

## MIND diet slows cognitive decline with aging

Martha Clare Morris<sup>a,\*</sup>, Christy C. Tangney<sup>b</sup>, Yamin Wang<sup>a</sup>, Frank M. Sacks<sup>c</sup>, Lisa L. Barnes<sup>d,e,f</sup>,  
David A. Bennett<sup>e,f</sup>, Neelum T. Aggarwal<sup>e,f</sup>

<sup>a</sup>Department of Internal Medicine at Rush University Medical Center, Chicago, IL, USA

<sup>b</sup>Department of Clinical Nutrition at Rush University Medical Center, Chicago, IL, USA

<sup>c</sup>Department of Nutrition, Harvard School of Public Health, Harvard University, Boston, MA, USA

<sup>d</sup>Department of Behavioral Sciences at Rush University Medical Center, Chicago, IL, USA

<sup>e</sup>Department of Neurological Sciences at Rush University Medical Center, Chicago, IL, USA

<sup>f</sup>Rush Alzheimer's Disease Center at Rush University Medical Center, Chicago, IL, USA

### Abstract

**Introduction:** The Mediterranean and dash diets have been shown to slow cognitive decline; however, neither diet is specific to the nutrition literature on dementia prevention.

**Methods:** We devised the Mediterranean-Dietary Approach to Systolic Hypertension (DASH) diet intervention for neurodegenerative delay (MIND) diet score that specifically captures dietary components shown to be neuroprotective and related it to change in cognition over an average 4.7 years among 960 participants of the Memory and Aging Project.

**Results:** In adjusted mixed models, the MIND score was positively associated with slower decline in global cognitive score ( $\beta = 0.0092$ ;  $P < .0001$ ) and with each of five cognitive domains. The difference in decline rates for being in the top tertile of MIND diet scores versus the lowest was equivalent to being 7.5 years younger in age.

**Discussion:** The study findings suggest that the MIND diet substantially slows cognitive decline with age. Replication of these findings in a dietary intervention trial would be required to verify its relevance to brain health.

© 2015 The Alzheimer's Association. Published by Elsevier Inc. All rights reserved.

### Keywords:

Cognition; Cognitive decline; Nutrition; Diet; Epidemiologic study; Aging

### 1. Introduction

Dementia is now the sixth leading cause of death in the United States [1] and the prevention of cognitive decline, the hallmark feature of dementia, is a public health priority. It is estimated that delaying disease onset by just 5 years will reduce the cost and prevalence by half [2]. Diet interventions have the potential to be effective preventive strategies. Two randomized trials of the cultural-based Mediterranean diet [3] and of the blood pressure lowering DASH diet (Dietary Approach to Systolic Hypertension) [4] observed protective

effects on cognitive decline [5,6]. We devised a new diet that is tailored to protection of the brain, called the Mediterranean-DASH diet intervention for neurodegenerative delay (MIND). The diet is styled after the Mediterranean and DASH diets but with modifications based on the most compelling findings in the diet-dementia field. For example, a number of prospective studies [7–10] observed slower decline in cognitive abilities with high consumption of vegetables, and in the two US studies, the greatest protection was from green leafy vegetables [7,8]. Furthermore, all these studies found no association of overall fruit consumption with cognitive decline. However, animal models [11] and one large prospective cohort study [12] indicate that at least one particular type of fruit—berries—may protect the brain against cognitive loss.

The authors have no relevant disclosures of potential conflicts of interest.

\*Corresponding author. Tel.: +1-312-942-3223; Fax: +1-312-942-2861.

E-mail address: [martha\\_c\\_morris@rush.edu](mailto:martha_c_morris@rush.edu)

<http://dx.doi.org/10.1016/j.jalz.2015.04.011>

1552-5260/© 2015 The Alzheimer's Association. Published by Elsevier Inc. All rights reserved.

Thus, among the unique components of the MIND diet score are that it specifies consumption of green leafy vegetables and berries but does not score other types of fruit. In this study, we related the MIND diet score to cognitive decline in the Memory and Aging Project (MAP) and compared the estimated effects to those of the Mediterranean and DASH diets; dietary patterns that we previously reported were protective against cognitive decline among the MAP study participants [13].

## 2. Methods

### 2.1. Study population

The analytic sample is drawn from the Rush MAP, a study of residents of >40 retirement communities and senior public housing units in the Chicago area. Details of the MAP study were published previously [14]. Briefly, the ongoing open cohort study began in 1997 and includes annual clinical neurologic examinations. At enrollment, participants are free of known dementia [15,16] and agree to annual clinical evaluation and organ donation after death. We excluded persons with dementia based on accepted clinical criteria as previously described [15,16]. Participants meeting criteria for mild cognitive impairment [17] ( $n = 220$ ) were not excluded except in secondary analyses. From February 2004 to 2013, the MAP study participants were invited to complete food frequency questionnaires (FFQs) at the time of their annual clinical evaluations. During that period, a total of 1545 older persons had enrolled in the MAP study, 90 died and 149 withdrew before the diet study began, leaving 1306 participants eligible for these analyses. Of these, 1068 completed the dietary questionnaires of which 960 survived and had at least two cognitive assessments for the analyses of change. The analytic sample was 95% white and 98.5% non-Hispanic. The Institutional Review Board of Rush University Medical Center approved the study, and all participants gave written informed consent.

