Published in final edited form as:

J Alzheimers Dis. 2020 ; 78(2): 827–835. doi:10.3233/JAD-200392.

Adherence to dietary patterns and risk of incident dementia: Findings from the Atherosclerosis Risk in Communities Study

Emily A. Hu, PhD, MHS[a], **Aozhou Wu, PhD**[a], **Jennifer L. Dearborn, MD**[b], **Rebecca F. Gottesman, MD PhD**[c], **A. Richey Sharrett, MD DrPH**[a], **Lyn M. Steffen, PhD**[d], **Josef Coresh, MD PhD**[a], **Casey M. Rebholz, PhD**[a]

[a]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland [b]Department of Neurology, Yale University School of Medicine, New Haven, Connecticut [c]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland [d]Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, Minnesota

Abstract

Background: Previous studies have suggested that adherence to healthy dietary patterns during late life may be associated with improved cognition. However, few studies have examined the association between healthy dietary patterns during midlife and incident dementia.

Objective: Our study aimed to determine the association between adherence to healthy dietary patterns at midlife and incident dementia.

Methods: We included 13,630 adults from the Atherosclerosis Risk in Communities (ARIC) Study in our prospective analysis. We used food frequency questionnaire responses to calculate 4 dietary scores: Healthy Eating Index-2015 (HEI-2015), Alternative Healthy Eating Index-2010 (AHEI-2010), alternate Mediterranean (aMed) diet, and Dietary Approaches to Stop Hypertension (DASH). Participants were followed until the end of 2017 for incident dementia. Cox regression models adjusted for covariates were used to estimate risk of incident dementia by quintile of dietary scores.

Results: Over a median of 27 years, there were 2,352 cases of incident dementia documented. Compared with participants in quintile 1 of HEI-2015, participants in quintile 5 (healthiest) had a 14% lower risk of incident dementia (hazard ratio, HR: 0.86, 95% confidence interval, CI: 0.74–0.99). There were no significant associations of incident dementia with the AHEI-2010, aMed, or DASH scores. There were no significant interactions by sex, age, race, education, physical activity, hypertension, or obesity.

Corresponding author: Dr. Casey M. Rebholz, Welch Center for Prevention, Epidemiology, and Clinical Research, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2024 East Monument Street, Suite 2-500, Baltimore, Maryland 21287, Phone: 410-502-2359, crebhol1@jhu.edu.

Authorship: EAH and CMR designed research plan; EAH and CMR analyzed data; EAH wrote paper; EAH and CMR had primary responsibility for final content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Conflict of Interest/Disclosures: RFG is the Associate Editor for Neurology.

Conclusion: Adherence to the HEI-2015, but not the other dietary scores, during midlife was associated with lower risk of incident dementia. Further research is needed to elucidate whether timing of a healthy diet may influence dementia risk.

Keywords

dietary pattern; HEI-2015; AHEI-2010; Mediterranean; DASH; dementia; cognition

INTRODUCTION

It has been estimated that 47 million people worldwide lived with dementia in 2016 [1]. With an aging population, this number is projected to increase to at least 131 million people by the year 2050 [1]. The economic burden of dementia is also growing, and the total estimated cost of dementia worldwide is $818 billion and is expected to increase.

Prevention of dementia is critical due to the lack of effective treatments. Diet is a low-cost, modifiable, and potentially effective primary prevention strategy to reduce the risk and burden of dementia. While many studies have examined the association of individual nutrients and foods with cognition [2–4], fewer studies have examined dementia risk in relation to dietary patterns, which account for nutrient interactions and represent real-life behavior. Increasing evidence suggests that adherence to a Mediterranean-style diet may be associated with a reduced risk of cognitive decline [5–7]. This dietary pattern has been found to be associated with improvements in global cognition and several cognitive domains, such as episodic memory, working memory, delayed recall, immediate recall, attention, processing speed, and verbal fluency [8]. The cognitive benefit of the Mediterranean diet may work through cardiovascular mechanisms, as the diet has been found to be associated with reduced risk of cardiovascular disease and potentially obesity, hypertension, and dyslipidemia [9–12].

Although many of these previous studies examined cognitive function based on cognitive testing, fewer have assessed incident dementia. The outcome of dementia has the advantage over cognitive decline or function in that it captures cases that may be missed from cognitive assessments that rely on in-person visits. Furthermore, previous studies were conducted mostly among older populations and had short follow-up periods. Therefore, these studies may have missed a biologically relevant time window, as dementia has a long preclinical period. A recent study found that among 8,225 participants who were dementia-free, there was no association between adherence to a healthy dietary pattern during midlife and risk of subsequent dementia over a median follow-up period of 25 years [13]. Conversely, the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, Mediterranean diet, and Dietary Approaches to Stop Hypertension (DASH) diet have been found to be associated with lower risk of developing incident Alzheimer’s disease [14].

