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Neuroprotective diets are associated with better cognitive function: the Health and Retirement Study

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1 ABSTRACT

Objective: Evidence suggests that adherence to the Mediterranean (MedDiet) or MIND diet is
neuroprotective but the association between these dietary patterns and cognition has not been
evaluated in a nationally representative population of older US adults.

5 **Design:** Population-based cross-sectional study.

6 Participants/setting: Community-dwelling older adults from the Health and Retirement Study (n
7 = 5,907).

8 Measurements: Adherence to dietary patterns was determined from food frequency 9 questionnaires using *a priori* criteria to generate diet scores for MedDiet (range = 0-55) and MIND 10 diet (range 0-15). Cognitive performance was measured using a composite test score of global 11 cognitive function (range 0-27). Linear regression was used to compare cognitive performance 12 across tertiles of dietary pattern. Logistic regression was used to examine the association between 13 dietary patterns and clinically significant cognitive impairment. Models were adjusted for age, 14 gender, race, educational attainment and other health and lifestyle covariates.

Results: Mean age of participants was 68 ± 10.8 years. Compared to those with low MedDiet score, participants with mid and high score were less likely to have poor cognitive performance (OR 0.85; 95% CI 0.71, 1.02: P = 0.08, and OR 0.65; 95% CI: 0.52, 0.81: P < 0.001, respectively) in fully adjusted models. Results for the MIND diet were similar. Higher score in each dietary pattern was independently associated with significantly better cognitive function (P < 0.001) in a dose-response manner (P_{TREND} < 0.001).

Conclusion: In a large nationally representative population of older adults, greater adherence to
the MedDiet and MIND diet was independently associated with better cognitive function and lower
risk of cognitive impairment. Clinical trials are required to elucidate the role of dietary patterns in
cognitive aging.

25 Key words: dietary patterns, cognitive performance.

26 INTRODUCTION

Dementia is a major cause of death and disability in older Americans¹ and there is considerable
interest in identifying lifestyle approaches, such as diet, for prevention of cognitive decline during
aging².

30

The Mediterranean diet (MedDiet), rich in fruit, vegetables, wholegrains, nuts, olive oil and fish, 31 is proven to have vascular³ and anti-inflammatory⁴ benefits and may also be neuroprotective. 32 Greater adherence to the MedDiet is associated with slower rate of cognitive decline⁵⁻⁶, reduced 33 risk of cognitive impairment⁷⁻⁸ and dementia^{5,8} but findings are conflicting⁹⁻¹¹ largely owing to 34 significant heterogeneity between studies in terms of populations studied and methods used to 35 assess diet and cognition. Studies from the US have limited generalizability due to a lack of 36 representative study populations and multiple publications from the same cohorts. Additionally, 37 most prospective studies have used population-specific median food intake thresholds to measure 38 MedDiet adherence and this approach further limits the generalizability and comparability of 39 findings, as similar scores reflect different eating patterns in different cohorts¹². The MedDiet 40 score¹³ is a different approach which uses absolute food intake targets derived from a Greek 41 population and allows for more meaningful comparison between studies. Higher MedDiet score 42 has been associated with slower rate of cognitive decline¹⁴⁻¹⁶ in a small number of studies that have 43 used this dietary assessment method. 44

In summary, evidence to date is suggestive of a neuroprotective role for MedDiet but variation between studies makes it difficult to draw firm conclusions. Further investigation is needed to determine whether the MedDiet represents an optimal dietary pattern for protection against neurodegeneration in representative populations. Another proposed neuroprotective dietary pattern, called MIND (Mediterranean-DASH diet Intervention for Neurodegeneration Delay), has been recently described¹⁶. The MIND diet is a modified version of MedDiet but incorporates additional foods based on current evidence in the diet-dementia field¹⁶. In one population-based study, the MIND score was more predictive of cognitive decline than the MedDiet score¹⁶ and higher MIND score was associated with reduced Alzheimer's disease (AD)¹⁷. While these results in mostly older white females are encouraging, they require confirmation in other populations.

56

We aimed to determine the association between proposed neuroprotective dietary patterns characterized by the MedDiet and MIND scores, and objectively measured cognitive performance in a large sample of older adults from the nationally-representative population-based Health and Retirement Study (HRS).

