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Review

Diet and biomarkers of Alzheimer's disease: a systematic review and meta-analysis

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ABSTRACT

Alzheimer's disease (AD) risk increases with age and lacks efficacious pharmacological options. Summaries of the existing evidence reveal an association between Mediterranean-style diet adherence and reduced AD incidence; however, no review has investigated this relationship with respect to the hallmark AD biomarkers (tau and beta-amyloid) that manifest decades before clinical symptomatology. MEDLINE, PubMed, PsycINFO, Google Scholar, and SCOPUS databases were systematically searched to identify peer-reviewed articles investigating diet and AD biomarkers in the last 2 decades. Two thousand seven hundred twenty-six records were extracted, quality assessed, and double-blind screened by 2 authors. Fifteen studies met the inclusion criteria and 13 studies found a significant relationship. Of these, 4 studies found a high-glycemic load was related to an increase in AD biomarker burden; 6 found adherence to a Mediterranean or "AD-protective" dietary pattern conferred a reduction in AD biomarker burden. Meta-analysis revealed a small but significant effect of diet on AD biomarkers ($\beta = 0.11$ [95% CI 0.04–0.17], $p = 0.002$). This systematic review supports the notion that diet and nutrition display potential for nonpharmacological AD prevention.

1. Introduction

Dementia incidence exponentially increases with age, doubling approximately every 5 years (Jorm and Jolley, 1998). Alzheimer's disease (AD) is the leading cause of dementia, accounting for 60%–70% of all cases (Fratiglioni and Rocca, 2001) and is a global public health priority. The *Alzheimer's Disease International* World Alzheimer Report 2015 estimated 46.8 million people living with dementia worldwide, and this number is expected to reach 131.5 million by 2050 (Prince et al., 2015). Current pharmacological approaches, including cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, are focused on treating AD symptomatology and are lacking therapeutic efficacy. Clinical trials that focus on reducing the pathological burden of AD biomarkers are failing (Mehta et al., 2017). Given the resistance to treatment, a growing body of research is now focusing on the preventative potential of modifiable risk factors in the AD pathology before the emergence of clinical symptoms.

Nonmodifiable risk factors for AD include family history, aging, head injury, and carrying the epsilon 4 allele of the apolipoprotein E gene (APOE-ε4). The *2017 Lancet Commission on Dementia Prevention, Intervention and Care* found that approximately 35% of dementia is attributable to potentially modifiable lifestyle risk factors (Livingston et al., 2017). Epidemiological evidence indicates that up to 3 million AD cases worldwide could be prevented with a 10%–25% reduction in known modifiable midlife risk factors (Barnes and Yaffe, 2011).

Diet and nutrition may offer potential for nonpharmacological prevention in AD. Epidemiological findings are consistent in showing that high adherence to dietary patterns characterized by high intake of fruit, vegetables, cereals and legumes and low intake of meat, high-fat dairies, and sweets are consistently associated with a lower risk of AD (Feart et al., 2009; Gardener et al., 2012; Gu and Scarmeas, 2011; Scarmeas et al., 2006, 2007). Prospective studies have also suggested that low to moderate alcohol consumption (Piazza-Gardner et al., 2013), lower carbohydrate consumption (Seneff et al., 2011), and increased vitamin intake (Engelhart et al., 2002) are associated with a decreased risk for AD. In Australia, increased adherence to a Mediterranean diet (MeDi) has been associated with changes in mini-mental state examination over 18 months (Gardener et al., 2012) and a reduction in risk for

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cognitive decline (Gardener et al., 2015). An ecological study found AD prevalence in Japan was associated with a prolonged nutritional transition from the traditional Japanese diet to the Western diet, where AD rates rose from 1% in 1985 to 7% in 2008 (Grant, 2014).

In AD, the onset of clinical symptoms is preceded by a preclinical prodromal phase of neurochemical, neuropathological, functional, and structural brain changes (Amieva et al., 2008; Jack et al., 2013). Therefore, the identification of presymptomatic divergence from normal brain aging is important as this may serve as a marker for early detection of people that may benefit from preventative intervention strategies. Central to the AD pathogenesis is the proliferation, aggregation, and deposition of 2 proteins in the brain: beta-amyloid (Aβ) and the microtubule-associated protein tau (Holtzman et al., 2011). Biomarkers provide unique insights into the underlying neuropathology of AD, at times operating independently of the clinical and neuropsychological manifestations.