Other healthy dietary patterns include the Healthy Eating Index (HEI), Alternative Healthy Eating Index (AHEI), and DASH diet. These dietary patterns have some overlapping components and different scoring methods. They have been found to be associated with lower risk of cardiovascular disease and therefore may also reduce the risk of dementia as vascular risk factors have been found to be associated with dementia [15–18].

We aimed to examine whether adherence to healthy dietary patterns, assessed using the HEI-2015, AHEI-2010, alternate Mediterranean (aMed) diet, and DASH scores, was associated with incident dementia in the Atherosclerosis Risk in Communities (ARIC) study.

MATERIALS AND METHODS

Study population

Participants in this analysis were men and women from the ARIC study, a community-based prospective cohort of 15,792 participants from 4 U.S. communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis suburbs, Minnesota) [19]. Participants were aged 45–64 years old when they were recruited in 1987–1989 (visit 1). They were also seen in-person in 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), 2011–2013 (visit 5), 2016–2017 (visit 6), 2018–2019 (visit 7), visit 8 is in progress, and had annual follow-up telephone interviews. The Institutional Review Boards of participating institutions approved the ARIC study and participants provided written informed consent at each site.

In the present analysis, participants who were neither black nor white (n=48) or black and from Minneapolis, Minnesota or Washington County, Maryland (n=55) were excluded due to small numbers resulting in a lack of adequate representation of these groups within these study centers. Additionally, participants who did not fill out more than 15 food frequency questionnaire (FFQ) responses (n=46), had extreme energy intakes (women: <500 or >3,500 kcal/d; men: <700 or >4,500 kcal/d [n=268]), had a history of stroke at baseline (n=267), were missing data on covariates of interest (n=1,234), or did not have sufficient data to calculate all 4 dietary scores (n=244), were excluded. The final study population included 13,630 participants.

Diet assessment and computation of diet scores

Diet was assessed at visit 1 (1987–1989) and visit 3 (1993–1995). The 66-item semi-quantitative FFQ, modified from the Willett questionnaire [20], has been previously validated in ARIC [21, 22]. Trained interviewers asked participants how often, on average, they consumed food items of a given portion size in the preceding year. Total energy intake and nutrient intakes were calculated using data from the US Department of Agriculture. Only visit 1 data was used if participants developed incident dementia prior to visit 3 or did not have dietary data available at visit 3; otherwise, the averages of food and nutrient responses from visits 1 and 3 were used [23]. Total energy intake was calculated using the same method.

The HEI-2015 score reflects the recommendations from the *2015–2020 US Dietary Guidelines for Americans* [24]. It consists of 13 food and nutrient components that are scored based on energy-adjusted cutoffs (Supplemental Table 1). Possible scores range from 0 to 100.

The AHEI-2010 score includes foods and nutrients that have been found to be associated with risk of major chronic diseases [25]. There are 11 components that each range from 0 to 10, allowing for a total maximum score of 110 points (Supplemental Table 1).

The aMed score reflects food and nutrients common in a Mediterranean-style diet and has been adapted for the US population [26]. There are 9 components that are scored 0 or 1 based on sex-specific cutoffs; total possible score ranges from 0 to 9 (Supplemental Table 1).

The DASH score was created based on foods that were emphasized or discouraged in the DASH trial [27]. There are 8 components that are scored 1 to 5 based on quintiles of each component (Supplemental Table 1). The total score ranges from 8 to 40.

For our main analysis, we categorized participants by quintile of each score to assess trends and potential dose-response associations between diet and dementia.

Dementia ascertainment

Methods for ascertaining dementia in ARIC have been described in depth elsewhere [15, 28]. In brief, dementia was defined by at least one of the following criteria: 1) adjudicated dementia based on a complete neuropsychological battery, informant interviews and expert review at ARIC Neurocognitive Study visits (visits 5 and 6); 2) dementia determined from telephone interviews with participant or informant; or 3) dementia based on a prior hospitalization or death code for dementia. If participants met more than one of the criteria, the earliest date of dementia was used. Due to a possible lag in ascertainment of dementia identified by informant interviews, hospitalization, and death, six months was subtracted from the date dementia was ascertained by these methods.

Assessment of covariates

Age, sex, race, education, and physical activity were self-reported at visit 1 through an interviewer-administered questionnaire. Race and center were combined into an interaction variable to account for the unequal distribution of blacks and whites by each study site. Physical activity was measured via the Baecke questionnaire and exercise during leisure time was scored from 1 to 5 [29, 30]. Apolipoprotein (*APOE)* ε4 genotype and carriers were defined based on the number of ε4 alleles present (0, 1, or 2). Smoking status, alcohol status, and clinical variables were recorded at baseline. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as BMI ≥30 kg/m^2. Plasma total cholesterol level was measured using enzymatic methods [31, 32]. Systolic blood pressure was calculated as the average of the second and third measurements, which were taken after 5 minutes of rest using a random-zero sphygmomanometer. Anti-hypertensive medication use and prevalent coronary heart disease were self-reported. Diabetes was defined as fasting glucose level ≥126 mg/dL, non-fasting glucose level ≥200 mg/dL, self-report of physician diagnosis, or use of anti-diabetic medications.