### 2.2. Cognitive assessments

Each participant underwent annual structured clinical evaluations including cognitive testing. Technicians, trained and certified according to standardized neuropsychological testing methods, administered 21 tests, 19 of which summarized cognition in five cognitive domains (episodic memory, working memory, semantic memory, visuospatial ability, and perceptual speed) as described previously [18]. Composite scores were computed for each cognitive domain and for a global measure of all 19 tests. Raw scores for each test were standardized using the mean and standard deviation from the baseline population scores, and the standardized scores averaged. The number of annual cognitive assessments analyzed for participants ranged from 2 to 10 with 52% of sample participants having five or more cognitive assessments.

### 2.3. Diet assessment

FFQs were collected at each annual clinical evaluation. For these prospective analyses of the estimated dietary effects on cognitive change, we used the first obtained FFQ to relate dietary scores to cognitive change from that point forward. Longitudinal analyses of change in MIND diet score using all available FFQs in a linear mixed model indicated a very small but statistically significant decrease in MIND score of  $-0.026$  ( $P = .02$ ) compared to the intercept MIND diet score of 7.37.

Diet scores were computed from responses to a modified Harvard semiquantitative FFQ that was validated for use in older Chicago community residents [19]. The FFQ ascertains usual frequency of intake over the previous 12 months of 144 food items. For some food items, natural portion sizes (e.g., one banana) were used to determine serving sizes and calorie and nutrient levels. Serving sizes for other food items were based on sex-specific mean portion sizes reported by the oldest men and women of national surveys.

### 2.4. MIND diet score

The MIND diet score was developed in three stages: (1) determination of dietary components of the Mediterranean and DASH diets including the foods and nutrients shown to be important to incident dementia and cognitive decline through detailed reviews of the literature [20–22], (2) selection of FFQ items that were relevant to each MIND diet component, and (3) determination of daily servings to be assigned to component scores guided by published studies on diet and dementia. Among the MIND diet components are 10 brain healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine) and five unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). Olive oil consumption was scored 1 if identified by the participant as the primary oil usually used at home and 0 otherwise. For all other diet score components, we summed the frequency of consumption of each food item portion associated with that component and then assigned a concordance score of 0, 0.5, or 1 (Table 1). The total MIND diet score was computed by summing over all 15 of the component scores.

### 2.5. DASH and Mediterranean diet scores

We used the DASH diet scoring of the Exercise and Nutrition Interventions for Cardiovascular Health (ENCORE) trial [23] in which 10 dietary components were each scored 0, 0.5, or 1 and summed for a total score ranging from 0 (lowest) to 10 (highest) diet concordance. The Mediterranean diet score was that described by Panagiotakos et al. [3] that includes 11 dietary components each scored 0–5 that are summed for a total score ranging from 0 to 55 (highest dietary concordance). We used serving quantities specific to the traditional Greek Mediterranean diet [3] to score

Table 1  
MIND diet component servings and scoring

Diet component	0	0.5	1
Green leafy* vegetables	≤2 servings/wk	>2 to <6/wk	≥6 servings/wk
Other vegetables†	<5 serving/wk	5 to <7 wk	≥1 serving/d
Berries‡	<1 serving/wk	1/wk	≥2 servings/wk
Nuts	<1/mo	1/mo to <5/wk	≥5 servings/wk
Olive oil	Not primary oil		Primary oil used
Butter, margarine	>2 T/d	1–2/d	<1 T/d
Cheese	7 + servings/wk	1–6/wk	<1 serving/wk
Whole grains	<1 serving/d	1–2/d	≥3 servings/d
Fish (not fried)¶	Rarely	1–3/mo	≥1 meals/wk
Beans§	<1 meal/wk	1–3/wk	>3 meals/wk
Poultry (not fried)¶	<1 meal/wk	1/wk	≥2 meals/wk
Red meat and products#	7 + meals/wk	4–6/wk	<4 meals/wk
Fast fried foods**	4 + times/wk	1–3/wk	<1 time/wk
Pastries and sweets††	7 + servings/wk	5–6/wk	<5 servings/wk
Wine	>1 glass/d or never	1/mo–6/wk	1 glass/d
Total score			15

Abbreviation: MIND, Mediterranean-DASH diet intervention for neurodegenerative delay.

\*Kale, collards, greens; spinach; lettuce/tossed salad.

†Green/red peppers, squash, cooked carrots, raw carrots, broccoli, celery, potatoes, peas or lima beans, tomatoes, tomato sauce, string beans, beets, corn, zucchini/summer squash/eggplant, coleslaw, potato salad.

‡Strawberries.

§Beans, lentils, soybeans.

¶Tuna sandwich, fresh fish as main dish; not fried fish cakes, sticks, or sandwiches.

¶Chicken or turkey sandwich, chicken or turkey as main dish, and never eat fried at home or away from home.

