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Long-Term Adherence to the Mediterranean Diet Is Associated with Overall Cognitive Status, but Not Cognitive Decline, in Women[1–3]

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Abstract

In this large-scale prospective epidemiological study, we examined associations of long-term adherence to the Mediterranean diet (MeDi) and subsequent cognitive function and decline. We included 16,058 women from the Nurses' Health Study, aged ≥70 y, who underwent cognitive testing by telephone 4 times during 6 y, beginning in 1995–2001, and provided repeated information on diet between 1984 and the first cognitive exam. Primary outcomes were the Telephone Interview for Cognitive Status (TICS) and composite scores of verbal memory and global cognition. MeDi adherence was based on intakes of: vegetables, fruits, legumes, whole grains, nuts, fish, red and processed meats, moderate alcohol, and the ratio of monounsaturated:saturated fat. Long-term MeDi exposure was estimated by averaging all repeated measures of diet (>13 y, on average). In primary analyses of cognitive change, the MeDi was not associated with decline in global cognition or verbal memory. In a secondary approach examining cognitive status in older age, determined by averaging all 4 repeated measures of cognition, each higher quintile of long-term MeDi score was linearly associated with better multivariable-adjusted mean cognitive scores [differences in mean Z-scores between extreme quintiles of MeDi = 0.06 (95% CI: 0.01, 0.11); = 0.05 (95% CI: 0.01, 0.08); and = 0.06 (95% CI: 0.03, 0.10) standard units; *P*-trends = 0.004, 0.002, and <0.001 for TICS, global cognition, and verbal memory, respectively]. These associations were similar to those observed in women 1–1.5 y apart in age. In summary, long-term MeDi adherence was related to moderately better cognition but not with cognitive change in this very large cohort of older women. J. Nutr. 143: 493–499, 2013.

Introduction

The Mediterranean diet (MeDi)[7] has been related in various populations to a lower risk of cardiovascular disease mortality (1–3) and could therefore help reduce cognitive decline and dementia, both of which have strong vascular components (4). The MeDi refers to the traditional diet of Greece and southern Italy and includes high consumption of plant foods, moderate consumption of fish and wine, low consumption of dairy products and meat, and intake of MUFAs as the primary fat source (largely in the form of olive oil) (5). In 2 U.S. cohorts with modest adherence to the MeDi pattern, a higher MeDi score was associated with lower risk of Alzheimer disease (6), mild cognitive impairment (7), and slower cognitive decline (8); surprisingly, in contrast, MeDi score was not related to dementia but only with less cognitive decline in a French cohort with greater adherence to the MeDi (9). Additionally, several other observational studies did not report any association between MeDi adherence and cognitive function (10,11) or incidence of mild cognitive impairment or dementia (12,13). Thus, overall, existing data from limited studies with relatively modest sample size ($n < 4000$) are conflicting, and more studies are needed to clarify the relation of MeDi to cognition (14). Importantly, although long-term diet is most relevant to brain aging, which takes many years to occur (15), no study to our knowledge has examined long-term MeDi adherence (e.g., from mid to late life) and cognitive decline.

We therefore examined the association of long-term MeDi adherence to cognitive function and decline during 6 y among 16,058 women from the Nurses' Health Study.

Materials and Methods

Study population

The NHS began in 1976 when 121,700 female registered nurses aged 30–55 y, residing in 11 U.S. states, completed a mailed questionnaire about their health and lifestyle. Follow-up questionnaires are sent every 2 y; follow-up of the cohort remains at ~90% to date. In 1980, participants completed a 61-item, semiquantitative FFQ (16). In 1984,

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[3] Supplemental Tables 1–3 and Supplemental Methods are available from the ''Online Supporting Material'' link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
[7] Abbreviations used: A-MeDi, alternate Mediterranean diet; EBMT, East Boston Memory Test; MeDi, Mediterranean diet; TICS, Telephone Interview for Cognitive Status.
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the FFQ was expanded to 116 items and similar FFQs were sent in 1986 and every 4 y thereafter. From 1995 to 2001, a cognitive substudy was initiated in participants who were ≥70 y and free of stroke. Among eligible women, 19,415 (93%) completed the first telephone-based cognitive assessment. Follow-up assessments were performed 3 times at 2-y intervals, with a high participation rate (>90% among those remaining alive at each follow-up point). The study was approved by the Institutional Review Board of Brigham and Women's Hospital (Boston, MA).