Cognitive testing, performed at visit 2, used the Delayed Word Recall Test, the Digit Symbol Substitution Test, and the Word Fluency Test. A z-score at visit 2 was calculated by averaging the 3 test-specific z-scores.

Statistical analysis

Descriptive statistics were used to compare baseline characteristics of study participants across quintiles of each dietary score. Cox regression models were used to quantify

associations between dietary scores and incident dementia by estimating hazard ratios (HR) and 95% confidence intervals (CI). Follow-up time accumulated from visit 1 to the event date, date of death, or December 31, 2017, whichever occurred first. The proportional hazard assumption was assessed via Schoenfeld residuals test. Model 1 was adjusted for age, sex, race-center, total energy intake, education level, *APOE* ε4 genotype, smoking status, physical activity, and alcohol status (for HEI-2015 and DASH scores since they do not include alcohol in their scoring). Model 2 was further adjusted for BMI, total cholesterol, systolic blood pressure, antihypertensive medication use, diabetes status, and history of coronary heart disease. Model 3 was additionally adjusted for 3-test cognitive score at visit 2. Model 3 was considered our primary model. *P* for trend was assessed using the median score of each quintile. We used likelihood ratio tests to test for interactions by potential effect modifiers (sex, age, race, education, physical activity, hypertension, and obesity). We also implemented competing risk models to account for the competing risk of death [33]. Stata version 14 was used for all analyses (StataCorp, College Station, Texas.)

RESULTS

Baseline characteristics of participants by quintile of HEI-2015 score are shown in Table 1. Participants who had higher HEI-2015 scores, indicating healthier dietary intake, were more likely to be female, have a college education, be a never smoker, never drinker, be more physically active, have a lower total energy intake, and have a higher baseline cognitive 3-test z-score compared with participants with the lowest HEI-2015 scores. Those in higher quintiles of HEI-2015 were also more likely to have diabetes, take antihypertensive medication, and have a history of CHD compared with participants in quintile 1. Characteristics were mostly similar by quintile of AHEI-2010 (Supplemental Table 2) and aMed (Supplemental Table 3), with some exceptions. Some noteworthy exceptions were that those at higher levels of adherence to AHEI-2010 were more likely to be current drinkers, consumed higher levels of total energy intake, and were not different on the basis of anti-hypertensive medication use (Supplemental Table 2). Those in higher quintiles of aMed were not different according to sex, were more likely to consume alcohol, and consumed higher levels of total energy intake (Supplemental Table 3). Characteristics were very similar by quintile of DASH (Supplemental Table 4).

There were 2,352 cases of incident dementia over a median follow-up of 27 years. In model 1, there was a significant association between HEI-2015 score and risk of incident dementia comparing quintile 5 to quintile 1 (HR: 0.86, 95% CI: 0.75–0.99) (Table 2). The association of the other quintiles (2, 3, 4) of HEI-2015 with dementia compared with quintile 1 were not significant, but a test for trend was statistically significant. After additionally adjusting for clinical covariates in Model 2, the association remained significant. In model 3, which additionally adjusted for the 3-test cognitive score at visit 2, participants in quintile 5 had a 14% lower risk of dementia compared with participants in quintile 1 (HR: 0.86, 95% CI: 0.74–0.99), but the *P* for trend was non-significant (*P*=0.1). There were no significant associations for AHEI-2010, aMed, or DASH scores and incident dementia (Table 2). Comparing quintile 5 to quintile 1 in model 3, the association between AHEI-2010 (HR: 1.04, 95% CI: 0.91–1.20), aMed (HR: 1.01, 95% CI: 0.88–1.16), and DASH (HR: 1.10, 95% CI: 0.96–1.26) scores were non-significant. In competing risk models to account for the

competing risk of death, per standard deviation increase in each score, the hazard ratio was 0.95, CI% 0.87–1.04 for HEI-2015, 1.06, 95% CI: 0.98–1.16 for AHEI-2010, 1.01, 95% CI: 0.92–1.11 for aMed, and 1.00, 95% CI: 0.92–1.09 for DASH.

There were no consistent interactions between the dietary scores and dementia by sex, age, race, education, physical activity, hypertension, or obesity (all *P* for interactions>0.05).

DISCUSSION

In our study population of 13,630 black and white participants from four U.S. communities, we found that a better HEI-2015 score was weakly associated with less incident dementia, but there were no significant associations for AHEI-2010, aMed, or DASH scores. For all four scores, there were no significant trends in dementia risk by quintile of dietary scores and the results were consistent by subgroups.

