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* |

interventional studies

* intervention was not diet related

| | |
|---|---|
| | association not examined |
| | no significant association |
| | negative association |
| | positive association |

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.

## 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, 2014; King et al. 2014; Pase et al. 2017; Suwa et al. 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 et al. 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). And 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 et al. 2017), different vitamins and micronutrients (Hooshmand et al. 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 et al. 2015; Willey et al. 2014). Similarly, no association with CBF or LDL cholesterol level was reported (Birdsill et al. 2013). Despite these discrepancies, the majority of reviewed studies have linked cerebrovascular abnormalities with at least one ‘unhealthy’ dietary marker.

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.

# 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.

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.

| | **GM volume** | **WM volume** | **GM functional connectivity** | **WM connectivity** | **Cerebro-vascular markers** |
|---|---|---|---|---|---|
| **Main Exposures:** | *(Main ROIs: temporal, frontal and parietal lobe, cingulate and entorhinal cortex, hippocampus)* | *Main ROIs: temporal and frontal WM* | *Main ROIs: DMN, sensorimotor and attention network* | *Main ROIs: SLF, ILF, CC and IFOF* | *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)


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.

## 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 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 et al. 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 et al. 2017) have been related to deficits in cognitive performance (Kharabian Masouleh et al. 2018; Zamroziewicz et al. 2016) such as working memory performance (Boraxbekk et al. 2015; Meusel et al. 2017; Witte, Kerti, Margulies, et al. 2014), attention (Kohn et al. 2016), and episodic memory performance (Boraxbekk et al. 2015; Kharabian Masouleh et al. 2018; Prehn et al. 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 et al. 2017; Zwilling et al. 2019), improved cognition (e.g. Bajerska et al. 2014; Martínez-Lapiscina et al. 2013; Wengreen et al. 2013; Ye et al. 2013) and decreased risk for MCI and dementia (Galbete et al. 2015; Morris et al. 2015; Psaltopoulou et al. 2013; Scarmeas, Stern, Mayeux, et al. 2006; Scarmeas, Stern, Tang, et al. 2006; Trichopoulou et al. 2015), and progressing from MCI to Alzheimer's dementia (Singh et al. 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 et al. 2012) and the American Heart Association, but in this review, we summarise 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.

### 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
Figure 2, 45 studies). Thus, conclusions about middle-aged (6 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.

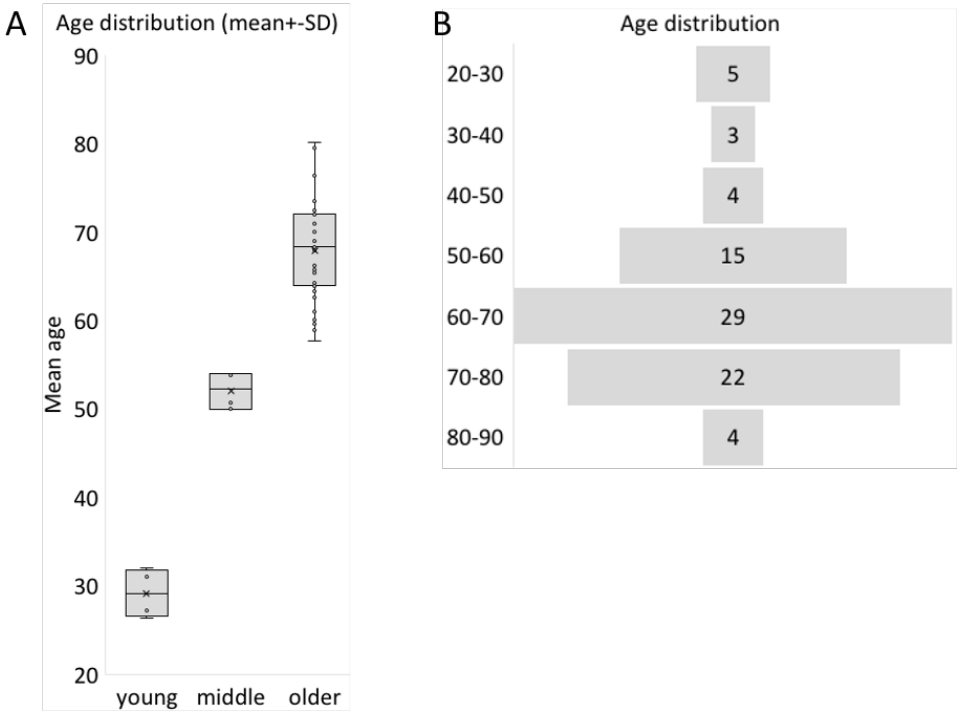


Figure 2: Age distribution in the reviewed samples of 52 articles. **A** shows the mean age and standard deviation (SD) of young (20-35 years), middle (36-55 years) and older adults (56 years and older). **B** shows the age distribution in quantiles considering the age range of each study.

