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Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 535-541

Alzheimer's & Dementia

Featured Article

Dietary patterns and β-amyloid deposition in aging Australian women

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Abstract

Introduction: Evidence indicates that associations between diet and Alzheimer's disease may occur through biomarker pathways such as amyloid-β (Aβ); however, few studies have investigated dietary/Aβ relationships, and no study has investigated this relationship in women.
Methods: Dietary patterns were extrapolated for 115 participants from the Women's Health Aging Project. Aβ deposition was measured via *in vivo* F-18 florbetaben positron emission tomography scanning.
Results: Participants were, on average, aged 70 years (±2.63 SD), had 13 years of education (±3.57 SD), a BMI of 28 kg/m^2 (±5.46 SD), and a daily energy intake of 5161 kJ (±1679.03 SD). Four dietary patterns were identified: high fat, Mediterranean, junk food, and low fat. Adherence to the junk food diet was a significant predictor of Aβ deposition ($\beta = .10$, $P = .03$).
Discussion: This study highlights the potential of diet to influence neurodegenerative disease and as a potential modifiable lifestyle risk factor for Alzheimer's disease.
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Keywords: Biomarkers; Alzheimer's disease; Neuropathology; β-amyloid protein; Diet; Nutrition; Dietary pattern; Factor analysis; Women

1. Introduction

Diet may play a substantial role in the Alzheimer's disease (AD) symptomatology and offer great potential for non-pharmacological prevention. Epidemiological evidence has suggested increased adherence to a Mediterranean diet [1], low glycemic index [2,3], and higher consumption of omega-3 polyunsaturated fatty acids [4] were associated with a decrease in AD biomarker burden. Systematic review found 50 out of 64 studies revealed an association between diet and AD incidence [5]; however, only one study has used *a priori* analysis to analyze dietary associations with the hallmark cerebral protein implicated in AD, β-amyloid (Aβ). In this study, dietary pattern analysis identified a pattern characterized by a higher intake of fresh fruit, vegetables, whole grains, fish, and low-fat dairies, and a lower intake of sweets, fried potatoes, processed meat, and butter was negatively associated with *in vivo* cerebral Aβ [6].

Furthermore, male and mixed cohort studies predominate the research, and to date, no study has investigated this relationship specifically in women. Women are more likely than men to develop AD [7], have a higher penetrance for the apolipoprotein ε-4 (APOE-ε4) allele [8], and are more likely to progress from mild cognitive impairment to AD [8]. Impacts of higher male mortality, vascular risk factors, and the postmenopausal loss of estrogenic neuroprotection suggest females are 1.5 times more likely to develop AD than men [9]. Given sex differences in AD risk, research is needed for those at greater risk of disease.

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https://doi.org/10.1016/j.trci.2018.09.007
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Studies investigating *in vivo* AD biomarkers are needed to clarify how nutrition promotes healthy brain aging and to identify neuroprotective patterns for those at the greatest risk of AD. The objectives of this study were to identify dietary patterns using an *a priori* approach and investigate their associations with Aβ deposition in healthy aging Australian women. We previously reported on a lack of a relationship between a healthy Mediterranean diet and Aβ deposition [10] and hypothesized this was due to limitations of the self-reported food frequency questionnaire in measuring the potentially beneficial phytochemicals in olive oil. Given high-fat, high-glycemic diets have been associated with increased AD biomarker burden, we hypothesized that a dietary pattern characterized by high-fat, high-sugar content would be associated with an increase in cerebral Aβ pathology.

2. Methods

2.1. Study population

Participants were sought from the 2012 follow-up of the Women's Health Ageing Project (WHAP), an epidemiologically sourced prospective study of healthy aging Australian women. WHAP is an extension of the Melbourne Women's Midlife Health Project. Briefly, 438 women within the Melbourne metropolitan area were identified by random digit dialing in 1991. Women were eligible for the cohort if they were Australian-born, aged 45–55 years, had menstruated in the three months before recruitment, and were not taking estrogen-containing hormone replacement therapy. In 2012, participants were re-contacted and invited to participate in a late-life health study. Clinical assessments were conducted on 252 participants by trained field researchers. The clinical assessments included a battery of validated measures of physical health, sociodemographics, lifestyle, cognitive function, psychological health, and biomarkers. A complete methodology has been published elsewhere [11].