Our study results are consistent with other studies that also found a null association between dietary patterns and dementia. A previous analysis in the ARIC study, using derived dietary patterns from principal components analysis (a Western diet pattern and prudent diet pattern), found no significant associations with 20-year change in cognitive function or with incident dementia [34]. An analysis of 8,225 participants from the Whitehall II study found that there was no association between a healthy diet at midlife, assessed by the AHEI-2010 score and derived dietary patterns, and incident dementia over a median follow-up of 24.8 years [13]. Other studies conducted in Bordeaux, France and Minnesota, USA that assessed adherence to the Mediterranean diet did not find an association with incident dementia among dementia-free older adults [35, 36].

However, our results contradict previous observational studies that have suggested an inverse association between healthy dietary patterns and cognitive decline. A meta-analysis of 32 studies from 25 unique cohorts concluded that most observational studies conducted found that adherence to a Mediterranean diet was associated with improved cognitive function, decreased risk of cognitive impairment, and decreased risk of dementia [5]. However, most previous studies were conducted among older populations (>65 years) and had short follow-up periods [37–43]. A recent review examined different dietary patterns [e.g. the Mediterranean diet, DASH diet, and Mediterranean/DASH Intervention for Neurodegenerative Delay (MIND) diet] and included 56 total studies [6]. Although many of the observational studies suggested that better adherence to these dietary patterns was associated with improved cognitive function, the evidence for dementia was too limited to draw firm conclusions. Furthermore, the results from randomized controlled trials were mixed [44–47].

Several reasons may explain why our findings differed from those of some previous studies. Many of the previous studies were conducted among older adults (>65 years) and assessed diet during late life, while our study assessed diet during midlife. Since diet was assessed during midlife and participants were followed for a median of 27 years, dietary behavior may have changed over time during the preclinical phase of dementia [48]. If participants were experiencing cognitive decline later in life, they may have changed from a healthy

eating pattern to an unhealthy pattern perhaps due to the difficulty with preparing healthy foods because of impaired cognitive function. Therefore, the studies conducted among elderly adults may have found an inverse association between healthy diet and dementia due to reverse causation.

We found that the HEI-2015, but not the other scores, was associated with lower risk of dementia. The key differences between the HEI-2015 and the other patterns are the individual components for refined grains, all dairy, total protein, and added sugars. Refined grains and added sugars are scored negatively but are not penalized in the other scores. Fish is accounted for in both the total protein and seafood/plant protein components in the HEI-2015. In the aMed score, fish is its own category and it is not included in the AHEI-2010 or DASH scores. Fish is a high source of omega-3 fatty acids and vitamin D, and is hypothesized to be a key factor in previous associations between Mediterranean diet and improved cognition [49]. Omega-3 fatty acids reduce inflammation and oxidative stress, which are both associated with cognitive function [50, 51]. There is also evidence that severe deficiency of vitamin D, found in meat and fish sources, may increase risk of dementia [52, 53]. Olive oil and nuts, which contain high amounts of phenolic compounds, have been hypothesized to improve cognition through improving cerebrovascular blood flow and stimulation of neurogenesis [54]. The MIND diet, which emphasizes brain healthy foods such as berries, leafy green vegetables, fish, and olive oil, has been found to be associated with reduced risk of Alzheimer's disease risk and cognitive decline (tertile 3 vs. tertile 1 HR: 0.47, 95% CI: 0.26–0.76) [14, 55]. Due to the questions in the ARIC FFQ not specifying berries or olive oil, we could not calculate the MIND score for comparison.

There were several limitations of our study. Diet was self-reported and therefore is subject to measurement error. However, the FFQ was administered by trained interviewers using a standard protocol. Diet was based on an average of dietary intake from visits 1 and 3, but we did not examine change in diet quality and risk of dementia. Future studies should examine how change in diet may be associated with dementia. There is also a possibility of residual confounding; however, covariates were measured using rigorous methods and were adjusted for in multivariable regression models. Additionally, there was potential misclassification of dementia cases since not all cases were adjudicated by the expert committee.

Our study also had several strengths. The study included a long follow-up time, which allowed us to evaluate the effects of midlife diet and capture more cases of incident dementia than previous studies given the lengthy preclinical phase of dementia. We leveraged repeated measurements of dietary intake by using the average of food and nutrient intakes from visits 1 and 3, allowing for a more precise measure. Lastly, we had rigorous ascertainment of dementia, and had a formal adjudication process for cases captured from in-person visits.

In summary, the results of our study suggest that adherence to the HEI-2015 dietary pattern during midlife may be associated with lower risk of dementia in later life. More research is warranted to further elucidate the relationship between midlife diet and incident dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Ms. Hu is supported by a grant from the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (training grant T32 HL007024). Dr. Gottesman is supported by K24 AG052573. Dr. Rebholz is supported by a mentored research scientist development award from the National Institute of Diabetes and Digestive and Kidney Diseases (K01 DK107782) and a grant from the National Heart, Lung, and Blood Institute (R21 HL143089). The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). Neurocognitive data is collected by U01 2U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, 2U01HL096917 from the NIH (NHLBI, NINDS, NIA and NIDCD), and with previous brain MRI examinations funded by R01-HL70825 from the NHLBI. The authors thank the staff and participants of the ARIC study for their important contributions.

