HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

J Alzheimers Dis. 2018 ; 64(1): 281–290. doi:10.3233/JAD-171121.

Mediterranean diet, its components and amyloid imaging biomarkers

Maria Vassilaki, MD, MPH, PhD[a], **Jeremiah A. Aakre, MPH**[a], **Jeremy A. Syrjanen, MS**[a], **Michelle M. Mielke, PhD**[a,b], **Yonas E. Geda, MD, MSc**[a,c], **Walter K. Kremers, PhD**[a], **Mary M. Machulda, PhD**[d], **Rabe E. Alhurani, MBBs, MS**[b], **Sara C. Staubo**[a,e], **David S. Knopman, MD**[b], **Ronald C. Petersen, MD, PhD**[a,b], **Val J. Lowe, MD**[f], **Clifford R. Jack Jr, MD**[f], and **Rosebud O. Roberts, MB ChB, MS**[a,b]

[a]Department of Health Sciences Research, Rochester, MN, USA

[b]Department of Neurology, Rochester, MN, USA

[c]Department of Psychiatry and Psychology and Department of Neurology, Mayo Clinic, Scottsdale, Arizona

[d]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota

[e]Charles University in Prague, Faculty in Hradec Kralove, Hradec Kralove, Czech Republic

[f]Department of Radiology, Mayo Clinic, Rochester, Minnesota

Abstract

Background—There is accumulating evidence suggesting that diet may play a role in preventing or delaying cognitive decline and dementia, but the underlying biological mechanisms are not well understood.

Correspondence: Maria Vassilaki, MD, MPH, PhD, Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, 200 First Street S.W., Rochester, MN 55905 USA. Telephone: (507) 293-7472; Fax: (507) 284-1516; vassilaki.maria@mayo.edu.

CONFLICT OF INTEREST/DISCLOSURE STATEMENT

Maria Vassilaki – Receives research funding from Roche and Biogen
Jeremiah Aakre – Reports no disclosures
Jeremy Syrjanen – Reports no disclosures
Rabe Alhurani – Reports no disclosures
Sara Staubo - Reports no disclosures
Walter Kremers – Receives research funding from Department of Defense, NIH, Astra Zeneca, Biogen and Roche
Michelle Mielke – Consults for Eli Lilly and Lysosomal Therapeutics, Inc., receives unrestricted research grants from Biogen, Lundbeck, and Roche, and research funding from the NIH/NIA and Department of Defense
Yonas Geda – Receives funding from NIH and Roche, and serves on Lundbeck Advisory Board
M. Machulda – Receives NIH funding
David Knopman – serves on a Data Safety Monitoring Board for the DIAN study; is an investigator in clinical trials sponsored by Lilly Pharmaceuticals, Biogen and the Alzheimer's Treatment and Research Institute at USC; and receives research support from the NIH.
Val Lowe – Serves on scientific advisory boards for Bayer Schering Pharma, Piramal Life Sciences, Merck Research and receives research support from GE Healthcare, AVID Radiopharmaceuticals and the NIH (NIA, NCI).
Clifford Jack – receives research support from the NIH/NIA, and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation
Ronald Petersen – Consultant for Roche, Inc., Biogen, Inc., Merck, Inc., Eli Lilly and Company, and Genentech, Inc.; receives publishing royalties from *Mild Cognitive Impairment* (Oxford University Press, 2003), and receives research support from the National Institute of Health
Rosebud Roberts – Receives research funding from the NIH/NIA, Biogen, and Roche.

Objective—To examine the cross-sectional associations of the Mediterranean diet (MeDi) and its components with ^{11}C-PiB-PET scan measures of amyloid-β (Aβ) deposition.

Methods—The study consisted of 278 Mayo Clinic Study of Aging participants 70+ years old, who were cognitively unimpaired (CU) at the time of completion of the Food Frequency Questionnaire (FFQ) and when they underwent PET imaging. Adherence to the MeDi was assessed by computing the MeDi score for each participant. All scans were performed after the FFQ completion; median [IQR] time between FFQ and Aβ PET was 3.5 (1.4) years. Z-scores were created for component, macro- and micronutrients measured. Linear and logistic regression models were adjusted for age, sex, education, apolipoprotein E (APOE) ε4 allele carrier status, time interval between the FFQ completion and PET scan, and total energy intake.

Results—Participants' median age at FFQ was 77.7 years (55.8% men; 26.6% with an APOE ε4 allele). Higher MeDi score (linear regression slope (beta):−0.035, p=0.012; per standard deviation increase), vegetable intake (beta: −0.043, p=0.002), intake of vitamin A (beta: −0.041, p=0.003) or β-carotene (beta: −0.039, p=0.005) from food sources and moderate alcohol consumption (beta: −0.074, p=0.03) were associated with lower ^{11}C-PiB standardized uptake value ratio.

Conclusions—Findings are consistent with previous studies suggesting that higher adherence to a MeDi pattern and higher vegetable consumption are associated with better neuroimaging biomarker profile. Prospective studies are needed to validate current findings.

Keywords

Amyloid; cross-sectional study; Mediterranean diet; vegetables

INTRODUCTION

Accumulating evidence suggests [1, 2] that diet may play a role in preventing or delaying cognitive decline and dementia, but the underlying biological mechanisms are not well understood. A recent systematic review found growing evidence that combinations of foods and nutrients into certain dietary patterns may synergistically provide stronger health effects than their separate dietary components [3]. Higher adherence to the Mediteranean Diet (MeDi) [2, 4] has been associated with decreased cognitive decline; in addition the Dietary Approach to Stop Hypertension (DASH) and the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND) have been associated with slower rates of cognitive decline [3].

Neuroimaging biomarkers of Alzheimer's disease (AD) pathology could currently be used to provide in vivo evidence to support a clinical AD dementia [1]. These brain changes can be detected decades before cognitive decline is detected [5, 6], and modifiers of the underlying processes could potentially increase or reduce this lag time [6]. A limited number of studies have examined the association of diet and brain Aβ burden, a hallmark of AD pathology [7–11].