#Cheeseburger, hamburger, beef tacos/burritos, hot dogs/sausages, roast beef or ham sandwich, salami, bologna, or other deli meat sandwich, beef (steak, roast) or lamb as main dish, pork or ham as main dish, meatballs or meatloaf.

\*\*How often do you eat fried food away from home (like French fries, chicken nuggets)?

††Biscuit/roll, poptarts, cake, snack cakes/twinkies, Danish/sweet rolls/pastry, donuts, cookies, brownies, pie, candy bars, other candy, ice cream, pudding, and milkshakes/frappes.

concordance in contrast to the use of sex-specific within population median servings used by other studies so that the scoring metric aligned with the actual Mediterranean diet.

## 2.6. Covariates

Total energy intake was computed based on responses of frequency of consumption of the FFQ food items. Nondietary variables were obtained from structured interview questions and measurements at the participants' annual clinical evaluations. Age (in years) was computed from self-reported birth date and date of the first cognitive assessment in this analysis. Education was based on self-reported years of regular schooling. Apolipoprotein E genotyping was performed using high throughput sequencing as previously described [24]. Smoking history was categorized as never,

past, and current smoker. All other covariates were based on data collected at the time of each cognitive assessment and were modeled as time-varying covariates to represent updated information from participants' previous evaluations. A variable for frequency of participation in cognitively stimulating activities was computed as the average frequency rating, based on a 5-point scale, of different activities (e.g., reading, playing games, writing letters, visiting the library) [25]. Hours per week of physical activity was computed based on the sum of self-reported minutes spent over the previous two weeks on five activities (walking for exercise, yard work, calisthenics, biking, and water exercise) [26]. Number of depressive symptoms was assessed by a modified 10-item version of the Center for Epidemiological Studies-Depression scale [27] that has been related to incident dementia. Body mass index (BMI, weight in kg/height in m<sup>2</sup>) was computed from measured weight and height and modeled as two indicator variables, BMI ≤20 and BMI ≥30. Hypertension history was determined by self-reported medical diagnosis, measured blood pressure (average of 2 measurements ≥160 mm Hg systolic or ≥90 mm Hg diastolic), or current use of hypertensive medications. Myocardial infarction history was based on self-reported medical diagnosis or interviewer recorded use of cardiac glycosides (e.g., lanoxin, digitoxin). Diabetes history was determined by self-reported medical diagnosis or current use of medications. Medication use was based on interviewer inspection. Clinical diagnosis of stroke was based on clinician review of self-reported history, neurologic examination, and cognitive testing history [28].

## 2.7. Statistical methods

We used separate linear mixed models with random effects in SAS to examine the relations of the MIND diet score to change in the global cognitive score and in each cognitive domain score. The basic-adjusted model included terms for age, sex, education, apolipoprotein E (*APOE*) ε4, smoking history, physical activity, participation in cognitive activities, total energy intake, MIND diet score, a variable for time, and multiplicative terms between time and each model covariate, the latter providing the covariate effect on cognitive decline. For all analyses, we investigated both linear (MIND diet score modeled as a continuous term) and nonlinear associations (MIND diet score modeled in tertiles) with the cognitive scores. Because the study results were identical for the two sets of models, we report the effect estimates for the continuous linear term in tables and text and the tertile estimates in Fig. 1. Nonstatic covariates (e.g., cognitive and physical activities, BMI, depressive symptoms and cardiovascular conditions) were modeled as time-varying except when they were analyzed as potential effect modifiers in which case only the baseline measure for that covariate was modeled. Tests for statistical interaction by potential effect modifiers were computed in the basic-adjusted model by modeling two-way and three-way

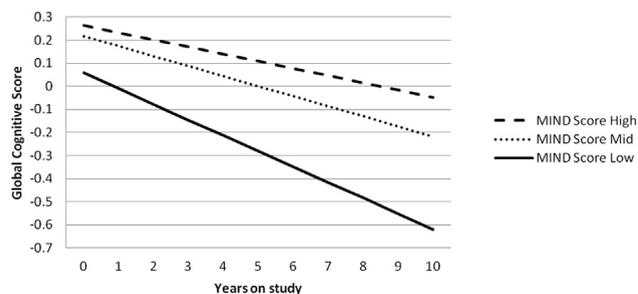


Fig. 1. Rates of change in global cognitive score over 10 years for MAP participants with MIND diet scores in the highest tertile of scores (---; median, 9.5; range, 8.5–12.5), the second tertile of scores (...; median, 7.5; range, 7.0–8.0), and the lowest tertile of scores (—; median, 6; range, 2.5–6.5). The rates of change were based on the mixed model with MIND diet score modeled as two indicator variables for tertile 2 and tertile 3 (tertile 1, the referent) and adjusted for age, sex, education, smoking, physical activity, participation in cognitively stimulating activities, and total energy intake. For tertile 3:  $\beta = 0.0366$ , standard error = 0.0101, and  $P = .003$  and for tertile 2:  $\beta = 0.0243$ , standard error = 0.0099, and  $P = .01$ . Abbreviations: MAP, Memory and Aging Project; MIND, Mediterranean-DASH diet intervention for neurodegenerative delay.

