

**TITLE**

Mediterranean diet adherence and cognitive function in older, UK adults: The EPIC-Norfolk study

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**RUNNING HEAD**

Mediterranean diet adherence and cognitive function

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**ABBREVIATIONS:**

BMI Body mass index

BP Blood pressure

CANTAB-PAL Paired Associates Learning Test from the Cambridge Neuropsychological Test Battery

CI Confidence interval

CVD Cardiovascular disease

EPIC-Norfolk European Prospective Investigation of Cancer, Norfolk

FFQ Food frequency questionnaire

HC Health Check

HVLT Hopkins Verbal Learning test

MEDAS Mediterranean Diet Adherence Screener

MedDiet Mediterranean dietary pattern

MRC-CFAS Medical Research Council Cognitive Function and Ageing study

OR Odds Ratio

PREDIMED Prevención con Dieta Mediterránea

RCT Randomised controlled trial

SE Standard error

SF-EMSE Short-form extended mental state exam

UK United Kingdom

VST Visual Sensitivity Test

## 1 **ABSTRACT**

### 2 **Background**

3 In Mediterranean countries, adherence to a traditional Mediterranean dietary pattern (MedDiet)  
4 is associated with better cognitive function and reduced dementia risk. It is unclear if similar  
5 benefits exist in non-Mediterranean regions.

6

### 7 **Objective**

8 To examine associations between MedDiet adherence and cognitive function in an older, UK  
9 population. To investigate whether associations differed between individuals with high versus  
10 low cardiovascular disease (CVD) risk.

11

### 12 **Design**

13 We conducted an analysis in 8009 older individuals with dietary data at Health Check 1 (1993-  
14 1997) and cognitive function data at Health Check 3 (2006-2011) of the European Prospective  
15 Investigation of Cancer, Norfolk (EPIC-Norfolk). Associations were explored between  
16 MedDiet adherence and global and domain specific cognitive test scores and risk of poor  
17 cognitive performance in the entire cohort, and when stratified according to CVD risk status.

18

### 19 **Results**

20 Higher MedDiet adherence defined by the Pyramid MedDiet score was associated with better  
21 global cognition ( $\beta \pm SE = -0.012 \pm 0.002$ ;  $P < 0.001$ ), verbal episodic memory ( $\beta \pm SE =$   
22  $0.009 \pm 0.002$ ;  $P < 0.001$ ), and simple processing speed ( $\beta \pm SE = -0.002 \pm 0.001$ ;  $P = 0.013$ ). Lower  
23 risk of poor verbal episodic memory (OR(95%CI)=0.784 (0.641,0.959);  $P = 0.018$ ), complex  
24 processing speed (OR(95%CI)=0.739 (0.601,0.907);  $P = 0.004$ ), and prospective memory  
25 (OR(95%CI)=0.841 (0.724,0.977);  $P = 0.023$ ) was also observed for the highest versus lowest

26 Pyramid MedDiet tertiles. The effect of a one-point increase in Pyramid score on global  
27 cognitive function was equivalent to 1.7 fewer years of cognitive ageing. MedDiet adherence  
28 defined by the MEDAS score (mapped using both binary and continuous scoring) showed  
29 similar, albeit less consistent, associations. In stratified analyses, associations were evident in  
30 individuals at higher CVD risk only ( $P<0.05$ ).

31

## 32 **Conclusions**

33 Higher adherence to the MedDiet is associated with better cognitive function and lower risk of  
34 poor cognition in older, UK adults. This evidence underpins the development of interventions  
35 to enhance MedDiet adherence, particularly in individuals at higher CVD risk, aiming to  
36 reduce the risk of age-related cognitive decline in non-Mediterranean populations.

