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Vegetables, Unsaturated Fats, Moderate Alcohol Intake, and Mild Cognitive Impairment

Rosebud O. Roberts[a] Yonas E. Geda[a, c] James R. Cerhan[a] David S. Knopman[d]
Ruth H. Cha[b] Teresa J.H. Christianson[b] V. Shane Pankratz[b] Robert J. Ivnik[c]
Bradley F. Boeve[d] Helen M. O'Connor[e] Ronald C. Petersen[a, d]

Divisions of [a]Epidemiology and [b]Biomedical Statistics and Informatics, Department of Health Sciences Research, Departments of [c]Psychiatry and Psychology and [d]Neurology, and [e]Office for Human Research Protection, College of Medicine, Mayo Clinic, Rochester, Minn., USA

Key Words

Mild cognitive impairment · Dietary intake · Moderate alcohol intake · Unsaturated fatty acids · Mediterranean diet · Longitudinal · Prevalence studies · Incidence studies · Population-based

Abstract

Background/Aims: To investigate associations of the Mediterranean diet (MeDi) components and the MeDi score with mild cognitive impairment (MCI). ***Methods:*** Participants (aged 70–89 years) were clinically evaluated to assess MCI and dementia, and completed a 128-item food frequency questionnaire. ***Results:*** 163 of 1,233 nondemented persons had MCI. The odds ratio of MCI was reduced for high vegetable intake [0.66 (95% CI = 0.44–0.99), p = 0.05] and for high mono- plus polyunsaturated fatty acid to saturated fatty acid ratio [0.52 (95% CI = 0.33–0.81), p = 0.007], adjusted for confounders. The risk of incident MCI or dementia was reduced in subjects with a high MeDi score [hazard ratio = 0.75 (95% CI = 0.46–1.21), p = 0.24]. ***Conclusion:*** Vegetables, unsaturated fats, and a high MeDi score may be beneficial to cognitive function.

Introduction

Mild cognitive impairment (MCI), a transitional stage between normal aging and dementia, offers an opportunity for reducing the public health burden of Alzheimer disease (AD) and other dementias through early detection and prevention [1, 2]. Several studies suggest that in part because of the association with vascular risk factors, certain dietary patterns may be associated with the risk of dementia and cognitive impairment [3–7]. One such diet is the Mediterranean diet (MeDi), a diet high in intake of vegetables, legumes, fruit, and nuts, and low in intake of meats and dairy products. Greater adherence to the MeDi was inversely associated with total mortality and death from coronary heart disease in a Greek population [8]. In addition, the MeDi has been associated with incident MCI and AD in a multiethnic community [9, 10]. However, there is little information on adherence to the MeDi in the US Midwest, or the association of adherence to the MeDi with MCI and its subtypes, in this setting. It has also been suggested that the MeDi approach may not be transferrable to communities that do not typically eat a MeDi [11]. The objective of this study is to describe adherence to the MeDi in a sample of subjects randomly selected from the Olmsted County, Minn., USA,

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Dr. Rosebud O. Roberts
Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic
200 First Street SW
Rochester, MN 55905 (USA)
Tel. +1 507 284 5656, Fax +1 507 284 1516, E-Mail roberts.rosebud@mayo.edu

community and evaluated for MCI, and to assess the association of the MeDi score and components of this diet with prevalent MCI and its subtypes, and with incident MCI and dementia during follow-up.

Materials and Methods

Study Participants

The study design and methodology have been previously published in detail [12]. Briefly, all residents from Olmsted County, Minn., USA, aged 70–89 years on October 1, 2004, were identified using the medical records-linkage system of the Rochester Epidemiology Project [13]. Of the 9,953 persons identified, 5,233 were randomly selected for participation. We excluded subjects who died before they could be contacted (n = 263), and subjects who were terminally ill and in hospice (n = 56); subjects with previously diagnosed confirmed dementia (n = 402), and subjects who could not be contacted (n = 114) were considered ineligible. The remaining 4,398 subjects were eligible; of the eligible subjects, 2,719 agreed to participate (61.8% response) by telephone (n = 669) or via a face-to-face evaluation (n = 2,050) that allowed characterization of dementia, MCI, and normal cognition. Information obtained from the medical records-linkage system showed that nonparticipants were more likely to be older, male, less educated, and to have greater comorbidity [12]. Subjects who participated by telephone only were not included in any nontelephone assessments. Of the 2,050 subjects who participated in the face-to-face evaluation, 67 were found to be demented at the time of evaluation, and 14 did not complete the evaluation and could not be assigned a diagnosis; these subjects were not eligible for future studies. The remaining subjects (n = 1,969) had a diagnosis of cognitively normal (n = 1,640) or had MCI (n = 329). All study protocols were approved by the Mayo Clinic and Olmsted Medical Center institutional review boards.

Measurements

Measurements included an interview by a nurse or study coordinator, a neurological evaluation by a physician, and neuropsychological testing. The interview included administration of the Clinical Dementia Rating (CDR) Scale to the participant and an informant and the Functional Activities Questionnaire to an informant [14]. The neurological evaluation included the Short Test of Mental Status [15], the Hachinski Scale, and a complete neurological examination. Neuropsychological testing was performed using 9 cognitive tests to assess 4 cognitive domains: memory [Logical Memory II (delayed recall) and Visual Reproduction II (delayed recall) from Wechsler Memory Scale-Revised, Auditory Verbal Learning Test [16]]; executive function (Trail Making Test B [17], Digit Symbol Substitution from Wechsler Adult Intelligence Scale-Revised); language (Boston Naming Test, Category Fluency [18]), and visuospatial skills (Picture Completion and Block Design from Wechsler Adult Intelligence Scale-Revised [19]). A neuropsychologist assessed impairment in cognition by comparing the age-corrected scaled scores for each participant with the norms determined for the same population from which subjects were recruited [20] taking into account the level of education, prior occupation, and other information. Scores of 1.0 standard deviation or more below the mean were considered potentially impaired, but a final decision about impairment in a domain was made by consensus. An expert panel of physicians, neuropsychologists, and the nurse or study coordinators who evaluated the participant reviewed all the information collected for each participant in order to reach a diagnosis of cognitively normal, MCI, or dementia by consensus.

