

# Mediterranean Diet and Mild Cognitive Impairment

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**Background:** Higher adherence to the Mediterranean diet (MeDi) may protect from Alzheimer disease (AD), but its association with mild cognitive impairment (MCI) has not been explored.

**Objective:** To investigate the association between the MeDi and MCI.

**Design, Setting, and Patients:** In a multiethnic community study in New York, we used Cox proportional hazards to investigate the association between adherence to the MeDi (0-9 scale; higher scores indicate higher adherence) and (1) the incidence of MCI and (2) the progression from MCI to AD. All of the models were adjusted for cohort, age, sex, ethnicity, education, APOE genotype, caloric intake, body mass index, and duration between baseline dietary assessment and baseline diagnosis.

**Main Outcome Measures:** Incidence of MCI and progression from MCI to AD.

**Results:** There were 1393 cognitively normal participants, 275 of whom developed MCI during a mean (SD)

follow-up of 4.5 (2.7) years (range, 0.9-16.4 years). Compared with subjects in the lowest MeDi adherence tertile, subjects in the middle tertile had 17% less risk (hazard ratio [HR]=0.83; 95% confidence interval [CI], 0.62-1.12;  $P=.24$ ) of developing MCI and those in the highest tertile had 28% less risk (HR=0.72; 95% CI, 0.52-1.00;  $P=.05$ ) of developing MCI (trend HR=0.85; 95% CI, 0.72-1.00;  $P$  for trend=.05). There were 482 subjects with MCI, 106 of whom developed AD during a mean (SD) follow-up of 4.3 (2.7) years (range, 1.0-13.8 years). Compared with subjects in the lowest MeDi adherence tertile, subjects in the middle tertile had 45% less risk (HR=0.55; 95% CI, 0.34-0.90;  $P=.01$ ) of developing AD and those in the highest tertile had 48% less risk (HR=0.52; 95% CI, 0.30-0.91;  $P=.02$ ) of developing AD (trend HR=0.71; 95% CI, 0.53-0.95;  $P$  for trend=.02).

**Conclusions:** Higher adherence to the MeDi is associated with a trend for reduced risk of developing MCI and with reduced risk of MCI conversion to AD.

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**T**HE CONCEPT OF MILD COGNITIVE impairment (MCI) was developed to identify subjects who are in the transitional stage between normal aging and dementia or Alzheimer disease (AD). Because of the high conversion rates, subjects with MCI constitute a population suited for study of dementia-AD risk factor epidemiology and for investigation of possible behavioral or pharmacological preventive interventions. Among behavioral traits, diet may play an important role in the cause and prevention of AD. However, epidemiological data on diet and AD have been conflicting.<sup>1,2</sup> Moreover, there is a paucity of research on the effect of dietary factors on both rates of development of MCI and rates of MCI conversion to AD.

We recently demonstrated that higher adherence to the Mediterranean diet (MeDi) (a diet characterized by high in-

take of fish, vegetables, legumes, fruits, cereals, and unsaturated fatty acids [mostly in the form of olive oil], low intake of dairy products, meat, and saturated fatty acids, and a regular but moderate intake of alcohol<sup>3</sup>) is associated with lower AD risk.<sup>4,5</sup> Some studies have investigated the effect of individual elements of the MeDi (ie, alcohol, fatty acids, and fish) in MCI and age-related cognitive decline<sup>6-12</sup> and have found conflicting results. Nevertheless, potential associations between the entire MeDi pattern and MCI have not been explored. We examined the association between the MeDi and MCI using data from the Washington Heights-Inwood Columbia Aging Project (WHICAP). We hypothesized that cognitively normal participants with higher adherence to the MeDi would have a lower risk of future development of MCI and that participants with MCI and higher MeDi adherence would have a lower risk of developing future AD.

## SAMPLE AND DIAGNOSES

The sample for the current study has been described in detail in recent studies exploring the frequency and course of MCI in our cohorts.<sup>13,14</sup> The study included participants of 2 related cohorts recruited in 1992 (WHICAP 1992) and 1999 (WHICAP 1999) who were identified (via ethnicity and age stratification processes) from a probability sample of Medicare beneficiaries residing in an area of 3 contiguous census tracts within a geographically defined area of northern Manhattan, New York.<sup>15</sup> The same assessments and study procedures were used in both cohorts. At entry, a physician elicited each subject's medical and neurological history and conducted a standardized physical and neurological examination. All available ancillary information (medical records, computed tomographic scans, or magnetic resonance images) was considered in the evaluation.

Each subject also underwent a structured in-person interview including an assessment of health and function and a neuropsychological battery. Functional assessment of instrumental activities of daily living included a disability and functional limitations scale.<sup>16,17</sup> The neuropsychological battery<sup>18</sup> contained tests of memory (short- and long-term verbal and nonverbal), orientation, abstract reasoning (verbal and nonverbal), language (naming, verbal fluency, comprehension, and repetition), and construction (copying and matching). A global summary score on the Clinical Dementia Rating (CDR)<sup>19</sup> was also assigned.

A consensus diagnosis for the presence or absence of dementia was made at a diagnostic conference of neurologists and neuropsychologists where information of all the above evaluations was presented. Evidence of cognitive deficit (based on the neuropsychological scores as described earlier), evidence of impairment in social or occupational function (as assessed by the Blessed Dementia Rating Scale, the Schwab and England Activities of Daily Living Scale, and the physician's assessment), and evidence of cognitive and social-occupational function decline were the criteria used for the diagnosis of dementia as required by the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*.<sup>20</sup> The type of dementia was subsequently determined. For the diagnosis of probable or possible AD, the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association<sup>21</sup> were used.