37

38

## 39 **KEYWORDS**

40 Mediterranean diet, cognitive function, cognitive decline, dementia risk, cardiovascular  
41 health, healthy ageing

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## 52 INTRODUCTION

53 The traditional Mediterranean diet (MedDiet) is characterised by a high intake of plant-based  
54 foods including fruits, vegetables, legumes, nuts and seeds, and whole grains. Olive oil is used  
55 as the principal cooking fat, and added liberally to salads, bread, and pasta. Additionally, fish  
56 and red wine are consumed in moderate amounts, whilst red meat, confectionery, and processed  
57 foods are consumed infrequently (1,2). Higher adherence to a MedDiet has been associated  
58 with numerous beneficial health outcomes, particularly in older people, including lower risk of  
59 cardiovascular diseases (CVD) (3), type II diabetes (4), and some cancers (5,6). Further,  
60 observational studies indicate a protective effect of the MedDiet against dementia, including  
61 Alzheimer’s disease (7,8), whilst results from the Navarra and Barcelona cohorts of the  
62 Prevención con Dieta Mediterránea (PREDIMED) randomised controlled trial (RCT) have  
63 demonstrated beneficial effects of a MedDiet intervention supplemented with additional nuts  
64 or extra virgin olive oil on cognitive function (9–11). Outside the Mediterranean basin, few  
65 studies have explored associations between MedDiet adherence and cognitive function and  
66 dementia incidence (12). Existing evidence is mixed, with some studies reporting positive  
67 associations (13–15) and other studies reporting no significant associations between MedDiet  
68 adherence and cognitive function (16–18). In the United Kingdom (UK) specifically, there is  
69 a paucity of research exploring associations between MedDiet adherence and cognitive  
70 function, with evidence limited to a cross-sectional study of participants from the 1936 Lothian  
71 Birth Cohort, which reported greater verbal ability with higher adherence to an *a posteriori*  
72 defined “Mediterranean-style” diet (19). A later analysis of this dataset also showed reduced  
73 brain atrophy with higher MedDiet adherence (20). Large scale, prospective analyses  
74 exploring associations between MedDiet adherence and cognitive function with more  
75 comprehensive measures of exposure to the MedDiet are warranted.

76

77 Poor cardiovascular health is associated with higher risk of cognitive impairment and  
78 dementia (21–23), which has been related to systemic cardio-metabolic (e.g. cerebral hypo-  
79 perfusion, dysfunctional glucose and lipid metabolism) and brain-specific (e.g. reduced  $\beta$ -  
80 amyloid clearance, elevated inflammation and oxidative stress, reduced neurogenesis and  
81 neuronal survival, greater white matter hyper-intensities) mechanisms (24). By protecting  
82 against one or more of these adverse effects, the MedDiet is likely to be particularly effective  
83 at reducing the risk of poor cognitive performance in individuals with higher CVD risk but  
84 this hypothesis has not been tested.

85

86 In the present study, we used data from the Norfolk Cohort of the European Prospective  
87 Investigation of Cancer and Nutrition (EPIC-Norfolk) to investigate longitudinal associations  
88 between MedDiet adherence and cognitive function/risk of poor cognitive performance in an  
89 older UK population. We tested whether associations between adherence to this dietary  
90 pattern and the risk of poor cognitive performance differed between individuals at lower and  
91 higher CVD risk.

92

## 93 **SUBJECTS AND METHODS**

### 94 **Study population and design**

95 EPIC is an ongoing, multi-centre prospective cohort study, exploring the relationship between  
96 diet and disease across 10 European countries (25). EPIC-Norfolk is one of two UK centres  
97 within EPIC. The design and methods of this study have been described comprehensively  
98 elsewhere (26). Briefly, EPIC-Norfolk included a baseline health examination (Health Check  
99 1; HC1) of 25,639 men and women aged 40-79 years, recruited from East Anglia in England  
100 via general practice registers, between 1993 and 1997. Participants were invited to a follow  
101 up assessment (Health Check 2; HC2) between 1998 and 2000, which included those tests



102 undertaken at baseline plus further variables such as bone health. Health Check 3 (HC3) was  
103 conducted between 2006 and 2011 in 8623 participants (aged 48–92 years at that time), to  
104 investigate conditions relevant to ageing, including cognitive function, loss of mobility, and  
105 loss of vision (27). Cognitive data were collected for 8585 individuals at HC3 (28).