multiplicative terms between MIND diet score, time, and the effect modifier, with the three-way multiplicative term test for interaction set at  $P \leq .05$ . We compared the relative effects of the MIND, Mediterranean and DASH diet scores on cognitive decline by computing standardized  $\beta$  coefficients ( $\beta$  to four decimal places/standard error) for each diet score based on the parameter estimates of the basic model. We then performed formal statistical tests using Meng et al.'s [29] revision of Hotelling's [30] procedure for comparing two nonindependent correlation coefficients, in this case, the correlations between the diet scores and cognitive change from the basic model. To provide an estimate of the equivalent age difference in years to the difference in decline rates for tertiles 3 and 1 of the MIND diet score, we computed the ratio of the beta coefficients [ $\beta$  (time  $\times$  age)]/ $\beta$  (time  $\times$  tertile 3 MIND score) in the basic-adjusted model.

### 3. Results

The analytic sample aged, on average, 81.4 years ( $\pm 7.2$ ), was primarily female (75%), had a mean educational level of 14.9 years ( $\pm 2.9$ ), and was demographically comparable with the entire MAP cohort of 1545 participants (mean age, 80.1 years; 73% female; mean education, 14.4 years). Computed MIND scores from food frequency data on MAP study participants averaged 7.4 (range, 2.5–12.5). MIND diet scores were positively correlated with both the Mediterranean ( $r = 0.62$ ) and the DASH ( $r = 0.50$ ) diet scores. MAP participants with the highest MIND diet scores tended to have a more favorable risk profile for preserving cognitive abilities including higher education, greater participation in cognitive and physical activities, and lower prevalence of cardiovascular conditions (Table 2).

The overall rate of change in cognitive score was a decline of 0.08 standardized score units per year. In mixed models adjusted for age, sex, education, total energy intake *APOE*  $\epsilon 4$ , smoking history, physical activity, and participation in cognitive activities, the MIND diet score was positively and statistically significantly associated with slower rate of cognitive decline (Table 3). Compared to the decline rate of participants in the lowest tertile of scores, the rate for participants in the highest tertile was substantially slower (Fig. 1). The difference in rates was the equivalent of being 7.5 years younger. The MIND diet score was statistically significantly associated with each cognitive domain, particularly for episodic memory, semantic memory, and perceptual speed (Table 3).

The Mediterranean and DASH diets have demonstrated effects on the reduction of cardiovascular conditions and risk factors [31–34], which raises the possibility that the association of the MIND diet with cognitive decline may be because of its effects on cardiovascular disease. To investigate potential mediation by these factors, we reanalyzed the basic model for the global cognitive score and each cognitive domain score with the inclusion of terms for hypertension, stroke, myocardial infarction, and diabetes; however, the effect estimates did not change (Table 3).

Depression and weight have complex relations with dementia; they are known both as risk factors (depression and obesity) and as outcomes of the disease (depressive symptoms and weight loss). Both factors are also affected by diet quality. Therefore, we examined in the basic model what impact additional control for these variables might have on the observed association between the MIND diet score and cognitive decline but these adjustments also did not change the results for any of the cognitive measures

Table 2

Baseline characteristics\* of analyzed MAP participants according to tertile of MIND diet score

Characteristic	n	MIND diet score tertile		
		Tertile 1	Tertile 2	Tertile 3
Age, mean y	960	81.9	81.7	80.5
Male, percent	960	28	26	23
<i>APOE</i> $\epsilon 4$ , percent	823	22	26	21
Education, mean y	960	14.3	15.1	15.6
Cognitive activities, mean	959	3.1	3.2	3.4
Total energy intake, mean kcal	960	1665	1788	1794
Smoking, percent never	960	40	38	42
Physical activity, mean h/wk	958	2.5	3.4	4.3
Depressive symptoms, mean number	959	1.4	0.9	0.9
BMI, mean	927	27.5	27.1	26.7
Hypertension, percent	954	79	76	72
Diabetes, percent	960	24	20	17
Heart disease history, percent	959	18	12	18
Clinical stroke history, percent	870	11	7	9

Abbreviations: MAP, Memory and Aging Project; MIND, Mediterranean-DASH diet intervention for neurodegenerative delay; *APOE*, apolipoprotein E; BMI, body mass index.

\*Characteristics were standardized by age in 5-year categories.

(e.g., for global cognitive function  $\beta = 0.0092$ , standard error = 0.0022,  $P < .0001$ ).

We also investigated potential modifications in the estimated effect of the MIND diet score on cognitive decline by age, sex, *APOE*  $\epsilon 4$ , education, physical activity, low weight (BMI  $\leq 20$ ), obese (BMI  $\geq 30$ ), and each of the cardiovascular-related conditions (hypertension, myocardial infarction, stroke, and diabetes). However, there was no statistical evidence that the diet effect on the global or individual domain cognitive scores differed by level or presence of any of these risk factors (data not shown).

To examine whether the observed MIND diet—cognitive decline relation—may be due to dementia effects on dietary behaviors or to reporting accuracy, we reanalyzed the data after eliminating 220 participants who had mild cognitive impairment at the baseline; the resulting decline rate for higher MIND diet score ( $\beta = 0.0104$ ,  $P < .00001$ ) was even more protective, by 9.5%, compared with that of the entire sample ( $\beta = 0.0095$ ).

