Published in final edited form as:
Arch Neurol. 2009 February ; 66(2): 216–225. doi:10.1001/archneurol.2008.536.

Mediterranean Diet and Mild Cognitive Impairment

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Abstract

Background—Higher adherence to the Mediterranean diet (MeDi) may protect from Alzheimer's disease (AD) but its association with Mild Cognitive Impairment (MCI) has not been explored.

Objective—To investigate the association between MeDi and MCI.

Design, Setting, Patients, Outcomes—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 higher adherence) and (1) incidence of MCI and (2) progression from MCI to AD. All models were adjusted for cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, body mass index and time duration between baseline dietary assessment and baseline diagnosis.

Results—There were 1393 cognitively normal participants, 275 of whom developed MCI during 4.5 (± 2.7, 0.9–16.4) years of follow-up. Compared to subjects in the lowest MeDi adherence tertile, subjects in the middle MeDi tertile had 17 % (HR, 0.83; 95% CI, 0.62 – 1.12; p=0.24) less risk of developing MCI, while those at the highest MeDi adherence tertile had 28 % (HR, 0.72; 95% CI, 0.52 – 1.00; p=0.05) less risk of developing MCI (trend HR, 0.85; 95% CI, 0.72 – 1.00; p for trend= 0.05). There were 482 subjects with MCI, 106 of whom developed AD during 4.3 (± 2.7, 1.0 – 13.8) years of follow-up. Compared to subjects in the lowest MeDi adherence tertile, subjects in the middle MeDi adherence tertile had 45 % (HR, 0.55; 95% CI, 0.34 – 0.90; p=0.01) less risk of developing AD, while those at the highest MeDi adherence tertile had 48 % (HR, 0.52; 95% CI, 0.30 – 0.91; p=0.02) less risk of developing AD (trend HR, 0.71; 95% CI, 0.53 – 0.95; p for trend= 0.02).

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

The concept of MCI was developed in order to capture subjects who are in the transitional stage between normal aging and dementia or AD. Because of the high conversion rates, MCI subjects 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 causation and prevention of AD. However, epidemiological data on diet and AD have been conflicting [1, 2]. Moreover, there is

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Disclosure: The authors report no conflicts of interest.

paucity of research on the effect of dietary factors on either rates of development of MCI or on rates of MCI conversion to AD.

We recently demonstrated that higher adherence to the MeDi (a diet characterized by high intake of fish, vegetables, legumes, fruits, cereals, unsaturated fatty acids [mostly in the form of olive oil], low intake of dairy products, meat, saturated fatty acids and a regular but moderate amount of ethanol [3]) is associated with lower AD risk [4, 5]. Some studies have investigated the effect of some individual elements of the MeDi (i.e. alcohol, fatty acids, fish) in MCI and age-related cognitive decline[6–12] with conflicting results. Nevertheless, potential associations between the whole MeDi pattern and MCI has not been explored. We examined the association between 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 lower risk for future development of MCI and that MCI participants with higher MeDi adherence would have lower risk for developing future AD.

SUBJECTS AND METHODS

Sample and diagnoses

The sample for the current study has been described in detail in recent studies describing frequency and course of MCI in our cohorts [13, 14]. The study included participants of 2 related cohorts recruited in 1992 (WHICAP 1992) and 1999 (WHICAP 1999) which 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 [15]. 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 charts, CTs or MRIs) 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 [16, 17]. The neuropsychological battery [18] contained tests of memory (short and long-term verbal and nonverbal); orientation; abstract reasoning (verbal and non-verbal); language (naming, verbal fluency, comprehension and repetition); and construction (copying and matching). A global summary score on the Clinical Dementia Rating (CDR) [19] 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 above), 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 (DSM-III-R). 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's Disease and Related Disorders Association [20] 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 MCI definition have been previously provided [13, 14]. Briefly, consistent with standard criteria [21], those considered for MCI were required to have following. First, a subjective

memory complaint (using items from the Disability and Functional Limitations Scale [16, 17], and the Blessed Functional Activities Scale [22]). Second, objective impairment in at least one cognitive domain. Using selected items from the neuropsychological battery, 4 cognitive domains (memory, executive, language, and visuospatial) were defined [13, 14]. 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, essentially preserved activities of daily living (defined above). Fourth, no diagnosis of dementia at the consensus conference. In order to further explore the association of MeDi to MCI, in the view of the original Petersen criteria [21, 23] (which focus on objective memory impairment), the overall MCI group was divided into two mutually exclusive MCI subtypes: (i) MCI with objective memory impairment (with or without objective impairment in other cognitive domains) and MCI without objective memory impairment (objective impairment in at least one of the three non-memory domains but 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 at intervals of approximately 1.5 years, repeating the baseline examination and consensus diagnosis at each follow-up.