61

62 METHODS

We used data from the HRS, a longitudinal, nationally representative survey in 30,000 communitydwelling adults aged > 50 years. The HRS commenced in 1992 to collect data on the antecedents and consequences of retirement in US adults and follows approximately 20,000 participants biennially. A detailed description of HRS has been published elsewhere¹⁸. The HRS was approved by the Health Sciences Institutional Review Board at the University of Michigan. All participants provided their consent on enrollment.

69

This present study is a cross-sectional analysis of participants from a core wave 12 survey (2014) 70 who completed the HRS Health Care and Nutrition (HCNS) substudy (n = 8,035). The HCNS diet 71 assessment was conducted between November 2013 and May 2014, and cognitive, demographic 72 and covariate data were drawn from the core 2014 survey. We excluded respondents who required 73 a by-proxy core 2014 interview and those with missing or incomplete cognitive data (n = 981). 74 75 We also excluded those who reported extreme energy intakes outside of predefined levels (<800 or >8000 kcal/d for men and <600 or >6000 kcal/d for women) (n =291) and those who reported 76 dementia or AD (n = 140) or stroke (n = 430), and those with missing covariates (n = 286). After 77 exclusions, the final analytic sample was 5,907 participants. 78

79

80 Dietary assessment

Dietary intake was assessed using a validated 163-item semi-quantitative Harvard Food Frequency Questionnaire (FFQ)^{19,20}. Adherence to MedDiet and MIND dietary patterns was assessed by calculating summary scores using predefined criteria^{13,16} (as shown in Supplementary Table S1 and S2). First, we selected FFQ food item(s) to create dietary components relevant for each dietary pattern. Next, we assigned individual scores for dietary components based on the frequency of
recommended intake servings.

87

88 MedDiet score

MedDiet score¹³ comprises 11 dietary components corresponding to consumption frequency of 89 foods consistent with the traditional MedDiet. Dietary components were scored 0-5 in agreement 90 91 with predefined frequencies of serving for each point value and then summed to obtain a total score 92 ranging from 0 to 55. Scores for dietary components consistent with the MedDiet (nonrefined grains, fruits, vegetables, potatoes, legumes, fish, olive oil) increase as consumption frequency 93 94 increases and scores for food groups not characteristic of a MedDiet (red meat, poultry, full fat dairy products) decrease as consumption frequency increases. Alcohol intake was determined 95 using frequency of alcoholic drinks daily (1 drink equivalent to 150mls; approximately 12g 96 ethanol) and scored nonlinearly, with a score of 0 for no consumption or >4.5 drinks/day through 97 to a maximum score of 5 for up to 2 drinks/day. Overall, higher MedDiet score indicates greater 98 adherence to the traditional MedDiet. 99

100

101 MIND score

102 MIND score¹⁶ consists of 15 dietary components in which 10 are considered brain healthy food 103 groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, 104 poultry, olive oil, and wine) and five are considered unhealthy food groups (red meats, butter and 105 stick margarine, cheese, pastries and sweets, and fried/fast food). Dietary components were scored 106 0, 0.5, or 1 depending on level of consumption. Olive oil use was scored 1 if intake \geq 1 tbsp. daily 107 and 0 otherwise. Scores for the 10 healthy components increased monotonically with higher consumption of reported servings, and scores were reversed for the five unhealthy components.
Dietary component scores were then summed to obtain an overall score ranging from 0-15, where
higher scores indicate greater adherence to the MIND diet.

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112 Cognitive assessment

113 Cognitive performance was assessed by a global cognition score comprising three items: (1) 114 immediate and delayed recall of 10 words from a word list randomly assigned for each participant 115 (0-20 points), (2) backward counting (0-2 points), and, (3) serial seven subtraction (0-5 points)²¹. 116 Possible scores ranged from 0 to 27, with higher scores indicating better overall cognitive function 117 in domains of episodic memory, attention and working memory²². Clinically significant poor 118 cognitive performance was defined as ≥ 1 SD below the mean global cognition score.