2.2. Diet

Participants completed a validated food frequency questionnaire entitled the Dietary Questionnaire for Epidemiological Studies Version 2 (DQES v2) [12]. The DQES v2 incorporates 80 food items with frequency response options on 74 of these items. The DQES v2 covers five types of dietary intake: cereals/sweets/snacks, dairy/meat/fish, fruits, vegetables, and alcoholic beverages. Data collected by the DQES v2 was used to calculate daily energy and nutrient intakes by the Cancer Council of Victoria based on Australian nutrient composition data from NUTTAB95, collated via the Composition of Foods, Australia [13]. Individuals were removed if their energy intake was reported as below 3000 kJ/day or above 20,000 kJ/day. All food items were reported in grams per day and placed into 33 food groups defined *a priori* (Table 1) that was similar to those used by others [14,15]. Dietary patterns were extrapolated from food groupings using iterated principal factor analysis with oblique varimax rotation due to the presumed intercollinearity and nonindependence of dietary patterns.

2.3. Imaging

In the 2012 follow-up, all WHAP participants were offered the opportunity to have cerebral imaging. Aβ deposition was measured via *in vivo* F-18 Florbetaben positron

Table 1
Food groupings from Dietary Questionnaire for Epidemiological Studies Version 2 (DQES v2)

Food group	Items in the DQES v2
Whole grains	All bran, bran flakes, high fiber white bread, muesli, multigrain bread, porridge, rye bread, Weet-Bix, wholemeal bread
Refined grains	Corn flakes, crackers, pasta, rice, white bread
Red meats	Beef, lamb, pork, veal
Processed meats	Bacon, salami, sausages
Poultry	Chicken
Takeaway foods	Hamburger, meat pies, pizza
Fried fish	Fried fish
Other fish	Fish (nonfried), tinned fish
Fried potatoes	Chips (French fries)
Other potato	Potatoes
Yellow or red vegetables	Capsicum, carrots, pumpkin
Legumes	Baked beans, green beans, other beans, peas, tofu
Cruciferous vegetables	Broccoli, cabbage, cauliflower
Leafy green vegetables	Lettuce, spinach
Other vegetables	Bean sprouts, beetroot, celery, cucumber, garlic, mushrooms, onion, zucchini
Tomato	Tomatoes
Fresh fruit	Apples, apricots, avocado, bananas, mango, melon, oranges, peaches, pears, pineapple, strawberries
Canned fruit	Tinned fruit
Cakes, biscuits, sweet pastries	Cakes, sweet biscuits
Low-fat dairy products	Flavored milk drink, low-fat cheese, reduced fat milk, ricotta cheese, cottage cheese, skim milk
Full-fat dairy products	Cream cheese, firm cheese, full-cream milk, hard cheese, ice cream, soft cheese, yoghurt
Soya milk	Soya milk
Confectionery	Chocolate
Added sugar	Jam, sugar
Crisps	Crisps
Nuts	Nuts, peanut butter
Eggs	Eggs
Fruit juice	Fruit juice
Saturated spreads	Butter, butter-margarine blends, margarine
Unsaturated spreads	Monounsaturated margarine, polyunsaturated margarine
Alcohol–beer	Heavy beer, light beer
Alcohol–wine	Red wine, white wine
Alcohol–spirits	Fortified wines, spirits

emission tomography (PET) at the Austin Health Centre for PET in Victoria, Australia. Participants received 250 MBq of 18F-florbetaben intravenously, with a 20-minute acquisition commencing 90 minutes after injection. Standardized uptake values (SUVs) were calculated for all brain regions examined, and standard uptake value ratios (SUVRs) were generated by normalizing regional SUVs by the cerebellar cortex with atrophy correction from structural magnetic resonance imaging. Neocortical SUVR, a global index of Aβ burden, is expressed as the average SUVR of the area-weighted mean. Area-weighted means were calculated for each participant by averaging the frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions. This protocol has been described elsewhere [11].