Evaluation

Predictors

Diet: Dietary data regarding average food consumption over the past year were obtained using a 61-item version of Willett's semi-quantitative food frequency questionnaire (SFFQ) (Channing Laboratory, Cambridge, MA) [24]. Trained interviewers administered the SFFQ 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 SSFQ in WHICAP [25–27].

Similarly to our previous work [4, 5, 28], we followed a method previously described [3] for the construction of the MeDi score. More specifically, we first regressed caloric intake (kcal) and calculated the derived residuals of daily gram intake [29] for each of the following seven categories [3]: dairy, meat, fruits, vegetables, legumes, cereals and fish. A value of 0 or 1 was assigned to each of the seven above groups, using sex-specific medians as cut-offs. 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 was 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 was assigned a value of 0. For fat intake (8^{th} food category) we used the ratio of daily consumption (in grams) of monounsaturated lipids to saturated lipids [3] (again using sex-specific median cutoffs for assignment values of 0 for low and 1 for high). For alcohol intake (9^{th} food category), subjects were assigned a score of 0 for either no (0 g/day) or more than moderate (≥30 g/day) consumption, and a value of 1 for mild-moderate alcohol consumption (>0 to <30 g/day). This is in agreement with previous reports [3], that consider moderate amount of alcohol consumption as another characteristic component of the MeDi. We classified alcohol consumption dichotomously, also because of the skewed distribution of alcohol in our population (68% reporting no alcohol intake, 31% reporting less than 30 gm/day [mild to moderate intake], and 1% reporting ≥30 g/day [heavy intake]). The MeDi score was generated for each participant by adding the scores in the food categories (theoretically ranging 0–9) with higher score indicating higher adherence to the MeDi.

We used 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

partially based on availability of neuropsychological assessment their ascertainment was not always synchronous with the dietary assessments. For the incident MCI analyses, the time of 1st dietary assessment coincided (+/− 1.5 years) with the time of 1st assessment of cognitively normal status for 82% of the subjects, was performed more than 1.5 years earlier for 14% of the subjects and more than 1.5 years later for only 4%. For the incident AD analyses the time of 1st dietary assessment coincided (+/− 1.5 years) with the time of 1st assessment of MCI status for 84% of the subjects, was performed more than 1.5 years earlier for 11% of the subjects and more than 1.5 years later for only 5%. Summarizing, the timing of MeDi adherence assessment and cognitively normal/MCI assessments overlapped to a significant degree. Despite the above, in all survival models we included a term adjusting for the difference in time between 1st diet and 1st cognitive status assessment.

Covariates: Age (years), education (years), caloric intake (kcal), and body mass index (BMI; weight in kilograms divided by height in square meters [kg/m^2]) [30] were used as continuous variables. We also considered cohort (1992 cohort as reference), and gender (men as reference). Ethnic group was based on self-report using the format of the 1990 census [31]. Participants were then assigned to one of four 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 (APOE) genotype was used dichotomously: absence of ε4 allele vs. presence of either one or two ε4 alleles.

Statistical analyses—Baseline characteristics of subjects by missing dietary data, by outcome of interest and by MeDi tertiles were compared using t-test or ANOVA for continuous variables and χ^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 time from 1st cognitive normal status to 1st visit of MCI diagnosis. Subjects diagnosed with MCI and then reverting back to normal were considered cases and their 1st MCI diagnostic visit was considered the event visit. Persons who did not develop MCI were censored at the time of their last follow-up (i.e. all subject-visits before the last follow-up were used in the analyses). The main predictor was MeDi score (from the 1st dietary evaluation) as a continuous variable initially and in tertiles form subsequently (used for trend test calculation). We simultaneously adjusted for the following variables: cohort, age at intake in the study, gender, ethnicity, education, APOE, BMI and time between 1st dietary and 1st 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 Willet et al.[29]). All predictors were used as time-constant covariates. In additional analyses we recalculated the models using the two different types of MCI as the outcomes: MCI with and MCI 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 time from 1st MCI status to 1st visit of AD diagnosis. Subjects diagnosed with AD and then reverting back to MCI, were considered cases and their 1st 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 (i.e. all subject-visits before the last follow-up were used in the analyses). Predictors and covariates were the same as in the 'cognitively normal to incident MCI' models described above. In additional analyses we recalculated the models using the two different types of MCI (with and without memory impairment) as the starting point.