Diagnostic Criteria

Cases. MCI was defined according to the following criteria: cognitive concern by participant, physician, nurse, or informant (from CDR); impairment in 1 or more of the 4 cognitive domains (including nonmemory domains) from the cognitive testing battery; essentially normal functional activities from the CDR and Functional Activities Questionnaire; and absence of dementia as previously published [1]. Participants were characterized as having amnestic MCI (a-MCI) if they had impairment in the memory domain and nonamnestic MCI (na-MCI) if they had impairment in any 1 or more of the nonmemory cognitive domains.

Dementia. A diagnosis of dementia was made according to the DSM-IV criteria [21]. Subjects with dementia were excluded from the present study.

Controls. Subjects who did not meet the criteria for MCI or dementia were characterized as cognitively normal according to published criteria [20].

Measurement of Dietary Food Intake

We assessed dietary intake via the modified Block 1995 Revision of the Health Habits and History Questionnaire [22] that included 128 items: 103 food items and 25 beverages. The self-administered questionnaire was mailed to the homes of participants with an addressed, stamped envelope for its return. Participants were asked to provide information on usual eating habits during the previous year. For each food item, respondents were asked to indicate (1) their usual portion size consumed (small, medium, large), with the medium serving provided as a specific amount, and (2) how often they had consumed each food (never or <1 per month, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 1 per day, 2–3 per day, 4–5 per day, 6+ per day). The Food Processor SQL nutrition analysis software program (version 10.0.0, ESHA Research, Salem, Oreg., USA) was used to calculate the total nutrient, food group, and energy (caloric) intake per day, under the supervision of a registered dietician (H.M.O.).

MeDi Adherence

We assessed adherence to a MeDi by computing a MeDi score using a previously developed scale [8, 10]. We calculated the energy-adjusted nutrient and food group values using the residual method by regressing the log(energy) on log(nutrient) to derive the residual [23]. We computed the daily intake of nutrients and food groups as the sum of the residual and the mean log(nutrient) value determined from the regression model. Using the sex-specific median from the distribution as the cutoff, we assigned a value of 0 for consumption below the median and 1 for consumption at or above the median for beneficial components (vegetables, legumes, fruits, cereal, and fish). For components presumed to have adverse effects (meat, dairy products), we assigned a value of 1 for consumption below the median and 0 for consumption at or above the median. For fat intake, we used the ratio of monounsaturated fatty acids (MUFA) to saturated fatty acids (SFA), with a value of 1 for high and 0 for low intake. We scored alcohol intake as 0 for intake of 0

or ≥30 g per day and 1 for >0 to <30 g per day. The total possible MeDi score ranged from 0 (minimal) to 9 (maximal adherence).

Covariates

We ascertained date of birth, years of education, marital status, and vascular comorbidities (diabetes, hypertension, coronary heart disease, stroke) by interview. We assessed medication use from medication bottles that participants were asked to bring to the evaluation. We validated self-report of vascular comorbidities from the medical record [13], and considered the medical record the gold standard. A history of depressive symptoms was assessed by interview of an informant using the Neuropsychiatric Inventory Questionnaire [24]. We assessed the frequency of moderate physical exercise in the year prior to recruitment (≤1 per month, 2–3 times per month, 1–2 times per week, 3–4 times per week, 5–6 times per week, and daily) [25]. Weight and height were measured and body mass index (BMI) was calculated (kg/m^2). A blood draw was performed to assess Apolipoprotein E (ApoE) ε4 genotype, and biomarkers including HbA1c, total cholesterol, triglycerides, and C-reactive protein were also measured using standard methods.

Statistical Analyses

We investigated the associations between components of the MeDi score, MeDi score tertiles, and MCI using multiple logistic regression models. We determined cutpoints for the MeDi score from the distribution of scores for cases and controls combined; these tertile cutpoints were consistent with cutpoints in other studies [9, 10]. The base model was adjusted for age, years of education, and total caloric intake (as continuous variables), and sex; the fully adjusted model included variables in the base model and stroke, ApoE ε4 allele status (ApoE ε4+ vs. ApoE ε4–), coronary heart disease, and depressive symptoms. BMI, diabetes, and hypertension were not associated with MCI in our sample, and since their inclusion in the analyses did not alter the results, those results are not presented. We included total caloric intake in all the logistic regression models to avoid spurious associations [26] and also examined potential confounding by physical exercise, and potential effect modification by age, sex, and years of education, and ApoE ε4 allele. We also investigated associations of the MeDi with a-MCI and na-MCI.

To adjust for potential nonparticipation bias, we used a propensity score approach to develop a logistic regression model that predicted the probability of participation [27, 28]. We included demographic (age, sex, years of education) and clinical (diabetes, stroke, depressive symptoms, MCI status) characteristics for subjects included and excluded from the study, and used the reciprocal of the predicted probabilities as weights in all the logistic regression models presented.

Secondary Analyses

Because polyunsaturated fatty acid (PUFA) is a primary source of beneficial unsaturated fatty acids in non-Mediterranean regions [29, 30], we examined the use of the (MUFA + PUFA):SFA ratio as the measure of fat intake in the calculation of the MeDi score. We also examined the use of sex-specific cutpoints for moderate alcohol intake (5 to <25 g/day for women and 10 to <50 g/day for men), fruit and nut intake [8, 31] in the calculation of the MeDi score. We conducted additional analyses with the MeDi score as a continuous variable or as quartiles on account of the skewness of the MeDi score distribution.

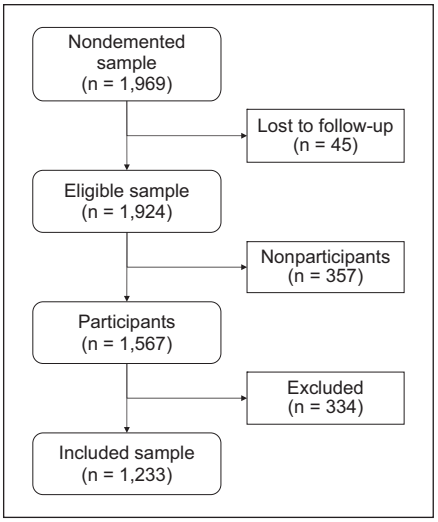

Fig. 1. Flow chart for study participants. Losses to follow-up: 22 died, 22 refused further participation, 1 was non-English speaking, and 357 did not return questionnaire. Exclusions: 268 had missing responses on more than 10 questions on frequency of consumption, 56 reported extreme caloric intake (<800 or >6,000 kcal per day for 32 men and <600 or >5,000 kcal per day for 24 women), and 10 were demented at the time of the evaluation.