106

107 The present study evaluated associations between MedDiet adherence, quantified using food  
108 frequency questionnaire (FFQ) data obtained at HC1, and cognitive function, as determined  
109 via a comprehensive cognitive testing battery at HC3. This analysis involved 8009 individuals  
110 who completed both dietary assessments at HC1 and cognitive measures at HC3  
111 (**Supplementary Figure 1**). The study was approved by the Norwich District Ethics  
112 Committee (HC1 & HC2: 98CN01; HC3: 05/Q0101/191) and East Norfolk and Waveney NHS  
113 Research Governance Committee (2005EC07L). Participants provided informed consent.

114

### 115 **Dietary assessment and calculation of Mediterranean diet scores**

116 A 130-item, semi-quantitative FFQ, extensively used and validated in previous research (29–  
117 31), was used to evaluate the habitual diet of participants over the past year at HC1. Food  
118 intake values were calculated from the FFQ data using validated computer programs (32,33),  
119 and foods were grouped into relevant categories which were used for the creation of the various  
120 MedDiet scores (e.g. total fruit intake or total vegetable intake). Dietary data were energy-  
121 adjusted (2000 kcal/d (8.4 MJ/d)) via the residuals method (34) to allow evaluation of diet  
122 quality independent of diet quantity (35). Briefly, log transformed dietary variables were used  
123 to create residuals with more consistent variance across the levels of total energy intake. Values  
124 were back-transformed by adding the residuals to a constant, equivalent to the predicted value  
125 for the log of 2000 kcal, and then calculating the antilog. Three MedDiet scores were then  
126 calculated as measures of adherence to the MedDiet pattern. These were: i) the MEDAS score

127 (categorical), ii) the MEDAS Continuous score, and iii) the MedDiet pyramid (Pyramid) score.  
128 The MEDAS score is a 14-point score used to track MedDiet adherence in the aforementioned  
129 PREDIMED RCT (3). As recently validated for use in UK populations (36), the standard  
130 MEDAS score was calculated with participants allocated 0 or 1 points per food item depending  
131 on whether they achieved the cut off for the dietary target. The MEDAS Continuous score was  
132 developed as part of the current analysis to provide greater sensitivity. It was calculated using  
133 the same dietary targets as the standard MEDAS score but with points allocated on a continuous  
134 basis (i.e. between 0 and 1) depending on closeness to the dietary target. The Pyramid score  
135 is a 15-point scoring system proposed by the Mediterranean Diet Foundation (1) that was used  
136 previously for the EPIC-Norfolk cohort by Tong et al. (35). It is also coded on a continuous  
137 basis. Details of the calculations used for each of the MedDiet scores are provided in  
138 **Supplementary Tables 1 and 2.**

139

#### 140 **Assessment of cognitive function**

141 Tests were selected to cover a range of different cognitive domains (37). The number of  
142 participants for whom both dietary data at HC1 and cognitive test data for each specific  
143 outcome at HC3 are available is as follows:

- 144 1) **Global cognitive function:** Total score from a shortened version of the Extended  
145 Mental State Exam (SF-EMSE; n = 7917).
- 146 2) **Verbal episodic memory:** Total score from the Hopkins Verbal Learning test (HVLN;  
147 n = 7589).
- 148 3) **Non-verbal episodic memory:** The first trial memory score of the Paired Associates  
149 Learning Test from the Cambridge Neuropsychological Test Battery (CANTAB-PAL;  
150 n = 6970).

- 151 4) **Attention:** Accuracy score (number of targets correctly identified – number missed)  
152 from the Letter Cancellation Task, as applied in the Medical Research Council  
153 Cognitive Function and Ageing study (MRC-CFAS; n = 7847).
- 154 5) **Simple processing speed:** Mean response time of the Simple Visual Sensitivity Test  
155 (VST; n = 6685).
- 156 6) **Complex processing speed and visual deficits contributing to cognitive**  
157 **impairment:** Mean response time of the Complex VST (n = 6685).
- 158 7) **Memory:** Pass or fail of the Prospective Memory Test, as also described in the MRC-  
159 CFAS (n = 7841).