The evidence suggests that anatomical or hormonal differences between men and women may influence the effect of obesity on brain volume and connectivity (Mueller et al. 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 et al. 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 (Boraxbekk et al. 2015; Pottala et al. 2014; Prehn et al. 2016) showed similar diet marker - 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 et al. 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 (Figure 3). Three studies controlled their analyses for the ethnicity of the participants (Akbaraly et al. 2018; Berti et al. 2015; Gu et al. 2015), but only two of these studies examined the brain

- diet markers relationship among multiple (more than two) ethnic groups, including white, African American and Hispanic participants (Berti et al. 2015; Gu et al. 2015). No reviewed sample was acquired in South America, Africa or Australia which could bias the conclusions from this review (Figure 3). In general, there was insufficient data to estimate differences between countries in terms of existing diet markers - 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. 2013a) compared to the US population (Gu et al., 2005) may explain the significant result of Gu et al. (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 et al. 2010; Scarmeas et al. 2009) covary with obesity, and are risk factors for cognitive decline or neurodegeneration (discussed in Ronan et al. 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 et al. 2015; Haller et al. 2018; Jacka et al. 2015, 2015; Luciano et al. 2017; Pottala et al. 2014), most studies failed to include socioeconomic variables. Thus, it is difficult to draw conclusions about whether the DM marker - brain associations described here were driven, at least in part, by socioeconomic status and geography.

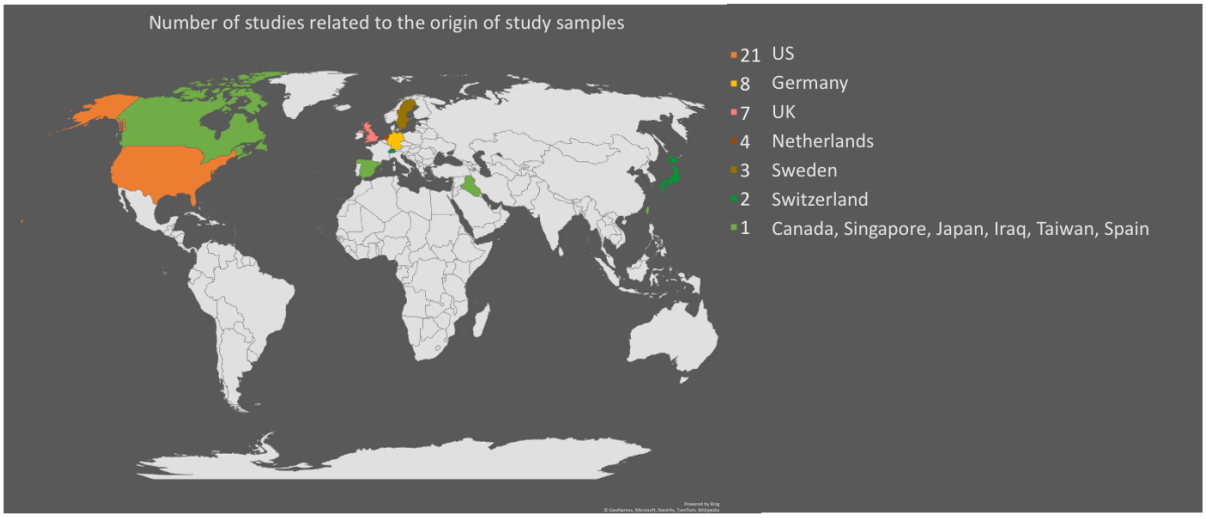


Figure 3: Origin of samples in the studies examined in this review and covered samples sizes. The figure shows the number of studies in each country/region in the world. The sample size of each country in percent in relation to the whole reviewed sample is for the US: 52.6%, Germany: 4.5%, UK: 5.7%, 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%.

### 4.3.4 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, Wieczorek, and Muglia 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 sequence and appropriate preprocessing steps. Future studies should consider the importance of subcortical structures in association with diet markers.

# 5 Conclusion

The 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 marker - brain associations.

Studies investigated 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 in 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).