Because the current study had started before the concept of MCI was developed, diagnosis of MCI was not part of the standard consensus conference procedure but was retrospectively applied after the consensus conference for each visit among nondemented individuals. Details on the MCI definition have been previously provided.<sup>13,14</sup> Briefly, consistent with standard criteria,<sup>22</sup> subjects considered for MCI were required to have the following. First, they had a subjective memory complaint (using items from the Disability and Functional Limitations Scale<sup>16,17</sup> and the Blessed Functional Activities Scale<sup>23</sup>). Second, they had objective impairment in at least 1 cognitive domain. Using selected items from the neuropsychological battery, 4 cognitive domains (memory, executive, language, and visuospatial) were defined.<sup>13,14</sup> Impairment was defined based on the average of the scores on the neuropsychological measures within that domain and a 1.5-SD cutoff using corrections for age, years of education, ethnicity, and sex and based on the previously established norms. Third, they had essentially preserved activities of daily living (defined earlier). Fourth, they had no diagnosis of dementia at the consensus conference. To further explore the association of the MeDi to MCI, in the view of the original criteria by Petersen et al<sup>22,24</sup> (which focus on objective memory impairment), the overall MCI group was divided into 2 mutually ex-

clusive MCI subtypes: (1) MCI with objective memory impairment (with or without objective impairment in other cognitive domains), and (2) MCI without objective memory impairment (objective impairment in  $\geq 1$  of the 3 nonmemory domains but a memory domain composite score within norms). Dietary data were not available to the consensus panel and were not considered in the MCI diagnostic process. Subjects were followed up at intervals of approximately 1.5 years, repeating the baseline examination and consensus diagnosis at each follow-up.

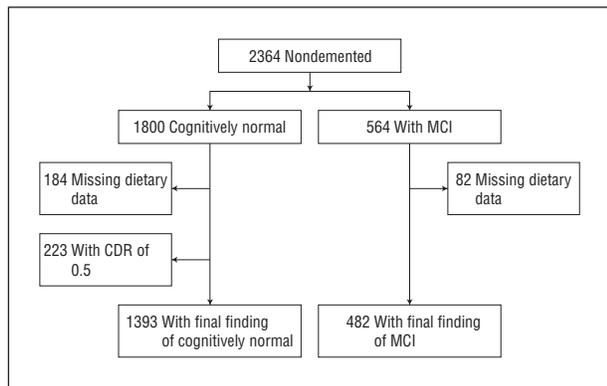
## PREDICTORS

## Diet

Dietary data regarding average food consumption during the past year were obtained using a 61-item version of the semiquantitative food frequency questionnaire by Willett et al<sup>25</sup> (Channing Laboratory, Cambridge, Massachusetts). Trained interviewers administered the semiquantitative food frequency questionnaire in English or Spanish. We have previously reported validity (using two 7-day food records) and reliability (using two 3-month frequency assessments) of various components of the semiquantitative food frequency questionnaire in the WHICAP.<sup>26-28</sup>

Similar to our previous work,<sup>4,5,29</sup> we followed a method previously described<sup>3</sup> for the construction of the MeDi score. More specifically, we first regressed caloric intake (in kilocalories) and calculated the derived residuals of daily gram intake<sup>30</sup> for each of the following 7 categories<sup>3</sup>: dairy, meat, fruits, vegetables, legumes, cereals, and fish. A value of 0 or 1 was assigned to each of the 7 groups using sex-specific medians as cutoffs. For beneficial components (fruits, vegetables, legumes, cereals, and fish), persons whose consumption was below the median were assigned a value of 0 and persons whose consumption was at or above the median were assigned a value of 1. For components presumed to be detrimental (meat and dairy products), persons whose consumption was below the median were assigned a value of 1 and persons whose consumption was at or above the median were assigned a value of 0. For fat intake (eighth food category), we used the ratio of daily consumption (in grams) of mono-unsaturated lipids to saturated lipids<sup>3</sup> (again using sex-specific median cutoffs for assignment values of 0 for low and 1 for high). For alcohol intake (ninth food category), subjects were assigned a score of 0 for either no consumption (0 g/d) or more than moderate consumption ( $\geq 30$  g/d) and a value of 1 for mild to moderate alcohol consumption ( $>0$  to  $<30$  g/d). This is in agreement with previous reports<sup>3</sup> that consider a moderate amount of alcohol consumption as another characteristic component of the MeDi. We also classified alcohol consumption dichotomously because of the skewed distribution of alcohol consumption in our population (68% reporting no alcohol intake, 31% reporting  $<30$  g/d [mild to moderate intake], and 1% reporting  $\geq 30$  g/d [heavy intake]). The MeDi score was generated for each participant by adding the scores in the food categories (theoretically ranging from 0-9) with a higher score indicating higher adherence to the MeDi.