We also investigated the potential effects of dietary changes over time on the observed associations of baseline MIND diet score with cognitive change. We reanalyzed the data after excluding 144 participants whose MIND diet scores either improved (top 10%) or decreased (bottom 10%) over the study period. The protective estimates of effect of the MIND diet score on change in global cognitive score increased considerably ( $\beta = 0.0120$ ,  $P < .00001$ ) in the basic-adjusted model. The estimated effects of the MIND diet on the individual cognitive domains also increased by 30%–78% with the exception of visuospatial ability, which had little change ( $\beta = 0.0072$ ,  $P = .02$ ).

In a previous study of the MAP participants [35], we observed protective relations of both the MedDiet and DASH diet scores to cognitive decline. A comparison of these diet components and scores is provided in [Supplementary Table 1](#). We analyzed the data for these two diet scores in separate basic-adjusted models of the global cognitive scores and compared the standardized regression coefficients for all three diet scores. The MIND diet score was more predictive of cognitive decline than either of the other diet scores; the standardized  $\beta$  coefficients of the estimated diet effects were 4.39 for MIND, 2.46 for the MedDiet, and 2.60 for DASH. The correlation between the MIND score with cognitive change was statistically significantly higher compared with that for either the MedDiet ( $P = .02$ ) or the DASH ( $P = .03$ ) scores.

#### 4. Discussion

In this community-based study of older persons, we investigated the relation of diet to change in cognitive function using an *á priori*-defined diet composition score (MIND) based on the foods and nutrients shown to be protective for dementia. Higher MIND diet score was associated with slower decline in cognitive abilities. The rate reduction for persons in the highest tertile of diet scores compared with the lowest tertile was the equivalent of being 7.5 years

younger. Strong associations of the MIND diet were observed with the global cognitive measure as well as with each of the five cognitive domains. The strength of the estimated effect was virtually unchanged after statistical control for many of the important confounders, including physical activity and education as well as with the exclusion of individuals with the lowest baseline cognitive scores.

The MIND diet was based on the dietary components of the Mediterranean and DASH diets, including emphasis on natural plant-based foods and limited intake of animal and high saturated fat foods. However, the MIND diet uniquely specifies consumption of berries and green leafy vegetables and does not specify high fruit consumption (both DASH and Mediterranean), high dairy (DASH), high potato consumption, or  $>1$  fish meal per week (Mediterranean). The MIND modifications highlight the foods and nutrients shown through the scientific literature to be associated with dementia prevention [21,22,36]. A number of prospective cohort studies found that higher consumption of vegetables was associated with slower cognitive decline [7–10] with the strongest relations observed for green leafy vegetables [7,8]. Green leafy vegetables are sources of folate, vitamin E, carotenoids, and flavonoids, nutrients that have been related to lower risk of dementia and cognitive decline. There is a vast literature demonstrating neuroprotection of the brain by vitamin E, rich sources of which are vegetable oils, nuts, and whole grains [21]. Dietary intakes of berries were demonstrated to improve memory and learning in animal models [11] and to slow cognitive decline in the Nurses' Health Study [12]. However, the prospective epidemiologic studies of cognitive decline or dementia do not observe protective benefit from the consumption of fruits in general [7–10]. These dietary components have been demonstrated to protect the brain through their antioxidant and anti-inflammatory properties (vitamin E) [37,38] and inhibition of  $\beta$ -amyloid deposition (vitamin E, folate, flavonoids, and carotenoids) [38–42] and neurotoxic death (vitamin E and flavonoids) [43]. Studies of fish consumption observed lower risk of dementia with just one fish meal a week with no additional benefit evident for higher servings per week [44–46]. Thus, the highest possible score for this component of the MIND diet score is attributed to one or more servings per week. Mediterranean diet interventions supplemented with either nuts or extra-virgin olive oil were effective in maintaining higher cognitive scores compared with a low-fat diet in a substudy of PREDIMED [6], a randomized trial designed to test diet effects on cardiovascular outcomes among Spaniards at high cardiovascular risk. The MIND diet components directed to limiting intake of unhealthy foods for the brain target foods that contribute to saturated and trans fat intakes; these include red meat and meat products, butter and stick margarine, whole fat cheese, pastries and sweets, and fried/fast foods. Fat composition that is higher in saturated and trans fats and lower in polyunsaturated and monounsaturated fats lead to blood-brain barrier dysfunction and

Table 3

Estimated effects ( $\beta$ )\* of the MIND diet score on the rate of change in global cognitive score and change in five cognitive domains among MAP participants over an average 4.7 years of follow-up in adjusted\* mixed models