REFERENCES

[1]. Alzheimer's Disease International (2016) World Alzheimer Report 2016: Improving healthcare for people living with dementia.

[2]. Gomez-Pinilla F (2008) Brain foods: the effects of nutrients on brain function. Nat Rev Neurosci 9, 568–578. [PubMed: 18568016]

[3]. Otaegui-Arrazola A, Amiano P, Elbusto A, Urdaneta E, Martinez-Lage P (2014) Diet, cognition, and Alzheimer's disease: food for thought. Eur J Nutr 53, 1–23.

[4]. Scarmeas N, Anastasiou CA, Yannakoulia M (2018) Nutrition and prevention of cognitive impairment. Lancet Neurol 17, 1006–1015. [PubMed: 30244829]

[5]. Petersson SD, Philippou E (2016) Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review of the Evidence. Adv Nutr 7, 889–904. [PubMed: 27633105]

[6]. van den Brink AC, Brouwer-Brolsma EM, Berendsen AAM, van de Rest O (2019) The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diets Are Associated with Less Cognitive Decline and a Lower Risk of Alzheimer's Disease-A Review. Adv Nutr 10, 1040–1065. [PubMed: 31209456]

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

[8]. Loughrey DG, Lavecchia S, Brennan S, Lawlor BA, Kelly ME (2017) The Impact of the Mediterranean Diet on the Cognitive Functioning of Healthy Older Adults: A Systematic Review and Meta-Analysis. Adv Nutr 8, 571–586. [PubMed: 28710144]

[9]. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB (2009) Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. Circulation 119, 1093–1100. [PubMed: 19221219]

[10]. Ginter E, Simko V (2015) Recent data on Mediterranean diet, cardiovascular disease, cancer, diabetes and life expectancy. Bratisl Lek Listy 116, 346–348. [PubMed: 26084734]

[11]. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Fito M, Gea A, Hernan MA, Martinez-Gonzalez MA, Predimed Study Investigators (2018) Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med 378, e34. [PubMed: 29897866]

[12]. Salas-Salvado J, Bullo M, Babio N, Martinez-Gonzalez MA, Ibarrola-Jurado N, Basora J, Estruch R, Covas MI, Corella D, Aros F, Ruiz-Gutierrez V, Ros E, Predimed Study Investigators (2011) Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the

PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care 34, 14–19. [PubMed: 20929998]

[13]. Akbaraly TN, Singh-Manoux A, Dugravot A, Brunner EJ, Kivimaki M, Sabia S (2019) Association of Midlife Diet With Subsequent Risk for Dementia. JAMA 321, 957–968. [PubMed: 30860560]

[14]. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT (2015) MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimers Dement 11, 1007–1014. [PubMed: 25681666]

[15]. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, Deal JA, McKhann GM, Mosley TH, Sharrett AR, Schneider ALC, Windham BG, Wruck LM, Knopman DS (2017) Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. JAMA Neurol 74, 1246–1254. [PubMed: 28783817]

[16]. Hu EA, Steffen LM, Coresh J, Appel LJ, Rebholz CM (2019) Adherence to the Healthy Eating Index-2015 and Other Dietary Patterns May Reduce Risk of Cardiovascular Disease, Cardiovascular Mortality, and All-Cause Mortality. J Nutr.

[17]. Liese AD, Krebs-Smith SM, Subar AF, George SM, Harmon BE, Neuhouser ML, Boushey CJ, Schap TE, Reedy J (2015) The Dietary Patterns Methods Project: synthesis of findings across cohorts and relevance to dietary guidance. J Nutr 145, 393–402. [PubMed: 25733454]

[18]. Schwingshackl L, Hoffmann G (2015) Diet quality as assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension score, and health outcomes: a systematic review and meta-analysis of cohort studies. J Acad Nutr Diet 115, 780–800 e785. [PubMed: 25680825]

[19]. The ARIC Investigators (1989) The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol 129, 687–702. [PubMed: 2646917]

[20]. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE (1985) Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 122, 51–65. [PubMed: 4014201]

[21]. Stevens J, Metcalf PA, Dennis BH, Tell GS, Shimakawa T, Folsom AR (1996) Reliability of a food frequency questionnaire by ethnicity, gender, age and education. Nutrition Research 16, 735–745.