We used the MeDi score from the first time the dietary assessment was performed as the main predictor in the survival analyses. Because the cognitively normal and MCI definitions were partly based on availability of neuropsychological assessments, their ascertainment was not always synchronous with the dietary assessments. For the incident MCI analyses, the time of the first dietary assessment coincided ( $\pm 1.5$  years) with the time of the first assessment of cognitively normal status for 82% of the subjects, was more than 1.5 years earlier for 14% of the subjects, and was more than 1.5 years later for only 4%. For the incident AD analyses, the time of the first dietary assessment coincided ( $\pm 1.5$  years) with the time of the first assessment of MCI status for 84% of the subjects, was more than 1.5 years earlier



**Figure 1.** Flowchart describing the sample. MCI indicates mild cognitive impairment; CDR, Clinical Dementia Rating.

for 11% of the subjects, and was more than 1.5 years later for only 5%. To summarize, the timing of the MeDi adherence assessment and the cognitively normal or MCI assessments overlapped to a significant degree. Despite this, in all of the survival models we included a term adjusting for the difference in the time between the first dietary assessment and the first cognitive status assessment.

### Covariates

Age (in years), education (in years), caloric intake (in kilocalories), and body mass index (BMI) (weight in kilograms divided by height in meters squared)<sup>31</sup> were used as continuous variables. We also considered cohort (1992 cohort as the reference) and sex (men as the reference). Ethnic group was based on self-report using the format of the 1990 census.<sup>32</sup> Participants were then assigned to 1 of 4 groups: black (non-Hispanic), Hispanic, white (non-Hispanic), or other. Ethnicity was used as a dummy variable with white (non-Hispanic) as the reference. Apolipoprotein E (*APOE*) genotype was used dichotomously: absence of the  $\epsilon 4$  allele vs presence of either 1 or 2  $\epsilon 4$  alleles.

### STATISTICAL ANALYSES

Baseline characteristics of subjects by missing dietary data, by outcome of interest, and by MeDi adherence tertiles were compared using *t* test or analysis of variance for continuous variables and  $\chi^2$  test for categorical variables.

#### Cognitively Normal to Incident MCI

We calculated Cox proportional hazards models with MCI as the dichotomous outcome. The time-to-event variable was the time from the first cognitively normal status to the first visit with an MCI diagnosis. Subjects diagnosed with MCI and then reverting back to normal were considered cases, and their first MCI diagnostic visit was considered the event visit. Persons who did not develop MCI were censored at the time of their last follow-up (ie, all subject visits before the last follow-up were used in the analyses). The main predictor was the MeDi score (from the first dietary evaluation) as a continuous variable initially and in tertiles subsequently (used for trend test calculation). We simultaneously adjusted for the following variables: cohort, age at intake in the study, sex, ethnicity, education, *APOE* genotype, BMI, and time between the first dietary assessment and the first cognitive status assessment. Although caloric intake-adjusted residuals were used in the MeDi score calculation, we also included caloric intake as a covariate in the models (as recommended by Willett and Stampfer<sup>30</sup>). All of the predictors were

used as time-constant covariates. In additional analyses, we recalculated the models using the 2 different types of MCI as the outcomes: with and without memory impairment.

### MCI to Incident AD

We calculated Cox proportional hazards models with AD as the dichotomous outcome. The time-to-event variable was the time from the first MCI status to the first visit with an AD diagnosis. Subjects diagnosed with AD and then reverting back to MCI were considered cases, and their first AD diagnostic visit was considered the event visit. Therefore, censored subjects never developed AD at any of their follow-up visits. Persons who did not develop AD were censored at the time of their last follow-up (ie, all of the subject visits before the last follow-up were used in the analyses). Predictors and covariates were the same as in the earlier-described models for cognitively normal to incident MCI. In additional analyses, we recalculated the models using the 2 different types of MCI (with and without memory impairment) as the starting point.

## RESULTS

### MISSING DATA ANALYSES

Among all of the potential participants in both WHICAP cohorts, 2364 individuals were considered for this study because of sufficient data for MCI diagnosis and available follow-up<sup>14</sup> (**Figure 1**). As previously reported,<sup>14</sup> in comparison with 1329 subjects who were not considered because of missing data or lack of follow-up, these 2364 subjects were slightly younger, were more likely to be women, and had higher cognitive performance but did not differ in ethnicity. Among the 2364 subjects, 1800 were cognitively normal (nondemented, non-MCI) at the initial evaluation (serving for calculation of the effect of the MeDi on the incidence of MCI) and 564 were diagnosed with MCI at the initial evaluation (serving for calculation of the effect of the MeDi on the MCI conversion to AD).

#### Cognitively Normal to Incident MCI Analyses

Among the 1800 subjects who were cognitively normal at the initial evaluation, dietary information was missing for 184 subjects (partly because the dietary assessment component was added after initiation of the study) (Figure 1). To have an even cleaner sample for the incident MCI analyses, we additionally excluded 223 subjects who, despite not meeting our MCI criteria, had a CDR of 0.5 at the first evaluation. Compared with the 184 subjects with missing dietary information, the 1393 cognitively normal subjects (with a CDR of 0.0 and available dietary information) used for the incident MCI analyses had lower BMIs (28.5 vs 27.5, respectively;  $P = .02$ ) and borderline higher cognitive performance (composite cognitive *z* score, 0.37 vs 0.46, respectively;  $P = .05$ ). The groups did not differ in sex, age, ethnicity, education, or *APOE* status. As expected, compared with the 223 subjects with a CDR of 0.5, the 1393 cognitively normal subjects (with a CDR of 0.0 and available dietary information) used for the incident MCI analyses were younger (79.0 vs 76.7 years, respectively;  $P < .001$ ), were more educated (6.8 vs 10.8 years of school, respectively;  $P < .001$ ), had higher cognitive per-