160

#### 161 **Assessment of other covariates**

162 At each health check, a self-administered questionnaire was used to capture participant  
163 demographics, lifestyle, and health characteristics. Physical activity over the past year was  
164 determined via a simple, validated questionnaire, and a four-level index which was validated  
165 against heart rate was derived (38). Trained nurses measured the weight, height, waist  
166 circumference and blood pressure (BP) of participants, and obtained blood samples.

167

#### 168 **Statistical analyses**

169 All statistical analyses were conducted using SPSS version 24. Statistical significance was  
170 defined as  $P < 0.05$ .

171

#### 172 **Cohort characteristics**

173 Cohort characteristics at HC1 were compared between low, medium and high MedDiet  
174 adherence groups for each MedDiet score using the Kruskal-Wallis test for ordered and non-  
175 normally distributed continuous variables and the chi squared test for nominal variables.

176 **Mediterranean diet adherence and cognitive function**

177 Linear regression was used to investigate associations between MedDiet adherence at HC1 and  
178 cognitive function at HC3, with adjustment for relevant covariates (see *statistical models*).  
179 Scores for the SF-EMSE and HVLТ were negatively skewed, and therefore transformed  
180 variables were derived and used for subsequent analyses as  $NEWVARIABLE = \log_{10}(K - X)$ ,  
181 where  $NEWVARIABLE$  is the new variable name,  $K$  is equal to the maximum test score + 1,  
182 and  $X$  is equal to the untransformed score. Lower transformed scores on these tests reflect  
183 better cognitive performance (i.e. greater original scores). VST-Simple and VST-complex  
184 scores were log transformed ( $\log_{10}$ ). Lower scores on this test reflect faster processing speed.  
185 Untransformed variables were used for the CANTAB-PAL and Letter Cancellation Task, with  
186 higher scores reflecting better performance. Results are presented as  $\beta$ -coefficients and  
187 standard errors (SE). The prospective memory test was not included in the linear regression  
188 analyses because it is binary (scored as pass or fail).

189

190 **Mediterranean diet adherence and risk of poor cognitive performance in the whole cohort**  
191 **and when stratified by CVD risk status**

192 Using the same cognitive data, but now categorised into normal and poor performance,  
193 associations between MedDiet adherence and risk of poor cognitive performance were  
194 explored via logistic regression. Poor performance on any test was defined as a score below  
195 the 10<sup>th</sup> percentile of the population distribution for each of the cognitive tests (28). Because  
196 19% of the population failed the prospective memory task, this was used as the lower cut-point  
197 for this outcome.

198

199 Given the well documented associations between poor cardiovascular health and cognitive  
200 impairment (21–23), we performed stratified analyses which tested the hypothesis that the

201 effects of MedDiet adherence on risk of poor cognitive performance differed by CVD risk  
202 group. Lower and higher CVD risk was defined as below and above the median QRISK2 score  
203 (which is indicative CVD risk in the next 10 years (39)). Results are presented as odds ratios  
204 (OR) with 95% confidence intervals.

205

### 206 **Statistical models**

207 A series of statistical models was used to investigate associations between MedDiet adherence  
208 and cognitive function or risk of poor cognitive performance. Models were adjusted for a range  
209 of covariates measured at the same point as the dietary exposure. Additional covariates were  
210 added to the model as we progressed from Model 1 to Model 4 (i.e., basic to maximal  
211 adjustment) as follows: Model 1 adjusted for age, sex, body mass index (BMI), waist  
212 circumference, marital status, and employment status; Model 2 adjusted additionally for self-  
213 reported medical conditions (heart attack, stroke, arrhythmia, diabetes, depression, and other  
214 psychological illness), self-reported medication (BP lowering, lipid lowering, steroids, diabetes  
215 medication), HDL and LDL cholesterol, triglycerides, smoking status, physical activity status,  
216 systolic BP and diastolic BP; Model 3 adjusted additionally for education; and, Model 4  
217 adjusted additionally for *APOE* genotype (presence or absence of the *APOE4* allele).