In the present study, we included 16,058 women who completed at least 1 FFQ among the 2 initial longer versions in 1984 and 1986, at least 1 cognitive assessment, and no missing data for energy intake and physical activity (2 main potential confounders).

Cognitive assessment

Cognitive testing was performed by trained interviewers using validated telephone interviews. The cognitive battery included: *1*) the Telephone Interview for Cognitive Status (TICS); *2*) immediate; and *3*) delayed recalls of the East Boston Memory test (EBMT); *4*) delayed recall of the TICS 10-word list; *5*) category fluency; and 6) digit span-backward. In the initial cognitive interview, we administered only the TICS and gradually added the 5 other tests. Thus, the sample size slightly differs across tests, but the participation rate remained identical for all tests.

The TICS (17) (range 0–41 points) is a telephone adaptation of the Mini-Mental State Examination (18), which assesses global cognitive performance. The EBMT (19) (range 0–12 points) assesses verbal (episodic) memory. The delayed recall of the TICS 10-word list (range 0–10 points) also assesses verbal memory. A category fluency test assesses language and executive function (20) by scoring performance naming as many animals as possible during 1 min. Finally, the digit-span backward test (range 0–12 points), in which women repeat backward increasingly long series of digits, assesses working memory and attention.

The primary outcomes were the TICS and composite scores of global cognition and verbal memory. A global cognitive score was computed as the mean of Z-scores of all 6 cognitive tests in the cognitive battery. A verbal memory score was calculated as the mean of Z-scores of the 4 tests assessing verbal memory (i.e., immediate and delayed recalls of both the EBMT and the TICS 10-word list). We calculated Z-scores at each time point using the distribution of scores at the first cognitive assessment. To allow for comparability of findings across the composite scores and TICS, we converted TICS scores into Z-scores as well.

Dietary assessment and the MeDi score

For each item of the FFQ, possible responses ranged from "never or <1 time/mo" to "≥6 times/d"; a standardized portion size was specified for each food to estimate the quantity consumed daily. Where relevant, food intake estimations were converted into nutrient intakes by multiplying the consumption of each food by its nutrient content by using the database of the USDA.

In this study, we used the 1984, 1986, 1990, 1994, and 1998 FFQs to estimate daily energy intake and to construct, at each of these time points, an alternate MeDi (A-MeDi) 9-point-score, using a methodology previously described (2). This score slightly enhanced the original MeDi score by Trichopoulou et al. (5). The A-MeDi includes 9 components: vegetables (excluding potatoes), fruits, nuts, whole grains, legumes, fish, red and processed meats, moderate alcohol, and the MUFA:SFA ratio. For each component hypothesized to benefit health (i.e., vegetables, fruits, nuts, whole grains, legumes, fish, and MUFA:SFA ratio), 1 point was given if intake was greater than the median, 0 otherwise; for alcohol, 1 point was given if intake was between 5 and 15 g/d. For items hypothesized to be detrimental to health (i.e., red/processed meats), 1 point was given if intake was less than the median, 0 otherwise. The long-term A-MeDi score was computed as the mean of scores across all dietary assessments from 1984 (or 1986, if 1984 FFQ was missing) to the questionnaire immediately preceding the first cognitive exam.

Other variables

Socio-demographic, lifestyle, and health-related covariates were obtained from the questionnaires. Covariates were determined at the time of the first cognitive exam, except physical activity and energy intake, for which values were averaged across multiple assessments over time, similar to diet.

Physical activity was assessed in 1986, 1988, 1992, and every 2 y thereafter by estimating mean energy expended per week (in metabolic equivalent-hours); long-term physical activity was calculated by averaging energy expenditures from 1986 to the questionnaire preceding baseline cognitive assessment.