**Table 1. Demographic and Clinical Characteristics During the First Evaluation for All Subjects**

Characteristic	Cognitively Normal (n=1393)	MCI (n=482)	All Subjects (n=1875)	P Value
Men, No. (%)	447 (32)	156 (32)	603 (32)	.91
Age, mean (SD), y	76.7 (6.5)	77.5 (6.6)	76.9 (6.5)	.02
Ethnicity, No. (%)				
White	434 (31)	124 (26)	558 (30)	].001
Black	479 (34)	144 (30)	623 (33)	
Hispanic	473 (34)	214 (44)	687 (36)	
Other	7 (1)	0	7 (1)	
Education, mean (SD), y	10.8 (4.6)	9.1 (4.9)	10.4 (4.7)	<.001
≥1 ε4 allele, No. (%)	327 (27)	127 (30)	454 (28)	.18
BMI, mean (SD)	27.5 (5.5)	27.2 (5.3)	27.4 (5.4)	.34
Energy, mean (SD), kcal	1426.1 (498.0)	1421.8 (591.9)	1425.0 (523.6)	.88
MeDi score, mean (SD)	4.37 (1.69)	4.31 (1.62)	4.36 (1.67)	.47

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MCI, mild cognitive impairment; MeDi, Mediterranean diet.

**Table 2. Demographic and Clinical Characteristics During the First Evaluation for All Subjects by Mediterranean Diet Adherence Tertiles**

Characteristic	MeDi Adherence Tertile			P Value
	Low (n=609)	Middle (n=775)	High (n=491)	
Men, No. (%)	442 (69)	532 (69)	318 (65)	.23
Age, mean (SD), y	76.9 (6.6)	76.8 (6.5)	77.2 (6.2)	.48
Ethnicity, No. (%)				
White	182 (30)	223 (29)	153 (31)	].001
Black	234 (38)	260 (33)	139 (26)	
Hispanic	190 (31)	289 (37)	208 (42)	
Other	3 (1)	3 (1)	1 (1)	
Education, mean (SD), y	10.5 (4.5)	10.3 (4.7)	10.4 (4.9)	.77
≥1 ε4 allele, No. (%)	146 (27)	179 (27)	129 (29)	.70
BMI, mean (SD)	27.7 (5.8)	27.4 (5.2)	27.1 (5.3)	.19
Energy, mean (SD), kcal	1494.9 (608.2) <sup>a</sup>	1395.4 (472.5) <sup>a</sup>	1385.1 (477.4) <sup>a</sup>	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MeDi, Mediterranean diet.

<sup>a</sup>P<.05 for all MeDi adherence tertiles according to post hoc Scheffé test.

formance (composite cognitive z score, -0.46 vs 0.46, respectively;  $P < .001$ ), and were more likely to be white (11% vs 31%, respectively) and less likely to be Hispanic (60% vs 34%, respectively) ( $P < .001$ ). The groups did not differ in sex, BMI, or APOE status.

#### MCI to Incident AD Analyses

Compared with the 82 subjects with MCI and missing dietary information, the 482 subjects with MCI and available dietary information included in the incident AD analyses had borderline higher education (8.0 vs 9.1 years of school, respectively;  $P = .05$ ) and borderline higher cognitive performance (composite cognitive z score, -0.40 vs -0.27, respectively;  $P = .05$ ). The groups did not differ in sex, age, ethnicity, APOE status, or BMI.

#### CLINICAL, DEMOGRAPHIC, AND DIETARY CHARACTERISTICS

At the first evaluation, compared with subjects who were cognitively normal, subjects with MCI were older, less educated, more likely to be Hispanic, and less likely to

be white (**Table 1**). Cognitively normal subjects and subjects with MCI did not differ in sex, APOE genotype, BMI, total caloric intake, and MeDi adherence.

Hispanic subjects adhered more to the MeDi, black subjects adhered less, and white subjects' adherence was in between (**Table 2**). The higher the MeDi adherence was, the lower the total caloric intake was. There was no association between the MeDi score and age, sex, education, APOE genotype, or BMI.

#### MeDi AND RISK FOR INCIDENT MCI

Despite somewhat lower scores in subjects with MCI (as compared with cognitively normal subjects) at baseline (Table 1), the groups did not significantly differ cross-sectionally. Longitudinal analyses (particularly with use of survival models) are a much more powerful method of detecting predictor differences because they can combine in a single statistic 2 different risk dimensions: (1) the proportion of subjects who reach an event (convert to MCI or AD), and (2) duration (how soon subjects convert or nonconvert to MCI or AD).

**Table 3. Cox Proportional Hazard Ratios for Incidence of Mild Cognitive Impairment for Subjects Who Were Cognitively Normal at the First Evaluation by Mediterranean Diet Score**

Predictor	HR (95% CI)	P Value
Unadjusted <sup>a</sup>		
MeDi continuous	0.93 (0.87-1.00)	.06
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.87 (0.66-1.14)	.33
High	0.73 (0.53-1.00)	.05
Trend	0.85 (0.73-1.00)	.05
Adjusted <sup>b</sup>		
MeDi continuous	0.92 (0.85-0.99)	.04
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.83 (0.62-1.12)	.24
High	0.72 (0.52-1.00)	.05
Trend	0.85 (0.72-1.00)	.05

Abbreviations: CI, confidence interval; HR, hazard ratio; MeDi, Mediterranean diet; NA, not applicable.