218

### 219 **Missing data**

220 At HC1, covariate data were missing for  $\leq 0.5$  % of participants for socioeconomic, lifestyle,  
221 anthropometric and BP data,  $\leq 1.1$  % for self-reported medical conditions,  $\leq 7.4$  % for  
222 circulating cholesterol and triglyceride concentrations, and 11.0 % for *APOE* genotype. The  
223 missing data were imputed simultaneously using the SPSS multiple imputations procedure.  
224 Estimates from 10 datasets were pooled under Rubin's rules in all subsequent analyses, unless  
225 otherwise stated.

## 226 **Sensitivity analyses**

227 Sensitivity analyses were conducted to test the robustness of associations between MedDiet  
228 adherence and cognitive function/poor cognitive performance using dietary data obtained at  
229 HC2 instead of HC1. In addition, to assess whether any individual components of the MedDiet  
230 drove the beneficial effects observed, we repeated the primary analyses (i.e. maximally  
231 adjusted linear regression models) in which a significant effect on cognition was observed after  
232 removing each MedDiet component from the total score, sequentially. We also conducted a  
233 sensitivity analysis in which participants with potentially implausible energy intakes (i.e. over-  
234 or under-reporters) according to the Goldberg cut offs (40) were excluded from the main  
235 analysis. As an alternative method of exploring whether associations between MedDiet  
236 adherence and risk of poor cognitive performance differed by CVD risk status, we also  
237 performed analyses where we included an interaction term (diet \* CVD risk group) in  
238 maximally adjusted models. Finally, we explored differences in cohort characteristics between  
239 participants with and without complete cognitive testing data, to identify potential issues with  
240 selection bias.

241

## 242 **RESULTS**

### 243 **Cohort characteristics**

244 Baseline participant characteristics are in **Table 1**, with additional details also provided in  
245 **Supplementary Table 3**. Participants with high adherence to the MedDiet were less likely to  
246 be smokers, and more likely to be female, unmarried, more physically active, and have a higher  
247 education status compared with individuals with low MedDiet adherence. In addition,  
248 individuals with a high MedDiet adherence were more likely to have lower BMI, waist  
249 circumference, systolic and diastolic BP, triglyceride concentrations, and QRISK2 score, and

250 higher HDL-cholesterol concentrations, compared with individuals with low MedDiet  
251 adherence (all  $P < 0.05$ ).

252

253 **\*\*INSERT TABLE 1 HERE\*\***

254

### 255 **Associations between MedDiet adherence and cognitive function**

256 Associations between MedDiet adherence and cognitive performance are shown in **Table 2**.

257 In the maximally adjusted linear regression models (model 4), higher MedDiet adherence, as  
258 characterised by all three MedDiet scores, was associated with significantly better performance

259 on the SF-EMSE (global cognition; MEDAS:  $\beta \pm SE = -0.004 \pm 0.002$ ,  $P = 0.018$ ; MEDAS

260 Continuous:  $\beta \pm SE = -0.005 \pm 0.002$ ,  $P = 0.008$ ; Pyramid:  $\beta \pm SE = -0.012 \pm 0.002$ ,  $P < 0.001$ ).

261 Higher adherence to the MedDiet (assessed using the Pyramid score) was also associated with  
262 significantly better performance on the HVLTL (verbal episodic memory;  $\beta \pm SE = -0.009 \pm$

263  $0.002$ ,  $P < 0.001$ ) and VST-Simple (simple processing speed;  $\beta \pm SE = -0.002 \pm 0.001$ ,  $P =$

264  $0.013$ ). To put this into perspective, the effects of a one point increase in MedDiet score

265 (maximum 14-15 points) on SF-EMSE performance, a measure of global cognition, was

266 equivalent to 0.57, 0.71, and 1.7 fewer years of ageing for the MEDAS, MEDAS Continuous,

267 and Pyramid scores, respectively ( $\beta$  value for age in maximally adjusted models was 0.007,  $P$

268  $< 0.001$ ).