# 6 Appendices

## 6.1 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

## 6.2 A2: Study identification and selection process.

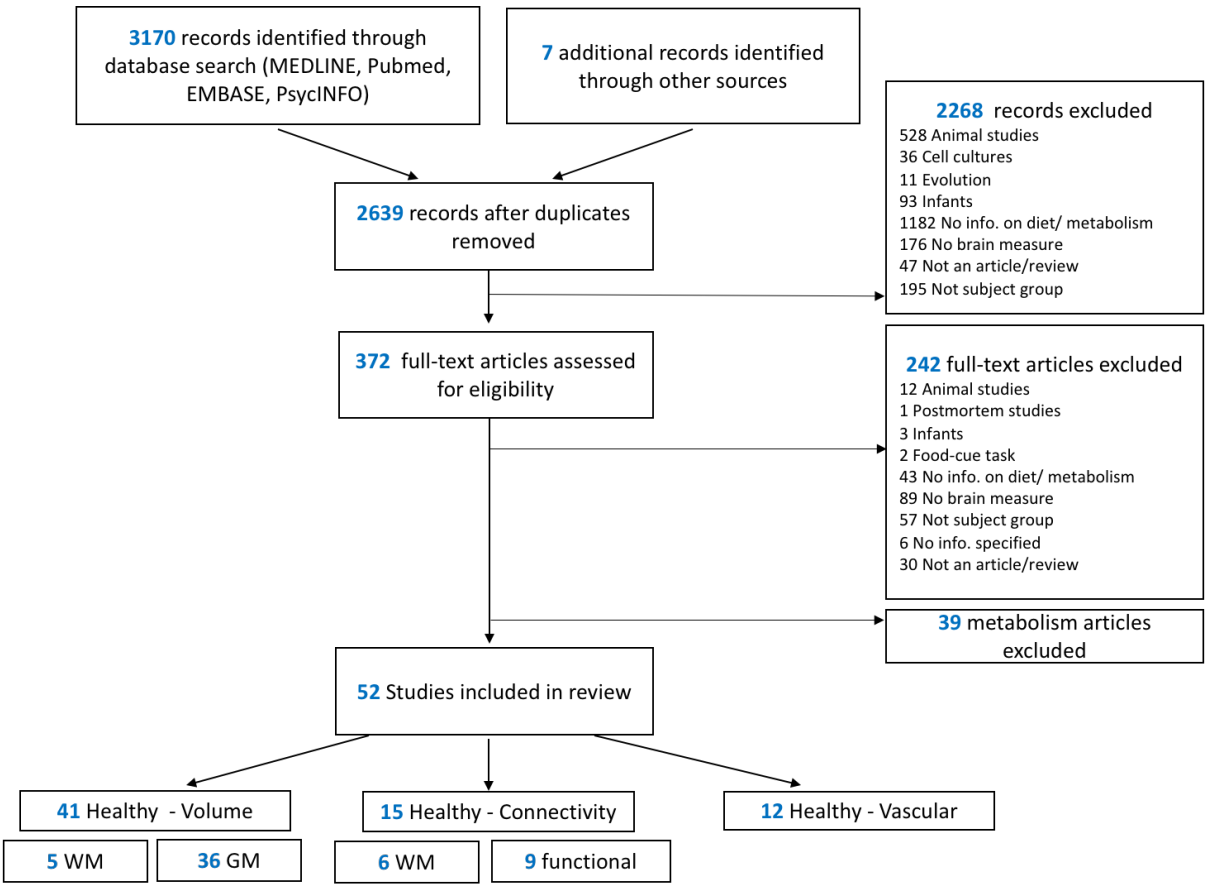


Figure A2: Study identification and selection process.

## 6.3 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 et al. 2013 | good |
| Dickie et al. 2016 | good |
| Erickson et al. 2008 | good |
| Gonzales et al. 2011 | fair |
| Gu et al. 2015 | good |
| Haller et al. 2018 | fair |
| Del C Valdes Hernandez et al. 2017 | fair |
| Hoogendam et al. 2012 | good |
| Hooshmand et al. 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 et al. 2011 | fair |
| Lindbergh et al. 2018 | good |
| Luciano et al. 2017 | good |
| Meusel et al. 2017 | fair |
| Mosconi et al. 2018 | fair |
| Mueller et al. 2011 | good |
| Mueller et al. 2015 | good |
| Narita et al. 2009 | fair |
| Ottino-González et al. 2017 | fair |
| Pase et al. 2017 | good |
| Petrie et al. 2017 | good |
| Pottala et al. 2014 | good |
| Prehn et al. 2016 | fair |
| Raz et al. 2012 | good |
| Spielberg et al. 2017 | good |
| Suwa et al. 2015 | fair |
| Talukdar et al. 2018 | good |
| Titova et al. 2013a | good |
| Titova et al. 2013b | good |
| Walhovd et al. 2014 | good |
| Ward et al. 2005 | fair |
| Willey et al. 2014 | good |
| Williams et al. 2013 | good |
| Witte et al. 2014 | good |
| Witte et al. 2014 | good |
| Zamroziewicz et al. 2016 | good |
| Zamroziewicz et al. 2018 | good |
| Zwilling et al. 2019 | good |

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

**Mediterranean diet (MeDi) score** was studied in four articles (Gu et al. 2015; Luciano et al. 2017; Mosconi et al. 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 et al. 2015; Luciano et al. 2017; Mosconi et al. 2014; Titova et al. 2013b).

In Gu et al. (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 to 30 g/day) was assigned a value of 1.

In Mosconi et al. (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 et al. (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 et al. (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 et al. (2013). 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 et al. 2017; Topiwala et al. 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 et al. (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 et al. 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).

## 7 Acknowledgments

DEAJ conducted the meta-analysis and wrote the manuscript. SS supervised the work and gave analysis advice 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.

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## 9 Conflict of interest

The authors declare no competing financial interests.

## 10 References

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