In recent years, the use of positron emission tomography (PET) scans for the in vivo measurement of cerebral AD biomarkers has been increasingly utilized, and the validity of Aβ PET radiotracers for the diagnosis of AD has been documented (Morris et al., 2016). Increased amyloid-PET positivity and low cerebrospinal fluid Aβ have been shown to precede clinical AD manifestations by many years (Jack et al., 2013); however, neuroimaging lacks cost-effectiveness and (cerebrospinal fluid) CSF extraction is invasive. A robust inverse relationship has been observed between cortical Aβ binding and levels of CSF Aβ42 in cognitively normal individuals (Fagan et al., 2006). Research has suggested that central and peripheral pools of Aβ may be in a state of equilibrium and that the changes in blood levels of Aβ42 may be reflected in cerebral Aβ deposition (DeMattos et al., 2002). More recently, the utility of plasma to detect AD pathophysiology has been clinically validated using independent data sets in Australia and Japan (Nakamura et al., 2018). The stability and sensitivity of plasma Aβ measurements have also been reported to suggest a blood-brain transportation mechanism of Aβ (Ovod et al., 2017). In the NIA-AA Research Framework (Jack et al., 2018), blood-based biomarkers were regarded as showing promise as a future screening tool for AD, given they are less invasive and expensive than existing cerebral and CSF biomarkers.

Summaries of the existing evidence reveal an association between healthy diet adherence and reduced AD incidence and prevalence. A recent systematic review found 50 of 64 studies revealed a significant association between diet and AD incidence (Yusufov et al., 2017); however, no review has investigated this relationship with respect to the hallmark AD biomarkers that manifest decades before clinical symptomatology. The aims of this systematic review were to summarize the evidence relating diet and nutrition to the hallmark AD biomarkers (tau and beta-amyloid), identify methodological constraints, and provide future research directions.

2. Materials and methods

We searched published scientific literature for prospective cohort studies and randomized controlled trials of adult human participants reporting diet/nutritional intake and AD biomarkers. This systematic review adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement guidelines (Moher et al., 2009) (Supplementary Table 1). The protocol was designed a priori and was registered with PROSPERO (CRD42017076389).

2.1. Search strategy and article selection

Searches were conducted in MEDLINE, PubMed, PsycINFO, Google Scholar, and SCOPUS databases to identify peer-reviewed articles that examined the relationship between diet and/or nutrition and AD biomarkers in the last 2 decades (January 1, 1997-September 12, 2017). Articles were extracted, quality assessed, and double-blind screened by 2 authors (EH/AG) and were included if they reported on associations between diet/nutrition and physiological AD biomarkers. The National Institutes of Health (NIH) quality assessment tool was used to assess bias within included studies (Supplementary Table 2). For all 4 databases, the exact search date was from January 1, 1997 through September 12, 2017 and updated thereafter. Google Scholar searches were performed to identify additional articles.

Depending on the mesh headings, keywords, and database requirements, a Boolean search strategy was conducted with the general following logic: ("diet" OR "dietary patterns" OR "dietary factors" OR "food" OR "nutrition") AND ("tau" OR "p-tau" OR "t-tau" OR "Aβ42" OR "Aβ40" OR "Aβ" OR "βA" OR "amyloid" OR "β amyloid" OR "β-amyloid" OR "amyloid-β" OR "amyloid β") NOT (rat OR rats OR mice OR mouse OR cell OR cells) OR AB(rat OR rats OR mice OR mouse OR cell OR cells). Studies were included in the review if they (1) were original studies; (2) contained multiple subjects (no case reports); (3) included human subjects only; (4) utilized a self-reported dietary/nutritional measure (no pathological nutritional marker); and (5) examined the AD biomarker (tau/amyloid) in cerebral, CSF, or plasma levels. No limitations were set on study cohort, cohort classification (cognitively normal [NL]/AD/mild cognitive impairment [MCI]), country, or setting. Cross-sectional, longitudinal, and interventional studies were included.

2.2. Data extraction

Data extraction involved the first author extracting the following characteristics from the articles: lead author, year of publication, followup period, country/setting, sample size, sex, mean age (and standard deviation) in years, cohort name, cohort classification, diet/nutrient measure, evaluation of AD biomarker, covariates, statistical methodology, effect size, standardized beta coefficients (where available), and standard error (where available). To clarify variables that may have influenced outcomes, subgroup analysis was performed by grouping the data according to cohort classification (NL vs. MCI vs. AD), dietary measure (Glycemic vs. MeDi vs. Nutrients vs. Omega-3 vs. Folic vs. Vit D), AD biomarker (tau vs. Aβ), and in vivo method of AD biomarker procurement (cerebral vs. CSF vs. plasma).

2.3. Quantitative analysis

For the quantitative analysis, where populations were drawn from the same participant pool we excluded the earliest publication (Bayer-Carter et al., 2011; Freund-Levi et al., 2009), we excluded studies where global coefficient values were not reported (Berti et al., 2015, 2018; Matthews et al., 2014) and randomized control trials (RCTs) that administered dietary interventions that were not comparable to other studies (Baker et al., 2012; Chen et al., 2016; Freund Levi et al., 2014; Hanson et al., 2013; Matthews et al., 2014; Miller et al., 2016). For studies using comparable dietary assessment methods, we extracted standardized beta-coefficients and error estimate data (where available) of dietary effects on AD biomarkers. Because of heterogeneity in the direction of the effect of diet on AD biomarkers, we reversed the effect size for 1 RCT (Taylor et al., 2017) that investigated a high glycemic load diet and sugar/carbohydrate intake on cerebral Aβ deposition. Given the small number of eligible studies, studies that defined specific dietary patterns (e.g., MeDi) or nutrients known to be AD-protective (higher intake of fresh fruit and vegetables, whole grains fish and low-fat dairies; and a lower intake of sweets, fried potatoes, high-