269

270 **\*\*INSERT TABLE 2 HERE\*\***

271

### 272 **Associations between MedDiet adherence and risk of poor cognitive performance**

273 Associations between MedDiet adherence and risk of poor cognitive performance are presented

274 in **Figure 1** and **Supplementary Table 4**. In maximally adjusted models (model 4), high

275 compared with low MedDiet adherence as defined by the MEDAS Continuous score was  
276 associated with reduced risk of poor cognitive performance on the SF-EMSE (global cognition;  
277 OR (95% CI) = 0.828 (0.696, 0.985),  $P = 0.033$ ) and HVLТ (verbal episodic memory; OR  
278 (95% CI) = 0.797 (0.653, 0.973),  $P = 0.026$ ). Higher MedDiet adherence defined by the  
279 Pyramid score was associated with a lower risk of poor performance in the HVLТ (OR (95%  
280 CI) = 0.784 (0.641, 0.959),  $P = 0.018$ ), VST-Complex (OR (95% CI) = 0.739 (0.601, 0.907),  
281  $P = 0.004$ ), and Prospective memory task (Prospective memory; OR (95% CI) = 0.841 (0.724,  
282 0.977),  $P = 0.023$ ). Moderate MedDiet adherence defined by the MEDAS Continuous score  
283 and the Pyramid score was also associated with a lower risk of poor performance on the VST-  
284 Complex task (complex processing speed; MEDAS Continuous: OR (95% CI) = 0.803 (0.660,  
285 0.977),  $P = 0.029$ ; Pyramid: OR (95% CI) = 0.820 (0.675, 0.995),  $P = 0.045$ ).

286

287 **\*\*INSERT FIGURE 2 HERE\*\***

288

289 When participants were grouped by CVD risk (below and above the median QRISK2 score;  
290 **Figure 2; Supplementary Table 5**), no associations between MedDiet adherence and risk of  
291 poor cognitive performance in individuals with low CVD risk emerged. However, in  
292 individuals at high CVD risk, MedDiet adherence as defined by the MEDAS Continuous score  
293 was associated with lower risk of poor HVLТ performance (verbal episodic memory; OR (95%  
294 CI) = 0.756 (0.596, 0.958),  $P = 0.021$ ). Additionally, in high CVD risk individuals, moderate  
295 MedDiet adherence defined by the MEDAS Continuous score was associated with lower risk  
296 of poor VST-Complex performance (complex processing speed; OR (95% CI) = 0.728 (0.565,  
297 0.939),  $P = 0.015$ ). Both moderate and high MedDiet adherence defined by the Pyramid score  
298 were associated with lower risk of poor VST-Complex performance in individuals with high



299 CVD risk (Moderate: OR (95% CI) = 0.707 (0.551, 0.908),  $P = 0.007$ ; High: OR (95% CI) =  
300 0.667 (0.551, 0.871),  $P = 0.003$ ).

301

302 **\*\*INSERT FIGURE 2 HERE\*\***

303

### 304 **Sensitivity analyses**

305 To test the robustness of associations between MedDiet adherence and cognitive function/ risk  
306 of poor cognitive performance, we used dietary data from HC2 instead of HC1  
307 (**Supplementary Table 6 and 7**). Higher MedDiet adherence defined by one or more of the  
308 MedDiet scores was associated with better performance and/or lower risk of poor cognitive  
309 performance across several different cognitive tests ( $P < 0.05$ ; SF-EMSE, VST-Simple, and  
310 VST-Complex). However, unexpectedly, performance was worse in the Letter Cancellation  
311 task ( $P < 0.05$ ; attention) with high MedDiet adherence defined by the MEDAS and MEDAS  
312 Continuous scores at HC2, and the risk of poor performance on this test was greater with high  
313 MedDiet adherence defined by the MEDAS score ( $P < 0.05$ ).