119

120 Covariates

Covariates of age, gender and race (white, black or other) were included. We also selected health 121 and lifestyle covariates previously identified as potential modifiable risk factors for cognitive 122 decline and dementia²: smoking, hypertension, diabetes, depression, low educational attainment, 123 physical inactivity and obesity. Depressive symptoms were determined using a Center for 124 Epidemiologic Studies Depression (CES-D8) short form score (score 0-8) with active depression 125 symptoms defined as a CES-D8 cut point of $\geq 4^{23}$. Low educational attainment was classified as 126 127 completing less than high school education and physical inactivity was defined as engaging in vigorous activity less than twice weekly, as used in a previous HRS analysis²⁴. Obesity was defined 128 as a Body Mass Index (BMI) \geq 30 kg/m². 129

130 Statistical analysis

Participant characteristics were compared with tertiles of dietary pattern scores using descriptive 131 statistical tests. Analysis of variance with Bonferroni post hoc comparison was used for continuous 132 variables and chi-square test was used for categorical variables, with corresponding tests for linear 133 trend. Pearson's correlation coefficient was used to examine correlations for continuous variables. 134 A multivariable general linear model was applied to investigate associations between dietary 135 patterns (MedDiet and MIND score modelled in tertiles) and global cognition score. Participants 136 137 in tertile 1 (lowest diet adherence) were the reference group for each analysis. Models were 138 adjusted firstly for classic confounders age, gender, race and educational attainment (less than high school vs high school or more), and subsequently for potential mediators total wealth as a measure 139 140 of socioeconomic status (total assets - total debt), hypertension (Yes/No), diabetes (Yes/No), current smoking (Yes/No), depression (CES-D8 \geq 4), physical inactivity (Yes/No), obesity (BMI 141 \geq 30 vs BMI <30) and total energy intake (kcals/day). The risk of poor cognitive performance 142 143 associated with adherence to each dietary pattern was estimated by using binary logistic regression 144 analyses with corresponding odds ratios (OR) and 95% confidence intervals (CI), adjusted for covariates using the same approach described above. Sensitivity analyses were carried out after 145 removal of individuals classified as demented on the global cognition score. In addition, analyses 146 were repeated after applying a priori defined Greek cut-points to MedDiet tertiles (0-20, 21-35 147 and 36-55). Analyses were performed using SPSS version 22 (IBM SPSS, Chicago, IL). 148

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151 **RESULTS**

The mean (SD) age of the 5, 907 participants was 68 ± 10.8 years at the core 2014 survey. Overall, 152 60% were women and 78% were white. Mean diet score was 27.6 \pm 5.4 for MedDiet and 7.3 \pm 1.8 153 for MIND, indicating moderate adherence for each dietary pattern. Average MedDiet score was 154 similar to that reported in a Greek population 26.3 ± 3.2^{13} . As shown in Table 1, participants with 155 highest MedDiet adherence were younger, more likely to be physically active and less likely to be 156 157 hypertensive, diabetic or obese, with higher educational attainment and fewer reported depressive symptoms, compared with those with lowest adherence. Demographics were similar for MIND, 158 but there was no observed difference in diabetes across tertiles of MIND score. 159

160

Both diet scores were positively correlated (r = 0.68, P < 0.001) and showed a fair level of agreement in the population (Cohen's kappa 0.36, P < 0.001).Weekly servings of wholegrains, vegetables, fruit, fish, nuts and olive oil increased linearly across tertiles for each dietary pattern ($P_{TREND} < 0.001$) with individuals in the high tertile consuming between 2-3 times more than those in the low tertile. Conversely, weekly consumption of red meat decreased linearly across tertiles of diet score ($P_{TREND} < 0.001$).

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Table 2 shows unadjusted and adjusted global cognition score across tertiles of dietary patterns. Compared to participants with mid or low levels of adherence, those with high adherence to MedDiet or MIND had significantly better cognitive performance (P < 0.001 for both dietary patterns). In fully adjusted models, these associations were attenuated but individuals with highest diet adherence had significantly better cognitive scores (by 1.0 and 0.8 points for MedDiet and MIND respectively) than those with mid and low adherence and these associations showed a doseresponse relationship (P_{TREND} < 0.001).