fat dairies, and processed meat and butter) were pooled for analysis. Studies that provided multiple nutritional or dietary relationships with both Aβ and tau were separated by AD biomarker. Where studies did not provide estimates of error, standard error (SE) was estimated using a simulation model. For each cohort, baseline summary statistics and variable distribution were used to reproduce the study cohort by applying a probabilistic model. Regression models were then constructed following the methodology described in each study and at least 500 simulations were run to generate a reliable estimate of SEs. Meta-regression was then conducted in STATA on Windows operating system. Heterogeneity was assessed using Cochran's Q-test and I2-statistic.

3. Results

3.1. Study characteristics

3.1.1. Description of studies

A total of 2726 records were screened (Fig. 1). Fifteen studies met the inclusion criterion for qualitative analysis (7 RCTs, 7 cross-sectional, 1 longitudinal), and 5 studies were included in the quantitative analysis (5 cross-sectional). Table 1 provides sample and study characteristics for the 15 included studies. Eleven of the 15 studies (73.3%) were conducted in the United States, 2 in Sweden, 1 in China, and 1 in Australia. Several studies recruited participants from larger population pools; however, as the cohorts reported unique sample sizes, dietary/nutritional measures, and AD biomarker outcomes, these studies were included in the systematic review. A total of 2068 (68% female) subjects were included in the studies, sample sizes ranged from 24 to 1219 participants. Thousand six hundred ninety-eight of these were defined as cognitively normal and 370 subjects were defined as MCI, amnestic MCI (aMCI), or AD. Seven studies were RCTs with a dietary intervention range of 4 weeks–6 months. Seven studies were cross-sectional and one longitudinal observational study was identified. Fourteen studies provided age in years with standard deviation and mean sample ages were 63.4 (SD = 8.2) years. Although heterogeneous, the identified studies were of modest methodological quality and adjusted for a similar battery of covariates (Supplementary Table 2). The main sources of reduced quality of the included studies were nonreporting of statistical power/variability, exposure-outcome order, and multiple exposure measurements.

Thirteen studies reported a significant relationship. Of these, 4 studies pooled from 3 cohorts found in a higher glycemic load was related to increased AD biomarker burden in CSF (Baker et al., 2012; Bayer-Carter et al., 2011; Hanson et al., 2013) and the brain (Taylor et al., 2017), 3 studies pooled from 2 cohorts reported beneficial supplementation effects in CSF (Freund Levi et al., 2014; Freund-Levi et al., 2009) and plasma (Miller et al., 2016) and 6 studies pooled from 5 cohorts found adherence to a MeDi or "AD-protective" (Berti et al., 2015) dietary pattern conferred a reduction in Aβ/tau burden or ratio (Berti et al., 2015, 2018; Gu et al., 2012; Matthews et al., 2014; Merrill et al., 2016; Mosconi et al., 2014). Two studies did not report a significant effect (Freund-Levi et al., 2009; Hill et al., 2018).

3.1.2. Dietary measures

The studies included in this systematic review generated a total of 11 unique dietary models. Of the 15 studies, 3 studies investigated the intake of nutrients that had been previously associated with AD or cognitive function (Berti et al., 2015; Gu et al., 2012; Mosconi et al., 2014). Four studies measured glycemic indices and their relationship to Aβ40/42 in CSF (Baker et al., 2012; Bayer-Carter et al., 2011; Hanson et al., 2013) and the brain (Taylor et al., 2017).