314

315 In analyses where diet scores were derived after sequential removal of individual MedDiet  
316 components, the significant positive associations with cognition remained reasonably stable  
317 (**Supplementary Table 8 and 9**), except for the removal of wine or fruit from the MEDAS  
318 score and wine from the MEDAS Continuous score, after which associations with SF-EMSE  
319 performance were no longer present ( $P > 0.05$ ; global cognition). When potential under- and  
320 over-reporters were excluded from the analysis according to the Goldberg cut offs, higher  
321 MedDiet adherence defined by the Pyramid score remained significantly associated with better  
322 SF-EMSE (global cognition), HVLT (verbal episodic memory), and VST-Simple (simple  
323 processing speed) performance, and was additionally significantly associated with higher VST-

324 Complex (complex processing speed) performance. Higher MedDiet adherence defined by the  
325 MEDAS continuous score was now significantly associated with higher HVLIT performance,  
326 but associations with SF-EMSE performance were no longer significant. Associations between  
327 the MEDAS and SF-EMSE performance were no longer significant (**Supplementary Table**  
328 **10**). When we included an interaction term in the model for MedDiet \* CVD risk category,  
329 we found the MedDiet was more effective in individuals with high versus low CVD risk at  
330 reducing the risk of poor cognitive performance (**Supplementary Table 11**), confirming the  
331 results from our stratified analyses. Finally, when we compared cohort characteristics between  
332 participants with and without complete cognitive testing data, we found that participants who  
333 completed all cognitive tests were overall significantly younger, more physically active, had a  
334 higher educational attainment, and lower systolic BP and QRISK2 score (all  $P < 0.05$ ;  
335 **Supplementary table 12**).

336

## 337 **DISCUSSION**

338 Using data on 8009 middle and older aged participants from EPIC-Norfolk, we found that  
339 higher adherence to the MedDiet was associated with better cognitive function and lower risk  
340 of poor cognitive performance across several cognitive tests/domains. In stratified analyses,  
341 higher MedDiet adherence was associated with a lower risk of poor cognitive performance only  
342 in individuals at higher CVD risk.

343

### 344 **MedDiet and cognitive function/ risk of poor cognitive performance**

345 This is the first, large-scale prospective study exploring associations between an *a priori*  
346 defined MedDiet and cognitive function/poor cognitive performance in a UK population. We  
347 found that higher MedDiet adherence defined by one or more MedDiet scores was associated  
348 with better global cognition, verbal episodic memory, and simple processing speed, together

349 with a lower risk of poor global cognition, verbal episodic memory, complex processing speed,  
350 and prospective memory. To put this into perspective, compared with the effects of age, which  
351 is the strongest determinant of cognitive decline (41), a 3 point increase in Pyramid score is  
352 equivalent to ~ 5 fewer years of ageing on global cognitive function. These findings are  
353 consistent with a recent study conducted in Greece by Anastasiou et al. (42), who reported that  
354 higher adherence to the Mediterranean lifestyle (encompassing the MedDiet plus physical  
355 activity, sleep, and daily activities) reduced risk of low global cognitive function equivalent to  
356 2.7 fewer years of ageing. Delaying the onset of dementia by two- or five-years would reduce  
357 UK dementia prevalence by 19% and 33% by 2050, and result in much lower prevalence of  
358 severe dementia (43).

359

360 In a previous, cross-sectional investigation conducted in 882 participants in the Lothian Birth  
361 Cohort 1936 study (19), higher adherence to a “Mediterranean-style” diet was associated with  
362 significantly better verbal ability in maximally adjusted models. Other studies, conducted in  
363 non-Mediterranean countries, have shown inconsistent associations, with some investigations  
364 reporting positive associations (13–15) and others documenting no significant associations  
365 between MedDiet adherence and cognitive function (16–18). Potential reasons for these  
366 conflicting findings could include differences in MedDiet capture, cognitive tests employed  
367 (e.g. varying sensitivity, assessment of different domains), study design (e.g. cross-sectional  
368 versus prospective) and follow up duration, and participant groups (e.g. divergent age profiles,  
369 healthy versus non-healthy cohorts).