2.4. Covariates

Age (in years), education (in years), and body mass index (BMI) were collected as part of the clinical assessments in 2012. Total energy intake in kilojoules was calculated by the Cancer Council of Victoria from the DQES v2. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Savings Score was used as a valid indicator of cognitive ability [16]—it has been suggested as the most reliable index in differentiating cognitively normal individuals from AD [17]. Participants' APOE genotype was determined by direct sequencing and were dichotomized as an APOE ε4 carrier (APOE ε2/ε4, APOE ε3/ε4, and APOE ε4/ε4) or a noncarrier. Adherence to identified dietary patterns was converted from weighted factor loadings to binary adherence to minimize the intracorrelations between variables. All analyses were adjusted for age in years, education in years, energy intake (kJ/day), cognition (CERAD Savings), and binary presence of the APOE ε4 allele.

2.5. Statistical analysis

All analyses were conducted in STATA software on Windows operating system. Complete data were available for 115 WHAP participants, and there were no significant differences between the included (n = 115) and excluded (n = 137) cohorts. PET SUVRs displayed a positive skew that was rectified using 1/square transformation; therefore, results should be interpreted as inverse coefficient derivatives. Generalized linear models were used to assess associations between Aβ deposition and dietary patterns scores. Generalized linear models were adjusted for age in years, education in years, cognition (CERAD Savings), and binary presence of the APOE ε4 allele.

3. Results

Four dietary patterns were identified: high fat, Mediterranean, junk food, and low fat. Factor loadings (Table 2 and Fig. 1) indicated that the high-fat diet loaded heavily on food groups such as processed meats, fried fish, red meats, fried potatoes, and poultry. The Mediterranean style diet loaded chiefly on whole grains, vegetables, nuts, fish, and wine as the main source of alcohol. The unhealthy junk food pattern was characterized by high consumption of takeaway foods, added sugar, confectionary and cakes, biscuits, and sweet pastries, whereas the low-fat diet loaded heavily on low-fat dairy products, vegetables, and unsaturated spreads.

Table 2
Dietary pattern factor loadings for all WHAP participants in 2012 (n = 224)

Variable	High fat	Mediterranean	Junk food	Low fat
Eigenvalue	3.03802	2.13623	1.80738	1.55595
Variance	2.15252	2.00648	1.58108	1.39511
Proportion	0.3164	0.2949	0.2324	0.2051
Whole grains		0.3668	0.2096	0.1387
Refined grains	0.1598	0.1673	0.1247	
Red meats	0.5464			0.1128
Processed meats	0.7281			
Poultry	0.4130	0.1302		0.1549
Takeaway foods	0.2021	−0.2543	0.3427	
Fried fish	0.4662	0.2473		
Other fish	0.4029	0.3867		
Fried potatoes	0.4195			
Other potato	0.1803		0.1127	0.3143
Yellow or red vegetables	0.1675	0.2594	0.1480	0.5034
Legumes			0.2923	0.3134
Cruciferous vegetables		0.2117	−0.1027	0.4114
Leafy green vegetables		0.5466		
Other vegetables	0.1961	0.6869		0.1286
Tomato	−0.2459	0.2255		
Fresh fruit	−0.2786	0.3381	0.1887	
Canned fruit			0.1337	
Cakes, biscuits, sweet pastries			0.6350	
Low-fat dairy products	−0.2222			0.5117
Full-fat dairy products	0.1754		0.1255	−0.4775
Soya milk		0.1843		−0.1101
Confectionery	−0.1195	0.2484	0.5211	
Added sugar	0.1263		0.4327	
Crisps	0.1405	0.1229		
Nuts		0.4485	0.1703	
Eggs	0.1083	0.1448		
Fruit juice	−0.1134			
Saturated spreads				−0.2113
Unsaturated spreads				0.2165
Alcohol–beer	0.1540	−0.1618		−0.1272
Alcohol–wine	0.1345	0.1586	−0.2868	

Rotated factor loadings for iterated principal factor analysis with oblique promax rotation. Blanks represent absent loadings (<0.1). Alcohol–spirits not shown due to not loading (>0.1) on any factor.

