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

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1 **ABSTRACT**

2 **Objective:** Evidence suggests that adherence to the Mediterranean (MedDiet) or MIND diet is
3 neuroprotective but the association between these dietary patterns and cognition has not been
4 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.

15 **Results:** Mean age of participants was 68 ± 10.8 years. Compared to those with low MedDiet
16 score, participants with mid and high score were less likely to have poor cognitive performance
17 (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)
18 in fully adjusted models. Results for the MIND diet were similar. Higher score in each dietary
19 pattern was independently associated with significantly better cognitive function ($P < 0.001$) in a
20 dose-response manner ($P_{\text{TREND}} < 0.001$).

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

25 **Key words:** dietary patterns, cognitive performance.

26 INTRODUCTION

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

30

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

45 In summary, evidence to date is suggestive of a neuroprotective role for MedDiet but variation
46 between studies makes it difficult to draw firm conclusions. Further investigation is needed to
47 determine whether the MedDiet represents an optimal dietary pattern for protection against
48 neurodegeneration in representative populations.

49 Another proposed neuroprotective dietary pattern, called MIND (Mediterranean-DASH diet
50 Intervention for Neurodegeneration Delay), has been recently described¹⁶. The MIND diet is a
51 modified version of MedDiet but incorporates additional foods based on current evidence in the
52 diet-dementia field¹⁶. In one population-based study, the MIND score was more predictive of
53 cognitive decline than the MedDiet score¹⁶ and higher MIND score was associated with reduced
54 Alzheimer's disease (AD)¹⁷. While these results in mostly older white females are encouraging,
55 they require confirmation in other populations.

56

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

61

62 **METHODS**

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

69
70 This present study is a cross-sectional analysis of participants from a core wave 12 survey (2014)
71 who completed the HRS Health Care and Nutrition (HCNS) substudy (n = 8,035). The HCNS diet
72 assessment was conducted between November 2013 and May 2014, and cognitive, demographic
73 and covariate data were drawn from the core 2014 survey. We excluded respondents who required
74 a by-proxy core 2014 interview and those with missing or incomplete cognitive data (n = 981).
75 We also excluded those who reported extreme energy intakes outside of predefined levels (<800
76 or >8000 kcal/d for men and <600 or >6000 kcal/d for women) (n = 291) and those who reported
77 dementia or AD (n = 140) or stroke (n = 430), and those with missing covariates (n = 286). After
78 exclusions, the final analytic sample was 5,907 participants.

79

80 **Dietary assessment**

81 Dietary intake was assessed using a validated 163-item semi-quantitative Harvard Food Frequency
82 Questionnaire (FFQ)^{19,20}. Adherence to MedDiet and MIND dietary patterns was assessed by
83 calculating summary scores using predefined criteria^{13,16} (as shown in Supplementary Table S1
84 and S2). First, we selected FFQ food item(s) to create dietary components relevant for each dietary

85 pattern. Next, we assigned individual scores for dietary components based on the frequency of
86 recommended intake servings.

87

88 MedDiet score

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

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

108 consumption of reported servings, and scores were reversed for the five unhealthy components.
109 Dietary component scores were then summed to obtain an overall score ranging from 0-15, where
110 higher scores indicate greater adherence to the MIND diet.

111

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**

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

130 **Statistical analysis**

131 Participant characteristics were compared with tertiles of dietary pattern scores using descriptive
132 statistical tests. Analysis of variance with Bonferroni post hoc comparison was used for continuous
133 variables and chi-square test was used for categorical variables, with corresponding tests for linear
134 trend. Pearson's correlation coefficient was used to examine correlations for continuous variables.
135 A multivariable general linear model was applied to investigate associations between dietary
136 patterns (MedDiet and MIND score modelled in tertiles) and global cognition score. Participants
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
139 school vs high school or more), and subsequently for potential mediators total wealth as a measure
140 of socioeconomic status (total assets – total debt), hypertension (Yes/No), diabetes (Yes/No),
141 current smoking (Yes/No), depression (CES-D8 ≥ 4), physical inactivity (Yes/No), obesity (BMI
142 ≥ 30 vs BMI < 30) and total energy intake (kcal/day). The risk of poor cognitive performance
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
145 covariates using the same approach described above. Sensitivity analyses were carried out after
146 removal of individuals classified as demented on the global cognition score. In addition, analyses
147 were repeated after applying *a priori* defined Greek cut-points to MedDiet tertiles (0-20, 21-35
148 and 36-55). Analyses were performed using SPSS version 22 (IBM SPSS, Chicago, IL).