[22]. Shimakawa T, Sorlie P, Carpenter MA, Dennis B, Tell GS, Watson R, Williams OD (1994) Dietary intake patterns and sociodemographic factors in the atherosclerosis risk in communities study. ARIC Study Investigators. Prev Med 23, 769–780. [PubMed: 7855109]

[23]. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC (1999) Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 149, 531–540. [PubMed: 10084242]

[24]. Krebs-Smith SM, Pannucci TE, Subar AF, Kirkpatrick SI, Lerman JL, Tooze JA, Wilson MM, Reedy J (2018) Update of the Healthy Eating Index: HEI-2015. J Acad Nutr Diet 118, 1591–1602. [PubMed: 30146071]

[25]. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ, Willett WC (2012) Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 142, 1009–1018. [PubMed: 22513989]

[26]. Fung TT, McCullough ML, Newby PK, Manson JE, Meigs JB, Rifai N, Willett WC, Hu FB (2005) Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr 82, 163–173. [PubMed: 16002815]

[27]. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB (2008) Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med 168, 713–720. [PubMed: 18413553]

[28]. Knopman DS, Gottesman RF, Sharrett AR, Wruck LM, Windham BG, Coker L, Schneider AL, Hengrui S, Alonso A, Coresh J, Albert MS, Mosley TH Jr. (2016) Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Alzheimers Dement (Amst) 2, 1–11. [PubMed: 26949733]

[29]. Baecke JA, Burema J, Frijters JE (1982) A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 36, 936–942. [PubMed: 7137077]

[30]. Folsom AR, Arnett DK, Hutchinson RG, Liao F, Clegg LX, Cooper LS (1997) Physical activity and incidence of coronary heart disease in middle-aged women and men. Med Sci Sports Exerc 29, 901–909. [PubMed: 9243489]

[31]. Sharrett AR, Patsch W, Sorlie PD, Heiss G, Bond MG, Davis CE (1994) Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease. The Atherosclerosis Risk in Communities (ARIC) Study. Arterioscler Thromb 14, 1098–1104. [PubMed: 8018665]

[32]. Siedel J, Hagele EO, Ziegenhorn J, Wahlefeld AW (1983) Reagent for the enzymatic determination of serum total cholesterol with improved lipolytic efficiency. Clin Chem 29, 1075–1080. [PubMed: 6851096]

[33]. Austin PC, Lee DS, Fine JP (2016) Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation 133, 601–609. [PubMed: 26858290]

[34]. Dearborn-Tomazos JL, Wu A, Steffen LM, Anderson CAM, Hu EA, Knopman D, Mosley TH, Gottesman RF (2019) Association of Dietary Patterns in Midlife and Cognitive Function in Later Life in US Adults Without Dementia. JAMA Netw Open 2, e1916641. [PubMed: 31800068]

[35]. Feart C, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues JF, Scarmeas N, Barberger-Gateau P (2009) Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. JAMA 302, 638–648. [PubMed: 19671905]

[36]. Roberts RO, Geda YE, Cerhan JR, Knopman DS, Cha RH, Christianson TJ, Pankratz VS, Ivnik RJ, Boeve BF, O'Connor HM, Petersen RC (2010) Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment. Dement Geriatr Cogn Disord 29, 413–423. [PubMed: 20502015]

[37]. Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, Stern Y (2009) Physical activity, diet, and risk of Alzheimer disease. JAMA 302, 627–637. [PubMed: 19671904]

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

[39]. Samieri C, Grodstein F, Rosner BA, Kang JH, Cook NR, Manson JE, Buring JE, Willett WC, Okereke OI (2013) Mediterranean diet and cognitive function in older age. Epidemiology 24, 490–499. [PubMed: 23676264]

[40]. Samieri C, Okereke OI, Devore EE, Grodstein F (2013) Long-term adherence to the Mediterranean diet is associated with overall cognitive status, but not cognitive decline, in women. J Nutr 143, 493–499. [PubMed: 23365105]

[41]. Tangney CC, Li H, Wang Y, Barnes L, Schneider JA, Bennett DA, Morris MC (2014) Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons. Neurology 83, 1410–1416. [PubMed: 25230996]

[42]. Tangney CC, Kwasny MJ, Li H, Wilson RS, Evans DA, Morris MC (2011) Adherence to a Mediterranean-type dietary pattern and cognitive decline in a community population. Am J Clin Nutr 93, 601–607. [PubMed: 21177796]

[43]. Gu Y, Luchsinger JA, Stern Y, Scarmeas N (2010) Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. J Alzheimers Dis 22, 483–492. [PubMed: 20847399]

[44]. Knight A, Bryan J, Wilson C, Hodgson JM, Davis CR, Murphy KJ (2016) The Mediterranean Diet and Cognitive Function among Healthy Older Adults in a 6-Month Randomised Controlled Trial: The MedLey Study. Nutrients 8.