Participants' characteristics are found in Table 3. Participants in the Mediterranean diet group (n = 31) displayed the highest level of education (14.10 ± 3.87 years), highest CERAD Savings score (72.97 ± 31.07), and lowest level of Aβ deposition (PET SUVR 1.0834 ± 0.14). Daily energy intake was highest in the high-fat group (5443.46 ± 2116.50 kJ/day) and lowest in the Mediterranean group (4677.26 ± 1242.79 kJ/day). Significant group differences were observed in education, energy intake, and CERAD

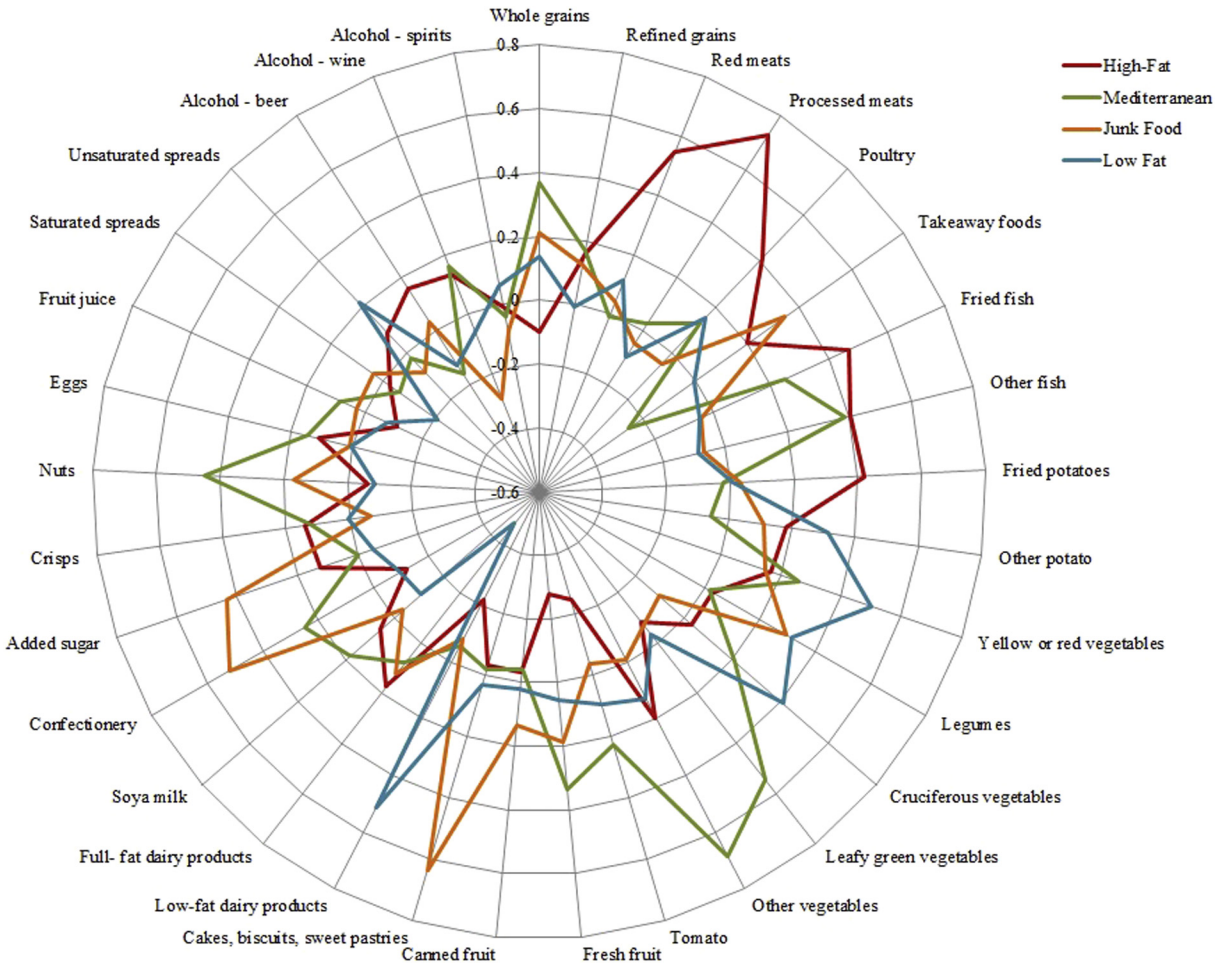

Fig. 1. Spider diagram of factor loadings by dietary patterns.

Savings and were therefore adjusted for in all generalized linear models.