RESULTS

Missing data analyses

Among all potential participants in both WHICAP cohorts, 2364 individuals were considered for the present study because of sufficient data for MCI diagnosis and available follow-up [14] (figure 1). In comparison to 1329 subjects who were not considered because of missing data or lack of follow-up, these 2364 subjects were slightly younger, more likely to be women, had higher cognitive performance, while they did not differ in ethnicity. The above have been previously reported in detail [14]. Among the 2364 subjects, 1800 were cognitively normal (non-demented, non-MCI) at initial evaluation (serving for calculation of the effect of MeDi on incidence of MCI) and 564 were diagnosed with MCI at initial evaluation (serving for calculation of the effect of MeDi on MCI conversion to AD).

Cognitively normal to incident MCI analyses (figure 1)—Among the 1800 subjects who were cognitively normal at initial evaluation dietary information was missing for 184 (partially because the dietary assessment component was added after initiation of the study). In order 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 rating of CDR = 0.5 at the 1st evaluation. Compared to the 184 subjects with missing dietary information, the 1393 cognitively normal subjects (with CDR=0 and available dietary information) used for the incident MCI analyses had lower BMI (27.5 vs. 28.5; p=0.02) and borderline higher cognitive performance (composite cognitive z-score 0.46 vs. 0.37; p=0.05). The groups did not differ in gender, age, ethnicity, education, or APOE status. As expected, compared to the 223 subjects with CDR=0.5, the 1393 cognitively normal subjects (with CDR=0 and available dietary information) used for the incident MCI analyses were younger (76.7 vs. 79.0; p<0.001), more educated (10.8 vs. 6.8 years; p<0.001), had higher cognitive performance (composite cognitive z-score 0.46 vs. −0.46; p<0.001) and were more likely to be Whites (31% vs. 11%) and less likely to be Hispanics (34% vs. 60%; p<0.001). The groups did not differ in gender, bmi, or APOE status.

MCI to incident AD analyses (figure 1)—Compared to the 82 MCI subjects with missing dietary information, the 482 MCI subjects with available dietary information used included for the incident AD analyses had borderline higher education (9.1 vs. 8.0 years of school; p=0.05) and borderline higher cognitive performance (composite cognitive z-score −0.27 vs. −0.40; p=0.05). The groups did not differ in gender, age, ethnicity, APOE status or BMI.

Clinical-demographic-dietary characteristics

At 1st evaluation, compared with subjects who were cognitively normal, MCI subjects were older, less educated, more likely to be Hispanic and less likely to be White (table 1). Cognitively normal and MCI subjects did not differ in gender, APOE genotype, BMI, total caloric intake and MeDi adherence.

Hispanics adhered more to the MeDi, Blacks less, while Whites were in between (table 2). The higher the MeDi adherence the lower the total caloric intake. There was no association between MeDi score and age, gender, education, APOE genotype or BMI.

MeDi and risk for incident MCI

Despite somewhat lower scores in MCI subjects (as compared to cognitively normal) at baseline (table 1) the groups did not significantly differ cross-sectionally. Longitudinal analyses (particularly with use of survival models) is a much more powerful method of detecting predictor differences since they can combine in a single statistic two different risk

dimensions: (i) proportion of subjects who reach an event (convert to MCI or AD) and (ii) time duration (how soon subjects convert or non-convert to MCI or AD).

Subjects who were cognitively normal at 1st evaluation were followed (until MCI incidence or last follow-up for subjects who remained cognitively normal) for an average of 4.5 (± 2.7, 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% (p=0.04) less risk of developing MCI. Compared to subjects in the lowest MeDi adherence tertile, subjects in the middle MeDi tertile had 17 % (p = 0.24) less risk of developing MCI, while those at the highest tertile (high adherence to the MeDi) had 28 % (p = 0.05) less risk 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 MeDi on development of different MCI subtypes is subject to power limitations, but it is still worth exploring. Overall 108 subjects developed incident MCI with memory impairment. In fully adjusted models, as compared to subjects in the lowest MeDi tertile, those in the middle MeDi tertile had a HR 0.90 (95% CI; 0.57 – 1.40; p = 0.64) for developing MCI with memory impairment, while those at the highest MeDi tertile had a HR 0.71 (95% CI: 0.43 – 1.17; p = 0.18). The overall MeDi HR trend was 0.84 (0.66 – 1.03); p for trend 0.18. MCI without memory impairment was developed by 133 subjects. In fully adjusted models, as compared to subjects in the lowest MeDi tertile, those in the middle MeDi tertile had a HR 0.79 (95% CI; 0.53 – 1.19; p = 0.27) for developing MCI without memory impairment, while those at the highest MeDi tertile had a HR 0.71 (95% CI: 0.46 – 1.12; p = 0.14). The overall MeDi HR trend was 0.84 (0.67 – 1.05); p for trend 0.13.