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Impaired cognitive performance, defined as > 1SD (4.3 points) below the mean global cognitive 176 score, was found in 831 (14%) participants. Figure 1 shows the adjusted likelihood of having poor 177 cognitive performance with adherence to the dietary patterns. Compared to participants with low 178 MedDiet score, those with mid score had 15 % lower odds of having poor cognitive performance 179 180 (OR 0.85; 95% CI: 0.71, 1.02: P = 0.08). The association was significantly stronger for those with highest MedDiet score who had 35% lower odds of having poor cognitive performance compared 181 to those with lowest score (OR 0.65; 95% CI: 0.52, 0.81: P < 0.001). Results were similar for 182 individuals with mid and high MIND score (OR 0.85; 95% CI 0.70, 1.03: P =0.10 and OR 0.70; 183 95% CI: 0.56, 0.86: P = 0.001, respectively) when compared to those with low MIND score. In 184 fully adjusted linear models, each 1 SD increase (5.4 units) in MedDiet was associated with 15% 185 lower odds of poor cognitive performance (OR 0.85; 95% CI 0.78, 0.93, P < 0.001) and each 1 SD 186 increase (1.8 units) in MIND diet was associated with 14% lower odds of poor cognitive 187 performance (OR 0.86; 95% CI 0.79, 0.94, P < 0.001). 188

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Analyses were repeated after removing participants with global cognition scores ≤ 6 (n = 143) but no notable changes were found in observed results. We also repeated the analyses using *a priori* defined cut-points for MedDiet tertiles derived from a Greek population¹³ and similar results were observed. In fully adjusted models, individuals in the highest Greek MedDiet tertile had 35% lower odds of cognitive impairment OR 0.65; 95% CI: 0.44, 0.98: P = 0.04) compared with those in the lowest Greek tertile.

196 **DISCUSSION**

In this large general population of community-dwelling older adults, neuroprotective dietary 197 patterns characterized by MedDiet and MIND score were significantly associated with moderately 198 better cognitive performance in a dose-response relationship. Individuals with the highest 199 adherence to neuroprotective diets had a 30-35% lower risk of cognitive impairment defined as > 200 1SD or 4.3 points below the population mean global cognition score. While, the incidence of 201 clinical cognitive impairment on the global cognition score was relatively low (14%) in this 202 203 healthy population, our findings lend support to the hypothesis that diet modification may be an important public health strategy to protect against neurodegeneration during aging. 204

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This study adds to the limited work done to investigate relations between dietary patterns and brain 206 health. Although previous prospective studies examining associations between MedDiet and 207 cognitive outcomes have largely reported contradictory findings, evidence is strengthened by 208 209 recent results from the PREDIMED trial sub-study which demonstrated small but significant improvements in cognitive function in response to increasing MedDiet adherence²⁶. To date, the 210 effects of MIND on cognitive health have not been evaluated, however, greater adherence to 211 MIND is linked with slower rates of cognitive decline¹⁶ and reduced risk of AD¹⁷. These studies 212 have been conducted exclusively in one older, largely female, population from the Rush Memory 213 and Aging Project and require replication in other cohorts. Our findings support a protective 214 215 association of MIND on cognitive performance in a general population.

216

217 MedDiet and MIND have similar dietary profiles and recommend high intakes of plant foods,
218 limited meat consumption, moderate intake of alcohol (wine in particular) and use of olive oil as

a primary fat source. Unique to MIND are green vegetables and berries which are independently 219 reported to offer protection against neurodegeneration¹². In contrast, the MedDiet places greater 220 emphasis on potatoes, fish and overall fruit and vegetable intake. Both dietary patterns are rich in 221 antioxidants, monounsaturated and n-3 fatty acids and low in saturated fat. These individual 222 nutrients have also been independently related to cognitive performance, for example, 223 observational evidence has shown association between monounsaturated fat and n-3 fatty acids 224 and a reduced risk of cognitive decline and dementia^{5,} whereas increased saturated fat intake is 225 shown to increase risk of cognitive decline and dementia²⁷. However, the biological mechanisms 226 for how dietary patterns exert neuroprotective effects are not clear. Several putative mechanisms 227 for the MedDiet have been proposed²⁸, and include beneficial impacts on neuronal cell signalling, 228 vascular, antioxidant and anti-inflammatory biological pathways, but more comprehensive 229 investigation is required. Furthermore, while the MedDiet and the new MIND diet have attracted 230 most attention in the literature, they may not reflect an optimal dietary pattern for protection against 231 232 neurodegeneration during aging.