Statistical analyses

Relation between long-term A-MeDi score and cognitive function. Statistical analyses utilized 2 complementary approaches. In the primary analysis, we modeled trajectories of the 4 repeated cognitive scores using linear mixed models (21). The linear mixed models included an intercept that represented the level of cognitive score at baseline and a slope that represented the annual change in scores over time as well as a random intercept and random slope to account for inter-individual variability. We examined linear trends across quintiles of the A-MeDi score using a continuous variable in which participants in a given category were assigned the median value.

In a secondary approach, we averaged the 4 repeated measures of cognitive function to create an outcome representing overall cognitive status at older ages and modeled the association of A-MeDi score with cognitive status using linear regression models. Averaging repeated measures of cognition was relevant to our data, as it attenuates variability in each single cognitive assessment, which may be helpful when cognition is measured over a relatively short follow-up in largely healthy, educated participants such as ours.

Adjustment for potential confounding factors was performed in 2 stages. Models were first adjusted for age and education (model 1). In a second model (model 2), we subsequently added long-term energy intake and physical activity, BMI, smoking, history of depression, multivitamin use, and vascular risk factors (history of diabetes, hypertension, hypercholesterolemia, and myocardial infarction).

For BMI and multivitamin use, data were missing for >4% of the sample (4.4 and 7.1%, respectively); thus, a specific missing category was created for these 2 variables. For all other covariates, participants with missing information were <1% of the sample and were assigned to the reference group.

Secondary analyses: relation between A-MeDi score components and cognitive function. To determine whether the association between A-MeDi score and cognitive function was due to a specific food group, we additionally evaluated A-MeDi components separately (**Supplemental Methods**).

Values in the text for cognitive outcomes are mean standard units. All analyses were carried out by using SAS version 9.2 (SAS Institute) and a *P*-value of <0.05 was considered significant. Values in the text are mean ± SD unless otherwise indicated.

Results

Individual long-term A-MeDi scores (4.3 ± 1.4 points) were calculated from 4.4 dietary reports during 13 y, on average. At the first cognitive assessment, the mean age of participants was 74.3 ± 2.3 y and the mean TICS score was 33.8 ± 2.7 points (maximum = 41 points). The mean cognitive scores at each cognitive visit during 6 y of follow-up are presented in **Supplemental Table 1**.

Women with higher long-term A-MeDi adherence had higher education, lower BMI, and greater physical activity (**Table 1**). They were also less likely to report history of myocardial infarction or diabetes and were less often current smokers. They were slightly more likely to report a history of hypercholesterolemia (likely suggesting that women with high cholesterol adopted a MeDi). In general, there was a large distribution in intake of each dietary component from the bottom to top quintiles of the A-MeDi score.

Between 1984 and 1998 (the period during which we measured repeated dietary assessments), meat and alcohol intakes slightly decreased and the MUFA:SFA ratio slightly increased (**Table 2**). Median intakes of the other A-MeDi components, as well as mean A-MeDi scores, were stable during this period.

TABLE 1 Characteristics of the participants in the Nurses' Health Study cognitive subcohort by quintiles of long-term A-MeDi score (n = 16,058)[1]