MeDi and Risk for MCI conversion to AD

Subjects with MCI at 1st evaluation were followed (until AD incidence or last follow-up for subjects who did not develop AD) for an average of 4.3 (± 2.7, 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% (p=0.09) less risk of developing AD. Compared to subjects in the lowest MeDi adherence tertile, subjects in the middle MeDi tertile had 45 % (p = 0.01) less risk of developing AD, while those at the highest tertile (high adherence to the MeDi) had 48 % (p = 0.02) less risk 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 1st evaluation 175 subjects had MCI with memory impairment and 49 of them developed AD at follow-up. In fully adjusted models, as compared to MCI subjects with memory impairment belonging to the lowest MeDi tertile, MCI subjects with memory impairment in the middle MeDi tertile had a HR 0.48 (95% CI; 0.22 – 1.04; p = 0.06) for developing AD, while those MCI subjects with memory impairment at the highest MeDi tertile had a HR 0.71 (95% CI: 0.32 – 1.59; p = 0.41). The overall MeDi HR trend was 0.84 (0.55 – 1.29) p for trend 0.45. At 1st evaluation 234 subjects had MCI without memory impairment and 47 of them developed AD at follow-up. In fully adjusted models, as compared to MCI subjects without memory impairment belonging to the lowest MeDi tertile, MCI subjects without memory impairment in the middle MeDi tertile had a HR 0.49 (95% CI; 0.24 – 1.01; p = 0.05) for developing AD, while those MCI subjects without memory impairment at the highest MeDi

tertile had a HR 0.25 (95% CI: 0.10 – 0.63; p = 0.003). The overall MeDi HR trend was 0.50 (0.35 – 0.79); p for trend 0.003.

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[32, 33] of the Charlson Index of Comorbidity [34]. 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 malignancy. There was no difference in comorbidities between subjects who remained cognitively normal during follow-up and those who developed MCI during follow-up (1.9 vs. 1.9; p = 0.91) or between those who had MCI at baseline and those who developed AD during follow-up (2.0 vs. 2.1; p = 0.66). Similarly, the comorbidity index did not differ among different levels of MeDi adherence: 1.9 for lowest, 1.9 for middle and 1.9 for highest adherence tertiles; p = 0.75). Including the comorbidity index (simultaneously with all the other covariates) in the incident MCI analyses did not appreciably change the results: middle MeDi adherence tertile HR 0.83 [0.61–1.12], p=0.23; highest tertile HR 0.74 [0.53–1.04], p=0.08; overall MeDi tertile HR trend 0.86 [0.72–1.02], p for trend=0.08. Including the comorbidity index (simultaneously with all the other covariates) in the incident AD analyses produced similar results: middle tertile HR 0.59 [0.36–0.97], p=0.04, highest tertile HR 0.56 [0.32–0.97], p=0.04; overall MeDi tertile HR trend 0.74 [0.55–0.98], p for trend=0.04.

In additional supplementary analyses we used age (rather than duration from cognitive assessment) as the time-to-event variable. In these analyses the directionality of the effect was similar but the strength was significantly attenuated: incident MCI HR MeDi continuous 0.94 [0.87–1.0], p=0.09; MeDi middle tertile 0.91 [0.69–1.19], p=0.49; MeDi highest tertile 0.76 [0.56–1.04], p=0.09; MeDi tertile trend 0.87 [0.75–1.02], p for trend=0.09.

DISCUSSION

This study suggests that higher adherence to the MeDi is associated with (i) a borderline reduction in risk for developing MCI and (ii) a reduction in risk for 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 risk for development of MCI and of MCI conversion to AD did not attenuate even when simultaneously adjusting for many commonly considered potential confounders, such as age, gender, ethnicity, education, APOE genotype, caloric intake and BMI. Adherence to MeDi did not seem to differentially affect risk for development of MCI with or without memory impairment. The association between higher adherence to the MeDi and lower risk for conversion to AD was much more prominent for MCI subjects without memory impairment.

Higher adherence to the MeDi has been related to lower risk for AD [4, 5]. MCI has been described as a predictor or a transitional stage between normal cognition and AD [35, 36]. Thus, we expected that higher adherence to the MeDi would be related to MCI. The association between MeDi and MCI incidence was similar for MCI with and without memory impairment, while the protective MeDi effect for AD conversion was stronger for MCI subjects without memory impairment. Vascular comorbidity, including diabetes, hypertension, dyslipidemia and white matter abnormalities have been related to MCI [37–47] and it has been proposed that non-amnestic MCI in particular may be related to cerebrovascular disease [35, 36, 48]. There is an increasing recognition of vascular comorbidity regarding AD risk [49, 50] and there is strong evidence relating the MeDi to lower risk of vascular risk factors such as dyslipidemia [51, 52], hypertension [51–54] and coronary heart disease [3, 52, 55, 56]. Therefore the stronger effect of

the MeDi for non-memory MCI conversion rates to AD may relate to underlying vascular mechanisms. Nevertheless, non-vascular biological mediating mechanisms (i.e. metabolic, oxidative and inflammatory) may also potentially mediate the epidemiological MeDi MCI associations[4].