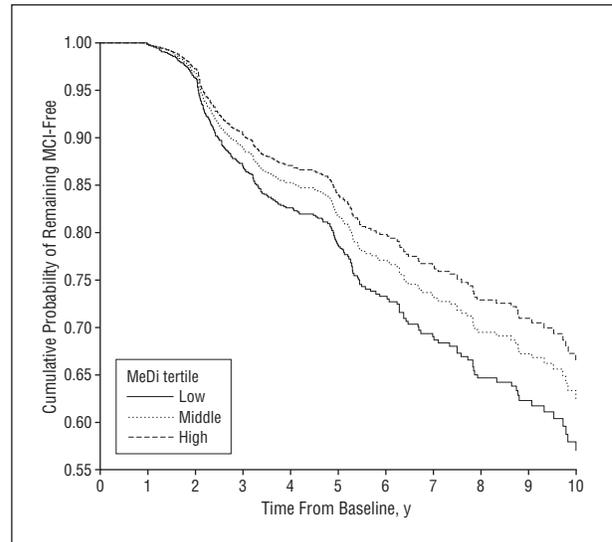
<sup>a</sup>A total of 1393 subjects were cognitively normal at the first evaluation; 275 subjects developed incident mild cognitive impairment.

<sup>b</sup>A total of 1199 subjects were cognitively normal at the first evaluation; 241 subjects developed incident mild cognitive impairment. Adjusted models include a slightly lower number of subjects because of missing data in some of the covariates; they simultaneously control for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment.

Subjects who were cognitively normal at the first evaluation were followed up (until MCI incidence or the last follow-up for subjects who remained cognitively normal) for a mean (SD) of 4.5 (2.7) years (range, 0.9-16.4 years). Overall, 275 subjects developed incident MCI.

Higher adherence to the MeDi was associated with a borderline trend for lower risk of developing MCI (**Table 3** and **Figure 2**). The results were similar in adjusted and unadjusted models. Each additional unit of the MeDi score was associated with 8% less risk ( $P = .04$ ) of developing MCI. Compared with subjects in the lowest MeDi adherence tertile, subjects in the middle tertile had 17% less risk ( $P = .24$ ) of developing MCI and those in the highest tertile had 28% less risk ( $P = .05$ ) of developing MCI. Among the other covariates in the model, younger age and higher education were the only protective factors for development of MCI.

The effect of the MeDi on development of different MCI subtypes is subject to power limitations but is still worth exploring. Overall, 108 subjects developed incident MCI with memory impairment. In fully adjusted models, as compared with subjects in the lowest MeDi adherence tertile, those in the middle tertile had a hazard ratio (HR) of 0.90 (95% confidence interval [CI], 0.57-1.40;  $P = .64$ ) for developing MCI with memory impairment, whereas those in the highest tertile had an HR of 0.71 (95% CI, 0.43-1.17;  $P = .18$ ). The overall MeDi HR trend was 0.84 (95% CI, 0.66-1.03;  $P$  for trend = .18). A total of 133 subjects developed MCI without memory impairment. In fully adjusted models, as compared with subjects in the lowest MeDi adherence tertile, those in the middle tertile had an HR of 0.79 (95% CI, 0.53-1.19;  $P = .27$ ) for developing MCI without memory impair-



**Figure 2.** Survival curves based on Cox analysis comparing cumulative mild cognitive impairment (MCI) incidence in subjects who were cognitively normal at the first evaluation by each Mediterranean diet (MeDi) adherence tertile ( $P$  for trend = .05). The figure is derived from a model that is adjusted for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment. Duration of follow-up is truncated at 10 years. Results of log-rank tests for pairwise comparisons are as follows: middle vs low tertile,  $\chi^2 = 0.91$ ,  $P = .33$ ; low vs high tertile,  $\chi^2 = 3.72$ ,  $P = .05$ ; and middle vs high tertile,  $\chi^2 = 1.22$ ,  $P = .26$ .

ment and those in the highest tertile had an HR of 0.71 (95% CI, 0.46-1.12;  $P = .14$ ). The overall MeDi HR trend was 0.84 (95% CI, 0.67-1.05;  $P$  for trend = .13).

#### MeDi AND RISK FOR MCI CONVERSION TO AD

Subjects with MCI at the first evaluation were followed up (until AD incidence or last follow-up for subjects who did not develop AD) for a mean (SD) of 4.3 (2.7) years (range, 1.0-13.8 years). Overall, 106 subjects developed AD.

Higher adherence to the MeDi was associated with lower risk of developing AD (**Table 4** and **Figure 3**). The results were similar in adjusted and unadjusted models. Each additional unit of the MeDi score was associated with 11% less risk ( $P = .09$ ) of developing AD. Compared with subjects in the lowest MeDi adherence tertile, subjects in the middle tertile had 45% less risk ( $P = .01$ ) of developing AD and those in the highest tertile had 48% less risk ( $P = .02$ ) of developing AD. Among the other covariates in the model, younger age, higher education, and higher BMI were the only protective factors for development of AD.