	Quintile 1, [2.5 (2.0–2.8)] n = 3400	Quintile 2, [3.5 (3.3–3.8)] n = 2685	Quintile 3, [4.3 (4.0–4.6)] n = 3624	Quintile 4, [5.2 (5.0–5.4)] n = 3182	Quintile 5, [6.3 (6.0–6.8)] n = 3167
Sociodemographic and health variables					
Age at first cognitive exam, *y*	74.2 ± 2.3	74.3 ± 2.3	74.2 ± 2.3	74.4 ± 2.3	74.3 ± 2.3
Educational level, *n (%)*					
Registered nurse	2856 (84.0)	2153 (80.2)	2852 (78.7)	2351 (73.9)	2236 (70.6)
Bachelor	394 (11.6)	390 (14.5)	550 (15.2)	603 (19.0)	675 (21.3)
Master or doctorate	150 (4.4)	142 (5.3)	222 (6.1)	228 (7.2)	256 (8.1)
BMI at first cognitive exam,[2] *n (%)*					
≤21, kg/m^2	640 (18.8)	526 (19.6)	693 (19.1)	611 (19.2)	700 (22.1)
22–24, kg/m^2	777 (22.9)	673 (25.1)	912 (25.2)	857 (26.9)	887 (28.0)
25–29, kg/m^2	1154 (33.9)	893 (33.3)	1204 (33.2)	1060 (33.3)	1040 (32.8)
≥30, kg/m^2	665 (19.6)	493 (18.4)	657 (18.1)	511 (16.1)	403 (12.7)
Long-term physical activity, *metabolic equivalent-h/wk*	12.1 ± 12.6	14.8 ± 13.5	16.6 ± 14.6	19.9 ± 17.7	23.0 ± 18.3
Smoking, *n (%)*					
Never	1539 (45.3)	1194 (44.5)	1693 (46.7)	1530 (48.1)	1518 (47.9)
Former	1454 (42.8)	1220 (45.4)	1663 (45.9)	1467 (46.1)	1536 (48.5)
Current	407 (12.0)	271 (10.1)	268 (7.4)	185 (5.8)	113 (3.6)
History of myocardial infarction, *n (%)*	219 (6.4)	183 (6.8)	227 (6.3)	176 (5.5)	164 (5.2)
History of hypertension, *n (%)*	1936 (56.9)	1490 (55.5)	1993 (55.0)	1794 (56.4)	1677 (53.0)
History of hypercholesterolemia, *n (%)*	2122 (62.4)	1740 (64.8)	2372 (65.5)	2145 (67.4)	2123 (67.0)
History of diabetes, *n (%)*	382 (11.2)	284 (10.6)	392 (10.8)	304 (9.6)	249 (7.9)
History of depression, *n (%)*	309 (9.1)	291 (10.8)	354 (9.8)	283 (8.9)	273 (8.6)
Multivitamin use,[3] *n (%)*	1729 (50.9)	1561 (58.1)	2145 (59.2)	2015 (63.3)	2108 (66.6)
Long-term dietary variables[4]					
Daily energy intake, *kcal*	1470 ± 384	1592 ± 373	1687 ± 395	1811 ± 394	1964 ± 402
A-MeDi food components intake, *servings/d*					
Vegetables	1.9 ± 0.8	2.6 ± 1.0	3.1 ± 1.1	3.7 ± 1.3	4.6 ± 1.5
Legumes	0.3 ± 0.2	0.3 ± 0.2	0.4 ± 0.2	0.5 ± 0.2	0.6 ± 0.3
Fruits	1.7 ± 0.8	2.2 ± 0.9	2.6 ± 1.0	3.1 ± 1.1	3.6 ± 1.2
Whole grains	0.8 ± 0.7	1.2 ± 0.7	1.4 ± 0.8	1.7 ± 0.9	2.1 ± 1.0
Nuts	0.2 ± 0.2	0.2 ± 0.3	0.3 ± 0.3	0.3 ± 0.3	0.4 ± 0.3
Fish	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.2	0.4 ± 0.2	0.5 ± 0.2
Red and processed meats	0.8 ± 0.4	0.8 ± 0.4	0.7 ± 0.4	0.7 ± 0.4	0.6 ± 0.4
MUFA:SFA ratio	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.2	1.2 ± 0.2	1.2 ± 0.2
Alcohol intake, *g/d*	5.2 ± 10.3	5.4 ± 9.1	5.3 ± 8.8	5.6 ± 8.0	6.4 ± 7.5

[1] Values are mean ± SD unless otherwise noted. A-MeDi scores [median (IQR)] are provided in brackets for each quintile. A-MeDi, alternate Mediterranean score.
[2] Missing data in quintiles 1 to 5 of A-MeDi score were found in 4.8, 3.7, 4.4, 4.5, and 4.3% of the sample, respectively.
[3] Missing data in quintiles 1 to 5 of A-MeDi score were found in 9.0, 6.1, 6.5, 6.8, and 6.7% of the sample, respectively.
[4] Mean intake across all dietary assessments from 1984 (or 1986, if 1984 FFQ was missing) to the questionnaire immediately preceding the first cognitive exam (in 1995–2001).