Both MCI and the MeDi have been associated with metabolic abnormalities. MCI has been linked to dysregulation of glucose and insulin homeostasis [57–61] and diabetes [37–41]. At the same time, according to the vast majority of the literature (but see [62, 63]), higher adherence to the MeDi seems to improve carbohydrate metabolism and in interventional studies it has been associated with significant reductions in plasma glucose [52, 54], serum insulin and insulin resistance [54, 64].

Oxidative stress could be another biological mechanisms relating MCI and the MeDi. Higher oxidative stress has been clearly invoked in MCI [65–70]. Complex phenols and many other substances with important antioxidant properties such as olive oil [71, 72], wine, fruits and vegetables, vitamins C, E and carotenoids [73–78] are found in high concentrations in the typical components of the MeDi [79]. Typical Mediterranean meals [80] or meals rich in typical Mediterranean food elements [81, 82] have been shown to increase enzymes with antioxidant properties such as paroxonase and plasma carotenoids [80]. Intervention studies with Mediterranean-type foods, have indicated significant reductions of markers of oxidative stress, such as isoprostanes [79, 83].

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 [84–88]. Two small studies reported no effect of MeDi on inflammatory markers such as CRP [62, 63] or IL-6 [62]. Higher adherence to the MeDi has been associated with lower CRP in multiple large both observational [51, 89, 90] and interventional [54, 80] studies. As another example, tyrosol and caffeic acid, both found in extra virgin olive oil and in wine, (which are essential components of the MeDi), have been shown to significantly reduce IL-6 production from peripheral blood mononuclear cells of healthy volunteers [91]. Higher adherence to the MeDi has been associated with lower IL-6 levels in both observational [5190] and interventional [54] studies. Higher adherence to the MeDi is in general associated with significant reduction in a series of other inflammatory markers including white blood cell counts etc [51].

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 [7, 11], fish [10], PUFA [10, 11] (also for age-related cognitive decline [8]), and lower SFA [10]. Interestingly, in other studies alcohol [7, 12], PUFA [6] or other nutrients such as vitamin E [92, 93] 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 MMSE]) may partially 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 (i.e. potential additive and interactive effects among nutritional components).

Although Hispanics reported higher adherence to the MeDi they also have higher risk for MCI [14] and AD [94]. A particular ethnic group may have a mixture of multiple protective and risk factors, the overall interaction of which determine the probability of developing a complex disease, such as AD. For example, the Hispanics may be placed at risk by their low education and by their SORL1 gene status [95], while they may be protected by their dietary habits and by the lack of detrimental effect of the APOE genotype [94]. At the same time there may be multiple

other genes or behavioral traits unique to the Hispanics that may contribute to AD, resulting in an overall higher risk in this ethnic group.

Study limitations regarding duration of follow-up, demographics of subjects with either missing data for MCI diagnostic assignment or missing follow-up have been discussed in detail in a previous publication [14]. Subjects excluded from the present analyses because of missing dietary information had slightly lower cognitive performance, were less educated and had higher BMI. Worse cognition and lower educational level indicate that these subjects were more likely at higher risk for MCI and AD, but 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 (i.e. use of an a priori dietary pattern score, equal weighing of underlying food categories, underestimation of total food and caloric intake etc) have been discussed in detail in previous publications [4, 5]. All models were adjusted for total caloric intake (largely determined by (i) metabolic efficiency, (ii) BMI and (iii) 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[29]. Nevertheless, we cannot completely exclude the possibility that physical activity may partially account for some of the MeDi's effect. Although adherence to the MeDi was not related to education or to 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 only addressed 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 MeDi we cannot completely exclude the possibility that the noted associations are confounded by age. Finally, because the current study had started before the concept of MCI was developed, diagnosis of MCI was retrospectively applied in already collected data (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 (i.e. dietary habits being affected by cognitive status rather than the opposite). Nevertheless, in two previous publications, using a subset of 390 subjects with repeated (2 – 4) dietary assessments over a course of ~8 (and up to 13) years, we demonstrated that adherence to the MeDi is remarkably stable over time [4, 5]. Therefore, we consider it more likely that the MeDi adherence reported reflects our population's longstanding dietary habits. Finally, since this is the 1st study 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 assessment and standard research criteria. The patients were followed 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 for MCI conversion to AD. Possible biological mechanisms underlying this association remain to be

explored. 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 risk of cognitive impairment and AD.