MeDi is characterized by high intake of vegetables, legumes, fruits, nuts, cereals, and unsaturated fatty acids [mostly in the form of olive oil], moderate to high intake of fish, low to moderate intake of dairy products, low intake of meat, and saturated fatty acids, and

regular but moderate intake of alcohol [2, 12]. Lower adherence to MeDi was associated with greater ^{11}C-Pittsburgh compound B (^{11}C-PiB) Positron-Emission Tomography (PET) retention in cognitively unimpaired (CU) volunteers [9] and higher adherence to a MeDi-type diet was associated with lower 2-(1-(6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile (FDDNP) PET scans assessing plaque/tangle binding in volunteers with subjective memory impairment or MCI [10]. In addition, previous MRI studies showed that a MeDi dietary pattern was associated with higher cortical thickness and larger brain volumes [13–15].

Diet is an important modifiable lifestyle factor and there is increasing evidence of its association with cognitive impairment and dementia. The current study examined the cross-sectional associations of the MeDi and its components with ^{11}C-PiB PET scan measures of amyloid deposition.

MATERIALS AND METHODS

Study design and participants

The details of the population-based Mayo Clinic Study of Aging (MCSA) have previously been published [16]. In brief, all residents from Olmsted County, Minn., USA, aged 70–89 years on October 1, 2004, were identified using the medical records-linkage system of the Rochester Epidemiology Project (REP) [17]. Potential participants were selected using an age- and sex-stratified random sampling strategy, and eligible participants (without dementia, not in hospice or terminally ill) were recruited. Food Frequency Questionnaires (FFQ)[18] were mailed to the first MCSA sample of the 2004 enumeration of all Olmsted County residents (1,924 participants) beginning in 2006. A total of 1,567 (81.4%) participants returned the FFQ, and of those 334 questionnaires were not included in further analysis (i.e., 268 questionnaires had more than 10 missing responses, 56 reported extremely high or low caloric intake, and 10 participants had dementia) [19]. Excluded participants were older, had fewer years of education, and had a higher frequency of stroke, diabetes, depressive symptoms and MCI [19]. PET imaging was offered to participants at the clinical evaluation beginning in 2008. For the current study, we excluded 163 participants who had MCI at the time of FFQ. Consequently, analysis included 278 (70+ years old) CU persons with completed FFQ at time of PET scanning. 792 CU individuals with available FFQ did not undergo PET scanning.

Standard Protocol Approvals, Registrations, and Patient Consent

The study was approved by the Institutional Review Boards of the Mayo Clinic and of Olmsted Medical Center. Written informed consent was obtained prior to participation in the study.

Clinical evaluation

Each participant underwent neuropsychological testing by a psychometrist and was also evaluated by a nurse or a study coordinator, and a physician. Details of the evaluation are presented in previous reports [16]. The nurse or study coordinator, the physician and a neuropsychologist adjudicated the final diagnosis of mild cognitive impairment (MCI) or

dementia by consensus decision following a review of all the data for each participant and according to published criteria.[16, 20] A diagnosis of CU was established for subjects who performed in the normative range and did not meet criteria for MCI [21] or dementia [22]. Depressive symptoms were assessed from the Beck Depression Inventory II and apolipoprotein E (APOE) ε4 allele was measured from a blood draw at baseline.

Measurement of dietary food intake and MeDi adherence

A detailed description of the FFQ has been published previously [19]. In brief, a modified Block 1995 Revision of the Health habits FFQ [18], including 128 items, was used by participants to report dietary intakes for the last 12 months. FFQ data were analyzed by The Food Processor SQL nutrition analysis software program (version 10.0.0; ESHA Research, Salem, Oregon, USA) and daily intake of foods, macro- and micronutrients, total daily caloric intake, and percentage of total caloric intake from each macronutrient (% protein, % fat, and % carbohydrate) was computed [15, 19].

Adherence to the MeDi was assessed by computing the MeDi score [12, 19, 23]. Energy-adjusted nutrient intakes were computed from the residual of each nutrient regressed on total caloric intake (kcal) [15, 24]. Using a sex-specific median cutoff, a value of 0 was assigned for consumption below and 1 for values at or above the median for beneficial foods (vegetables, legumes, fruit, cereal/grains, and fish). A value of 1 was assigned for consumption below, and 0 for consumption above the median for foods considered unfavorable in excess (meat and dairy products). The ratio of MUFA to saturated fats (SFA) estimated fat intake; a value of 1 was assigned for a ratio at or above the median and 0 otherwise. Alcohol intake was assigned a score of 1 for intake of 5 to <25 g/d for women and 10 to <50 g/d for men, and 0 otherwise. The total MeDi score, that is the sum of the individual scores, ranged from 0 to 9 (maximum adherence).

^{11}C-PiB PET acquisition

Details are presented in previous publications [25–27]. In brief, amyloid PET imaging was performed using Pittsburgh Compound B [28]. A CT image was obtained for attenuation correction. Late uptake PET images were acquired 40–60 minutes after injection. PET images were analyzed using the in-house fully automated image processing pipeline [29], where image voxel values are extracted from automatically labeled regions of interest (ROIs) propagated from an MRI template. An amyloid PET standardized uptake value ratio (SUVR) was formed from the voxel-number weighted average of the median uptake in the parietal, temporal, anterior, prefrontal, orbitofrontal and posterior cingulate and precuneus ROIs normalized to the cerebellar crus gray median [30]. The scans of all participants were performed using the same device and parameters. An abnormal (elevated) ^{11}C-PiB-PET retention ratio was defined as SUVR >1.42 [30].

Statistical Analyses

Participant characteristics at time of FFQ completion were compared by Aβ status using two-tailed Wilcoxon rank sum tests for continuous variables and chi-square or Fisher exact tests for categorical variables. Dietary variables were log-transformed (linolenic acid, linoleic acid, vitamin B1, B2, B6, and folate) or square root-transformed (vegetables and

grains/cereal) where necessary (i.e. substantially skewed), and standardized by the mean and standard deviation to create z-scores, because of the differences in units and distributions of the dietary variables (foods [g/d], macronutrients [g/d or %], micronutrients [mg/d or mcg/d]) [15].

During the clinical evaluation, each participant underwent neuropsychological testing using nine tests to assess cognitive performance in four domains: (i) memory (ii) attention / executive function (iii) language and (iv) visuospatial skills [16, 20]. The raw scores for tests in each domain were centered and scaled to create domain-specific cognitive z-scores. A global z-score for overall performance was also created by averaging and scaling the four domain z-scores.