Cognitive decline in later life. When we examined the relation of A-MeDi score, averaged from mid-life to later life, to change in cognition over the 4 repeated measures, the A-MeDi score was not significantly associated with change over time in the TICS, global cognitive score or verbal memory score in either age- and education-adjusted models (P-trend = 0.37, 0.33, and 0.36, respectively, or after multivariable adjustment (P-trend = 0.31, 0.84, and 0.70, respectively) (**Table 3**).

Mean cognition in later life. In a secondary approach, we examined the relation of long-term A-MeDi score to overall cognitive status at older ages, represented by the mean of all 4 repeated measures of cognition. We found that higher long-term A-MeDi score was linearly related to better performance on the TICS (P-trend = 0.004), global cognition (P-trend = 0.002), and verbal memory (P-trend < 0.001) (model 2, **Table 4**). The mean differences in mean TICS and global and verbal memory Z-scores between the top and bottom quintiles of the A-MeDi score were 0.06, 0.05, and 0.06 standard units, respectively (model 2, Table 4). To help interpret these mean differences, we compared the mean differences we found for TICS and global and verbal scores across categories of A-MeDi score with the mean differences in cognition we observed in this study population for each 1 y difference in age. Specifically, we found that each increase of 1 y of age in these participants was related to a mean difference of −0.08 standard units for the TICS, −0.05 standard units for the global score, and –0.05 standard units for the verbal memory score; thus, the effect estimates we found comparing extreme quintiles of A-MeDi were cognitively equivalent to ~1 y of aging. In other words, higher adherence to the A-MeDi appeared to delay cognitive aging by ~1 y.

Secondary analyses. In secondary analyses, we considered the relation of each of the 9 A-MeDi components to cognitive

TABLE 2 Mean A-MeDi score and median intake of A-MeDi score components for the years during which the FFQ was administered[1]

	1984	1986	1990	1994	1998
n	14,749	13,971	14,288	15,013	14,832
A-MeDi score	4.2 ± 1.8	4.3 ± 1.8	4.3 ± 1.8	4.7 ± 1.8	4.2 ± 1.8
A-MeDi food components intake, *servings/d*					
Vegetables	2.8 (1.9, 3.9)	3.2 (2.2, 4.6)	2.8 (1.9, 3.9)	3.0 (2.0, 4.2)	2.4 (1.6, 3.5)
Legumes	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)	0.3 (0.1, 0.4)
Fruits	2.2 (1.4, 3.1)	2.7 (1.8, 3.8)	2.4 (1.6, 3.3)	2.5 (1.7, 3.4)	2.4 (1.6, 3.3)
Whole grains	0.8 (0.3, 1.4)	1.1 (0.6, 2.0)	1.4 (0.8, 2.3)	1.3 (0.6, 2.1)	1.1 (0.6, 2.0)
Nuts	0.1 (0.1, 0.4)	0.1 (0.0, 0.1)	0.1 (0.0, 0.3)	0.1 (0.1, 0.4)	0.1 (0.0, 0.4)
Fish	0.2 (0.1, 0.4)	0.3 (0.1, 0.5)	0.3 (0.1, 0.5)	0.2 (0.1, 0.4)	0.1 (0.1, 0.3)
Red and processed meats	0.8 (0.5, 1.1)	0.7 (0.4, 1.1)	0.6 (0.4, 0.9)	0.6 (0.4, 0.9)	0.4 (0.2, 0.7)
MUFA:SFA ratio	1.0 (0.9, 1.1)	1.1 (1.0, 1.2)	1.2 (1.0, 1.3)	1.2 (1.0, 1.3)	1.2 (1.0, 1.3)
Alcohol intake, *g/d*	2.0 (0.0, 9.5)	1.8 (0.0, 7.8)	1.0 (0.0, 6.0)	0.9 (0.0, 6.0)	0.0 (0.0, 5.6)