149

150

151 **RESULTS**

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

160

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

167

168 Table 2 shows unadjusted and adjusted global cognition score across tertiles of dietary patterns.
169 Compared to participants with mid or low levels of adherence, those with high adherence to
170 MedDiet or MIND had significantly better cognitive performance ($P < 0.001$ for both dietary
171 patterns). In fully adjusted models, these associations were attenuated but individuals with highest
172 diet adherence had significantly better cognitive scores (by 1.0 and 0.8 points for MedDiet and

173 MIND respectively) than those with mid and low adherence and these associations showed a dose-
174 response relationship ($P_{\text{TREND}} < 0.001$).

175

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

189

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

196 **DISCUSSION**

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

205

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

219 a primary fat source. Unique to MIND are green vegetables and berries which are independently
220 reported to offer protection against neurodegeneration¹². In contrast, the MedDiet places greater
221 emphasis on potatoes, fish and overall fruit and vegetable intake. Both dietary patterns are rich in
222 antioxidants, monounsaturated and n-3 fatty acids and low in saturated fat. These individual
223 nutrients have also been independently related to cognitive performance, for example,
224 observational evidence has shown association between monounsaturated fat and n-3 fatty acids
225 and a reduced risk of cognitive decline and dementia⁵, whereas increased saturated fat intake is
226 shown to increase risk of cognitive decline and dementia²⁷. However, the biological mechanisms
227 for how dietary patterns exert neuroprotective effects are not clear. Several putative mechanisms
228 for the MedDiet have been proposed²⁸, and include beneficial impacts on neuronal cell signalling,
229 vascular, antioxidant and anti-inflammatory biological pathways, but more comprehensive
230 investigation is required. Furthermore, while the MedDiet and the new MIND diet have attracted
231 most attention in the literature, they may not reflect an optimal dietary pattern for protection against
232 neurodegeneration during aging.

233

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

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

248

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

255

256

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258 **Conflict of Interest.** The authors have no relevant financial or personal conflicts to declare. Dr.
259 Yaffe serves on Data Safety and Monitoring Boards for Takeda, Inc. and an NIH sponsored study,
260 and she is a member of the Alzheimer's Association Medical and Scientific Advisory Council and
261 a Senate member of the Council of the German Center for Neurodegenerative Diseases.

262

263 **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)

Table 1: Participant Characteristics by Tertiles of MedDiet and MIND Diet Scores (n = 5,907)

	MedDiet Score ^a				MIND Score ^b			
	Tertile 1 (LOW; ≤25)	Tertile 2 (MID; 26-30)	Tertile 3 (HIGH; >30-55)	<i>P for Trend</i>	Tertile 1 (LOW; ≤6.5)	Tertile 2 (MID; >6.5-8.0)	Tertile 3 (HIGH; >8.0-15.0)	<i>P for Trend</i>
	<i>n</i> 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)		1790 (80)	1406 (77)	1393 (75)	
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 high school, n (%)	397 (19)	243 (12)	195 (11)	<0.001	369 (17)	270 (15)	196 (11)	<0.001
Current smoker, n (%)	332 (16)	207 (10)	93 (5)	<0.001	355 (16)	172 (9)	105 (6)	<0.001
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
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, n (%)	1732 (82)	1517 (74)	1058 (61)	<0.001	1724 (80)	1349 (74)	1184 (64)	<0.001
Diet components, mean (SD), serving/week								
Wholegrains	4.9 (6.1)	6.9 (6.6)	9.0 (7.9)	<0.001	4.9 (5.8)	6.5 (6.5)	9.7 (8.1)	<0.001
Vegetables	9.8 (7.1)	17.2 (10.4)	26.8 (14.2)	<0.001	11.3 (8.5)	16.1 (10.7)	26.6 (14.5)	<0.001
Fruit	6.8 (6.1)	10.3 (7.8)	15.4 (10.8)	<0.001	6.6 (6.3)	10.1(8.1)	16.1(10.3)	<0.001
Red meat	5.8 (4.2)	5.4 (4.0)	4.2 (3.4)	<0.001	6.2 (4.4)	5.0 (3.8)	4.0 (3.2)	<0.001
Fish	0.5 (0.6)	0.9 (0.9)	1.4 (1.3)	<0.001	0.5 (0.6)	0.8 (0.9)	1.4 (1.4)	<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

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

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

		MedDiet score				MIND diet score			
		LOW	MID	HIGH	<i>P for Trend</i>	LOW	MID	HIGH	<i>P for Trend</i>
		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

^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 ≥ 30 kg/m²), hypertension, diabetes, physical inactivity; depression (CES-D8 ≥ 4) and total energy intake (kcal/d).