Logistic regression (for dichotomous abnormal amyloid outcome) and linear regression (for continuous SUVR outcome; average of right and left ROIs) models were fit to determine associations between dietary measures and Aβ. These models were adjusted for age, sex, education, APOE ε4 allele status, time interval between the FFQ completion and PET scan, and total energy intake (model type 1). We built separate models (model type 2) which in addition to the variables in model type 1, adjusted also for body mass index, cardiovascular diseases (CVD; e.g., diabetes, hypertension, coronary heart disease, peripheral vascular disease, congestive heart failure, atrial fibrillation, dyslipidemia, stroke) and depressive symptoms. We recognize that including these variables (i.e. CVD) that might be in the causal pathway between diet and AD biomarkers of brain pathology in the models could result in overadjustment.

Our primary analysis was to examine the association of the MeDi score with the amyloid PET measures. In case of significance of the MeDi score we next considered without adjustment for multiple comparisons, analyses examining the associations between daily intake of foods and amyloid PET measures, and then associations between macro- and micronutrients, and percentage of total caloric intake from each macronutrient and amyloid PET measures (i.e., % carbohydrates and % sugar, % protein, % total fat, linolenic acid, linoleic acid, monounsaturated-saturated fatty acids ratio, vitamins A, B1, B2, B6, B12, C, E, β-carotene and folate from food sources), to understand which component could be responsible for this association. For further consideration we calculated p-values adjusting for multiple comparisons using the Holm method and calculated p-values in each step using permutations. Associations were considered significant at a two-tailed p value < 0.05. Analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina) and Stata/SE statistical software version 15.1 (StataCorp LP, College Station, Texas).

RESULTS

Population characteristics

There were 278 participants (median age (IQR): 77.7 (7.9); 55.8% men) with available FFQ and ^{11}C-PiB PET scan data (Table 1). Participants with abnormal ^{11}C-PiB PET were older (p=0.02), had a significantly higher frequency of APOE ε4 genotype (p<0.001), lower global z-score (p=0.06) and lower daily alcohol consumption (p=0.08). Compared with CU

individuals who did not undergo PET scanning (N=792), CU individuals with PET (N=278) were younger (p<0.001), had higher education (p=0.007), were less likely to have hypertension (p=0.013), stroke (p=0.004), atrial fibrillation (p=0.005), congestive heart failure (p<0.001), and be current or ex-smokers (p=0.03), had a higher global cognitive score (p<0.001), and higher fish (p=0.02) and fruit intake (p=0.02) (data not shown).

Association of MeDi score, its components and macro-/micronutrients with amyloid deposition

In the tables we present analyses for associations of MeDi score, all Medi score components and % of daily calories (carbohydrates, protein, total fat and sugar) with Aβ. In addition, we present estimates for the statistically significant associations between micronutrients and Aβ, which included β-carotene and vitamin A (other vitamins did not present significant associations with Aβ and estimates are not presented).

Higher levels of the primary dietary measure, the MeDi score, were associated with lower brain Aβ levels (slope: −0.035, 95% confidence interval [CI] −0.063, −0.008, p=0.012, per standard deviation (SD) increase). Regarding the individual components of the MeDi score, vegetable consumption and moderate alcohol intake (5 to <25 g/d for women and 10 to <50 g/d for men vs. other (reference)) were associated with lower Aβ levels (slope: −0.043, 95% CI −0.070, −0.016, p=0.002 (per SD increase), and slope= −0.074, 95%CI −0.141, −0.007, p=0.03, respectively); these associations were adjusted for age at FFQ, sex, education, APOE ε4 allele status, time interval between FFQ completion and PET scan, and total energy intake (Table 2). Participants with higher vegetable consumption had significantly lower odds of Aβ abnormality (Odds ratio (OR) 0.77; 95% confidence interval 0.60, 1.00; p=0.051 per SD increase; Table 3).

Further estimates of association (per SD increase) were as follows: vitamin A (slope: −0.041, 95% CI −0.068, −0.015, p=0.003) and β-carotene intake from food (slope: −0.039, 95% CI −0.066, −0.012, p=0.005) were also associated with lower Aβ after adjusting for potential confounders (Table 2). Findings for β-carotene and vitamin A intake from food were consistent for both the dichotomous and continuous outcomes suggesting reduced odds of Aβ abnormality with higher intakes, however, statistical significance was not reached (possibly due to lower statistical power resulting from the dichotomization of the Aβ measure).

Adjusting for multiple comparisons among the MeDi components yielded p-values for vegetable consumption of 0.013 and for moderate alcohol consumption of 0.19. Inspecting the micronutrients, the adjusted p-values for vitamin A and β-carotene were 0.017 and 0.037 respectively; the other associations had larger p-values.

DISCUSSION

Our findings in this cohort of older adults suggest that cross-sectionally, higher MeDi score, vegetable consumption and moderate alcohol intake were associated with lower Aβ accumulation (as a continuous measure). In addition, vitamin A and β-carotene intake from food sources were associated with lower Aβ accumulation. Participants with higher

vegetable consumption had significantly lower odds of Aβ abnormality (dichotomous measure), but associations with moderate alcohol intake, vitamin A and β-carotene intake were not significant, although, their direction and magnitude is consistent with the estimates from the continuous measures.

We acknowledge the small sample size of the study (i.e., 278 of the 1,070 CU participants with FFQ underwent PET scanning) and that some of our findings in this cross-sectional analysis could simply be due to chance and require further validation in longitudinal studies. Although the findings might be of uncertain clinical significance, the agreement of current findings with previous studies suggesting a beneficial association between adherence to a MeDi and brain imaging biomarkers underscores the need for further exploration of these associations [8, 9, 13–15, 19]. There is currently insufficient evidence to determine effectiveness of dietary interventions and supporting such research is encouraged [31].