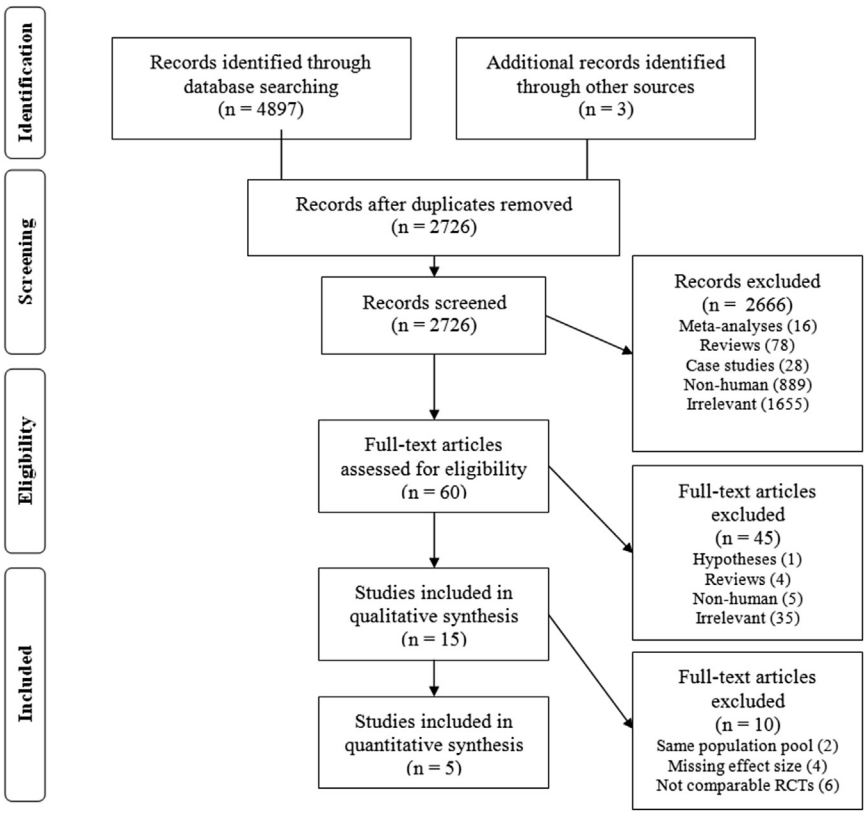

Fig. 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) diagram for systematic review of biomarkers of Alzheimer's disease and diet (Moher et al., 2009).

Table 1
Study characteristics of included studies

Study	Design (follow-up)	Country	n	Cohort	Age (years ± SD)	Measure (diet/ nutrition)	AD biomarker	Classification
Baker et al. (2012)	RCT (4 wk)	USA	41	Veteran Affairs Puget Sound Health Care System	67 ± 7	Low saturated fat/low glycemic index or a high saturated fat/high glycemic index	CSF: Tau, Aβ42	Normal, MCI (MSE)
Bayer-Carter et al. (2011)	RCT (4 wk)	USA	49	Veteran Affairs Puget Sound Health Care System	67 ± 7	Low saturated fat/low glycemic index or a high saturated fat/high glycemic index	CSF: Tau, Aβ40, Aβ42	Normal, aMCI
Berti et al. (2015)	XS	USA	52	New York University Langone School of Medicine	54 ± 12	Of 35 nutrients that have been associated with cognitive function and AD, 5 nutrient patterns (Harvard/ Willet FFQ) identified using PCA	PET: Aβ (^{11}C PiB)	Normal
Freund Levi et al. (2014)	RCT (6 mo)	Sweden	33	OmegAD		Supplementation of docosahexaenoic acid-rich omega-3 fatty acid preparation	CSF: P-tau, T-tau, Aβ42	AD
Freund-Levi et al. (2009)	RCT (6 mo)	Sweden	35	OmegAD	70.3 ± 8.2	Supplementation of docosahexaenoic acid-rich omega-3 fatty acid preparation	CSF: P-tau, T-tau, Aβ42	AD
Hanson et al. (2013)	RCT (4 wk)	USA	47	Veteran Affairs Medical Center	NL:69 ± 7 aMCI:67 ± 6	Low saturated fat/low glycemic index or a high saturated fat/high glycemic index	CSF: Lipid deleted Aβ40 Aβ42	Normal, aMCI
Matthews et al. (2014)	XS	USA	45	New York University Langone School of Medicine	54 ± 11	MeDi adherence (Harvard/Willett semi-quantitative FFQ) dichomitised into HIGH/LOW	PET: Aβ (^{11}C PiB)	Normal
Merrill et al. (2016)	XS	USA	44	University of California	62.6 ± 10.7	MeDi adherence (5-point Likert scale) dichotimised into HIGH/LOW	PET: FDDNP (Aβ and tau)	MCI, subjective memory impairment
Mosconi et al. (2014)	XS	USA	49	New York University - Alzheimer's Disease Core Center	54 ± 11	10 AD-related nutrients (Willett's semi-quantitative FFQ), alcohol, supplements	PET: Aβ (^{11}C PiB)	Normal
Gu et al. (2012)	XS	USA	1219	Washington Heights/ Hamilton Heights Columbia Aging Project	75.4 ± 6.1	10 nutrients (SFA, MUFA, ω-3 PUFA, ω-6 PUFA, vitamin E, vitamin C, β-carotene, vitamin B12, folate, and vitamin D)	Plasma: Aβ40 Aβ42	Normal
Chen et al. (2016)	RCT (6 mo)	China	121	TFA-AD Trial, Huanhu Hospital, Tianjin	68 ± 8	Folic acid daily (1.25 mg d) or placebo	Plasma: Aβ40 Aβ42 Aβ40/42	AD
Miller et al. (2016)	RCT (8 wk)	USA	24	Phoenix (Volunteers recruited)	64.3 ± 10.9	Vitamin D weekly supplementation (50,000 IUs of cholecalciferol) or placebo	Plasma: Aβ40	Normal
Taylor et al. (2017)	XS	USA	128	Alzheimer's Prevention through Exercise (APEX)	71.3 ± 5.1	Sugar/carbohydrate intake and glycemic load (DHQ FFQ) HGLD Pattern (High glycemic load diet)	PET: Aβ (^{18}F Florbetapir)	Normal
Hill et al. (2018)	XS	Australia	111	Women's Healthy Aging Project	70.0 ± 2.6	MeDi adherence (DQES v2) on 0-18 point scale	PET: Aβ (^{18}F Florbetaben)	Normal
Berti et al. (2018)	LT	USA	70	New York University Langone School of Medicine	MeDi-: 50 ± 9 MeDi+ 49 ± 9	MeDi adherence (Harvard FFQ) dichotomised into MeDi+/MeDi-	PET: Aβ (^{11}C PiB)	Normal