[1] Values are mean ± SD for A-MeDi score and median (IQR) for other items. A-MeDi, alternate Mediterranean diet.

decline and overall cognitive status (**Supplemental Tables 2** and 3). In analyses of each A-MeDi component and cognitive decline over time, we found that higher long-term vegetable intake was related to less decline in global cognition (*P*-trend = 0.04 across quintiles for slope) and a higher MUFA:SFA ratio was related to less decline in global cognition and verbal memory (*P*-trend ≤ 0.001 across quintiles for slopes of change in both global cognition and verbal memory) (Supplemental Table 2). The other A-MeDi components were not associated with change in cognition.

In analyses of each A-MeDi component and average cognition, we found that greater intake of vegetables, fish, and nuts were significantly associated with higher mean cognitive function in later life (*P*-trend across categories of intake for global score and verbal memory score, respectively, = 0.03 and 0.003 for vegetables, 0.26 and 0.003 for fish, 0.02 and 0.05 for nuts) (Supplemental Table 3). In addition, we observed an unexpected relation between fruit intake and cognition, such that increasing intake of fruit was related to worse mean cognitive function (*P*-trend ≤ 0.001 for global cognition and verbal memory).

TABLE 3 Multivariable-adjusted mean differences in slopes of cognitive change by quintiles of long-term A-MeDi score[1,2]

	Model 1[3]	Model 2[4]
TICS (*n* = 14,560)		
Quintile 1	Ref	Ref
Quintile 2	0.001 (−0.013, 0.015)	0.003 (−0.011, 0.017)
Quintile 3	0.002 (−0.011, 0.015)	0.004 (−0.010, 0.017)
Quintile 4	0.013 (−0.001, 0.026)	0.015 (0.001, 0.029)
Quintile 5	0.002 (−0.012, 0.015)	0.004 (−0.011, 0.019)
P-trend	0.37	0.31
Global score (*n* = 14,337)		
Quintile 1	Ref	Ref
Quintile 2	−0.001 (−0.009, 0.007)	−0.001 (−0.009, 0.007)
Quintile 3	0.001 (−0.006, 0.009)	0.000 (−0.007, 0.008)
Quintile 4	0.006 (−0.002, 0.013)	0.004 (−0.004, 0.013)
Quintile 5	0.001 (−0.007, 0.009)	−0.001 (−0.010, 0.007)
P-trend	0.33	0.84
Verbal memory score (*n* = 14,341)		
Quintile 1	Ref	Ref
Quintile 2	−0.003 (−0.013, 0.006)	−0.003 (−0.013, 0.007)
Quintile 3	−0.000 (−0.009, 0.009)	−0.001 (−0.010, 0.008)
Quintile 4	0.006 (−0.004, 0.015)	0.004 (−0.005, 0.014)
Quintile 5	0.001 (−0.008, 0.010)	−0.001 (−0.011, 0.010)
P-trend	0.36	0.70

[1] Values are mean differences (95% CI) expressed in standard units/y. A-MeDi, alternate Mediterranean diet; Ref, reference; TICS, Telephone Interview of Cognitive Status.
[2] Median values and IQRs of A-MeDi scores in each quintile are presented in Table 1.
[3] Adjusted for age and education.
[4] Adjusted for age, education, long-term physical activity and energy intake, BMI, smoking, multivitamin use, and history of depression, diabetes, hypertension, hypercholesterolemia, or myocardial infarction.

Discussion

In this very large sample of older women, the largest investigation to date on the relation between the MeDi and cognition, we did not find evidence of an association between long-term adherence to the MeDi pattern and cognitive change after 6 y. However, long-term MeDi adherence was related to both average global cognitive function and verbal memory [a strong early predictor of Alzheimer disease at older age (22)]. To help provide context, in general, we found that higher adherence to the MeDi diet was equivalent to delaying cognitive aging by ~1 y. For further comparison, the effect estimates we found for the top compared with the bottom quintile of MeDi score were ~50–75% smaller than those we previously found in analyses of the top compared with the bottom quintile of physical activity in this cohort (23); thus, higher adherence to the MeDi appeared to have a substantially weaker association with cognition than did physical activity. In summary, the association identified in our study between MeDi adherence and cognitive function was modest; nonetheless, given the magnitude of burden imposed by adverse cognitive aging, even a small benefit of the MeDi pattern could have substantial public health implications.