At the first evaluation, 175 subjects had MCI with memory impairment; 49 of them developed AD at follow-up. In fully adjusted models, as compared with subjects who had MCI with memory impairment belonging to the lowest MeDi adherence tertile, those who had MCI with memory impairment in the middle tertile had an HR of 0.48 (95% CI, 0.22-1.04;  $P = .06$ ) for developing AD and those who had MCI with memory impairment in the highest tertile had an HR of 0.71 (95% CI, 0.32-1.59;  $P = .41$ ). The overall MeDi HR trend was 0.84 (95% CI, 0.55-1.29;  $P$  for trend = .45). At the first evaluation, 234 subjects had MCI without memory impairment; 47 of them developed AD at follow-up. In fully adjusted models, as

**Table 4. Cox Proportional Hazard Ratios for Incidence of Alzheimer Disease for Subjects With Mild Cognitive Impairment at the First Evaluation by Mediterranean Diet Score**

Predictor	HR (95% CI)	P Value
Unadjusted <sup>a</sup>		
MeDi continuous	0.95 (0.85-1.07)	.48
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.62 (0.39-0.98)	.04
High	0.69 (0.41-1.14)	.15
Trend	0.82 (0.63-1.07)	.15
Adjusted <sup>b</sup>		
MeDi continuous	0.89 (0.78-1.02)	.09
MeDi tertile		
Low	1 [Reference]	NA
Middle	0.55 (0.34-0.90)	.01
High	0.52 (0.30-0.91)	.02
Trend	0.71 (0.53-0.95)	.02

Abbreviations: CI, confidence interval; HR, hazard ratio; MeDi, Mediterranean diet; NA, not applicable.

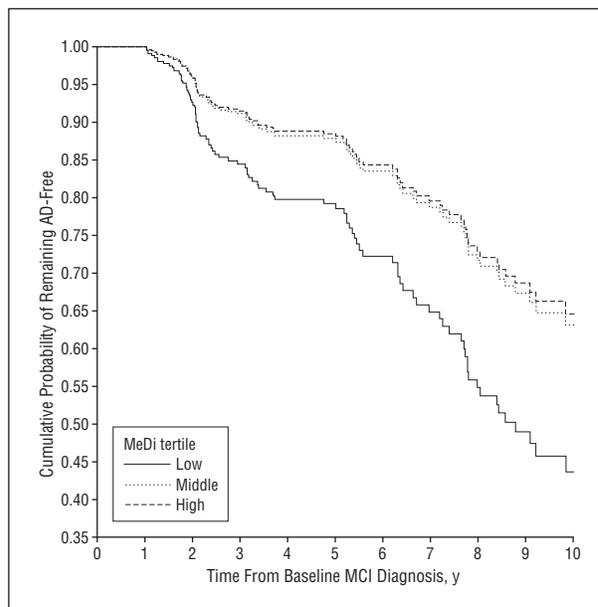
<sup>a</sup>A total of 482 subjects had mild cognitive impairment at the first evaluation; 106 subjects developed incident Alzheimer disease.

<sup>b</sup>A total of 409 subjects had mild cognitive impairment at the first evaluation; 96 subjects developed incident Alzheimer disease. Adjusted models include a slightly lower number of subjects because of missing data in some of the covariates; they simultaneously control for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment.

compared with subjects who had MCI without memory impairment in the lowest MeDi adherence tertile, those who had MCI without memory impairment in the middle tertile had an HR of 0.49 (95% CI, 0.24-1.01;  $P = .05$ ) for developing AD and those who had MCI without memory impairment in the highest tertile had an HR of 0.25 (95% CI, 0.10-0.63;  $P = .003$ ). The overall MeDi HR trend was 0.50 (95% CI, 0.35-0.79;  $P$  for trend = .003).

#### SUPPLEMENTARY ANALYSES

Considering the possibility of an overall healthier lifestyle behavior accounting for the MeDi effect, we considered a measure of overall comorbidity in the analyses: a modified version<sup>33,34</sup> of the Charlson Index of Comorbidity.<sup>35</sup> This measure includes items for myocardial infarct, congestive heart failure, peripheral vascular disease, hypertension, chronic renal disease, chronic obstructive pulmonary disease, arthritis, gastrointestinal disease, mild liver disease, diabetes, and systemic malignant neoplasms. There was no difference in comorbidity index between subjects who remained cognitively normal during follow-up and those who developed MCI during follow-up (1.9 vs 1.9, respectively;  $P = .91$ ) or between those who had MCI at baseline and those who developed AD during follow-up (2.0 vs 2.1, respectively;  $P = .66$ ). Similarly, the comorbidity index did not differ between levels of MeDi adherence: 1.9 for the lowest tertile, 1.9 for the middle tertile, and 1.9 for the highest tertile ( $P = .75$ ). Including the comorbidity index (simultaneously with all of the other covariates) in the incident MCI analyses did not appreciably change the results: the middle MeDi adherence tertile had an HR of 0.83 (95% CI, 0.61-1.12;  $P = .23$ ), the highest tertile had an HR



**Figure 3.** Survival curves based on Cox analysis comparing cumulative Alzheimer disease (AD) incidence in subjects with mild cognitive impairment (MCI) at the first evaluation by Mediterranean diet (MeDi) adherence tertile ( $P$  for trend = .02). The figure is derived from a model that is adjusted for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment. Duration of follow-up is truncated at 10 years. Results of log-rank tests for pairwise comparisons are as follows: middle vs low tertile,  $\chi^2 = 4.26$ ,  $P = .03$ ; low vs high tertile,  $\chi^2 = 1.39$ ,  $P = .23$ ; and middle vs high tertile,  $\chi^2 = 0.12$ ,  $P = .72$ .

of 0.74 (95% CI, 0.53-1.04;  $P = .08$ ), and the overall MeDi tertile HR trend was 0.86 (95% CI, 0.72-1.02;  $P$  for trend = .08). Including the comorbidity index (simultaneously with all of the other covariates) in the incident AD analyses produced similar results: the middle tertile had an HR of 0.59 (95% CI, 0.36-0.97;  $P = .04$ ), the highest tertile had an HR of 0.56 (95% CI, 0.32-0.97;  $P = .04$ ), and the overall MeDi tertile HR trend was 0.74 (95% CI, 0.55-0.98;  $P$  for trend = .04).