Acknowledgements

Federal NIA grants AG028506, P01-AG07232, RR00645.

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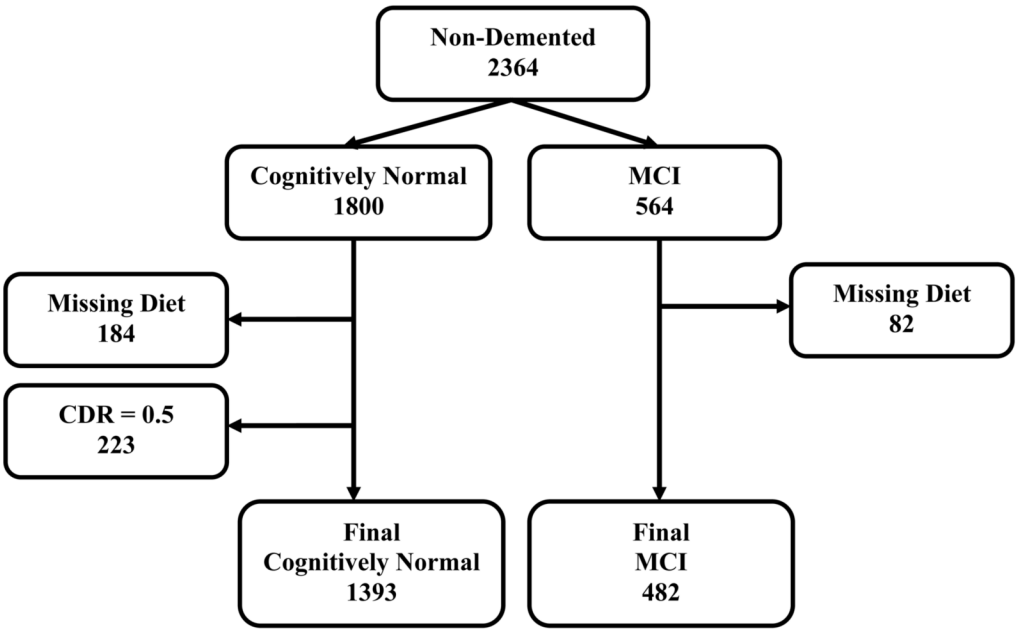

Figure 1.
Flow chart describing sample size.

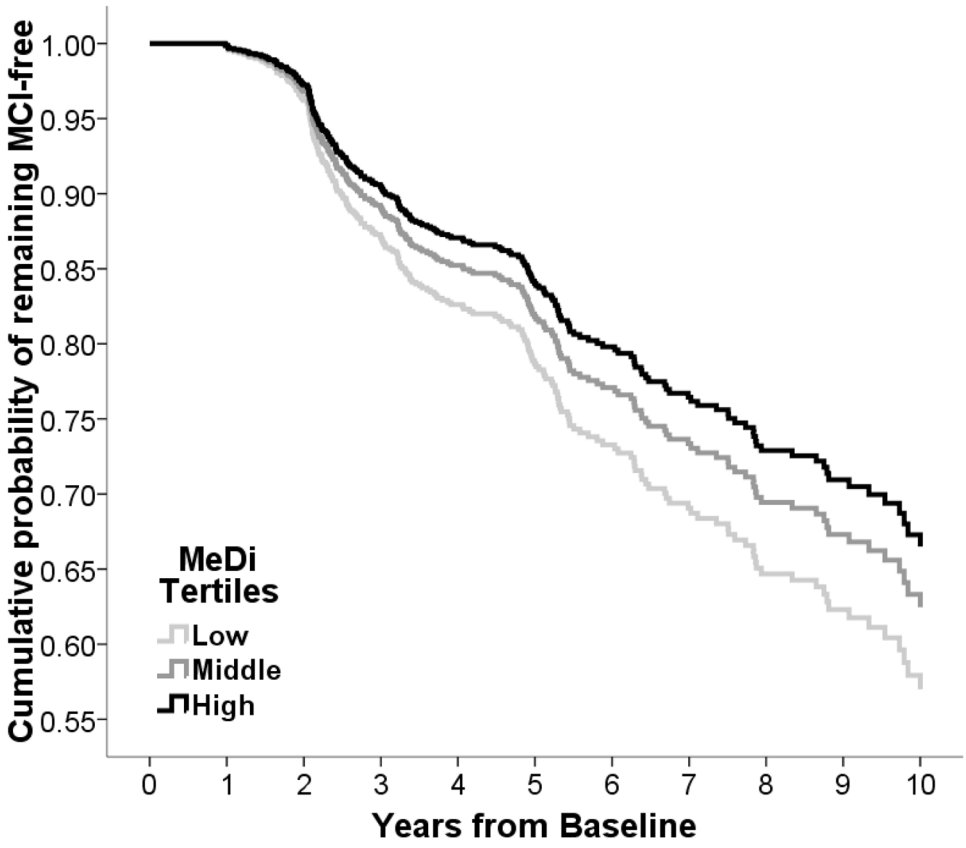

Figure 2.