Estimated effects	Global cognition	Episodic memory <sup>  </sup>	Semantic memory <sup>¶</sup>	Perceptual organization <sup>#</sup>	Perceptual speed <sup>**</sup>	Working memory <sup>††</sup>
Age-adjusted						
n <sup>†</sup>	960	949	945	932	934	957
$\beta$	0.0090	0.0079	0.0069	0.0057	0.0088	0.0049
Standard error	0.0023	0.0027	0.0026	0.0025	0.0024	0.0024
P value	.0001	.003	.007	.02	.0002	.04
Basic <sup>‡</sup>						
n <sup>†</sup>	818	808	804	793	794	816
$\beta$	0.0095	0.0080	0.0105	0.0077	0.0084	0.0050
Standard error	0.0023	0.0028	0.0027	0.0025	0.0024	0.0024
P value	<.0001	.004	.0001	.002	.0003	.04
Basic + cardiovascular conditions <sup>§</sup>						
n <sup>†</sup>	860	850	846	835	836	858
$\beta$	0.0106	0.0090	0.0113	0.0077	0.0097	0.0060
Standard error	0.0023	0.0028	0.0027	0.0025	0.0023	0.0024
P value	<.0001	.001	<.0001	.002	<.0001	.01

Abbreviations: MIND, Mediterranean-DASH diet intervention for neurodegenerative delay; MAP, Memory and Aging Project.

\* $\beta$  = beta coefficient from the model for the interaction term between MIND diet score and time.

†n = total number of participants with complete data for model.

‡Basic model includes age at the first cognitive assessment, Mind diet score, sex, education, participation in cognitive activities, *APOE*  $\epsilon 4$  (any  $\epsilon 4$  allele), smoking history (current, past, and never), physical activity hours per week, total energy intake, time and interaction terms between time and each model covariate.

§Basic model plus history of stroke, myocardial infarction, diabetes, hypertension, and interaction terms between each covariate and time.

|| Composite score of the following seven instruments: Immediate memory test and delayed memory test from Story A Logical Memory subset of the Wechsler memory scale-revised; immediate word recall and delayed word recall of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list recall; CERAD word list recognition; and immediate memory test and delayed memory test of the East Boston Story.

¶ Composite score of the following three instruments: Verbal fluency from CERAD; 15-item version of the Boston naming test; and 15-item reading test.

# Composite score of the 15-item version of judgment of line orientation and the 16-item version of standard progressive matrice.

\*\* Composite score of the following four measures: Oral version of the symbol digit modalities test; number comparison; and two indices from a modified version of the Stroop neuropsychological screening test.

†† Composite score of the following three instruments: digit span subtests-forward of the Wechsler memory scale-revised; digit span subtests-backward of the Wechsler memory scale-revised; and digit ordering.

increased A $\beta$  aggregation [22]. Fish are a rich source of long-chain n-3 fatty acids which have been shown to reduce A $\beta$  formation and oxidative damage and to increase synaptic proteins and dendritic spine density [47,48].

The study findings are supported by a number of strengths including the prospective study design with up to 10 years of follow-up, annual assessment of cognitive function using a battery of standardized tests, comprehensive assessment of diet using a validated questionnaire, and statistical control of the important confounding factors. Another important strength is that the MIND diet score was devised based on expansive reviews of studies relating diet to brain function [20–22,36]. None of the studies included in these reviews were conducted in the MAP study cohort. The fact that the food components were selected independently of the best statistical prediction of the outcome in the MAP study population lends validity to the MIND diet as a preventive measure for cognitive decline with aging.

A limitation of the study is that the dietary questionnaire had few questions to measure some of the dietary components and limited information on frequency of consumption. For example, a single item each provided information on consumption of nuts, berries (strawberries), beans, and olive oil.

However, this imprecision in the measurement of the MIND score would tend to underestimate the diet effect on cognitive decline. Another limitation is the self-report of diet which some studies suggest can lead to biased reporting in overweight [49] and cognitively impaired [50] adults. Concern that biased diet reporting could explain the findings is mitigated by the fact that statistical control for factors such as obesity, education, age, and physical activity had no impact on the estimated MIND diet effect and the association remained strong in analyses that omitted the participants with mild cognitive impairment and whose diet scores changed over the study period. Furthermore, we observed no modification in the effect by level of these potential confounders.

The primary limitation of the study is that it is observational and thus the findings cannot be interpreted as a cause-and-effect relation. Replication of the findings in other cohort studies is important for confirmation of the association; however, a diet intervention trial is required to establish a causal relation between diet and prevention of cognitive decline. Furthermore, the findings were based on an old, largely non-Hispanic white study population and cannot be generalized to younger populations or different racial/ethnic groups.

The MIND diet is a refinement of the extensively studied cardiovascular diets, the Mediterranean and DASH diets, with modifications based on the scientific literature relevant to nutrition and the brain. This literature is underdeveloped and, therefore, modifications to the MIND diet score would be expected as new scientific advances are made.

### Acknowledgment

The study was funded by grants (R01AG031553 and R01AG17917) from the National Institute on Aging.

### Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jalz.2015.04.011>.