Adherence to the junk food diet (Table 4) was a significant predictor of Aβ deposition (β = .10, P = .036) as was binary presence of the APOE ε4 allele (β = .11, P = .004). No significant interaction effects were observed in the combined effect of diet and APOE ε4 on Aβ deposition (P = .59). All other dietary patterns were not associated with Aβ deposition. Age, education, and cognition were also not significantly associated with Aβ deposition.

4. Discussion

In this cross-sectional study in Australian women, adherence to the junk food was a significant predictor of cerebral Aβ deposition. These results suggest that higher adherence to a high-fat, high-sugar style diet may be associated with an increased deposition of AD biomarkers and a higher risk for disease.

We observed similar cognitive status between dietary groups. However, women adhering to the Mediterranean dietary pattern displayed significantly higher cognitive scores than the other dietary groups. In the longitudinal Nurse's Health Study, women with higher Mediterranean diet adherence had significantly higher overall cognitive status [18]. Given evidence for the cardiovascular determinants of cognitive decline [19,20], there is clear evidence for an inverse relationship between Mediterranean diet adherence and cognition; however, the cross-sectional nature of this study limits our ability to address this relationship.

Our results contribute to the growing body of evidence linking diet with AD. A high-glycemic diet has been associated with greater amyloid burden in the brain [2] and cerebrospinal fluid measures [3,21,22]. A principal component analysis on nutrient intake patterns showed consumption of omega-3 fatty acids, zinc, vitamin B-12, and vitamin D was associated with decreased amyloid deposition [6,23]. Consumption of omega-3 fatty acid supplementation has been shown to be related to tau (phosphorylated and total) and amyloid biomarkers of AD in cerebrospinal fluid [24]. Serum docosahexaenoic acid has also been inversely associated with cerebral amyloid burden [25].

Research has established that diets with higher consumption of sugar, carbohydrates, and high-glycemic foods are

Table 3
Descriptive statistics for the included participants grouped by adherence to dietary patterns identified using IPFA

Variable	High fat (n = 24)	Mediterranean (n = 31)	Junk food (n = 24)	Low fat (n = 35)	Total (n = 115)
Age (in years)	69.79 ± 2.42	69.45 ± 2.23	70.41 ± 3.19	69.57 ± 2.70	69.76 ± 2.63
Education (in years)	12.88 ± 3.67	14.10 ± 3.87	11.50 ± 2.96	12.63 ± 3.36	12.84 ± 3.57
BMI	28.58 ± 6.75	27.43 ± 5.48	27.14 ± 5.58	29.29 ± 4.26	28.18 ± 5.46
Energy (kJ/day)	5443.46 ± 2116.50	4809.79 ± 1145.51	6035.40 ± 1993.21	4677.26 ± 1242.79	5160.53 ± 1679.03
APOE positive, n (%)	9 (37.5)	9 (29.0)	9 (37.5)	10 (28.57)	37 (32.46)
CERAD Savings Score (%)	72.93 ± 18.08	72.97 ± 31.07	65.57 ± 28.76	63.34 ± 28.62	68.45 ± 27.52
PET SUVR (raw)	1.1296 ± 0.1539	1.0835 ± 0.1427	1.2150 ± 0.2458	1.1300 ± 0.2336	1.1352 ± 0.2026
PET SUVR (transformed)	0.8185 ± 0.1770	0.8829 ± 0.1646	0.7389 ± 0.2174	0.8446 ± 0.2043	0.8273 ± 0.1959

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; PET, positron emission tomography; SUVR, standard uptake value ratio.

NOTE. If not otherwise described, data are presented as mean ± standard deviation of the mean.

associated with impaired glucose metabolism [26]. Disrupted glucose metabolism affects the production and clearance of Aβ and tau phosphorylation [27], and both insulin resistance [28] and type-2 diabetes [29] are risk factors for AD. Several animal studies have illustrated that a high-fat diet causes brain Aβ accumulation in wild-type rabbits [30] and transgenic mice [31,32]. Furthermore, human APOE isoforms have been shown to modulate glucose and metabolic pathways, with the APOE ε3/ε4 variants showing markedly reduced glucose uptake and metabolism in mouse models [33]. APOE ε2 brains demonstrated a more robust metabolic profile than APOE ε3/ε4, suggesting a physiological mechanism for its protective role against AD [33].