[45]. Martinez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvado J, San Julian B, Sanchez-Tainta A, Ros E, Valls-Pedret C, Martinez-Gonzalez MA (2013) Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry 84, 1318–1325. [PubMed: 23670794]

[46]. Martinez-Lapiscina EH, Clavero P, Toledo E, San Julian B, Sanchez-Tainta A, Corella D, Lamuela-Raventos RM, Martinez JA, Martinez-Gonzalez MA (2013) Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. J Nutr Health Aging 17, 544–552. [PubMed: 23732551]

[47]. Smith PJ, Blumenthal JA, Babyak MA, Craighead L, Welsh-Bohmer KA, Browndyke JN, Strauman TA, Sherwood A (2010) Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. Hypertension 55, 1331–1338. [PubMed: 20305128]

[48]. Wagner M, Grodstein F, Proust-Lima C, Samieri C (2020) Long-Term Trajectories of Body Weight, Diet, and Physical Activity From Midlife Through Late Life and Subsequent Cognitive Decline in Women. Am J Epidemiol 189, 305–313. [PubMed: 31781745]

[49]. Hooper C, De Souto Barreto P, Pahor M, Weiner M, Vellas B (2018) The Relationship of Omega 3 Polyunsaturated Fatty Acids in Red Blood Cell Membranes with Cognitive Function and Brain Structure: A Review Focussed on Alzheimer's Disease. J Prev Alzheimers Dis 5, 78–84. [PubMed: 29405237]

[50]. Steele M, Stuchbury G, Munch G (2007) The molecular basis of the prevention of Alzheimer's disease through healthy nutrition. Exp Gerontol 42, 28–36. [PubMed: 16839733]

[51]. Frisardi V, Panza F, Seripa D, Imbimbo BP, Vendemiale G, Pilotto A, Solfrizzi V (2010) Nutraceutical properties of Mediterranean diet and cognitive decline: possible underlying mechanisms. J Alzheimers Dis 22, 715–740. [PubMed: 20858954]

[52]. Crowe FL, Steur M, Allen NE, Appleby PN, Travis RC, Key TJ (2011) Plasma concentrations of 25-hydroxyvitamin D in meat eaters, fish eaters, vegetarians and vegans: results from the EPIC-Oxford study. Public Health Nutr 14, 340–346. [PubMed: 20854716]

[53]. Chai B, Gao F, Wu R, Dong T, Gu C, Lin Q, Zhang Y (2019) Vitamin D deficiency as a risk factor for dementia and Alzheimer's disease: an updated meta-analysis. BMC Neurol 19, 284. [PubMed: 31722673]

[54]. Bullo M, Lamuela-Raventos R, Salas-Salvado J (2011) Mediterranean diet and oxidation: nuts and olive oil as important sources of fat and antioxidants. Curr Top Med Chem 11, 1797–1810. [PubMed: 21506929]

[55]. Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA, Aggarwal NT (2015) MIND diet slows cognitive decline with aging. Alzheimers Dement 11, 1015–1022. [PubMed: 26086182]

Table 1.

Baseline characteristics of ARIC participants by quintile of HEI-2015 score[a].

Characteristic	HEI-2015 Quintile					P[b]
	Q1 n=2,726	Q2 n=2,726	Q3 n=2,726	Q4 n=2,726	Q5 n=2,726	
HEI-2015 score	60 ± 4	67 ± 1	72 ± 1	76 ± 1	83 ± 3	<0.001
Age, years	54 ± 6	54 ± 6	54 ± 6	54 ± 6	55 ± 6	<0.001
Female, %	41	51	56	62	68	<0.001
Black, %	25	28	28	24	23	<0.001
College education, %	25	32	38	40	46	<0.001
Smoking status, %						<0.001
Never smoker	30	39	44	47	49	
Former smoker	30	31	32	32	36	
Current smoker	40	29	24	21	15	
Alcohol status, %						<0.001
Never drinker	20	24	26	27	28	
Former drinker	22	18	17	18	17	
Current drinker	58	58	57	55	55	
Physical activity index (1–5)[c]	2.2 ± 0.7	2.4 ± 0.8	2.4 ± 0.8	2.5 ± 0.8	2.6 ± 0.8	<0.001
APOE ε4 (1–2 alleles), %	29	29	31	30	34	0.004
BMI, kg/m^2	27 ± 5	28 ± 5	28 ± 6	28 ± 5	27 ± 5	0.03
Total cholesterol, mg/dL	213 ± 42	213 ± 41	213 ± 40	216 ± 42	217 ± 44	<0.001
Diabetes, %	9	11	12	12	13	<0.001
Systolic blood pressure, mmHg	121 ± 19	122 ± 19	121 ± 18	121 ± 18	120 ± 18	0.2
Antihypertensive medication, %	25	27	32	32	32	<0.001
Coronary heart disease, %	4	4	4	4	6	<0.001
Average total energy intake, kcal/d	1,617 ± 593	1,566 ± 541	1,450 ± 496	1,434 ± 483	1,326 ± 414	<0.001
Visit 2 global cognitive z-score	−0.1 ± 1	−0.1 ± 1	0 ± 1	0.1 ± 1	0.2 ± 1	<0.001

[a]Values for categorical variables are given as percentage; for continuous variables, mean ± standard deviation. Higher quintiles indicate greater adherence to a healthy dietary pattern.