### RESEARCH IN CONTEXT

1. Systematic review: We performed extensive reviews of the literature on nutrition and neurodegenerative diseases and cognitive decline to devise a brain healthy diet called MIND. The reviews included animal models, prospective epidemiologic studies, and randomized trials of nutrients, individual foods, and whole diets.
2. Interpretation: The MIND diet builds on previously tested diets, particularly the Mediterranean and DASH diets, for prevention of dementia outcomes by incorporating specific foods and intake levels that reflect the current state of knowledge in the field.
3. Future directions: In the present study, the MIND diet was strongly associated with slower cognitive decline and had greater estimated effects than either the Mediterranean diet or the DASH diet. Future studies should evaluate and confirm the preventive relation of the MIND diet to cognitive change in other populations. As the field develops, the MIND dietary components should be modified to reflect new knowledge on nutrition and the brain.

### References

- [1] 2013 Alzheimer's Disease Facts and Figures. Volume 9, Issue 2. 2013. Alzheimer's Association, Chicago.
- [2] Changing the trajectory of Alzheimer's disease: How a treatment by 2025 saves lives and dollars. Chicago: Alzheimer's Association; 2015.
- [3] Panagiotakos DB, Pitsavos C, Arvaniti F, Stefanadis C. Adherence to the Mediterranean food pattern predicts the prevalence of hypertension, hypercholesterolemia, diabetes and obesity, among healthy adults; the accuracy of the MedDiet score. *Prev Med* 2007;44:335–40.
- [4] Sacks FM, Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, et al. A dietary approach to prevent hypertension: A review of the dietary approaches to stop hypertension (DASH) study. *Clin Cardiol* 1999;22:III6–10.
- [5] Smith PJ, Blumenthal JA, Babyak MA, Craighead L, Welsh-Bohmer KA, Browndyke JN, et al. Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. *Hypertension* 2010;55:1331–1338.
- [6] Martinez-Lapiscina EH, Clavero P, Toledo E, Estruc R, Salas-Salvado J, San JB, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. *J Neurol Neurosurg Psychiatry* 2013;84:1318–1325.
- [7] Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Associations of vegetable and fruit consumption with age-related cognitive change. *Neurology* 2006;67:1370–1376.
- [8] Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. *Ann Neurol* 2005;57:713–720.
- [9] Nooyens AC, Bueno-de-Mesquita HB, van Boxtel MP, van Gelder BM, Verhagen H, Verschuren WM. Fruit and vegetable intake and cognitive decline in middle-aged men and women: The Doetinchem cohort study. *Br J Nutr* 2011;106:752–761.
- [10] Chen X, Huang Y, Cheng HG. Lower intake of vegetables and legumes associated with cognitive decline among illiterate elderly Chinese: A 3-year cohort study. *J Nutr Health Aging* 2012;16:549–552.
- [11] Willis LM, Shukitt-Hale B, Joseph JA. Recent advances in berry supplementation and age-related cognitive decline. *Curr Opin Clin Nutr Metab Care* 2009;12:91–94.
- [12] Devore EE, Kang JH, Breteler MM, Grodstein F. Dietary intakes of berries and flavonoids in relation to cognitive decline. *Ann Neurol* 2012;72:135–143.
- [13] Tangney CC, Li H, Wang Y, Barnes LL, Schneider JA, Bennett DA, et al. Relation of DASH- and Mediterranean-like dietary patterns on cognitive decline in older persons. *Neurology* 2014;83:1410–1416.
- [14] Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS. Overview and findings from the rush memory and aging project. *Curr Alzheimer Res* 2012;9:646–663.
- [15] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–944.
- [16] Bennett DA, Schneider JA, Aggarwal NT, Arvanitakis Z, Shah RC, Kelly RF, et al. Decision rules guiding the clinical diagnosis of Alzheimer's disease in two community-based cohort studies compared to standard practice in a clinic-based cohort study. *Neuroepidemiology* 2006;27:169–176.
- [17] Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, et al. Natural history of mild cognitive impairment in older persons. *Neurology* 2002;59:198–205.
- [18] Wilson RS, Arnold SE, Tang Y, Bennett DA. Odor identification and decline in different cognitive domains in old age. *Neuroepidemiology* 2006;26:61–67.
- [19] Morris MC, Tangney CC, Bienias JL, Evans DA, Wilson RS. Validity and reproducibility of a food frequency questionnaire by cognition in an older biracial sample. *Am J Epidemiol* 2003;158:1213–1217.
- [20] Barnes JL, Tian M, Edens NK, Morris MC. Consideration of nutrient levels in studies of cognitive decline: A review. *Nutr Rev* 2014;72:707–719.
- [21] Morris MC. Nutritional determinants of cognitive aging and dementia. *Proc Nutr Soc* 2012;71:1–13.
- [22] Morris MC, Tangney CC. Dietary fat composition and dementia risk. *Neurobiol Aging* 2014;35 Suppl 2:S59–64.
- [23] Epstein DE, Sherwood A, Smith PJ, Craighead L, Caccia C, Lin PH, et al. Determinants and consequences of adherence to the dietary approaches to stop hypertension diet in African-American and white