Key: ADAS-Cog, Alzheimer disease assessment scale; ANOVA, analysis of variance; ANCOVA, analysis of covariance; APOE-ε4, apolipoprotein E epsilon 4 allele; BMI, body mass index; CI, confidence interval; DHQ, diet history questionnaire; FDDNP, 2-(1-{6-[(2-[fluorine-18]fluoroethyl) (methyl)amino]-2-naphthyl}-ethylidene)malononitrile; FFQ, food frequency questionnaire; HGLD, high glycemic load diet; LT, longitudinal; MeDi, Mediterranean diet; MET, metabolic equivalent of task; MSE, modified mini-mental status examination; MUFA, monounsaturated fatty acid; NL-ENIGMA, effect of a specific nutritional intervention on cerebral glucose metabolism in early Alzheimer's disease; NPI, neuropsychiatric inventory; OR, odds ratio; PA, physical activity; PCA, principal component analysis; PCC, posterior cingulate cortex; PET, positron emission tomography; PiB, Pittsburgh compound-B; PLS, partial least squares; P-tau, phosphorylated tau; PUFA, polyunsaturated fatty acid; RCT, randomized control trial; SE, standard error; SFA, saturated fatty acid; SUVR, standardized uptake value ratio; T-tau, total tau.

Table 2
Summary of results grouped by dietary pattern

Dietary pattern	Number of studies	Cohort classification	AD biomarker	Design	Significant results reported?	Significant Y/N (%)	Direction of effect
Glycemic	4	1 NL 2 NL and aMCI 1 NL and MCI	1 CSF Aβ, 2 CSF Aβ and Tau, 1 PET Aβ	3 RCTs, 1 XS	Yes	4/0 (100%)	Low glycemic diet increased Aβ in CSF. High glycemic diet associated with increased cerebral Aβ burden.
MeDi	4	3 NL 1 MCI	4 PET Aβ	3 XS, 1 LT	Yes	3/4 (75%)	Adherence to MeDi associated with reduction in cerebral Aβ burden.
Nutrients	3	3 NL	2 PET Aβ, 1 plasma Aβ	3 XS	Yes	3/3 (100%)	Higher intake of vitamin B12, vitamin D, ω-3 PUFA associated with lower cerebral Aβ burden. Lower cerebral Aβ burden associated with higher intakes of fresh fruit and vegetables, whole grains fish and low-fat dairies; and a lower intake of sweets, friend potatoes, high-fat dairies, processed meat and butter.
Omega-3	2	2 AD	2 CSF Aβ and Tau	2 RCTs	Yes	1/2 (50%)	Supplementation of docosahexaenoic acid associated with decrease in CSF tau.
Folic	1	1 AD	1 plasma Aβ	1 RCT	Yes	1/1 (100%)	Supplementation of folic acid decreased plasma Aβ
Vit D	1	1 NL	1 plasma Aβ	1 RCT	Yes	1/1 (100%)	Supplementation of vitamin D increased plasma Aβ in vitamin D insufficient older adults.

Key: AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; CSF, cerebrospinal fluid; LT, longitudinal; MCI, mild cognitive impairment; MeDi, Mediterranean diet; NL, cognitively normal; PET, positron emission tomography; PUFA, polyunsaturated fatty acid; RCT, randomized control trial; XS, cross sectional.

Four studies investigated adherence to the MeDi on a 2 (Berti et al., 2018; Matthews et al., 2014), 5 (Merrill et al., 2016), or 19 (Hill et al., 2018) point scale. Four studies investigated nutritional supplementation, omega-3(Freund-Levi et al., 2009; Freund Levi et al., 2014), vitamin D (Miller et al., 2016), and folic acid (Chen et al., 2016).