Few studies have examined the association of diet and brain Aβ burden [7–11] and partly agree with current findings; specifically, that a healthier diet is associated with lower Aβ pathology [7–10]. Prospective studies have also suggested that higher adherence to MeDi is associated with reduced risk of developing MCI and dementia - which is in accord with present findings -, as well as, reduced risk of progression from MCI to AD [2, 32]. Higher adherence to MeDi has been associated with slower cognitive decline and lower mortality in AD dementia patients [33, 34]. In a recent systematic review [35], 50 of the 64 studies reviewed, supported a beneficial association between diet and AD incidence, suggesting that diet could be a modifiable risk factor for AD.

Higher adherence to a MeDi has been associated with lower levels of C-reactive protein and interleukin. This suggests a potential mechanism whereby a healthy diet may contribute to a healthy brain by reducing inflammation and oxidative stress [2]. As the brain has a high metabolic activity, it is vulnerable to oxidative stress and damage to neural tissue, which is associated also with the pathophysiology of neurodegenerative diseases [2, 36]. There is always the possibility that dietary patterns (and nutrients)[37] act directly (e.g. participating in defense mechanisms against aging or AD pathology) or act indirectly (e.g., having preventive effects against cardiovascular disease that are also beneficial for neurodegenerative diseases).

Current findings are in accord with previous MCSA findings in the participants with FFQ data, which cross-sectionally reported that high vegetable intake and moderate alcohol intake were associated with reduced odds of MCI [19]. In addition, previous MRI studies in CU or non-demented participants showed that a MeDi dietary pattern was associated with higher cortical thickness and larger brain volumes [13–15].

Studies have suggested that vegetable consumption has an inverse association with cognitive decline [38] and consumption of green leafy vegetables may help to slow cognitive decline with aging, plausibly due to the neuroprotective actions of micronutrients, including β-carotene [39]. The current study adds valuable new information in an area of research (i.e., the association of consumption of vegetables, brain pathology, and dementia), which needs further investigation [4].

Studies that have examined the association of diet and brain Aβ burden [7–11] did not find a significant association between β-carotene and vitamin A with Aβ burden but suggested that Vitamin B12 and vitamin D (studied alone[7] or as a combination of nutrients) [8] and ω-3 polyunsaturated fatty acids (PUFA) [7] were associated with lower Aβ burden in AD vulnerable regions. A recent cross-sectional study [11] found a significant association between low/moderate protein consumption and higher brain Aβ but our findings did not concur.

AD neuroimaging biomarkers available in the MCSA study allowed us to observe a glimpse of the complex associations between diet and its components and AD pathology. The brain has a high metabolic activity and rate of nutrient turnover, with multiple nutrient-specific systems of transportation, through the blood-brain barrier [32] and foods and nutrients act as physiological agents in concert and not in isolation [3]. The study detected a significant association between vitamin A and β-carotene intake from food sources with lower Aβ accumulation. Antioxidant nutrients (e.g., carotenoids, flavonoids, vitamin E, Vitamin C) might be more important to the brain relative to other organs as there are fewer antioxidant enzymes for neuronal protection.[36] Published studies present discordant results [35, 36, 40, 41], related to a protective association between high dietary intake of β-carotene, which is a major precursor of vitamin A, and cognitive decline or dementia [35, 39]. Researchers have suggested that β-carotene and vitamin A, which cross the blood-brain barrier, could help the aging brain through antioxidant or Aβ anti-oligomerization effects on Aβ [7, 42], affecting Aβ oligomers before the development of plaques. However, supportive evidence is still limited and additional studies are needed to evaluate the potential protective association between antioxidants and AD and their ability to fight oxidative stress and cognitive decline, as well [4].

The association between dementia and alcohol consumption is less clear based on previous reports [4, 43], at least due to great variability of consumption patterns, follow-up differences or interactions with other lifestyle factors. Fish consumption has been associated with a lower risk of dementia and cognitive decline in several prospective studies [36]; not all studies agree however, and type of fish or method of cooking could also influence this association.

Diet interventions have shown that the concentrations of AD related cerebrospinal fluid biomarkers could be altered by diet (e.g., changing the Aβ42 concentrations) [44], which might suggest that diet is an environmental factor that has potential to modify AD risk. This could be particularly important as the AD pathological cascade is triggered several years before the clinical presentation of the disease - although it is unclear what proportion will actually reach the symptomatic AD stage during their lifetime [45, 46] - and environmental factors (including nutrients) may play a role in this process [37]. Research on nutritional risk factors provides promising, but not definite findings related to nutritional patterns, macro and micronutrients and prevention of dementia [32]. We need to acknowledge that delineating the nature of these associations is quite complex with multiple nutrients, inter-dependent factors and associations going in both directions (i.e. nutrient status may contribute to AD and AD can influence nutrient status) [47]. To partly eliminate

bidirectional associations in the current cross-sectional study, we limited our analysis to CU participants.

The study has potential limitations. Due to its cross-sectional design, the study cannot assess causality. Although the 12-month recall period might be considered restrictive, FFQs reliably rank food and nutrient intake of individuals, are useful for large epidemiologic studies [48–50], and are more reliable in assessing diet intake over longer periods, as in our study, than short term recall.[51] As we assessed nutrition later in life, we cannot ascertain if preclinical AD changes or other conditions contributed to the reported dietary patterns. A subset of participants may had adopted dietary habits more recently, whereas others may have followed such dietary patterns for a prolonged time such that analysis stratified by duration of adherence to the reported dietary regimen would be beneficial, but it is beyond the current study's capabilities. However, our findings are in accordance with accumulating research of a beneficial association between adherence to a MeDi and brain imaging biomarkers. Participants with amyloid PET studies in general had better health and possibly higher self-care tendencies, suggesting potential non-participation bias by individuals with less beneficial nutrition patterns, resulting in a potential underestimation (although cannot be certain) of the present associations. In addition, study participants were primarily of northern European ancestry. Thus, findings may be generalizable to populations with similar characteristics and generalizability to other settings should be performed with caution. FFQ was not administered simultaneously with PET studies but all were administered before any PET imaging.

The study has also important strengths. Participants were CU and unaware of their Aβ biomarker status or the study hypothesis, thus minimizing the potential for recall bias. Evaluation of their clinical diagnosis (i.e., CU, MCI or dementia) was rigorously done by 3 independent evaluators who were blind to previous diagnoses, and state of the art PET imaging was used. When we adjusted for multiple comparisons the associations of vegetable consumption, vitamin A and β-carotene intake from food sources with amyloid PET standardized uptake value ratio remained statistically significant. The study was able to evaluate the association of MeDi adherence but also several food groups and dietary measures with measures of Aβ burden, providing valuable information for hypotheses generation and future longitudinal research. Prospective studies are needed to validate current findings.