233

Strengths of this study include its large sample size and community-based population of older 234 adults which increases the external validity of findings. In addition, an extensively validated semi-235 quantitative FFQ was used to assess the dietary exposure. Furthermore, we generated dietary 236 scores based on predefined absolute food intake thresholds and this approach increases the ability 237 to meaningfully compare our findings with studies that employ a similar standardized dietary 238 pattern methodology. A major limitation is the cross-sectional study design meaning we were 239 unable to establish a causal relationship between dietary patterns and cognitive outcomes. In 240 addition, dietary misclassification is possible as individuals may have changed their eating 241

behavior as a result of cognitive impairment or other disease, although in our sensitivity models, removal of those with low cognitive scores did not alter the findings. As with all observational study, residual confounding is a possibility even though we adjusted the analyses for known dietdementia confounders. Finally, the use of a summary cognition score allowed us to examine global cognitive function but not individual cognitive domains which may be differentially influenced by age and lifestyle factors.

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In conclusion, this study shows that greater adherence to MedDiet and MIND dietary patterns are associated with better overall cognitive function in older adults and lower odds of cognitive impairment that could have important public health implications for preservation of cognition during aging. Given the limited evidence base and lack of clear dietary recommendations for cognitive health, further prospective population-based studies and clinical trials are required to elucidate the role of dietary patterns in cognitive aging and brain health.

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256

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Conflict of Interest. The authors have no relevant financial or personal conflicts to declare. Dr.
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a Senate member of the Council of the German Center for Neurodegenerative Diseases.
Author Contributions: CTM, KY: study design. CTM, KY, HG: analysis and data interpretation.

264 CTM, KY, HG, KML: preparation of manuscript.

265

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LEGEND

Figure 1: Adjusted^a Odds Ratios (95% CI) for Poor Cognitive Performance by Mid and High

Tertiles Compared to Low Tertile (reference) of MedDiet and MIND Diet Scores

Supplementary Table S1: Dietary component servings and maximum scores for MedDiet pattern (range 0-55)

Supplementary Table S2: Dietary component servings and maximum scores for MIND dietary pattern (range 0-15)