3.1.3. AD biomarkers

Seven studies utilized PET imaging (4 used ^{11}C Pittsburgh compound B [PiB] (Berti et al., 2015, 2018; Matthews et al., 2014; Mosconi et al., 2014); 1 used ^{18}F Florbetapir (Taylor et al., 2017), 1 used ^{18}F Florbetaben (Hill et al., 2018), and 1 used FDDNP (Merrill et al., 2016)), 5 studies measured CSF levels (Baker et al., 2012; Bayer-Carter et al., 2011; Freund-Levi et al., 2009; Freund Levi et al., 2014; Hanson et al., 2013), and 3 studies measured plasma biomarkers of AD (Chen et al., 2016; Gu et al., 2012; Miller et al., 2016). All 15 studies investigated Aβ, whereas 5 investigated Aβ and tau (Baker et al., 2012; Bayer-Carter et al., 2011; Freund-Levi et al., 2009; Freund Levi et al., 2014; Merrill et al., 2016). Aβ was measured in CSF (Aβ40, Aβ42), plasma (Aβ40, Aβ42, and Aβ40/42) and PET scans (^{11}C PiB, FDDNP, and ^{18}F Florbetatben). Tau was measured in CSF (P-tau, T-tau) and PET scans (FDDNP binding).

3.2. Study findings

3.2.1. PET imaging

Results are summarized in Table 2. Six out of the 7 studies that investigated PET imaging found a significant relationship between their dietary model and brain AD biomarker (Berti et al., 2015, 2018; Hill et al., 2018; Matthews et al., 2014; Merrill et al., 2016; Mosconi et al., 2014; Taylor et al., 2017). Only 1 study utilized a non-NL cohort (Merrill et al., 2016). We identified 4 studies that utilized PiB = Pittsburgh Compound-B (PiB) PET imaging in a healthy (non-MCI/AD) community cohort based in New York (Berti et al., 2015; Matthews et al., 2014; Mosconi et al., 2014). In their cross-sectional analysis, Berti et al. (2015) utilized factor analysis to define nutrient patterns that were associated with PiB retention, defining an AD protective nutrient pattern was consistent with higher intake of fresh fruit and vegetables, whole grains fish and low-fat dairies; and a lower intake of sweets, fried potatoes, high-fat dairies, and processed meat and butter. Several years later, Berti et al. (2018) reported on the only longitudinal study to date investigating diet and AD biomarkers, finding the MeDi-group showed significantly higher PiB-PET Aβ deposition in AD-affected regions at baseline than the MeDi+ group. Longitudinally, the MeDi-group displayed significant increases in Aβ in these regions that were greater than those in the MeDi+ group (Berti et al., 2018). Matthews et al. (2014) dichotomized participants into high(+)/low(-) adherence to the MeDi, finding greater PiB retention in MeDi-compared with MeDi+. Mosconi et al. (2014) found higher intake of vitamin B_{12}, vitamin D, and ω-3 polyunsaturated fatty acids (PUFA) were associated with lower Aβ load as detected by PiB. Two studies, 1 in Australia (Hill et al., 2018) and 1 in the United States (Taylor et al., 2017), utilized ^{18}F radiotracers to investigate Aβ burden in elderly participants. Taylor et al. (2017) found a high glycemic diet was associated with higher global and regional Aβ burden as measured by ^{18}F florbetapir in cognitively normal participants. Independent glycemic measures such as sugar intake, carbohydrate intake, and glycemic load were also associated with global and regional Aβ burden. Hill et al. (2018) found no association between MeDi adherence and Aβ burden as measured by ^{18}F florbetaben in both APOE-ε4 +/- healthy female participants. One study utilized FDDNP to measure the relationship between self-reported adherence to a MeDi dietary pattern and Aβ burden in participants diagnosed with MCI or subjective memory impairment (SMI) (Merrill et al., 2016). Regardless of cognitive status (MCI/SMI), a MeDi-type dietary pattern was associated with lower FDDNP-PET Aβ binding in AD-associated regions such as the frontal, parietal, medial and lateral temporal, posterior cingulate (Merrill et al., 2016).

3.2.2. CSF biomarkers

This systematic review found 4 of the 5 included studies found a significant effect of diet/supplementation on CSF AD biomarkers. Two studies investigated AD cohorts (Freund-Levi et al., 2009; Freund Levi et al., 2014) and 3 studies investigated NL and MCI/aMCI (Baker et al., 2012; Bayer-Carter et al., 2011; Hanson et al., 2013). Four studies investigated either phosphorylated (P-) or total (T-) tau levels in CSF as well as Aβ (Baker et al., 2012; Bayer-Carter et al., 2011; Freund Levi et al., 2014; Freund-Levi et al., 2009), and 1