[b]Categorical variables were analyzed using chi-square test. Continuous variables were analyzed using analysis of variance (ANOVA) test.

[c]Physical activity index score was calculated based on intensity and time of sport and exercise during leisure time; 1-lowest and 5-highest.

APOE, apolipoprotein E; ARIC, Atherosclerosis Risk in Communities study; BMI, body mass index; CHD, coronary heart disease; HEI, Healthy Eating Index; mg/dL; milligrams per deciliter; mmHg, millimeters of mercury; Q, quintile.

J Alzheimers Dis. Author manuscript; available in PMC 2021 March 05.

J Alzheimers Dis. Author manuscript; available in PMC 2021 March 05.

Table 2.

Hazard ratio (95% CI) of dementia according to quintile of HEI-2015, AHEI-2010, aMed, and DASH scores[a].

HEI-2015						
	Q1: 61[b] n=2,726	**Q2: 67 n=2,726**	**Q3: 72 n=2,726**	**Q4: 76 n=2,726**	**Q5: 82 n=2,726**	***P*[c]**
No. events	445	447	474	474	512	
Model 1	1 (ref.)	0.89 (0.78–1.02)	0.91 (0.80–1.04)	0.89 (0.78–1.02)	0.86 (0.75–0.99)	0.05
Model 2	1 (ref.)	0.88 (0.77–1.00)	0.89 (0.78–1.01)	0.85 (0.74–0.97)	0.84 (0.73–0.96)	0.01
Model 3	1 (ref.)	0.86 (0.75–1.00)	0.89 (0.77–1.02)	0.90 (0.78–1.04)	0.86 (0.74–0.99)	0.1
AHEI-2010						
	Q1: 37 n=2,726	**Q2: 45 n=2,726**	**Q3: 51 n=2,726**	**Q4: 58 n=2,726**	**Q5: 67 n=2,726**	***P***
No. events	427	499	457	450	519	
Model 1	1 (ref.)	1.05 (0.93–1.20)	0.97 (0.85–1.11)	0.90 (0.78–1.03)	1.00 (0.88–1.15)	0.4
Model 2	1 (ref.)	1.06 (0.93–1.20)	0.94 (0.84–1.09)	0.88 (0.77–1.00)	0.98 (0.86–1.12)	0.2
Model 3	1 (ref.)	1.06 (0.93–1.22)	0.99 (0.86–1.13)	0.92 (0.80–1.06)	1.04 (0.91–1.20)	0.9
aMed						
	Q1: 2 n=2,545	**Q2: 3 n=2,443**	**Q3: 4 n=2,780**	**Q4: 5 n=2,524**	**Q5: 7 n=3,338**	***P***
No. events	404	402	467	454	625	
Model 1	1 (ref.)	1.00 (0.87–1.15)	0.97 (0.85–1.11)	0.96 (0.84–1.10)	0.98 (0.86–1.11)	0.6
Model 2	1 (ref.)	0.98 (0.86–1.13)	0.95 (0.83–1.09)	0.92 (0.81–1.06)	0.95 (0.83–1.08)	0.3
Model 3	1 (ref.)	1.04 (0.90–1.20)	1.02 (0.88–1.17)	0.99 (0.86–1.15)	1.01 (0.88–1.16)	0.9
DASH						
	Q1: 18 n=3,431	**Q2: 22 n=2,710**	**Q3: 24 n=2,037**	**Q4: 27 n=2,781**	**Q5: 30 n=2,671**	***P***
No. events	555	450	349	481	517	
Model 1	1 (ref.)	1.03 (0.91–1.17)	1.04 (0.91–1.20)	0.95 (0.83–1.08)	1.05 (0.92–1.20)	0.9
Model 2	1 (ref.)	1.01 (0.89–1.15)	1.00 (0.87–1.14)	0.90 (0.79–1.02)	1.02 (0.89–1.16)	0.6
Model 3	1 (ref.)	1.06 (0.93–1.21)	1.03 (0.89–1.20)	0.97 (0.85–1.11)	1.10 (0.96–1.26)	0.5

[a]Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI). Model 1 was adjusted for age, sex, race-center, total energy intake, education level, *APOE* ε4 genotype, smoking status, physical activity, and alcohol status (for HEI-2015 and DASH scores). Model 2 was additionally adjusted for BMI, total cholesterol, systolic blood pressure, antihypertensive medication use,

diabetes status, and history of coronary heart disease. Model 3 included model 2 covariates in addition to global cognitive score at visit 2. AHEI, Alternative Healthy Eating Index; aMed, alternate Mediterranean diet; DASH, Dietary Approaches to Stop Hypertension; HEI; Healthy Eating Index; no, number; ref, reference.

[b] Median score of tertile.

[c] Trend was tested using the median value within each tertile.

J Alzheimers Dis. Author manuscript; available in PMC 2021 March 05.