In additional supplementary analyses, we used age (rather than duration from cognitive assessment) as the time-to-incident MCI variable. In these analyses, the directionality of the effect was similar but the strength was significantly attenuated: the continuous MeDi HR was 0.94 (95% CI, 0.87-1.0;  $P = .09$ ), the middle MeDi adherence tertile had an HR of 0.91 (95% CI, 0.69-1.19;  $P = .49$ ), the highest tertile had an HR of 0.76 (95% CI, 0.56-1.04;  $P = .09$ ), and the overall MeDi tertile HR trend was 0.87 (95% CI, 0.75-1.02;  $P$  for trend = .09).

#### COMMENT

This study suggests that higher adherence to the MeDi is associated with a borderline reduction in the risk of developing MCI and a reduction in the risk of conversion from MCI to AD. The gradual reduction in risks for higher tertiles of MeDi adherence also suggests a possible dose-response effect. The associations between MeDi and the risk of developing MCI and of MCI conversion to AD did not attenuate even when simultaneously adjusting for many commonly considered potential confounders such as age,

sex, ethnicity, education, *APOE* genotype, caloric intake, and BMI. Adherence to the MeDi did not seem to differentially affect the risk of development of MCI with or without memory impairment. The association between higher adherence to the MeDi and lower risk of conversion to AD was much more prominent for subjects who had MCI without memory impairment.

Higher adherence to the MeDi has been related to lower risk of AD.<sup>4,5</sup> Mild cognitive impairment has been described as a predictor or a transitional stage between normal cognition and AD.<sup>36,37</sup> Thus, we expected that higher adherence to the MeDi would be related to MCI. The association between adherence to the MeDi and MCI incidence was similar for MCI with and without memory impairment, whereas the protective MeDi effect for AD conversion was stronger for subjects who had MCI without memory impairment. Vascular comorbidities, including diabetes, hypertension, dyslipidemia, and white matter abnormalities, have been related to MCI,<sup>38-48</sup> and it has been proposed that nonamnestic MCI in particular may be related to cerebrovascular disease.<sup>36,37,49</sup> There is increasing recognition of vascular comorbidity regarding AD risk,<sup>50,51</sup> and there is strong evidence relating the MeDi to a lower risk of vascular risk factors such as dyslipidemia,<sup>52,53</sup> hypertension,<sup>52-55</sup> and coronary heart disease.<sup>3,33,56,57</sup> Therefore, the stronger effect of the MeDi for non-memory-impaired MCI conversion rates to AD may relate to underlying vascular mechanisms. Nevertheless, nonvascular biological mediating mechanisms (ie, metabolic, oxidative, and inflammatory) may also mediate the epidemiological MeDi-MCI associations.<sup>4</sup>

Both MCI and the MeDi have been associated with metabolic abnormalities. Mild cognitive impairment has been linked to dysregulation of glucose and insulin homeostasis<sup>58-62</sup> and diabetes.<sup>38-42</sup> At the same time, according to the vast majority of the literature (but see the articles by Ambring et al<sup>63</sup> and Michalsen et al<sup>64</sup>), higher adherence to the MeDi seems to improve carbohydrate metabolism, and in interventional studies it has been associated with significant reductions in plasma glucose levels,<sup>53,55</sup> serum insulin levels, and insulin resistance.<sup>55,65</sup>

Oxidative stress could be another biological mechanism relating MCI and the MeDi. Higher oxidative stress has been clearly invoked in MCI.<sup>66-71</sup> Complex phenols and many other substances with important antioxidant properties such as olive oil,<sup>72,73</sup> wine, fruits and vegetables, vitamin C, vitamin E, and carotenoids<sup>74-79</sup> are found in high concentrations in the typical components of the MeDi.<sup>80</sup> Typical Mediterranean meals<sup>81</sup> or meals rich in typical Mediterranean food elements<sup>82,83</sup> have been shown to increase enzymes with antioxidant properties such as paroxonase and plasma carotenoids.<sup>81</sup> Intervention studies with Mediterranean-type foods have indicated significant reductions of markers of oxidative stress such as isoprostanes.<sup>80,84</sup>

Finally, the protective effect of the MeDi for MCI may be mediated via inflammatory pathways. Links between MCI and higher inflammatory states have been demonstrated.<sup>85-89</sup> Two small studies reported no effect of the MeDi on inflammatory markers such as C-reactive protein<sup>63,64</sup> or interleukin 6.<sup>63</sup> Higher adherence to the MeDi has been associated with lower levels of C-reactive pro-

tein in multiple large observational<sup>52,90,91</sup> and interventional<sup>55,81</sup> studies. As another example, tyrosol and caffeic acid, both found in extra-virgin olive oil and wine (which are essential components of the MeDi), have been shown to significantly reduce interleukin 6 production from peripheral blood mononuclear cells of healthy volunteers.<sup>92</sup> Higher adherence to the MeDi has been associated with lower interleukin 6 levels in both observational<sup>52,91</sup> and interventional<sup>55</sup> studies. Higher adherence to the MeDi is in general associated with significant reductions in a series of other inflammatory markers including white blood cell counts and others.<sup>52</sup>