In addition, there is a biological basis supporting potential benefits of the MeDi on cognitive health. Strong evidence indicates that a MeDi pattern improves cardiovascular risk factors and cardiovascular disease-related mechanisms, including blood pressure, insulin resistance, lipid profile, peripheral inflammation, and oxidative stress (24–26). Given that all these risk factors/mechanisms are also important determinants of cognitive decline and late-life dementia (27,28), there is a clear basis for hypothesizing that the MeDi may be inversely associated with cognitive outcomes.

Accordingly, we found individual associations between several A-MeDi components and cognitive decline (i.e., vegetable intake,

TABLE 4 Multivariable-adjusted mean differences in overall cognitive status at older ages by quintiles of long-term A-MeDi score (n = 16,058)[1,2]

	Model 1[3]	Model 2[4]
TICS		
Quintile 1	Ref	Ref
Quintile 2	0.04 (−0.00, 0.09)	0.02 (−0.02, 0.07)
Quintile 3	0.06 (0.02, 0.10)	0.03 (−0.01, 0.08)
Quintile 4	0.10 (0.06, 0.15)	0.06 (0.02, 0.11)
Quintile 5	0.11 (0.07, 0.16)	0.06 (0.01, 0.11)
P-trend	<0.001	0.004
Global score		
Quintile 1	Ref	Ref
Quintile 2	0.03 (−0.00, 0.06)	0.02 (−0.01, 0.05)
Quintile 3	0.04 (0.02, 0.07)	0.03 (−0.00, 0.06)
Quintile 4	0.07 (0.04, 0.09)	0.04 (0.01, 0.07)
Quintile 5	0.07 (0.04, 0.10)	0.05 (0.01, 0.08)
P-trend	<0.001	0.002
Verbal memory score		
Quintile 1	Ref	Ref
Quintile 2	0.01 (−0.02, 0.05)	0.01 (−0.03, 0.04)
Quintile 3	0.03 (0.00, 0.06)	0.03 (-0.01, 0.06)
Quintile 4	0.06 (0.02, 0.09)	0.04 (0.01, 0.08)
Quintile 5	0.07 (0.04, 0.11)	0.06 (0.03, 0.10)
P-trend	<0.001	<0.001

[1] Values are mean differences (95% CI) expressed in standard units. A-MeDi, alternate Mediterranean diet; Ref, reference; TICS, Telephone Interview for Cognitive Status.
[2] Median values and IQRs of A-MeDi score in each quintile are presented in Table 1.
[3] Adjusted for age and education.
[4] Adjusted for age, education, long-term physical activity and energy intake, BMI, smoking, multivitamin use, and history of depression, diabetes, hypertension, hypercholesterolemia, or myocardial infarction.

MUFA:SFA ratio) or average cognitive function in older age (i.e., intake of vegetables, fish, and nuts). Specifically, the MUFA:SFA ratio was strongly related to less decline in global cognition and verbal memory in our cohort. Replacing dietary SFA with MUFA has yielded decreases in blood pressure and improvements in blood lipid profile, insulin sensitivity, and glycemic control in other research (29), and all these mechanisms are relevant to cognitive decline and dementia (4). For example, in epidemiological studies, higher SFA intake was related to greater cognitive decline (30–32), although limited evidence exists on the relation between the MUFA:SFA ratio and cognitive function (33). Furthermore, vegetables are sources of antioxidants, and fish provides long-chain polyunsaturated omega(ω)3 fatty acids, nutrients which may benefit the aging brain through a variety of mechanisms, including antioxidant and antiinflammatory pathways (34); in the existing literature, relationships between greater intake of vegetables and fish and cognitive status are suggestive but not entirely consistent (35). Finally, we provide one of the first reports, to our knowledge, of novel evidence of a relation of cognitive function to nuts, which are sources of several types of "good" fats and antioxidants and deserve further research.