We speculate that the relationship observed between a high-fat, high-sugar diet and increased cerebral Aβ deposition may be modulated by impaired glucose metabolism in this female-only cohort. We believe our results suggest an impaired glucose metabolic pathway interacting with an APOE-Aβ physiological mechanism. Research has been shown that APOE ε4 confers a greater risk in women than men [8]. Women with a single APOE ε4 allele have up to a four-fold increase in risk when compared with women homozygous for APOE ε3; however, men with a single APOE ε4 allele have little to no increase in risk [34]. Given animal model evidence for an APOE-mediated glucose metabolism [33], females may experience greater AD risk due to a mechanistic action in their glucose metabolism. Further research is required to elucidate the physiological mechanisms that underpin this relationship, for example, to replicate animal evidence of glucose metabolism in human models of APOE ε4 isoforms.

Our findings strengthen the hypothesis of diet being a modifiable risk factor for AD by linking amyloid deposition with an unhealthy-type diet in a female-only cohort. These findings suggest a metabolic pathway linking diet with cerebral Aβ deposition and should motivate investigations into dietary impacts on glucose metabolism by variations in presence of the APOE ε2/ε3/ε4 alleles.

Table 4
Generalized linear model for independent variables (PET SUVR) and four dietary patterns identified using iterative principal factor analysis. (95% CIs shown; n = 114)

PET SUVR	Coefficient	Std. Err.	*P*	CI lower	CI higher
High fat	−0.00705	0.04372	.872	−0.09273	0.07864
Mediterranean	0.06390	0.04349	.142	−0.02135	0.14915
Junk food	−0.09740	0.04511	**.031**	−0.18582	−0.00898
Low fat	0.02338	0.03962	.555	−0.05428	0.10103
Age (in years)	−0.00120	0.00702	.864	−0.01495	0.01256
Education (in years)	0.00139	0.00502	.781	−0.00845	0.01125
BMI	−0.00076	0.00326	.816	−0.00714	0.00563
Energy (kJ/day)	−0.00001	0.00001	.309	−0.00003	0.00001
APOE Presence	−0.10916	0.03919	**.005**	−0.18598	−0.03233
CERAD Savings Score	0.00125	0.00065	.054	−0.00002	0.00252

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; PET, positron emission tomography; SUVR, standard uptake value ratio.

NOTE. Bold indicates statistical significance ($P < .05$). CIs are for coefficient. Analysis adjusted for age in years, education in years, cognition (CERAD Savings score), and binary presence of the APOE ε4 allele.

Acknowledgments

The authors would like to acknowledge the contribution of the participants and their supporters who have contributed their time and commitment for over 20 years to the university. A full list of all researchers contributing to the project and the membership of our Scientific Advisory Board is available at http://www.medrmhwh.unimelb.edu.au/Research/WHAP.html.

Funding sources: Funding for the Healthy Aging Program (HAP) has been provided by the National Health and Medical Research Council [NHMRC grants 547600, 1032350, and 1062133], Ramaciotti Foundation, Australian Healthy Aging Organisation, the Brain Foundation, the Alzheimer's Association [NIA320312], Australian Menopausal Society, Bayer Healthcare, Shepherd Foundation, Scobie and Claire Mackinnon Foundation, Collier Trust Fund, J.O. & J.R. Wicking Trust, Mason Foundation, and the Alzheimer's Association of Australia. Inaugural funding was provided by VicHealth and the NHMRC. The Principal Investigator of HAP (C.Sz.) is supported by the National Health and Medical Research Council. The authors thank Professor Graham Giles of the Cancer Epidemiology & Intelligence Division, Cancer Council Victoria, for permission to use the DQES

v2. E.H. would like to acknowledge support from the Australian Government Research Training Program Scholarship.

Ethical approval: This study received approval from the University of Melbourne Human Research Ethics Committee (HREC: 1750632.1, 010528, 010411, 1034765, and 1647448) and was carried out in accordance with the Declaration of Helsinki. All participants signed written informed consent before participation.

C.S. 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. The other authors have no conflict of interest to report.