The potentially beneficial effect of the MeDi may be the result of some of its individual food components. For example, potentially beneficial effects for MCI or MCI conversion to AD have been reported for alcohol,<sup>7,11</sup> fish,<sup>10</sup> polyunsaturated fatty acids<sup>10,11</sup> (also for age-related cognitive decline<sup>8</sup>), and lower levels of saturated fatty acids.<sup>10</sup> Interestingly, in other studies, alcohol,<sup>7,12</sup> polyunsaturated fatty acids,<sup>6</sup> or other nutrients such as vitamin E<sup>93,94</sup> have failed to be associated with protection for MCI or MCI conversion to AD. Differences in the definition of the outcome (MCI [objective cognitive cutoffs in different cognitive domains + memory complaint + absence of functional impairment + absence of dementia] vs age-related cognitive decline [only a particular cognitive cutoff on a summary cognitive score such as the Mini-Mental State Examination]) may partly account for the discrepancies. Nevertheless, it is also possible that a composite dietary pattern such as the MeDi may better capture nutritional dimensions that may be missed by single nutrients (ie, potential additive and interactive effects among nutritional components).

Although Hispanic subjects reported higher adherence to the MeDi, they also have higher risks for MCI<sup>14</sup> and AD.<sup>95</sup> A particular ethnic group may have a mixture of multiple protective and risk factors, the overall interaction of which determines the probability of developing a complex disease such as AD. For example, the Hispanic subjects may be placed at risk by their low education and *SORL1* gene status,<sup>96</sup> whereas they may be protected by their dietary habits and lack of a detrimental effect of the *APOE* genotype.<sup>95</sup> At the same time, there may be multiple other genes or behavioral traits unique to the Hispanic subjects that may contribute to AD, resulting in an overall higher risk in this ethnic group.

Study limitations regarding duration of follow-up and demographics of subjects with either missing data for MCI diagnostic assignment or missing follow-up have been discussed in detail in a previous article.<sup>14</sup> Subjects excluded from the present analyses because of missing dietary information had slightly lower cognitive performance, were less educated, and had higher BMIs. Worse cognition and a lower educational level indicate that these subjects were more likely at higher risk for MCI and AD, but a higher BMI indicates the opposite. Most important, these subjects did not differ in most other characteristics. Potential confounding from associations between adherence to the MeDi and total caloric intake or ethnicity was addressed by adjusting for these factors. Limitations relating to the construction of the MeDi score (eg, use of an a priori dietary pattern score, equal weighing of underlying food cat-

egories, and underestimation of total food and caloric intake) have been discussed in detail in previous articles.<sup>4,5</sup> All of the models were adjusted for total caloric intake (largely determined by metabolic efficiency, BMI, and physical activity). Given that metabolic efficiency is unmeasurable and that BMI was included as a covariate, when we adjust for total caloric intake we essentially adjust for physical activity.<sup>30</sup> Nevertheless, we cannot completely exclude the possibility that physical activity may partly account for some of the effect of the MeDi. Although adherence to the MeDi was not related to education or to the overall level of medical comorbidities in our data, it is possible that a better diet is related to higher socioeconomic status or to other habits or characteristics related to better health. Therefore, despite adjusting for multiple variables, the study is observational and we cannot completely exclude residual confounding or “healthy person bias” (that can be addressed only via the randomization of an interventional study). In conservative (for the study size and follow-up) models using age as the timing variable of survival models, the associations were significantly attenuated. Although age was not related to the MeDi, we cannot completely exclude the possibility that the noted associations are confounded by age. Finally, because the current study started before the concept of MCI was developed, diagnosis of MCI was retrospectively applied in data that had already been collected (rather than being applied synchronously with the diagnostic consensus conference).

Because of the synchronous timing of dietary and cognitive assessments and the relatively short follow-up, we cannot completely exclude reverse causation (ie, dietary habits being affected by cognitive status rather than the opposite). Nevertheless, in 2 previous articles<sup>4,5</sup> using a subset of 390 subjects with repeated (2-4) dietary assessments over a course of approximately 8 (and up to 13) years, we demonstrated that adherence to the MeDi is remarkably stable over time. Therefore, we consider it more likely that the reported MeDi adherence reflects our population’s longstanding dietary habits. Finally, because this is the first study to our knowledge demonstrating an association between the MeDi and MCI, replication in other populations is necessary.

Confidence in our findings is strengthened by the following factors. The study is community-based and the population is multiethnic, increasing the external validity of the findings. Dietary data were collected with an instrument that has been previously validated and has been used widely in epidemiological studies. The diagnosis of MCI and AD took place in a university hospital with expertise in such disorders and was based on comprehensive assessments and standard research criteria. The patients were followed up prospectively at relatively short intervals. Measures for multiple potential confounders were carefully recorded and adjusted for in the analyses.

Overall, the effects of dietary habits in MCI have not been adequately explored. These results provide support that MeDi-type habits may affect risk for both developing MCI and MCI conversion to AD. Possible biological mechanisms underlying this association remain to be investigated. Exploration of such mechanisms and potential future interventional studies will provide a more

complete and convincing picture of the conceivably important role of a healthy diet in the risk of cognitive impairment and AD.

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