| | | MedDiet | Score ^a | | MIND Score ^b | | | | |
|---------------------------------|------------------------|---------------------------|-----------------------------|----------------|--------------------------|------------------------------|--------------------------------|----------------|--|
| | Tertile 1 (LOW;≤25) | Tertile 2 (MID; 26-30) | Tertile 3 (HIGH; >30-55) | P for Trend | Tertile 1 (LOW; ≤6.5) | Tertile 2 (MID; >6.5-8.0) | Tertile 3 (HIGH; >8.0-15.0) | P for Trend | |
| n | 2110 | 2064 | 1733 | - | 2219 | 1825 | 1863 | - | |
| Age, mean (SD), y | 68.2 (10.6) | 67.8 (10.4) | 67.1 (10.7) | 0.001 | 68.5 (10.6) | 68.2 (10.6) | 66.5 (10.4) | < 0.001 | |
| Female, n (%) | 1261 (60) | 1215 (59) | 1072 (62) | 0.22 | 1235 (56) | 1067 (59) | 1246 (67) | < 0.001 | |
| Race, n (%) | | | | | | | | | |
| White | 1636 (78) | 1627 (79) | 1326 (77) | 0.004 | 1790 (80) | 1406 (77) | 1393 (75) | 0.004 | |
| Black | 360 (17) | 301 (15) | 233 (13) | < 0.001 | 299 (14) | 298 (16) | 297 (16) | < 0.001 | |
| Other | 114 (5) | 136 (7) | 174 (10) | | 130 (6) | 121 (7) | 173 (9) | | |
| Energy intake, mean (SD), kcals | | | | | | | | | |
| Male | 1940 (862) | 1899 (826) | 2167 (881) | < 0.001 | 1883 (801) | 2008 (889) | 2131 (899) | < 0.001 | |
| Female | 1641 (731) | 1693(762) | 2040 (815) | < 0.001 | 1617 (708) | 1784 (821) | 1935 (798) | < 0.001 | |
| Education less than | 397 (19) | 243 (12) | 195 (11) | < 0.001 | 369 (17) | 270 (15) | 196 (11) | < 0.001 | |
| high school, n (%) | | | | | | | | | |
| Current smoker, n | 332 (16) | 207 (10) | 93 (5) | < 0.001 | 355 (16) | 172 (9) | 105 (6) | < 0.001 | |
| (70) | | | | | | | | | |
| Clinically obese, n (%) | 1029 (49) | 959 (47) | 673 (39) | < 0.001 | 1034 (47) | 845 (46) | 782 (42) | 0.004 | |
| Hypertension n (%) | 1359 (64) | 1212 (59) | 933 (54) | <0.001 | 1384 (62) | 1103 (60) | 1017 (55) | <0.001 | |
| | 1555 (04) | 1212 (57) |)))) ()+) | <0.001 | 1564 (02) | 1105 (00) | 1017 (55) | <0.001 | |
| Diabetes, n (%) | 538 (26) | 421 (20) | 332 (19) | < 0.001 | 498 (22) | 413 (23) | 380 (20) | 0.13 | |
| CES-D8 depression, n (%) | 598 (28) | 424 (21) | 312 (18) | < 0.001 | 592 (27) | 392 (22) | 350 (19) | < 0.001 | |
| Physically inactive, | 1732 (82) | 1517 (74) | 1058 (61) | < 0.001 | 1724 (80) | 1349 (74) | 1184 (64) | < 0.001 | |
| n (%) | | | | | | | | | |
| Diet components, | | | | | | | | | |
| serving/week | | | | | | | | | |
| Wholegrains | 49(61) | 69(66) | 90(79) | <0.001 | 49(58) | 65(65) | 97(81) | <0.001 | |
| Vegetables | 98(71) | 17.2(10.4) | 268(142) | <0.001 | 113(85) | 161(107) | 26.6 (14.5) | <0.001 | |
| Fruit | 68(61) | 103(78) | 154(10.8) | <0.001 | 66(63) | 10.1(8.1) | 16 1(10 3) | <0.001 | |
| Red meat | 58(42) | 54(40) | 42(34) | <0.001 | 62(44) | 50(38) | 40(32) | <0.001 | |
| Fish | 0.5(0.6) | 0.9(0.9) | 14(13) | <0.001 | 0.2(1.1) | 0.8(0.9) | 14(14) | <0.001 | |
| Nuts | 1.3 (2.5) | 2.1 (3.3) | 3.8 (4.9) | < 0.001 | 1.1 (2.2) | 2.0 (3.3) | 4.2 (5.0) | < 0.001 | |
| | | | | | | | | | |

| Table 1: Participant Characteristics by Tertiles of MedDiet and MIND Diet Scores (n = 5,907) |
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MedDiet = Mediterranean Diet; MIND = Mediterranean-DASH diet Intervention for Neurodegenerative Delay; ^aPossible range 0-55; ^bPossible range 0-15; CES-D8 = Center for Epidemiologic Studies Depression short form

| | | MedDiet score | | | | MIND diet score | | | |
|---|----------------------|----------------|----------------|----------------|----------------|-----------------|----------------|----------------|----------------|
| | | LOW | MID | HIGH | P for Trend | LOW | MID | HIGH | P for Trend |
| | | n = 2110 | n = 2064 | n = 1733 | | n = 2219 | n = 1825 | n = 1863 | |
| Global cognition score ^a | Unadjusted | 14.5 (0.09) | 15.3 (0.09) | 16.0 (0.10) | <0.001 | 14.6 (0.09) | 15.2 (0.10) | 16.0 (0.10) | <0.001 |
| | Model 1 ^b | 14.7 (0.09) | 15.2 (0.09) | 15.9 (0.09) | < 0.001 | 14.8 (0.08) | 15.2 (0.09) | 15.8 (0.09) | < 0.001 |
| | Model 2 ^c | 14.8 (0.09) | 15.2 (0.08) | 15.7 (0.10) | < 0.001 | 14.9 (0.10) | 15.2 (0.09) | 15.6 (0.09) | < 0.001 |

Table 2: Unadjusted and Adjusted Mean (SE) of Global Cognition Score by Tertile of MedDietand MIND Diet Score (n = 5,907)

^aPossible range 0-27. ^bAdjusted for gender, age, race (white, black, other), low education attainment (less than high school completed), ^cModel 1 adjusted for current smoking, total wealth (= assets – debt), obesity (BMI \geq 30 kg/m²), hypertension, diabetes, physical inactivity; depression (CES-D8 \geq 4) and total energy intake (kcals/d).