Acknowledgments

The study was supported by the NIH (U01 AG006786, P50 AG016574, R01 AG011378, R01 AG041851, R01 NS097495), the GHR Foundation, the Elsie and Marvin Dekelboum Family Foundation, the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic, the Alice Weiner Postdoctoral Research Fellowship in Alzheimer's Disease Research, Mayo Foundation for Medical Education and Research, the Liston Award, the Schuler Foundation, and was made possible by the Rochester Epidemiology Project (R01 AG034676).

References

1. Mosconi L, McHugh PF. Let Food Be Thy Medicine: Diet, Nutrition, and Biomarkers' Risk of Alzheimer's Disease. Current nutrition reports. 2015; 4:126–135. [PubMed: 26167396]

2. Singh B, Parsaik AK, Mielke MM, Erwin PJ, Knopman DS, Petersen RC, Roberts RO. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. Journal of Alzheimer's disease : JAD. 2014; 39:271–282. [PubMed: 24164735]

3. Solfrizzi V, Custodero C, Lozupone M, Imbimbo BP, Valiani V, Agosti P, Schilardi A, D'Introno A, La Montagna M, Calvani M, Guerra V, Sardone R, Abbrescia DI, Bellomo A, Greco A, Daniele A, Seripa D, Logroscino G, Sabba C, Panza F. Relationships of Dietary Patterns, Foods, and Micro- and Macronutrients with Alzheimer's Disease and Late-Life Cognitive Disorders: A Systematic Review. J Alzheimers Dis. 2017; 59:815–849. [PubMed: 28697569]

4. Cao L, Tan L, Wang HF, Jiang T, Zhu XC, Lu H, Tan MS, Yu JT. Dietary Patterns and Risk of Dementia: a Systematic Review and Meta-Analysis of Cohort Studies. Molecular neurobiology. 2016; 53:6144–6154. [PubMed: 26553347]

5. Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, Fripp J, Tochon-Danguy H, Morandeau L, O'Keefe G, Price R, Raniga P, Robins P, Acosta O, Lenzo N, Szoeke C, Salvado O, Head R, Martins R, Masters CL, Ames D, Villemagne VL. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Neurobiology of Aging. 2010; 31:1275–1283. [PubMed: 20472326]

6. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. The Lancet Neurology. 2010; 9:119–128. [PubMed: 20083042]

7. Mosconi L, Murray J, Davies M, Williams S, Pirraglia E, Spector N, Tsui WH, Li Y, Butler T, Osorio RS, Glodzik L, Vallabhajosula S, McHugh P, Marmar CR, de Leon MJ. 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.

8. Berti V, Murray J, Davies M, Spector N, Tsui WH, Li Y, Williams S, Pirraglia E, Vallabhajosula S, McHugh P, Pupi A, de Leon MJ, Mosconi L. Nutrient patterns and brain biomarkers of Alzheimer's disease in cognitively normal individuals. The journal of nutrition, health & aging. 2015; 19:413–423.

9. Matthews DC, Davies M, Murray J, Williams S, Tsui WH, Li Y, Andrews RD, Lukic A, McHugh P, Vallabhajosula S, de Leon MJ, Mosconi L. Physical Activity, Mediterranean Diet and Biomarkers-Assessed Risk of Alzheimer's: A Multi-Modality Brain Imaging Study. Advances in molecular imaging. 2014; 4:43–57. [PubMed: 25599008]

10. Merrill DA, Siddarth P, Raji CA, Emerson ND, Rueda F, Ercoli LM, Miller KJ, Lavretsky H, Harris LM, Burggren AC, Bookheimer SY, Barrio JR, Small GW. Modifiable Risk Factors and Brain Positron Emission Tomography Measures of Amyloid and Tau in Nondemented Adults with Memory Complaints. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2016; 24:729–737. [PubMed: 27421618]

11. Fernando W, Rainey-Smith SR, Gardener SL, Villemagne VL, Burnham SC, Macaulay SL, Brown BM, Gupta VB, Sohrabi HR, Weinborn M, Taddei K, Laws SM, Goozee K, Ames D, Fowler C, Maruff P, Masters CL, Salvado O, Rowe CC, Martins RN, Group AR. Associations of Dietary Protein and Fiber Intake with Brain and Blood Amyloid-beta. J Alzheimers Dis. 2018; 61:1589–1598. [PubMed: 29376865]

12. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003; 348:2599–2608. [PubMed: 12826634]

13. Mosconi L, Murray J, Tsui WH, Li Y, Davies M, Williams S, Pirraglia E, Spector N, Osorio RS, Glodzik L, McHugh P, de Leon MJ. Mediterranean Diet and Magnetic Resonance Imaging-Assessed Brain Atrophy in Cognitively Normal Individuals at Risk for Alzheimer's Disease. The journal of prevention of Alzheimer's disease. 2014; 1:23–32.

14. Gu Y, Brickman AM, Stern Y, Habeck CG, Razlighi QR, Luchsinger JA, Manly JJ, Schupf N, Mayeux R, Scarmeas N. Mediterranean diet and brain structure in a multiethnic elderly cohort. Neurology. 2015; 85:1744–1751. [PubMed: 26491085]

15. Staubo SC, Aakre JA, Vemuri P, Syrjanen JA, Mielke MM, Geda YE, Kremers WK, Machulda MM, Knopman DS, Petersen RC, Jack CR Jr, Roberts RO. Mediterranean diet, micronutrients and macronutrients, and MRI measures of cortical thickness. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2017; 13:168–177.