Longitudinal Associations

In subjects who were cognitively normal or had MCI at baseline, we used proportional hazards models to investigate the association of the baseline MeDi score with incident MCI or dementia; subjects were censored at the time of death or loss to follow-up. All analyses were performed using SAS® (SAS Institute, Cary, N.C., USA).

Results

Of the 1,969 nondemented subjects who participated at baseline, 45 were lost to follow-up prior to the food frequency questionnaires being mailed out, 22 had died, 22 had refused participation since the baseline evaluation, and 1 person could not speak English and was therefore unable to complete the questionnaire (fig. 1). The food frequency questionnaire was mailed to the eligible 1,924 subjects. A total of 1,567 (81.4%) subjects returned the questionnaire; of these, we excluded subjects who had missing responses on more than 10 questions on frequency of consumption (n = 268), reported extreme caloric intake (<800 or >6,000 kcal per day for 32 men and <600 or >5,000 kcal per day for 24 women), or were demented at the time of the evaluation (n = 10). The remaining 1,233 subjects were included in the present study (fig. 1). Sub-

jects who were not included (n = 691) were similar to those included in regard to sex, history of hypertension, coronary heart disease, BMI, and ApoE ε4 allele status. However, there were modest differences: excluded subjects were older (median age = 82.2 vs. 80.1 years, $p < 0.0001$), had a higher frequency of stroke (14.2 vs. 10.1%, p = 0.007), diabetes (16.1 vs. 12.1%, p = 0.014), depressive symptoms (16.3 vs. 12.3%, p = 0.018), and MCI (23.9 vs. 13.2%, $p < 0.0001$), but were less likely to be married (52.5 vs. 64.9%, $p < 0.0001$) and had fewer years of education (median = 12 vs. 13 years, $p < 0.0001$). There were no differences between included and excluded MCI cases in regard to age, sex, years of education, and ApoE ε4 allele.

Table 1 presents the baseline demographic and clinical characteristics of MCI cases and controls included in the analyses. Questionnaires for these subjects were completed at a median of 3.3 months (interquartile range = 1.5–6.1) from the time of the evaluation. MCI cases were more likely to be older, male, to have fewer years of education, a history of stroke, depressive symptoms, and an ApoE ε4 allele. The baseline characteristics of the follow-up cohort by diagnostic status at follow-up are also presented.

Table 2 shows the distribution (median and interquartile range) of nutrient intakes for cases with MCI and controls overall and by sex. Among men and women combined, MCI cases had a slightly lower daily intake of vegetables (p = 0.06), a lower (MUFA + PUFA):SFA ratio (p = 0.05), and a lower frequency of moderate alcohol consumption (p = 0.05), but a higher daily caloric intake (p = 0.0005) than controls. The MeDi score did not differ between MCI cases and controls. Compared to women, men had a higher intake of legumes (p = 0.014), grains and cereals (p = 0.003), red meat ($p < 0.001$), and moderate alcohol ($p < 0.01$), but a lower intake of fruits and vegetables (p = 0.004). Among men, MCI cases had a marginally lower intake of fish (p = 0.06), but a higher daily caloric intake (p = 0.0001) than controls. Among women, the frequency of moderate alcohol intake was lower in MCI cases compared to controls (p = 0.005).

Table 3 presents the associations of the components of the MeDi score and the MeDi score tertiles with MCI. The odds ratio (OR) of MCI decreased significantly with higher vegetable intake (p for trend = 0.05), increasing (MUFA + PUFA):SFA ratio (p for trend = 0.01), and with moderate alcohol intake (p = 0.05). Fruit intake in the upper tertile was associated with an 11% reduced OR of MCI, and the OR of MCI decreased with increasing MeDi score, but neither the associations nor the trends were statistically significant. There was a dose-response association of increasing daily caloric intake with MCI (p for trend = 0.001). The results of the fully adjusted models were consistent with the base models suggesting no confounding by the additional variables, and the associations of vegetables and (MUFA + PUFA):SFA ratios with MCI were slightly stronger; additional adjustment for exercise did not materially change the results. In additional models, we included HbA1c, total cholesterol, and C-reactive protein since these could be potential confounders. There were no appreciable changes in the ORs for all except alcohol, although, given the increased number of variables now included in the model, the associations with vegetable intake and moderate alcohol were no longer statistically significant. The estimates of OR (95% CI) for the middle and upper tertiles compared to the lowest tertile were as follows: vegetable intake (middle tertile: OR = 0.58, 95% CI = 0.38–0.87; upper tertile: OR = 0.63, 95% CI = 0.41–0.96); moderate alcohol (OR = 1.22, 95% CI = 0.86–1.74); (MUFA + PUFA):SFA ratio (middle tertile: OR = 0.98, 95% CI = 0.66–1.46; upper tertile: OR = 0.52, 95% CI = 0.34–0.81); MeDi score 1 (middle tertile: OR = 1.07, 95% CI = 0.71–1.62; upper tertile: OR = 0.75, 95% CI = 0.47–1.20); MeDi score 2 (middle tertile: OR = 1.00, 95% CI = 0.46–1.50; upper tertile: OR = 0.72, 95% CI = 0.46–1.15). One could argue that these variables are related to diet and therefore may be in the causal pathway; including them in the model may represent overcontrolling. There was no significant interaction of the MeDi score with age, sex, years of education, and ApoE ε4 allele.

High intake of vegetables (upper tertile: OR = 0.57, 95% CI = 0.36–0.90, p for trend = 0.04), MUFA:SFA ratio (OR = 0.60, 95% CI = 0.39–0.93, p for trend = 0.03), and a higher (MUFA + PUFA):SFA ratio (OR = 0.48, 95% CI = 0.30–0.76, p for trend = 0.008) were significantly associated with a reduced OR of a-MCI but not with na-MCI (table 4).

Secondary Analyses

There were no significant associations of MCI with the MeDi score as quartiles (Q2: OR = 0.90, 95% CI = 0.58–1.42; Q3: OR = 1.17, 95% CI = 0.76–1.80; Q4: OR = 0.86, 95% CI = 0.57–1.31 compared to Q1; p for trend = 0.53) or as a continuous variable (OR = 0.98, 95% CI = 0.89–1.07, p = 0.63). The associations using the (MUFA + PUFA):SFA ratio were consistent with those based on the MUFA:SFA ratio (table 3), and there were no significant associations or trends when fruit and nuts or sex-specific cutpoints for alcohol intake were used in computing the MeDi score (these data are not presented).