study investigated lipid deleted Aβ40 and Aβ42 (Hanson et al., 2013). Freund-Levi et al. (2009) found no significant effect of a docosahexaenoic acid intervention on CSF biomarkers of AD (Aβ42, P-tau, T-tau); however, later reported a significant inverse correlation between levels of CSF P-tau/T-tau and levels of docosahexaenoic acid (Freund Levi et al., 2014). Three studies investigated glycemic indices and AD biomarkers of participants in the Veteran Affairs Puget Sound Health Care System (Bayer-Carter et al., 2011; Baker et al., 2012; Hanson et al., 2013). Bayer-Carter et al. (2011) found a low-saturated fat/low-glycemic index dietary intervention increased Aβ42 for amnestic MCI (aMCI) participants, yet decreased Aβ42 for the healthy adults. Conversely, the high-saturated fat/high-glycemic diet increased Aβ42 for healthy adults, yet had no significant effect on the aMCI participants (Bayer-Carter et al., 2011). In a later study drawn from the same participant pool, high levels of physical activity attenuated the effects of the high-saturated fat/high-glycemic diet on Aβ42 in healthy adults yet potentiated the effects of the low-saturated fat/low-glycemic index diet on MCI participants (Baker et al., 2012). Hanson et al. (2013) followed up by investigating lipid-deleted Aβ40 and Aβ42, finding the high-saturated fat/high-glycemic diet significantly increased lipid-deleted Aβ42, whereas the low-saturated fat/low-glycemic diet tended to be associated with a decrease in Aβ40.

3.2.3. Plasma

Three studies investigated plasma biomarkers of AD, and all of these described significant findings regarding dietary associations with plasma biomarkers of AD. Two studies investigated healthy NL participants (Gu et al., 2012; Miller et al., 2016) and 1 studied an AD cohort (Chen et al., 2016). Gu et al. (2012) investigated the cross sectional association of 10 nutrients with Aβ40 and Aβ42 in a large cohort (n = 1219) of healthy adults, finding that higher intake of ω-3 PUFA was significantly associated with a reduction in Aβ40 (unadjusted) and Aβ42. The other 2 studies investigating plasma AD biomarkers were RCTs, 1 investigating a 6 months folic acid intervention in China (Chen et al., 2016), the other was based in the United States investigating vitamin D supplementation (Miller et al., 2016). Given low folate levels have been associated with lower AD risk (Das, 2008) and patients with AD have low folate and vitamin B12, Chen et al. (2016) conducted an RCT on newly diagnosed patients with AD being treated with donepezil. Participants in the intervention group displayed significantly higher MMSE means, a higher Aβ42/Aβ40 ratio, and lower Aβ40 than the control group (Chen et al., 2016). In an 8-week trial in vitamin D insufficient adults, Miller et al. (2016) investigated whether vitamin D treatment (50,000 IU/week) had an impact on Aβ40 clearance. This study found vitamin D supplementation significantly enhanced brain Aβ transportation to the periphery. Miller et al. (2016) found a correlation between Aβ40 and total 25-hydroxyvitamin D in participants aged over 60 years, suggesting older individuals may have a stronger response to the treatment than their younger counterparts.

3.3. Quantitative analysis

Five studies were included in the meta-analysis (Gu et al., 2012; Hill et al., 2018; Merrill et al., 2016; Mosconi et al., 2014; Taylor et al., 2017). All 5 studies provided standardized effect sizes for the effect of diet on Aβ in either PET scans (Hill et al., 2018; Merrill et al., 2016; Mosconi et al., 2014; Taylor et al., 2017) or plasma measures (Gu et al., 2012). One study provided effect sizes and SEs for tau in addition to Aβ (Merrill et al., 2016); however, this was not comparable to any other study, therefore only the Aβ relationship is reported in the quantitative analysis. Pooled results suggest that dietary components are associated with a reduction in Aβ deposition. Based on 5 pooled studies with 19 effect sizes, the meta-analysis of Aβ deposition outcomes revealed a significant association between increased adherence to a MeDi or increased adherence to an "AD-protective" dietary pattern and a 0.11 (95% CI 0.04–0.17, $p = 0.002$) point lower deposition in Aβ. Results of the meta-analysis have been summarized in a forest plot (Supplementary Fig. 1) and funnel plot (Supplementary Fig. 2).

4. Discussion

Given the existing evidence reporting a dietary effect on AD prevalence, this systematic review and meta-analysis support the notion that diet and nutrition display potential for non-pharmacological prevention. Of the 15 studies that were identified during this systematic review of the evidence, 13 studies reported a statistically significant relationship, supporting the promising notion that diet may have preventative potential for AD. We identified substantial heterogeneity in dietary measures (11 unique models) and AD biomarkers (7 unique measures), although the studies adjusted for a similar battery of demographic, lifestyle, and physical covariates. Supplementation of vitamin D/folic/ω-3 and adherence to a dietary pattern emphasizing a higher intake of fruit, vegetables, whole grains, oily fish, and low-fat dairy was associated with a reduction in AD biomarker burden. Conversely, a diet characterized by consumption of high glycemic, high saturated fat foods were associated with an increase in AD biomarker burden. Meta-analysis revealed a small but significant association between increased adherence to a MeDi or "AD-protective" dietary pattern and lower AD biomarker burden. The findings of this review support the notion of diet as a potential modifiable risk factor for AD; however, the underlying mechanisms of dietary contributions to the mitigation of AD pathology remain a challenge for future research.