- adults with high blood pressure: Results from the ENCORE trial. *J Acad Nutr Diet* 2012;112:1763–73.
- [24] Buchman AS, Boyle PA, Wilson RS, Beck TL, Kelly JF, Bennett DA. Apolipoprotein E4 allele is associated with more rapid motor decline in older persons. *Alzheimer Dis Assoc Disord* 2009;23:63–9.
- [25] Wilson RS, Barnes LL, Krueger KR, Hoganson G, Bienias JL, Bennett DA. Early and late life cognitive activity and cognitive systems in old age. *J Int Neuropsychol Soc* 2005;11:400–7.
- [26] Buchman AS, Boyle PA, Wilson RS, Bienias JL, Bennett DA. Physical activity and motor decline in older persons. *Muscle Nerve* 2007;35:354–62.
- [27] Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D depression symptoms index. *J Aging Health* 1993;5:179–93.
- [28] Bennett DA. Secular trends in stroke incidence and survival, and the occurrence of dementia. *Stroke* 2006;37:1144–5.
- [29] Meng XL, Rosenthal R, Rubin DB. Comparison of correlated correlation coefficients. *Psychol Bull* 1992;111:172–5.
- [30] Hotelling H. The selection of variates for use in prediction, with some comments in the general problem of nuisance parameters. *Ann Math Stat* 1940;11:271–83.
- [31] Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997;336:1117–24.
- [32] Salas-Salvado J, Bullo M, Babio N, Martinez-Gonzalez MA, Ibarrola-Jurado N, Basora J, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: Results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care* 2011;34:14–9.
- [33] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–90.
- [34] Toledo E, Hu FB, Estruch R, Buil-Cosiales P, Corella D, Salas-Salvado J, et al. Effect of the Mediterranean diet on blood pressure in the PREDIMED trial: Results from a randomized controlled trial. *BMC Med* 2013;11:207.
- [35] Tangney CC, Li H, Barnes LL, Schneider JA, Bennett DA, Morris MC. Accordance to dietary approaches to stop hypertension (DASH) is associated with slower cognitive decline. *Alzheimers Dement* 2013;9:605–6.
- [36] Gillette GS, Bellan Van KG, Andrieu S, Salas-Salvado J, Berr C, Bonnefoy M, et al. IANA task force on nutrition and cognitive decline with aging. *J Nutr Health Aging* 2007;11:132–52.
- [37] Yamada K, Tanaka T, Han D, Senzaki K, Kameyama T, Nabeshima T. Protective effects of idebenone and alpha-tocopherol on beta-amyloid-(1–42)-induced learning and memory deficits in rats: Implication of oxidative stress in beta-amyloid-induced neurotoxicity in vivo. *Eur J Neurosci* 1999;11:83–90.
- [38] Jiang Q, Ames BN, Jiang Q, Lykkesfeldt J, Shigenaga MK, Shigeno ET, et al. Gamma-tocopherol, but not alpha-tocopherol, decreases proinflammatory eicosanoids and inflammation damage in rats. *FASEB J* 2003;17:816–22.
- [39] Chan A, Shea TB. Folate deprivation increases presenilin expression, gamma-secretase activity, and Aβ levels in murine brain: Potentiation by ApoE deficiency and alleviation by dietary S-adenosyl methionine. *J Neurochem* 2007;102:753–60.
- [40] Nishida Y, Ito S, Ohtsuki S, Yamamoto N, Takahashi T, Iwata N, et al. Depletion of vitamin E increases amyloid beta accumulation by decreasing its clearances from brain and blood in a mouse model of Alzheimer disease. *J Biol Chem* 2009;284:33400–8.
- [41] Katayama S, Ogawa H, Nakamura S. Apricot carotenoids possess potent anti-amyloidogenic activity in vitro. *J Agric Food Chem* 2011;59:12691–6.
- [42] Obulesu M, Dowlathabad MR, Bramhachari PV. Carotenoids and Alzheimer's disease: An insight into therapeutic role of retinoids in animal models. *Neurochem Int* 2011;59:535–41.
- [43] Jalsrai A, Numakawa T, Ooshima Y, Adachi N, Kunugi H. Phosphatase-mediated intracellular signaling contributes to neuroprotection by flavonoids of *Iris tenuifolia*. *Am J Chin Med* 2014;42:119–30.
- [44] Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Fish consumption and cognitive decline with age in a large community study. *Arch Neurol* 2005;62:1849–53.
- [45] Larrieu S, Letenneur L, Helmer C, Dartigues JF, Barberger-Gateau P. Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort. *J Nutr Health Aging* 2004;8:150–4.
- [46] Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: The Framingham Heart Study. *Arch Neurol* 2006;63:1545–50.
- [47] Lim GP, Calon F, Morihara T, Yang F, Teter B, Ubeda O, et al. A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. *J Neurosci* 2005;25:3032–40.
- [48] Calon F, Lim GP, Yang F, Morihara T, Teter B, Ubeda O, et al. Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. *Neuron* 2004;43:633–45.
- [49] Neuhouser ML, Tinker L, Shaw PA, Schoeller D, Bingham SA, Horn LV, et al. Use of recovery biomarkers to calibrate nutrient consumption self-reports in the Women's Health Initiative. *Am J Epidemiol* 2008;167:1247–59.
- [50] Bowman GL, Shannon J, Ho E, Traber MG, Frei B, Oken BS, et al. Reliability and validity of food frequency questionnaire and nutrient biomarkers in elders with and without mild cognitive impairment. *Alzheimer Dis Assoc Disord* 2011;25:49–57.