Table 1. Baseline characteristics of participants by diagnostic status at baseline and at follow-up, Mayo Clinic Study of Aging, 2004–2006

Variable	Baseline sample			Follow-up cohort[a]		
	MCI (n = 163)	no MCI (n = 1,070)	p	event (n = 116)	no event (n = 1,025)	p
Age						
Median (Q1, Q3), years	82.9 (78.3, 86.4)	79.6 (75.5, 84.1)	<0.0001	83.3 (78.7, 86.2)	79.7 (75.6, 84.2)	<0.0001
70–79 years	53 (32.5)	558 (52.1)	<0.0001	35 (30.2)	530 (51.7)	<0.0001
≥80 years	110 (67.5)	512 (47.9)		81 (69.8)	495 (48.3)	
Sex						
Male	97 (59.5)	544 (50.8)	0.04	76 (65.5)	527 (51.4)	0.004
Female	66 (40.5)	526 (49.2)		40 (34.5)	498 (48.6)	
Education						
Median (Q1, Q3), years	12 (12, 15)	13 (12, 16)	0.001	13 (12, 15.5)	13 (12, 16)	0.04
<9 years	22 (13.5)	43 (4.0)	<0.0001	8 (6.9)	51 (5.0)	0.29
9–12 years	63 (38.7)	414 (38.7)		49 (42.2)	379 (37.0)	
>12 years	78 (47.9)	613 (57.3)		59 (50.9)	595 (58.0)	
Marital status						
Married	104 (63.8)	696 (65.0)	0.76	74 (63.8)	673 (65.7)	0.69
Not married	59 (36.2)	374 (35.0)		42 (36.2)	352 (34.3)	
Body mass index[b]						
<25	53 (35.1)	336 (32.2)	0.31	43 (37.4)	328 (32.2)	0.37
25–29	65 (43.0)	419 (40.1)		40 (34.8)	421 (41.3)	
≥30	33 (21.9)	290 (27.8)		32 (27.8)	270 (26.5)	
Diabetes						
Yes	22 (13.5)	127 (11.9)	0.55	20 (17.2)	116 (11.3)	0.06
No	141 (86.5)	943 (88.1)		96 (82.8)	909 (88.7)	
Hypertension						
Yes	122 (74.8)	754 (70.5)	0.25	82 (70.7)	720 (70.2)	0.92
No	41 (25.2)	316 (29.5)		34 (29.3)	305 (29.8)	
Coronary heart disease						
Yes	51 (31.3)	282 (26.4)	0.19	28 (24.1)	280 (27.3)	0.46
No	112 (68.7)	788 (73.6)		88 (75.9)	745 (72.7)	
Stroke						
Yes	35 (21.5)	89 (8.3)	<0.0001	16 (13.8)	93 (9.1)	0.10
No	128 (78.5)	981 (91.7)		100 (86.2)	932 (90.9)	
Depression[c]						
Yes	41 (25.8)	107 (10.3)	<0.0001	23 (20.7)	106 (10.6)	0.002
No	118 (74.2)	935 (89.7)		88 (79.3)	895 (89.4)	
ApoE ε4[d]						
ε3ε4/ε4ε4	47 (31.1)	217 (21.5)	0.008	30 (28.0)	219 (22.6)	0.20
ε2ε2/ε2ε3/ε3ε3	104 (68.9)	793 (78.5)		77 (72.0)	752 (77.4)	
Smoking						
Never	82 (50.3)	552 (51.6)	0.95	59 (50.9)	534 (52.1)	0.92
Former	76 (46.6)	484 (45.2)		54 (46.6)	460 (44.9)	
Current	5 (3.1)	34 (3.2)		3 (2.6)	31 (3.0)	
Domain Z scores, median (Q1, Q3)						
Memory domain score[e]	−1.19 (−1.77, −0.72)	0.48 (−0.19, 1.17)	<0.0001	−0.80 (−1.22, −0.12)	0.48 (−0.25, 1.20)	<0.0001
Executive function domain score[f]	−1.01 (−1.79, −0.17)	0.42 (−0.13, 0.93)	<0.0001	−0.47 (−1.02, 0.12)	0.42 (−0.18, 0.93)	<0.0001
Visuospatial domain score[g]	−0.73 (−1.39, −0.03)	0.38 (−0.31, 0.94)	<0.0001	−0.46 (−1.16, 0.15)	0.38 (−0.27, 0.94)	<0.0001
Language domain score[h]	−0.75 (−1.58, −0.24)	0.32 (−0.20, 0.91)	<0.0001	−0.36 (−1.08, 0.21)	0.32 (−0.26, 0.91)	<0.0001

Q1 = Quartile 1; Q3 = quartile 3. Figures in parentheses are percentages unless indicated otherwise.

[a] Event = MCI or dementia during follow-up; no event = no MCI or dementia during follow-up. [b] 37 missing in the cross-sectional studies total cohort: 25 in the No MCI group, 12 in the MCI group; 7 missing in the longitudinal studies total cohort: 6 in the No event group, 1 in the Event group. [c] 32 missing in the cross-sectional studies total cohort: 28 in the No MCI group, 4 in the MCI group; 29 missing in the longitudinal studies total cohort: 24 in the No event group, 5 in the Event group. [d] 40 missing in the cross-sectional studies total cohort: 33 in the No MCI group, 7 in the MCI group; ε2ε4 was found in 5 (3.2%) in the MCI group, 27 (2.6%) in the No MCI group, and 32 (2.7%) among the total cohort. 34 missing in the longitudinal studies total cohort: 31 in the No event group, 3 in the Event group; ε2ε4 was found in 6 (5.3%) in the Event group, 23 (2.3%) in the No event group, and 29 (2.6%) in the total cohort. ε2ε4 was not included in the table due to small numbers. [e] 52 missing in the baseline sample: 39 in the No MCI group, 13 in the MCI group; 51 missing in the follow-up cohort: 45 in the No event group, 6 in the Event group. [f] 108 missing in the baseline sample: 81 in the No MCI group, 27 in the MCI group; 100 missing in the follow-up cohort: 89 in the No event group, 11 in the Event group. [g] 100 missing in the baseline sample: 78 in the No MCI group, 22 in the MCI group; 91 missing in the follow-up cohort: 85 in the No event group, 6 in the Event group. [h] 86 missing in the baseline sample: 67 in the No MCI group, 19 in the MCI group; 79 missing in the follow-up cohort: 75 in the No event group, 4 in the Event group.