RESEARCH IN CONTEXT

1. Systematic review: The authors previously conducted a systematic review that highlighted the paucity of research regarding dietary adherence and biomarkers of Alzheimer's disease. This review was conducted in accordance with PRISMA guidelines (PROSPERO: CRD42017076389) searching MEDLINE, PubMed, PsycINFO, Google Scholar, and SCOPUS databases.
2. Interpretation: Our findings contribute to the growing body of evidence linking diet with Alzheimer's disease. We speculate that the relationship observed between a high-fat, high-sugar diet and increased cerebral β-amyloid deposition is affected by impaired glucose metabolism. These findings suggest an apolipoprotein E (APOE)–mediated glucose metabolic pathway.
3. Future directions: Our research suggests a metabolic pathway linking diet with cerebral Aβ deposition and should motivate investigations into dietary impacts on glucose metabolism and Alzheimer's disease biomarker deposition by variations in presence of the APOE ε2/ε3/ε4 alleles.

References

[1] Merrill DA, Siddarth P, Raji CA, Emerson ND, Rueda F, Ercoli LM, et al. Modifiable risk factors and brain positron emission tomography measures of amyloid and tau in nondemented adults with memory complaints. Am J Geriatr Psychiatry 2016;24:729–37.
[2] Taylor MK, Sullivan DK, Swerdlow RH, Vidoni ED, Morris JK, Mahnken JD, et al. A high-glycemic diet is associated with cerebral amyloid burden in cognitively normal older adults. Am J Clin Nutr 2017;106:1463–70.
[3] Bayer-Carter JL, Green PS, Montine TJ, VanFossen B, Baker LD, Watson GS, et al. Diet intervention and cerebrospinal fluid biomarkers in amnestic mild cognitive impairment. Arch Neurol 2011;68:743–52.
[4] Gu Y, Schupf N, Cosentino SA, Luchsinger JA, Scarmeas N. Nutrient intake and plasma beta-amyloid. Neurology 2012;78:1832–40.
[5] Yusufov M, Weyandt LL, Piryatinsky I. Alzheimer's disease and diet: A systematic review. Int J Neurosci 2017;127:161–75.
[6] Berti V, Murray J, Davies M, Spector N, Tsui WH, Li Y, et al. Nutrient patterns and brain biomarkers of Alzheimer's disease in cognitively normal individuals. J Nutr Health Aging 2015;19:413–23.
[7] Pike KE, Ellis KA, Villemagne VL, Good N, Chételat G, Ames D, et al. Cognition and beta-amyloid in preclinical Alzheimer's disease: Data from the AIBL study. Neuropsychologia 2011;49:2384–90.
[8] Altmann A, Tian L, Henderson VW, Greicius MD. Sex modifies the APOE-related risk of developing Alzheimer disease. Ann Neurol 2014;75:563–73.
[9] Viña J, Lloret A. Why women have more Alzheimer's disease than men: Gender and mitochondrial toxicity of amyloid-β peptide. J Alzheimer's Dis 2010;20:527–33.
[10] Hill E, Szoeke C, Dennerstein L, Campbell S, Clifton P. Adherence to the Mediterranean Diet is not Related to Beta-Amyloid Deposition: Data from the Women's Healthy Ageing Project. J Prev Alzheimers Dis 2018;5:137–41.
[11] Szoeke C, Coulson M, Campbell S, Dennerstein L. Cohort profile: Women's Healthy Ageing Project (WHAP): A longitudinal prospective study of Australian women since 1990. Women's Midlife Heal 2016;2:5.
[12] Giles GG, Ireland PD. Dietary Questionnaire for Epidemiological Studies (Version 2). Melbourne, Australia: The Cancer Council of Victoria; 1996.
[13] Thomas S, Corden M. Metric Tables of Composition of Australian Foods. Canberra, Australia: Australian Government Publishing Service; 1977.
[14] Ambrosini GL, Fritschi L, De Klerk NH, Mackerras D, Leavy J. Dietary patterns identified using factor analysis and prostate cancer risk: A case control study in Western Australia. Ann Epidemiol 2008;18:364–70.
[15] Ambrosini GL, Oddy WH, Robinson M, O'Sullivan TA, Hands BP, De Klerk NH, et al. Adolescent dietary patterns are associated with lifestyle and family psycho-social factors. Public Health Nutr 2009;12:1807–15.
[16] Lamberty GJ, Kennedy CM, Flashman LA. Clinical utility of the CERAD word list memory test. Appl Neuropsychol 1995;2:170.
[17] Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. Neurology 1994;44:609–14.
[18] Samieri C, Okereke OI, Devore E, Grodstein F. Long-term adherence to the mediterranean diet is associated with overall cognitive status, but not cognitive decline, in women. J Nutr 2013;143:493–9.
[19] Grodstein F. Cardiovascular risk factors and cognitive function. Alzheimers Dement 2007;3:S16–22.
[20] Fotuhi M, Hachinski V, Whitehouse PJ. Changing perspectives regarding late-life dementia. Nat Rev Neurol 2009;5:649.
[21] Hanson AJ, Bayer-Carter JL, Green PS, Montine TJ, Wilkinson CW, Baker LD, et al. Effect of apolipoprotein E genotype and diet on apolipoprotein E lipidation and amyloid peptides: Randomized clinical trial. JAMA Neurol 2013;70:972–80.
[22] Baker LD, Bayer-Carter JL, Skinner J, Montine TJ, Cholerton BA, Callaghan M, et al. High-intensity physical activity modulates diet effects on cerebrospinal amyloid-β levels in normal aging and mild cognitive impairment. J Alzheimer's Dis 2012;28:137–46.
[23] Mosconi L, Murray J, Davies M, Williams S, Pirraglia E, Spector N, et al. Nutrient intake and brain biomarkers of Alzheimer's disease in at-risk cognitively normal individuals: A cross-sectional neuroimaging pilot study. BMJ Open 2014;4:e004850.
[24] Freund Levi Y, Vedin I, Cederholm T, Basun H, Faxen Irving G, Eriksdotter M, et al. Transfer of omega-3 fatty acids across the