Survival curves based on Cox analysis comparing cumulative MCI incidence in subjects cognitively normal at 1st evaluation by each Mediterranean diet (MeDi) tertile (p for trend 0.05). The figure is derived from a model that is adjusted for cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, body mass index and time between 1st dietary and 1st cognitive assessment. Duration of follow-up is truncated at 10 years. Log-rank test for pair-wise comparisons: middle vs. low MeDi tertile $x^2 = 0.91$, $p = 0.33$, low vs. high MeDi tertile $x^2 = 3.72$, $p = 0.05$, middle vs. high $x^2 = 1.22$, $p = 0.26$.

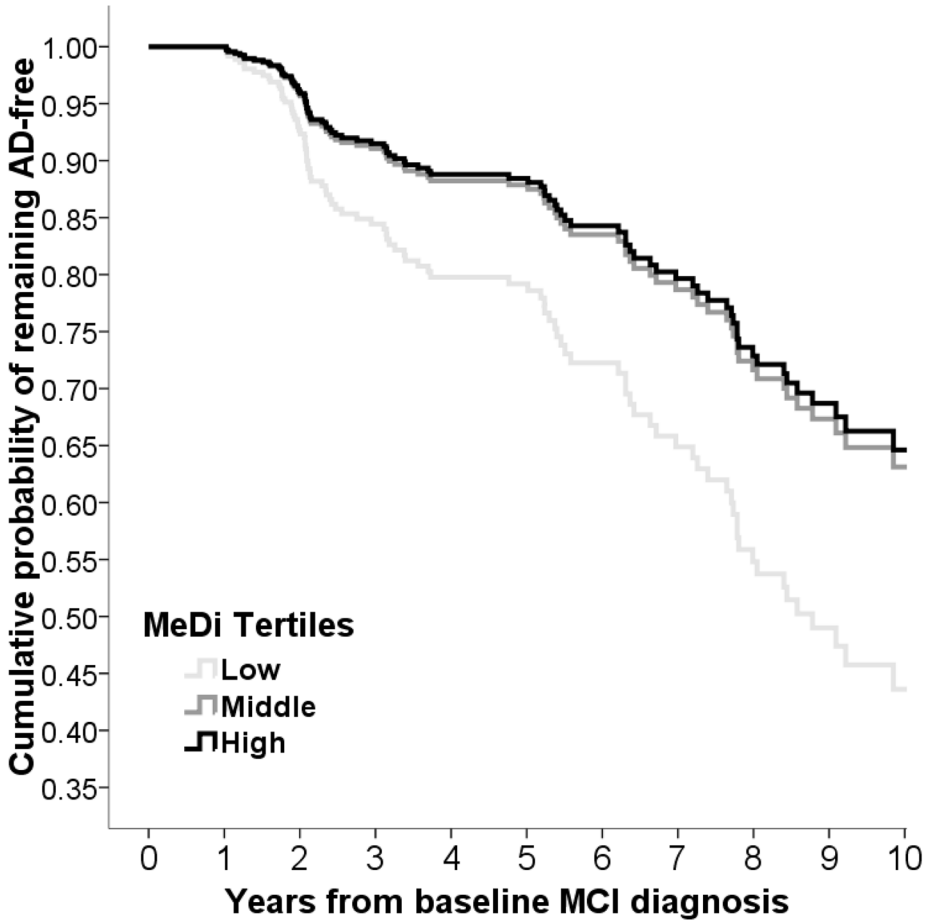

Figure 3.

Survival curves based on Cox analysis comparing cumulative AD incidence in subjects with MCI at 1st evaluation by Mediterranean diet (MeDi) tertile (p for trend 0.02). The figure is derived from a model that is adjusted for cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, body mass index and time between 1st dietary and 1st cognitive assessment. Duration of follow-up is truncated at 10 years. Log-rank test for pair-wise comparisons was as follows: middle vs. low MeDi tertile $x^2 = 4.2$, $p = 0.03$, low vs. high MeDi tertile $x^2 = 1.3$, $p = 0.23$, middle vs. high $x^2 = 0.12$, $p = 0.72$.

Table 1

Demographic and clinical characteristics during 1st evaluation for all subjects.