16. Roberts RO, Geda YE, Knopman DS, Cha RH, Pankratz VS, Boeve BF, Ivnik RJ, Tangalos EG, Petersen RC, Rocca WA. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. Neuroepidemiology. 2008; 30:58–69. [PubMed: 18259084]

17. St Sauver JL, Grossardt BR, Yawn BP, Melton LJI, Pankratz JJ, Brue SM, Rocca WA. Data Resource Profile: The Rochester Epidemiology Project (REP) medical records-linkage system. Int J Epidemiol. 2012; 41:1614–1624. [PubMed: 23159830]

18. Block G, Coyle LM, Hartman AM, Scoppa SM. Revision of dietary analysis software for the Health Habits and History Questionnaire. Am J Epidemiol. 1994; 139:1190–1196. [PubMed: 8209877]

19. Roberts RO, Geda YE, Cerhan JR, Knopman DS, Cha RH, Christianson TJ, Pankratz VS, Ivnik RJ, Boeve BF, O'Connor HM, Petersen RC. Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment. Dementia and geriatric cognitive disorders. 2010; 29:413–423. [PubMed: 20502015]

20. Petersen RC, Roberts RO, Knopman DS, Geda YE, Cha RH, Pankratz VS, Boeve BF, Tangalos EG, Ivnik RJ, Rocca WA. Prevalence of mild cognitive impairment is higher in men The Mayo Clinic Study of Aging. Neurology. 2010; 75:889–897. [PubMed: 20820000]

21. Petersen RC. Mild cognitive impairment as a diagnostic entity. Journal of Internal Medicine. 2004; 256:183–194. [PubMed: 15324362]

22. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association; Washington, DC: 1994.

23. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. Arch Neurol. 2009; 66:216–225. [PubMed: 19204158]

24. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol. 1986; 124:17–27. [PubMed: 3521261]

25. Lowe VJ, Kemp BJ, Jack CR Jr, Senjem M, Weigand S, Shiung M, Smith G, Knopman D, Boeve B, Mullan B, Petersen RC. Comparison of 18F-FDG and PiB PET in cognitive impairment. J Nucl Med. 2009; 50:878–886. [PubMed: 19443597]

26. Jack CR Jr, Lowe VJ, Senjem ML, Weigand SD, Kemp BJ, Shiung MM, Knopman DS, Boeve BF, Klunk WE, Mathis CA, Petersen RC. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. Brain. 2008; 131:665–680. [PubMed: 18263627]

27. Knopman DS, Jack CR Jr, Wiste HJ, Weigand SD, Vemuri P, Lowe V, Kantarci K, Gunter JL, Senjem ML, Ivnik RJ, Roberts RO, Boeve BF, Petersen RC. Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. Neurology. 2012; 78:1576–1582. [PubMed: 22551733]

28. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergstrom M, Savitcheva I, Huang GF, Estrada S, Ausen B, Debnath ML, Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Langstrom B. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 2004; 55:306–319. [PubMed: 14991808]

29. Senjem ML, Gunter JL, Shiung MM, Petersen RC, Jack CR Jr. Comparison of different methodological implementations of voxel-based morphometry in neurodegenerative disease. Neuroimage. 2005; 26:600–608. [PubMed: 15907317]

30. Jack CR Jr, Wiste HJ, Weigand SD, Therneau TM, Lowe VJ, Knopman DS, Gunter JL, Senjem ML, Jones DT, Kantarci K, Machulda MM, Mielke MM, Roberts RO, Vemuri P, Reyes DA, Petersen RC. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. Alzheimers Dement. 2017; 13:205–216. [PubMed: 27697430]

31. National Academies of Sciences E, and Medicine. Preventing Cognitive Decline and Dementia: A Way Forward. Washington (DC): The National Academies Press; 2017.

32. Morris MC. Nutrition and risk of dementia: overview and methodological issues. Annals of the New York Academy of Sciences. 2016; 1367:31–37. [PubMed: 27116239]

33. Solfrizzi V, Frisardi V, Seripa D, Capurso C, Vendemiale G, Pilotto A, Panza F. Dietary patterns and protection against Alzheimer disease and cognitive decline. Archives of neurology. 2010; 67:1285–1286. author reply 1287–1288. [PubMed: 20937964]

34. Scarmeas N, Luchsinger JA, Mayeux R, Stern Y. Mediterranean diet and Alzheimer disease mortality. Neurology. 2007; 69:1084–1093. [PubMed: 17846408]
35. Yusufov M, Weyandt LL, Piryatinsky I. Alzheimer's disease and diet: a systematic review. The International journal of neuroscience. 2017; 127:161–175. [PubMed: 26887612]
36. Morris MC. Symposium 1: Vitamins and cognitive development and performance Nutritional determinants of cognitive aging and dementia. Proceedings of the Nutrition Society. 2012; 71:1–13. [PubMed: 22067138]
37. Staehelin HB. Micronutrients and Alzheimer's disease. The Proceedings of the Nutrition Society. 2005; 64:565–570. [PubMed: 16313699]
38. Trichopoulou A, Kyrozis A, Rossi M, Katsoulis M, Trichopoulos D, La Vecchia C, Lagiou P. Mediterranean diet and cognitive decline over time in an elderly Mediterranean population. Eur J Nutr. 2015; 54:1311–1321. [PubMed: 25482573]
39. Morris MC, Wang Y, Barnes LL, Bennett DA, Dawson-Hughes B, Booth SL. Nutrients and bioactives in green leafy vegetables and cognitive decline: Prospective study. Neurology. 2018; 90:e214–e222. [PubMed: 29263222]
40. Devore EE, Kang JH, Stampfer MJ, Grodstein F. The association of antioxidants and cognition in the Nurses' Health Study. Am J Epidemiol. 2013; 177:33–41. [PubMed: 23221724]
41. Kang JH, Grodstein F. Plasma carotenoids and tocopherols and cognitive function: a prospective study. Neurobiol Aging. 2008; 29:1394–1403. [PubMed: 17433501]
42. Takasaki J, Ono K, Yoshiike Y, Hirohata M, Ikeda T, Morinaga A, Takashima A, Yamada M. Vitamin A has anti-oligomerization effects on amyloid-beta in vitro. Journal of Alzheimer's disease : JAD. 2011; 27:271–280. [PubMed: 21811022]
43. Piazza-Gardner AK, Gaffud TJ, Barry AE. The impact of alcohol on Alzheimer's disease: a systematic review. Aging & mental health. 2013; 17:133–146. [PubMed: 23171229]
44. Bayer-Carter JL, Green PS, Montine TJ, VanFossen B, Baker LD, Watson GS, Bonner LM, Callaghan M, Leverenz JB, Walter BK, Tsai E, Plymate SR, Postupna N, Wilkinson CW, Zhang J, Lampe J, Kahn SE, Craft S. Diet intervention and cerebrospinal fluid biomarkers in amnestic mild cognitive impairment. Archives of neurology. 2011; 68:743–752. [PubMed: 21670398]
45. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2011; 7:280–292.
46. Sperling R, Mormino E, Johnson K. The evolution of preclinical Alzheimer's disease: implications for prevention trials. Neuron. 2014; 84:608–622. [PubMed: 25442939]
47. Gustafson DR, Morris MC, Scarmeas N, Shah RC, Sijben J, Yaffe K, Zhu XW. New Perspectives on Alzheimer's Disease and Nutrition. Journal of Alzheimers Disease. 2015; 46:1111–1127.
48. Willett WC. Invited commentary: comparison of food frequency questionnaires. Am J Epidemiol. 1998; 148:1157–1159. discussion 1162–1155. [PubMed: 9867259]
49. Willett W. Commentary: Dietary diaries versus food frequency questionnaires-a case of undigestible data. Int J Epidemiol. 2001; 30:317–319. [PubMed: 11369736]
50. Roberts RO, Roberts LA, Geda YE, Cha RH, Pankratz VS, O'Connor HM, Knopman DS, Petersen RC. Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia. J Alzheimers Dis. 2012; 32:329–339. [PubMed: 22810099]
51. Shahar D, Fraser D, Shai I, Vardi H. Development of a food frequency questionnaire (FFQ) for an elderly population based on a population survey. The Journal of nutrition. 2003; 133:3625–3629. [PubMed: 14608085]