Table 2. Distribution of components of MeDi and MeDi score by MCI status and by sex

Variable	MCI cases (n = 163)	Controls (n = 1,070)	p	Men (n = 641)	Women (n = 592)	p
Vegetables, g/day	127.4 (84.2–204.8)	150.5 (95.1–225.3)	0.06	143.5 (88.9–215.8)	155.3 (96.1–229.0)	0.12
Legumes, g/day	43.6 (24.9–71.8)	46.3 (28.6–72.0)	0.33	47.2 (30.4–75.2)	43.0 (26.4–69.6)	0.014
Grains and cereals, g/day	190.9 (126.7–256.3)	171.8 (126.8–238.2)	0.18	182.3 (130.9–255.3)	168.1 (124.5–226.7)	0.003
Fruits, g/day	218.1 (128.6–313.1)	208.8 (128.1–320.5)	0.89	201.1 (123.2–294.4)	220.7 (137.4–333.5)	0.004
Fish, g/day	12.5 (6.3–23.8)	15.3 (7.0–26.2)	0.15	15.2 (7.2–26.2)	14.2 (6.3–25.7)	0.37
Red meat, g/day	104.4 (72.6–148.0)	107.7 (70.4–147.4)	0.81	120.6 (86.5–167.0)	91.5 (59.7–130.1)	<0.0001
Dairy, g/day	332.9 (181.4–530.7)	336.7 (188.7–559.8)	0.88	325.9 (187.6–542.9)	347.8 (188.0–569.7)	0.49
MUFA:SFA ratio	1.01 (0.89–1.14)	1.04 (0.91–1.17)	0.23	1.05 (0.92–1.17)	1.03 (0.90–1.16)	0.18
(MUFA + PUFA):SFA ratio	1.51 (1.28–1.70)	1.57 (1.33–1.81)	0.049	1.55 (1.32–1.78)	1.57 (1.31–1.82)	0.43
Moderate alcohol intake, n (%)[a]	95 (58.3)	706 (66.0)	0.05	438 (68.3)	363 (61.3)	0.01
Total calories[b]	2,060.1 (1,506.5–2,681.0)	1,791.6 (1,351.2–2,329.1)	0.0005	1,947.4 (1,522.1–2,507.9)	1,656.3 (1,220.2–2,190.8)	<0.0001
MeDi score 1[c]	5.0 (3.0–6.0)	5.0 (4.0–6.0)	0.37	5.0 (4.0–6.0)	5.0 (4.0–6.0)	0.42
MeDi score 2[d]	5.0 (3.0–6.0)	5.0 (4.0–6.0)	0.27	5.0 (4.0–6.0)	5.0 (3.0–6.0)	0.46

Figures are medians with interquartile ranges in parentheses unless indicated otherwise.

[a] Moderate alcohol intake was categorized as >0 and <30 g/day; intake was lower in female MCI cases [30 (45.5%)] vs. controls [333 (63.3%)]; p = 0.005.

[b] Caloric intake was greater for male MCI cases [2,231.4 (1,731.8–2,982.1)] vs. controls [1,898.1 (1,480.2–2,445.6)]; p = 0.0001. [c] MeDi score 1 = Moderate alcohol and MUFA:SFA ratio. [d] MeDi score 2 = Moderate alcohol and (MUFA + PUFA):SFA ratio.

Longitudinal Associations

Among 1,141 subjects who had MCI or were cognitively normal at baseline, and who completed ≥1 longitudinal clinical evaluation after assessment of dietary intake, there were 116 incident events (MCI, n = 93; dementia, n = 23). Due to the relatively short follow-up [median follow-up = 2.2 years (interquartile range = 1.7–2.6)], there was inadequate power to detect significant associations of the MeDi score components or the MeDi score with incident events. However, the hazard ratio (HR) for incident MCI or dementia was reduced 21% for subjects who had a MeDi score in the second tertile (HR = 0.79, 95% CI = 0.51–1.21, p = 0.28) and 25% for subjects in the upper tertile (HR = 0.75, 95% CI = 0.46–1.21, p = 0.24). The results were similar for MeDi score 2.

Discussion

In our cross-sectional findings, higher daily intake of vegetables, (MUFA + PUFA):SFA ratio, and moderate alcohol consumption were associated with a decreased OR of MCI and a-MCI (but not na-MCI). The OR of MCI decreased with higher intake of fruit and increasing MeDi score, but the trends were not statistically significant. The longitudinal findings showed a 25% reduced risk of MCI or dementia in subjects in the upper tertile of the MeDi score at baseline, but the association did not reach statistical significance.

Our findings are consistent with those of other investigators. High vegetable intake was associated with a slower rate of cognitive decline in the Chicago Health and Aging Project [32]; high intake of β-carotene, flavonoids, vitamins C and E, thiamine, and folate from dietary fruit and vegetables was associated with a lower risk of AD in the Rotterdam Study [33] and with better Mini-Mental State Exam (MMSE) scores [34]. Moderate alcohol intake has also been associated with a reduced incidence of dementia [35, 36], a decreased OR of MCI [37, 38], reduced progression of MCI to dementia [37], a lower risk of poor cognitive function [39], and higher MMSE scores [34]. The effects of fruits and vegetables, PUFA, MUFA, and moderate alcohol intake have been attributed to beneficial antioxidant effects on cerebrovascular disease risk and amyloid pathology. The adverse association of high caloric intake with MCI has also been observed with AD [40]. The association of dietary factors with MCI subtypes has not been evaluated. Our observation of associations of higher intake of vegetables and of higher MUFA:SFA and (MUFA + PUFA):SFA ratios with a-MCI is interesting and raises questions about the role of dietary factors in the pathogenesis of MCI and AD. However, given the cross-sectional design, the implications and relevance are not clear. We will examine these associations further in our longitudinal study of the cohort when we have a larger number of events and longer duration of follow-up.