Nonetheless, we did not find a relation between long-term MeDi and cognitive change, and the associations with overall cognitive status in older age were modest; there might be several explanations for these modest associations. Our participants had more education than those in the other studies that found strong associations between the MeDi and cognitive outcomes (6,8). Therefore, our participants may have a narrower distribution of cognitive function and decline, which could reduce the magnitude of association in our study. Moreover, they were followed for cognition for a relatively modest duration. Both these aspects could reduce our ability to detect associations with cognitive change. However, our length of follow-up was similar to a number of community-based cohort studies and there was an average decline in cognitive function in our cohort over the follow-up period. In addition, we previously demonstrated strong associations between cognitive change and dietary factors, some of which are components of the MeDi [e.g., alcohol intake (36), flavonoids, and berry intake (37)].

The modest association we found between long-term MeDi and late-life cognitive function may also be due to modest adherence to a Mediterranean-style diet in U.S. populations (38). For example, on average, the MUFA:SFA ratio is ~2.5 times higher in Mediterranean countries than in the US (38). However, even in French populations, with dietary habits closer to those of Mediterranean populations, the MeDi was associated with slower global cognitive decline, but not consistently for all cognitive tests, and was not associated with a reduced risk of dementia (9). In a Greek population, likely highly adherent to the MeDi pattern, MeDi adherence at late adulthood was also not associated with global cognitive function in late life (10). Thus, it is not clear that higher adherence to the MeDi in our population would have led to stronger associations.

Finally, it is possible that the association between the MeDi and brain health is truly modest. The 2 studies that found strong associations between MeDi adherence and cognitive outcomes were conducted in lower income U.S. populations (6,8). Because the MeDi pattern likely represents a Mediterranean-like food pattern but is also likely a marker of adherence to a healthier lifestyle, it is plausible that the magnitude of associations reported in previous studies may have been somewhat overestimated because of residual or uncontrolled confounding.

Other potential limitations of our study should also be considered. Our sample included female, mostly Caucasian, healthcare professionals with generally high levels of education. Therefore, our results may not be generalizable to older populations with different socio-demographic backgrounds; in particular, cognitive health appears worse in some minority populations (39), which may thus have differing risk factor patterns than our participants. Furthermore, a telephone assessment of cognitive function may have caused some misclassification. However, in a validation study, our telephone-based cognitive battery performed very well compared with detailed, in-person interviews (ρ = 0.81 comparing the 2 modes of assessment). Moreover, using cognitive scores from our telephone interview, we previously found clear associations with risk factors for cognitive decline, and the magnitude of associations we found were generally comparable with those observed using in-person cognitive interviews in other studies (40,41); both these aspects establish the high validity of our telephone interview method. Finally, although we adjusted for many potential confounders, we cannot exclude that residual confounding may persist.

In summary, our findings suggest that long-term adherence to the MeDi pattern is modestly associated with global cognitive function and verbal memory in later life but not with cognitive change after a 6-y period. Given that the MeDi improves many aspects of health (3) and cognitive aging is responsible for an increasingly large societal burden (42), even modest effects of the MeDi on cognition could have an important public health impact. Overall, there has been only limited research on dietary patterns and cognitive health despite agreement in other disciplines such as cardiovascular disease research that overall diet quality is both a strong predictor of disease and an optimized approach to implement efficient dietary counseling (43). Hence, further research on both the MeDi and other dietary patterns should be conducted to better identify dietary predictors of cognitive aging.

Acknowledgments

F.G., C.S., O.I.O., and E.E.D. designed and/or conducted research; C.S. analyzed data; F.G., C.S., O.I.O., and E.E.D. drafted or edited the manuscript; and C.S., F.G., O.I.O., and E.E.D. had primary responsibility for final content. All authors read and approved the final manuscript.

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