Table 1

Characteristics of participants at time of the food frequency questionnaire (FFQ) by abnormal amyloid.

Characteristics [§, ¶]	Total	Abnormal ^{11}C-PIB PET [*]		
	N=278	No N = 129	Yes N = 149	p
Age (years) at FFQ	77.7 (7.9)	76.8 (7.9)	77.9 (7.3)	0.02
Men, n (%)	155 (55.8)	76 (58.9)	79 (53.0)	0.32
Education (years)	14.0 (4.0)	14.0 (5.0)	14.0 (4.0)	0.96
APOE ε24/ε34/ε44, n (%)	74 (26.6)	20 (15.5)	54 (36.2)	<0.001
BMI (Kg/m^2)	27.3 (5.8)	26.4 (6.1)	28.1 (5.7)	0.36
Diabetes, n (%)	46 (16.5)	17 (13.2)	29 (19.5)	0.16
Hypertension, n (%)	205 (73.7)	92 (71.3)	113 (75.8)	0.39
Dyslipidemia, n (%)	232 (83. 5)	105 (81.4)	127 (85.2)	0.39
Stroke, n (%)	6 (2.2)	4 (3.1)	2 (1.3)	0.31
Congestive heart failure, n (%)	11 (4.0)	4 (3.1)	7 (4.7)	0.50
Coronary artery disease, n (%)	110 (39.6)	49 (38.0)	61 (40.1)	0.62
Smoking, former/current, n (%)	119 (42.8)	56 (43.4)	63 (42.3)	0.85
Depressive symptoms, n (%)[†]	9 (3.2)	5 (3.9)	4 (2.7)	0.58
Global z score [‡]	0.8 (1.2)	0.9 (1.2)	0.6 (1.1)	0.06
FFQ to PET(years)[^]	3.5 (1.4)	3.4 (1.3)	3.5 (1.5)	0.97
MeDi and its components				
MeDi score	4.0 (2)	5.0 (3.0)	4.0 (2.0)	0.18
Vegetables (without legumes)(g/d)	162.5 (164)	172.5 (145.7)	134.8 (164.9)	0.11
Legumes (g/d)	47.0 (58.5)	50.5 (53.5)	44.4 (59.3)	0.45
Fish (g/d)	15.5 (18.2)	15.3 (18.1)	16.7 (18.2)	0.97
Grains/cereal (g/d)	180.0 (127.0)	197.8 (132.1)	169.3 (124.3)	0.13
Fruit (no juice) (g/d)	218.4 (197.6)	205.5 (204.0)	223.0 (184.6)	0.38
Red meat (g/d)	108.2 (101.8)	109.7 (81.1)	105.2 (118.2)	0.91
Dairy (g/d)	345.9 (383.9)	366.5 (320.7)	339.5 (480.7)	0.63
Alcohol (g/d)	0.8 (6.4)	0.9 (8.3)	0.4 (4.9)	0.08

Abbreviations: ^{11}C-PIB, ^{11}C-Pittsburgh compound B; PET, positron emission tomography; APOE, Apolipoprotein E; BMI, body mass index; BDI, Beck Depression Inventory; MeDi, Mediterranean diet; FFQ, food frequency questionnaire. Data are based on participants with non-missing data only. P-values are based on the chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables.

[*] Abnormal amyloid ^{11}C-PIB PET was defined as standardized uptake value ratio >1.42.

[§] Median (IQR) unless otherwise described.

[¶] At the study visit closest to FFQ completion.

[†] BDI≥13; Depressive symptoms were assessed from the Beck Depression Inventory (BDI) II.

[‡] A global z-score for overall performance was created by averaging and scaling the four domain (memory, attention/executive function, language and visuospatial skills) z-scores.

[^] Time between completion of food frequency questionnaire and PET imaging.

Table 2

Association of total MeDi score and its components with amyloid.