Our preliminary longitudinal studies suggest that a high MeDi score is beneficial even in our cohort, but we

Table 3. Association of components of the MeDi and the MeDi score with MCI

Variable	Controls	Cases	OR[a]	95% CI[a]	p	p for trend	OR[b]	95% CI[b]	p	p for trend
Vegetables (without legumes)										
≤109.6 g/day	341 (31.9)	70 (42.9)	1.00	reference	–	–	1.00	reference	–	–
109.7–191.0 g/day	364 (34.0)	48 (29.4)	0.65	0.45–0.94	0.02	–	0.60	0.40–0.88	0.01	–
>191.0 g/day	365 (34.1)	45 (27.6)	0.71	0.48–1.04	0.08	0.05	0.66	0.44–0.99	0.05	0.02
Legumes										
≤33.5 g/day	353 (33.0)	58 (35.6)	1.00	reference	–	–	1.00	reference	–	–
33.6–61.3 g/day	359 (33.6)	53 (32.5)	0.95	0.65–1.39	0.80	–	0.99	0.67–1.48	0.98	–
>61.3 g/day	358 (33.5)	52 (31.9)	1.00	0.69–1.47	0.99	0.96	1.05	0.70–1.57	0.82	0.96
Fruits										
≤153.4 g/day	356 (33.3)	55 (33.7)	1.00	reference	–	–	1.00	reference	–	–
153.5–276.8 g/day	354 (33.1)	58 (35.6)	1.06	0.73–1.54	0.78	–	1.09	0.74–1.63	0.66	–
>276.8 g/day	360 (33.6)	50 (30.7)	0.89	0.61–1.32	0.57	0.68	0.92	0.61–1.38	0.68	0.69
Dairy										
≤235.2 g/day	358 (33.5)	53 (32.5)	1.00	reference	–	–	1.00	reference	–	–
235.3–467.2 g/day	358 (33.5)	54 (33.1)	1.02	0.70–1.50	0.91	–	0.97	0.65–1.46	0.90	–
>467.2 g/day	354 (33.1)	56 (34.4)	1.15	0.79–1.68	0.48	0.75	1.09	0.73–1.63	0.68	0.85
Grains and cereals										
≤141.6 g/day	359 (33.6)	52 (31.9)	1.00	reference	–	–	1.00	reference	–	–
141.7–212.9 g/day	363 (33.9)	49 (30.1)	0.99	0.67–1.46	0.95	–	0.94	0.63–1.42	0.77	–
>212.9 g/day	348 (32.5)	62 (38.0)	1.19	0.82–1.72	0.37	0.56	1.08	0.73–1.61	0.69	0.78
Meat										
≤83.2 g/day	357 (33.4)	54 (33.1)	1.00	reference	–	–	1.00	reference	–	–
83.3–132.2 g/day	353 (33.0)	59 (36.2)	1.15	0.79–1.68	0.46	–	1.16	0.78–1.72	0.46	–
>132.2 g/day	360 (33.6)	50 (30.7)	0.95	0.64–1.41	0.80	0.59	0.89	0.59–1.36	0.60	0.45
Fish										
≤8.7 g/day	353 (33.0)	58 (35.6)	1.00	reference	–	–	1.00	reference	–	–
8.8–21.2 g/day	354 (33.1)	58 (35.6)	1.10	0.76–1.60	0.60	–	1.02	0.69–1.51	0.93	–
>21.2 g/day	363 (33.9)	47 (28.8)	1.07	0.72–1.58	0.75	0.87	0.99	0.66–1.50	0.98	0.99
Alcohol										
No intake or ≥30	364 (34.0)	68 (41.7)	1.00	reference	–	–	1.00	reference	–	–
Moderate (>0 and <30)	706 (66.0)	95 (58.3)	0.73	0.53–1.00	0.05	0.05	0.82	0.58–1.15	0.25	0.25
MUFA:SFA ratio										
≤0.955	353 (33.0)	58 (35.6)	1.00	reference	–	–	1.00	reference	–	–
0.956–1.123	358 (33.5)	54 (33.1)	0.91	0.63–1.32	0.62	–	0.94	0.63–1.42	0.78	–
>1.123	359 (33.6)	51 (31.3)	0.82	0.56–1.20	0.31	0.60	0.79	0.52–1.20	0.27	0.52
(MUFA + PUFA):SFA ratio										
≤1.415	346 (32.3)	65 (39.9)	1.00	reference	–	–	1.00	reference	–	–
1.416–1.705	353 (33.0)	59 (36.2)	0.91	0.64–1.31	0.63	–	0.98	0.66–1.45	0.90	–
>1.705	371 (34.7)	39 (23.9)	0.56	0.38–0.83	0.004	0.010	0.52	0.33–0.81	0.004	0.007
Total energy										
≤1,525.9 kcal	369 (34.5)	42 (25.8)	1.00	reference	–	–	1.00	reference	–	–
1,526.0–2,142.5 kcal	367 (34.3)	45 (27.6)	0.98	0.65–1.47	0.92	–	1.12	0.72–1.73	0.62	–
>2,142.5 kcal	334 (31.2)	76 (46.6)	1.85	1.26–2.70	0.002	0.001	2.04	1.36–3.05	0.001	0.001
MeDi score 1[c]										
0–3	262 (24.5)	44 (27.0)	1.00	reference	–	–	1.00	reference	–	–
4–5	463 (43.3)	76 (46.6)	1.03	0.71–1.50	0.87	–	0.96	0.65–1.43	0.85	–
6–9	345 (32.2)	43 (26.4)	0.86	0.57–1.31	0.49	0.62	0.80	0.52–1.25	0.33	0.57
MeDi score 2[c]										
0–3	265 (24.8)	47 (28.8)	1.00	reference	–	–	1.00	reference	–	–
4–5	458 (42.8)	73 (44.8)	0.95	0.66–1.38	0.80	–	0.93	0.63–1.37	0.71	–
6–9	347 (32.4)	43 (26.4)	0.81	0.53–1.23	0.32	0.57	0.78	0.51–1.22	0.28	0.54

Figures in parentheses indicate percentages.

[a] Odds ratio (95% confidence intervals) adjusted for age, years of education, total energy (as continuous variables), and sex. All models were adjusted with propensity weights to take into account potential nonparticipation bias. The unweighted models were essentially the same and are not presented. [b] Adjusted for age, years of education, total energy (continuous variables), sex, ApoE ε4 (ε4+ vs. ε4–), stroke, coronary heart disease, and depressive symptoms. [c] Fat intake was determined from the MUFA:SFA ratio for MeDi score 1, and from the (MUFA + PUFA):SFA ratio for MeDi score 2.