In cross-sectional (Matthews et al., 2014; Merrill et al., 2016) and longitudinal (Berti et al., 2018) research, adherence to a MeDi was associated with lower Aβ deposition. These data indicate that diet may influence AD progression, and this review supports the notion of a possible pathophysiological relationship, as has been described in several clinical studies to date (Feart et al., 2009; Scarmeas et al., 2006).

Participants in the studies identified were predominantly cognitively normal; however, we did observe investigations along the disease spectrum (NL > MCI > AD). Subgroup analysis identified that all AD measurements were investigated in at least 1 cognitive classification (NL, MCI, or AD), and we observed no between-study difference in findings that investigated the same biomarker or method of measurement. However, we did observe within-study difference in 1 cohort consisting of multiple cognitive classifications. Bayer-Carter et al. (2011) reported an opposite effect for NL/MCI individuals adhering to a HIGH\LOW fat/glycemic index dietary intervention. The LOW diet increased CSF Aβ42 concentrations for the aMCI group, however, increased CSF Aβ42 for the NL group. Bayer-Carter et al. (2011) speculate this relationship may be due to a tipping point of CSF concentrations, as have been described in animal models (DeMattos et al., 2002).

We observed several RCTs (Freund-Levi et al., 2009; Freund Levi et al., 2014) and observational studies (Gu et al., 2012; Mosconi et al., 2014) reported a positive effect of ω-3 PUFA consumption on serum and CSF AD biomarker burden. Highly unsaturated fatty acids, such as ω-3 and ω-6, have been seen in lower levels in AD compared with controls (Tully et al., 2003); however, we observed significant and nonsignificant effects on PUFA supplementation. This systematic review supports the notion that the beneficial effects of ω-3 PUFA consumption could be explained by a biomarker mechanism; however, the relationship between ω-3 PUFA and AD

biomarkers may be mediated by another factor, such as cognitive function (Robinson et al., 2010), that were not measured in this systematic review. High glycemic loaded diets were a focus of the identified studies, whereas only 1 study specifically investigated carbohydrate consumption (Taylor et al., 2017). Only 3 studies utilized an a posteriori method of diet/nutritional measure. The utility of a posteriori approaches to investigating diet-disease associations has been well described (Hodge and Bassett, 2016); however, a paucity of studies in this systematic review utilized statistical methods to define their dietary model.

Previous research has suggested that AD prevalence is related to diet (Yusufov et al., 2017). Our systematic review has substantiated these findings with respect to the underlying pathophysiology of the hallmark AD biomarkers in plasma, CSF, and the brain. Taken together with prior literature, these findings are consistent that modifiable lifestyle risk factors are associated with in vivo biomarker burden as well as manifestations of AD incidence.

This systematic review and meta-analysis provides support for the notion of a physiological mechanism of a diet/AD relationship that has been reported in several clinical studies. We identified substantial heterogeneity in study protocols, an array of dietary measures, and multiple methods of tau/amyloid measurement. Our review was limited by a small number of identified studies. Studies were predominantly cross-sectional (14 of 15), limiting causal inferences from the available published findings. Given several studies pooled their cohorts from the same larger populations, the possibility of participants overlapping in separate studies may bias the strength of our findings; however, all cohorts analyzed in the systematic review were unique and were therefore not removed from qualitative analysis. Other mechanisms of neurodegeneration, such as white matter hyperintensities and atrophy, may also contribute to the clinical manifestation of disease progression, however, were outside the scope of this review.

Future research would benefit from a focus on dietary patterns with robust study designs and larger samples to clarify the therapeutic utility of diet in AD. There was only 1 longitudinal investigation that investigated dietary patterns and AD biomarkers at 2 distinct time points and only 3 studies that utilized an a posteriori method of dietary analysis. Future longitudinal research is of particular relevance to the development of preventative measures, as well-defined cohorts allow researchers to eliminate mediators of a potential diet-AD mechanism. Our findings support a relationship between diet/nutrition and biomarkers of AD; however, given biomarkers can manifest decades before symptomatology, it remains to be seen how long-term dietary choices can impact subsequent pathology.

5. Conclusions

The findings from this systematic review and meta-analysis suggest adherence to a MeDi-styled dietary pattern was associated with a reduction in AD biomarkers and subsequent pathology. Conversely, adherence to a high-glycemic, high saturated fat diet was associated with an increase in AD biomarker burden. These findings shed light on the pathophysiological processes that may underpin the association between diet and AD prevalence in previous studies.

Disclosure

CS has provided clinical consultancy and been on scientific advisory committees for the Australian Commonwealth Scientific and Industrial Research Organization, Alzheimer's Australia, University of Melbourne and other relationships that are subject to confidentiality clauses. She has been a named Chief Investigator on investigator driven collaborative research projects in partnership with Pfizer, Merck, Bayer, and GE. She may accrue revenues from patent in pharmacogenomics prediction of seizure recurrence. EH, AMG, and AG have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2018.12.008.

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