	^{11}C-PiB PET measurement~			
	Model 1 *		Model 2 §	
Dietary measures ¶	Slope (95% CI)	p	Slope (95% CI)	p
MeDi score	−0.035 (−0.063, −0.008)	0.012	−0.034 (−0.062, −0.005)	0.02
Fish	−0.027 (−0.055, 0.001)	0.06	−0.025 (−0.054, 0.003)	0.08
Red meat	−0.004 (−0.031, 0.023)	0.77	−0.003 (−0.031, 0.026)	0.85
Dairy	0.008 (−0.019, 0.035)	0.54	0.008 (−0.020, 0.036)	0.58
All vegetables#	−0.043 (−0.070, −0.016)	0.002	−0.045 (−0.073, −0.017)	0.002
Legumes	−0.019 (−0.047, 0.008)	0.16	−0.022 (−0.051, 0.007)	0.13
All fruits	−0.006 (−0.033, 0.021)	0.66	−0.007 (−0.035, 0.021)	0.62
Fruits, no juice	0.001 (−0.026, 0.028)	0.94	−0.000 (−0.028, 0.028)	1.00
Grains/cereal	−0.007 (−0.034, 0.020)	0.61	−0.006 (−0.034, 0.023)	0.69
Moderate alcohol intake †	−0.074 (−0.141, −0.007)	0.03	−0.072 (−0.143, −0.002)	0.044
% Carbohydrates‡	0.024 (−0.003, 0.052)	0.08	0.022 (−0.006, 0.050)	0.13
% Sugar	0.023 (−0.004, 0.050)	0.10	0.021 (−0.007, 0.048)	0.15
% Protein	−0.011 (−0.040, 0.017)	0.42	−0.010 (−0.038, 0.019)	0.52
% Total Fat	−0.008 (−0.036, 0.020)	0.59	−0.007 (−0.035, 0.022)	0.66
Vitamin A	−0.041(−0.068, −0.015)	0.003	−0.041(−0.068, −0.013)	0.004
β-carotene	−0.039 (−0.066, −.0012)	0.005	−0.038 (−0.066, −0.010)	0.008

Abbreviations: AD, Alzheimer disease; CI, confidence interval; OR, odds ratio; ^{11}C-PiB PET, Pittsburgh compound B positron emission tomography; MeDi, Mediterranean diet.

~Amyloid PET standardized uptake value (SUVR) formed from the voxel-number weighted average of the median uptake in the parietal, temporal, anterior, prefrontal, orbitofrontal and posterior cingulate, and precuneus ROIs normalized to the cerebellar crus gray median.

*Models were adjusted for age, sex, education, APOE ε4 carrier status, time interval between the food frequency questionnaire (FFQ) completion and PET scan, and total energy intake

§Models were adjusted for age, sex, education, APOE ε4 carrier status, body mass index, diabetes, hypertension, coronary heart disease, peripheral vascular disease, congestive heart failure, atrial fibrillation, dyslipidemia, stroke, depressive symptoms, time interval between the food frequency questionnaire (FFQ) completion and PET scan, and total energy intake.

¶Dietary measures were log or square root transformed where necessary, standardized and adjusted for caloric intake and estimates (excluding moderate alcohol intake) are presented per standard deviation increase.

#Variable “all vegetables” includes legumes; estimate for vegetable consumption without legumes: slope: −0.042, 95%CI −0.069, −0.015, p=0.002 (Model 1) and slope: −0.042, 95%CI −0.070, −0.015, p=0.003 (Model 2)

†Alcohol intake of 5 to <25 g/d for women and 10 to <50 g/d for men vs. other (ref.).

‡Percent of total calories/day.

Table 3

Association of total MeDi score and its components with abnormal amyloid.

	Abnormal ^{11}C- PiB PET *			
	Model 1 §		Model 2 ¶	
Dietary measures †	OR (95% CI)	p	OR (95% CI)	p
MeDi score	0.79 (0.61, 1.02)	0.07	0.76 (0.58, 0.99)	0.039
Fish	0.97 (0.75, 1.25)	0.79	0.95 (0.73, 1.23)	0.68
Red meat	1.02 (0.79, 1.31)	0.88	1.04 (0.80, 1.35)	0.75
Dairy	1.17 (0.91, 1.50)	0.23	1.18 (0.91, 1.53)	0.20
All vegetables#	0.77 (0.60, 1.00)	0.051	0.73 (0.56, 0.96)	0.022
Legumes	0.96 (0.75, 1.23)	0.74	0.94 (0.72, 1.23)	0.65
All fruits	1.07 (0.83, 1.37)	0.62	1.07 (0.83, 1.38)	0.61
Fruits, no juice	1.08 (0.83, 1.39)	0.57	1.06 (0.81, 1.37)	0.69
Grains/cereal	0.85 (0.66, 1.09)	0.20	0.82 (0.63, 1.06)	0.13
Moderate alcohol intake‡	0.68 (0.36, 1.26)	0.22	0.68 (0.36, 1.30)	0.24
% Carbohydrates^	1.01 (0.78, 1.29)	0.97	1.00 (0.77, 1.30)	0.98
% Sugar	1.18 (0.92, 1.52)	0.19	1.22 (0.94, 1.58)	0.14
% Protein	1.08 (0.83, 1.40)	0.58	1.09 (0.83, 1.42)	0.53
% Total Fat	1.02 (0.79, 1.32)	0.88	1.01 (0.77, 1.33)	0.93
Vitamin A	0.82 (0.64, 1.06)	0.13	0.79 (0.61, 1.03)	0.083
β-carotene	0.81 (0.62, 1.04)	0.10	0.78 (0.60, 1.01)	0.063

Abbreviations: ^{11}C-PiB PET, Pittsburgh compound B positron emission tomography; MeDi, Mediterranean diet; OR, odds ratio; CI, confidence interval.

*Abnormal amyloid ^{11}C-PiB PET was defined as standardized uptake value ratio >1.42.

§Models were adjusted for age, sex, education, APOE ε4 carrier status, time interval between the food frequency questionnaire (FFQ) completion and PET scan, and total energy intake.

¶Models were adjusted for age, sex, education, APOE ε4 carrier status, body mass index, diabetes, hypertension, coronary heart disease, peripheral vascular disease, congestive heart failure, atrial fibrillation, dyslipidemia, stroke, depressive symptoms, time interval between the food frequency questionnaire (FFQ) completion and PET scan, and total energy intake.

†Dietary measures were log or square root transformed where necessary, standardized and adjusted for caloric intake and estimates (excluding moderate alcohol intake) are presented per standard deviation increase.

#Variable “all vegetables” includes legumes; estimate for vegetable consumption without legumes: OR: 0.77, 95%CI 0.059, 0.99, p=0.045 (Model 1) and OR: 0.73, 95%CI 0.55, 0.95, p=0.021 (Model 2).

‡Alcohol intake of 5 to <25 g/d for women and 10 to <50 g/d for men vs. other (ref.).

^Percent of total calories/day.