Table 4. Association of select components of the MeDi and the MeDi score with a-MCI and na-MCI

Variable	Controls	Cases	OR[a]	95% CI[a]	p	p for trend	OR[b]	95% CI[b]	p	p for trend
a-MCI										
Vegetables (without legumes)										
≤109.6 g/day	341 (31.9)	54 (44.3)	1.00	reference	–	–	1.00	reference	–	–
109.7–191.0 g/day	364 (34.0)	39 (32.0)	0.70	0.46–1.07	0.10	–	0.66	0.42–1.02	0.06	–
>191.0 g/day	365 (34.1)	29 (23.8)	0.57	0.38–0.90	0.02	0.04	0.59	0.37–0.95	0.03	0.05
MUFA:SFA ratio										
≤0.955	353 (33.0)	50 (41.0)	1.00	reference	–	–	1.00	reference	–	–
0.956–1.123	358 (33.5)	35 (28.7)	0.63	0.40–0.97	0.03	–	0.64	0.41–1.02	0.06	–
>1.123	359 (33.6)	37 (30.3)	0.60	0.39–0.93	0.02	0.03	0.63	0.40–1.00	0.05	0.07
(MUFA + PUFA):SFA ratio										
≤1.415	346 (32.3)	51 (41.8)	1.00	reference	–	–	1.00	reference	–	–
1.416–1.705	353 (33.0)	42 (34.4)	0.81	0.53–1.22	0.31	–	0.86	0.56–1.34	0.51	–
>1.705	371 (34.7)	29 (23.8)	0.48	0.30–0.76	0.002	0.007	0.49	0.30–0.80	0.004	0.01
MeDi score 1[c]										
0–3	262 (24.5)	33 (27.0)	1.00	reference	–	–	1.00	reference	–	–
4–5	463 (43.3)	60 (49.2)	1.07	0.69–1.66	0.75	–	1.01	0.64–1.59	0.98	–
6–9	345 (32.2)	29 (23.8)	0.79	0.48–1.30	0.35	0.38	0.74	0.44–1.25	0.26	0.39
MeDi score 2[c]										
0–3	265 (24.8)	36 (39.5)	1.00	reference	–	–	1.00	reference	–	–
4–5	458 (42.8)	56 (45.9)	0.93	0.60–1.42	0.73	–	0.91	0.58–1.43	0.68	–
6–9	347 (32.4)	30 (24.6)	0.74	0.46–1.21	0.23	0.46	0.73	0.44–1.22	0.23	0.47
na-MCI										
Vegetables (without legumes)										
≤109.6 g/day	341 (31.9)	16 (39.0)	1.00	reference	–	–	1.00	reference	–	–
109.7–191.0 g/day	364 (34.0)	9 (22.0)	0.60	0.29–1.29	0.19	–	0.52	0.24–1.16	0.11	–
>191.0 g/day	365 (34.1)	16 (39.0)	1.41	0.73–2.74	0.31	0.09	1.18	0.58–2.39	0.64	0.13
MUFA:SFA ratio										
≤0.955	353 (33.0)	8 (19.5)	1.00	reference	–	–	1.00	reference	–	–
0.956–1.123	358 (33.5)	19 (46.3)	2.57	1.21–5.50	0.01	–	2.75	1.22–6.22	0.01	–
>1.123	359 (33.6)	14 (34.1)	1.74	0.78–3.87	0.18	0.05	1.70	0.71–4.08	0.23	0.04
(MUFA + PUFA):SFA ratio										
≤1.415	346 (32.3)	14 (34.1)	1.00	reference	–	–	1.00	reference	–	–
1.416–1.705	353 (33.0)	17 (41.5)	1.37	0.71–2.65	0.35	–	1.57	0.78–3.17	0.21	–
>1.705	371 (34.7)	10 (24.4)	0.73	0.34–1.54	0.41	0.22	0.63	0.27–1.47	0.29	0.07
MeDi score 1[c]										
0–3	262 (24.5)	11 (26.8)	1.00	reference	–	–	1.00	reference	–	–
4–5	463 (43.3)	16 (39.0)	0.95	0.47–1.94	0.90	–	1.03	0.47–2.22	0.95	–
6–9	345 (32.2)	14 (34.1)	1.28	0.61–2.69	0.51	0.65	1.41	0.63–3.16	0.40	0.60
MeDi score 2[c]										
0–3	265 (24.8)	11 (26.8)	1.00	reference	–	–	1.00	reference	–	–
4–5	458 (42.8)	17 (41.5)	1.05	0.52–2.12	0.89	–	1.19	0.55–2.54	0.66	–
6–9	347 (32.4)	13 (31.7)	1.21	0.57–2.56	0.63	0.87	1.37	0.60–3.10	0.45	0.75

Figures in parentheses indicate percentages.

[a] Odds ratio (95% confidence intervals) adjusted for age, years of education, total energy (as continuous variables), and sex. All models were adjusted with propensity weights to take into account potential nonparticipation bias. There were 122 cases with a-MCI and 41 cases with na-MCI.

[b] Adjusted for age, years of education, total energy (continuous variables), sex, ApoE ε4 (ε4+ vs. ε4–), stroke, coronary heart disease, and depressive symptoms.

[c] Fat intake was determined from the MUFA:SFA ratio for MeDi score 1, and from the (MUFA + PUFA):SFA ratio for MeDi score 2.