	Cognitively Normal N = 1393	MCI N = 482	All N = 1875	P
Gender-Men N (%)	447 (32)	156 (32)	603 (32)	0.91
Age yrs, mean (SD)	76.7 (6.48)	77.5 (6.58)	76.9 (6.5)	**0.02**
Ethnicity, N (%) White	434 (31)	124 (26)	558 (30)	<**0.001**
Black	479 (34)	144 (30)	623 (33)	
Hispanic	473 (34)	214 (44)	687 (36)	
Other	7 (1)	0 (0)	7 (1)	
Education yrs, mean (SD)	10.8 (4.6)	9.1 (4.9)	10.4 (4.7)	<**0.001**
At least 1 ε4, N (%)	327 (27)	127 (30)	454 (28)	0.18
BMI, mean (SD)	27.5 (5.49)	27.2 (5.28)	27.4 (5.4)	0.34
Energy (kcal), mean (SD)	1426.1 (498.0)	1421.8 (591.9)	1425.0 (523.6)	0.88
MeDi Score, mean (SD)	4.37 (1.69)	4.31 (1.62)	4.36 (1.67)	0.47

Table 2

Demographic and clinical characteristics during 1st evaluation for all subjects by MeDi tertiles.

	Low MeDi N = 609	Middle MeDi N = 775	High MeDi N = 491	P
Gender-Men N (%)	442 (69)	532 (69)	318 (65)	0.23
Age yrs, mean (SD)	76.9 (6.6)	76.8 (6.5)	77.2 (6.2)	0.48
Ethnicity, N (%) White	182 (30)	223 (29)	153 (31)	**0.001**
Black	234 (38)	260 (33)	139 (26)	
Hispanic	190 (31)	289 (37)	208 (42)	
Other	3 (1)	3 (1)	1 (1)	
At least 1 ε4, N (%)	146 (27)	179 (27)	129 (29)	0.70
Education yrs, mean (SD)	10.5 (4.5)	10.3 (4.7)	10.4 (4.9)	0.77
BMI, mean (SD)	27.7 (5.8)	27.4 (5.2)	27.1 (5.3)	0.19
Energy (kcal), mean (SD)	1494.9 (608.2)*	1395.4 (472.5)*	1385.1 (477.4)*	**<0.001**

*p<0.05 for all MeDi tertiles according to post-hoc Scheffe's test.

Table 3

Cox Proportional Hazard Ratios for incidence of MCI for subjects cognitively normal at 1st evaluation by MeDi score. Adjusted models include slightly lower number of subjects because of missing data in some of the covariates. Adjusted models simultaneously control for cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, body mass index and time between 1st dietary and 1st cognitive assessment.

Predictor	HR	95 % CI		P
Unadjusted: Cognitively Normal 1st evaluation (N = 1393) Incident MCI (N = 275)				
MeDi continuous	0.93	0.87	1.00	0.06
Low MeDi tertile	1 (ref)	-	-	-
Middle MeDi tertile	0.87	0.66	1.14	0.33
High MeDi tertile	0.73	0.53	1.00	0.05
MeDi tertile trend	0.85	0.73	1.00	0.05
Adjusted: Cognitively Normal 1st evaluation (N = 1199) Incident MCI (N = 241)				
MeDi continuous	0.92	0.85	0.99	0.04
Low MeDi tertile	1 (ref)	-	-	-
Middle MeDi tertile	0.83	0.62	1.12	0.24
High MeDi tertile	0.72	0.52	1.00	0.05
MeDi tertile trend	0.85	0.72	1.00	0.05

Table 4

Cox Proportional Hazard Ratios for incidence of AD for subjects with MCI at the 1st evaluation by MeDi score. Adjusted models include slightly lower number of subjects because of missing data in some of the covariates. Adjusted models simultaneously control for cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, body mass index and time between 1st dietary and 1st cognitive assessment.

Predictor	HR	95 % CI		P
Unadjusted: MCI 1st evaluation (N = 482) Incident AD (N = 106)				
MeDi continuous	0.95	0.85	1.07	0.48
Low MeDi tertile	1 (ref)	-	-	-
Middle MeDi tertile	0.62	0.39	0.98	0.04
High MeDi tertile	0.69	0.41	1.14	0.15
MeDi tertile trend	0.82	0.63	1.07	0.15
Adjusted: MCI 1st evaluation (N = 409) Incident AD (N = 96)				
MeDi continuous	0.89	0.78	1.02	0.09
Low MeDi tertile	1 (ref)	-	-	-
Middle MeDi tertile	0.55	0.34	0.90	0.01
High MeDi tertile	0.52	0.30	0.91	0.02
MeDi tertile trend	0.71	0.53	0.95	0.02