blood-brain barrier after dietary supplementation with a docosahexaenoic acid-rich omega-3 fatty acid preparation in patients with Alzheimer's disease: The OmegAD study. J Int Med 2014;275:428–36.

[25] Yassine HN, Feng Q, Azizkhanian I, Rawat V, Castor K, Fonteh AN, et al. Association of serum docosahexaenoic acid with cerebral amyloidosis. JAMA Neurol 2016;73:1208–16.

[26] Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health—a systematic review and meta-analysis: Relations between dietary glycemic properties and health outcomes–. Am J Clin Nutr 2008; 87:258S–68.

[27] Sato N, Morishita R. The roles of lipid and glucose metabolism in modulation of β-amyloid, tau, and neurodegeneration in the pathogenesis of Alzheimer disease. Front Aging Neurosci 2015;7:199.

[28] Matsuzaki T, Sasaki K, Tanizaki Y, Hata J, Fujimi K, Matsui Y, et al. Insulin resistance is associated with the pathology of Alzheimer disease The Hisayama Study. Neurology 2010;75:764–70.

[29] Huang C-C, Chung C-M, Leu H-B, Lin L-Y, Chiu C-C, Hsu C-Y, et al. Diabetes mellitus and the risk of Alzheimer's disease: A nationwide population-based study. PLoS One 2014;9:e87095.

[30] Sparks DL, Scheff SW, Hunsaker JC III, Liu H, Landers T, Gross DR. Induction of Alzheimer-like β-amyloid immunoreactivity in the brains of rabbits with dietary cholesterol. Exp Neurol 1994;126:88–94.

[31] Refolo LM, Pappolla MA, Malester B, LaFrancois J, Bryant-Thomas T, Wang R, et al. Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. Neurobiol Dis 2000;7:321–31.

[32] Ho L, Qin W, Pompl PN, Xiang Z, Wang J, Zhao Z, et al. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. FASEB J 2004;18:902–4.

[33] Keeney JT-R, Ibrahimi S, Zhao L. Human ApoE isoforms differentially modulate glucose and amyloid metabolic pathways in female brain: Evidence of the mechanism of neuroprotection by ApoE2 and implications for Alzheimer's disease prevention and early intervention. J Alzheimer's Dis 2015;48:411–24.

[34] Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease - A meta-analysis. JAMA 1997;278:1349–56.