Table 5. Distribution of components of the MeDi in the current study and other studies

Dietary variable	Median daily intake of selected foods common to the MeDi									
	Mayo Clinic Study of Aging			Trichopoulou et al. [8][a]		Trichopoulou et al. [29][a]		Mitrou et al. [41][b]		Scarmeas et al. [9][c]
	men median	women median	all median	men median	women median	men median	women median	men median	women median	all median
Vegetables, g/day	143.5	155.3	148.9	549.9	499.6	156.8	183.8	299.8	317.0	197
Legumes, g/day	47.2	43.0	45.5	9.1	6.7	3.3	10.7	8.6	6.1	57
Fruits, g/day	201.1	220.7	209.6	–	–	176.7	232.5	286.8	301.0	472
Fruits and nuts, g/day	208.7	230.6	216.7	362.5	356.3	–	–	292.3	304.2	–
Dairy, g/day	325.9	347.8	336.6	196.7	191.1	285.7	301.1	186.3	173.1	182
Grains and cereals, g/day	182.3	168.1	174.4	177.7	139.7	212.0	168.4	415.6	339.4	184
Fish, g/day	15.2	14.2	15.0	23.7	18.8	32.2	26.9	76.7	46.3	20
Meat, g/day	120.6	91.5	106.7	120.8	89.8	111.6	82.2	335.5	339.4	85
MUFA:SFA ratio	1.05	1.03	1.04	1.7	1.7	0.9	0.9	1.23	1.22	0.8
(MUFA + PUFA):SFA ratio	1.55	1.57	1.56	–	–	1.4	1.4	–	–	–
Moderate alcohol, %[d]	68.3	61.3	65.0	–	–	–	–	–	–	32
Total energy, kcal	1,947.4	1,656.3	1,811.9	2,354.4	1,863.0	2,296.6	1,860.9	1,889	1,455	1,428
MeDi score 1[e]	5.0	5.0	5.0	–	–	–	–	–	–	4.3
MeDi score 2[e]	5.0	5.0	5.0	–	–	–	–	–	–	–

[a] Greek populations.

[b] US population. Estimates in the published manuscript were presented in servings per day; we used our food frequency database to generate estimates in grams per day to enable us to compare the daily intakes on the same scale.

[c] Energy and MeDi score are the mean (demented subjects included); multiethnic US population.

[d] Alcohol intake of >0 and <30 g/day.

[e] Fat intake was determined from the MUFA:SFA ratio for MeDi score 1, and from the (MUFA + PUFA):SFA ratio for MeDi score 2.

may have had inadequate power to detect significant associations, possibly due to a low adherence to the MeDi. Lower adherence in our cohort is suggested by the comparison of our sample with 2 Mediterranean [8, 29] and 2 US samples [9, 41] where a significant association of MeDi score with cognition has been observed (table 5). Overall, daily intake of vegetables, fruit, and fish was lower, and red meat intake was higher than in 1 of the US samples. The MUFA:SFA ratio was low compared to 1 Greek sample, 1 US sample, and was also lower than a ratio of 2 for participants in the Italian Longitudinal Study of Aging [11].

Low adherence to MeDi in a community may limit the ability to detect a significant dose-response association of the MeDi score with cognition. Since the median intakes in a sample are used to determine the cutpoints for computing the MeDi score, a score in 1 community may not reflect intakes in a community with very different dietary habits [11]. Other cultural differences in the foods may also affect studies involving the MeDi score. For example, availability of fruits and vegetables year-round is different in Mediterranean regions than in a Midwestern US community.

Relatively few investigators have used the whole diet approach such as the MeDi to assess the impact of diet on cognitive function. In these studies, higher adherence to a MeDi was associated with decreasing cognitive decline assessed from the MMSE [31, 42], with prevalent AD [43], a reduced risk of AD and slower cognitive decline [9], and a reduced risk of AD mortality [44], and with a borderline reduced risk of MCI incidence and MCI conversion to dementia [10]. It is evident that different measures of cognition were used, and MCI criteria were retrospectively applied in some cases. However, the widespread health benefits of the MeDi are well noted. These include beneficial effects on survival [8, 29], cardiovascular risk factors and outcomes [5, 6], cancer [45], and inflammation [46]. Nonetheless, additional longitudinal studies are needed to confirm the associations with MCI in a population-based setting using reliable and valid ascertainment of both dietary exposure and MCI using specified criteria for MCI at the time of evaluation as in the present study. A longer duration of follow-up in our cohort may demonstrate significant associations.

Potential limitations of our findings include the possibility of recall bias in this elderly cohort, and our failure to validate the questionnaire in our cohort. Any effect of recall bias is likely to be minimal, and reporting of dietary intake is likely to be valid for the following reasons: (a) we excluded subjects with dementia who are unlikely to report valid dietary intake; (b) participants did not know about their cognitive status, reducing the potential for biased reporting; (c) MCI cases were very mild, with a median CDR sum of boxes of only 1.0 (interquartile range = 0.5–1.5), and (d) the results remained the same after excluding subjects in the lowest 5% of the memory domain score who could have provided unreliable data (data not presented). Also, others have observed that assessment of dietary intake over a longer period (prior 1 year) may be less susceptible to bias than short-term recall [47]. The modest differences between included and excluded subjects raises the question of potential nonparticipation bias. We addressed this by assigning included subjects who had the characteristics of the excluded subjects a heavier weight in all the logistic models to account for the propensity to participate in the study. The results were similar to those that were not adjusted for propensity to participate. The cross-sectional study design prevents our ability to assess causal associations. Given the number of tests assessed in the study, there is a potential for type 2 errors; a Bonferroni correction would require a p value of ≤ 0.004 for statistical significance. At this p value, the associations between the upper tertile of the (MUFA + PUFA):SFA ratio and total energy intake would remain statistically significant, but the other associations would no longer be significant. The preliminary longitudinal data based on the small number of incident events suggest a benefit of a higher MeDi score for MCI or dementia. Longitudinal follow-up of the sample will enable us to obtain more reliable estimates and will increase our power to detect significant associations. The findings may be generalizable to communities with similar demographic characteristics.

Our study has several strengths. The study sample was randomly selected from the community, thus reducing the potential for referral, selection, or volunteer bias. We used a previously validated questionnaire to ascertain dietary intake of foods. In addition to a whole-diet approach, we also assessed the association of individual components of the MeDi with MCI, and with MCI subtypes, and observed differences across the subtypes. The assessment of MCI was made using information from 3 independent evaluators, and the diagnosis of MCI or normal cognition was made by consensus, at the time of the evaluation, and was based on previously specified criteria. Our findings provide insight into the dietary habits of a Midwestern US community, and suggest that in this elderly cohort, adherence to a MeDi may be low. Despite this, we demonstrated beneficial associations of certain dietary components with MCI, and our preliminary longitudinal studies suggest that a high MeDi score may be beneficial. Thus, findings from our study and other studies provide insights into the role of the MeDi and components of this diet as a potential target for intervention in clinical trials to prevent MCI, and ultimately reduce the burden of dementia.

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