370

371 In stratified analyses, higher MedDiet adherence was associated with lower risk of poor  
372 cognitive performance only in participants with higher CVD risk. Mechanistically, this could  
373 be related to effects on both the systemic cardiovascular system and brain, including reduced

374 oxidative stress and inflammation (44), improved glucose and lipid metabolism (45), increased  
375 nitric oxide bioavailability, improved vascular function and brain perfusion (46,47). These  
376 findings have implications for the design of future RCTs, where individuals with higher CVD  
377 risk may represent a potentially responsive population group in which to study the cognitive  
378 benefits of the MedDiet. This is the strategy that has been adopted for the MedEx-UK trial  
379 (<https://clinicaltrials.gov/ct2/show/NCT03673722>), which will explore the feasibility and  
380 acceptability of a MedDiet and physical activity intervention for dementia risk reduction and  
381 will recruit participants with a high QRISK2 score (used routinely in primary care in the UK  
382 to establish CVD risk) and subjective memory complaints. Targeting individuals with and ‘at-  
383 risk’ cardiovascular profile to improve MedDiet adherence may have a “double benefit”, not  
384 only by reducing CVD risk (as established in studies such as PREDIMED (3)), but also by  
385 improving cognitive function.

386

### 387 **Strengths and limitations**

388 Study strengths include the large sample size and the comprehensive assessment of cognitive  
389 function using a range of previously validated tests which cover multiple different domains  
390 that are affected during the early stages of cognitive decline prior to dementia onset. Moreover,  
391 we used a prospective design in which dietary measures were obtained approximately 13 years  
392 before the cognitive assessments were made thus reducing the risk of reverse causality. A  
393 further strength of this study is that we used two previously published, robustly defined  
394 measures of exposure to the MedDiet. In addition, we created a novel derivative of the MEDAS  
395 score where we coded intake of foods continuously rather than on a binary basis, which was  
396 more sensitive at quantifying individual diet quality and showed stronger links with cognitive  
397 outcomes. However, although dietary data were derived from a validated FFQ, this instrument  
398 may not provide sufficient detail about the consumption of some foods key to the MedDiet

399 pattern, such as the type and intake of olive oil, consumption of sofrito, and the type of nuts  
400 consumed (12). Moreover, the scales we used to evaluate MedDiet adherence do not account  
401 for intake of supplements, which may contain several nutrients key to this dietary pattern (e.g.  
402 omega-3, 50% of which is obtained from supplements in the UK (48)). Furthermore, for our  
403 primary analysis, dietary intake was assessed between 1993-1997, whilst cognitive function  
404 was assessed 13 to 18 years later, and it is possible that participants may have altered their diet  
405 during this follow up period. Likewise, given cognitive function was only measured at one  
406 time point, we were unable to explore associations between MedDiet adherence and cognitive  
407 trajectories. In addition, despite adjusting for multiple covariates, our results may have been  
408 influenced by unmeasured variables. For example, we did not measure participant IQ, which  
409 influences both cognitive performance and dietary choices (19), but we included education as  
410 a covariate which, typically, shows good correlation with IQ (49). Finally, it is possible that  
411 there is a degree of selection bias in this study, which may limit the generalisability of our  
412 findings to the wider population. Indeed, participants with poorer cognition may have decided  
413 not to/ were unable to take part in data collection at HC3. Alternatively, these individuals may  
414 have only completed a sub-set of tests at this phase. In this regard, it is noteworthy that  
415 participants with incomplete cognitive data showed generally poorer health than those who  
416 completed all tests. It is difficult to speculate how this may have influenced our results, and  
417 future research is warranted to explore the impact of the MedDiet on cognition in different  
418 cohorts.

419

## 420 **Conclusions and implications**

421 This study provides evidence that higher MedDiet adherence is associated with better cognitive  
422 function and lower risk of poor cognitive performance in a UK population. In addition, we  
423 demonstrated that the MedDiet is particularly associated with lower risk of poor cognitive

424 performance in individuals with higher CVD risk. These results have implications for the  
425 development of dietary recommendations to facilitate healthy cognitive ageing. In addition, the  
426 findings suggests that individuals with higher CVD risk are a key population group for future  
427 RCTs testing lifestyle modifications to improve cognition during ageing.

428

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433 UK adults: Epidemiology and MedEx feasibility study'.

434

435

#### 436 **CONFLICT OF INTEREST STATEMENT**

437 All authors declare that they have no conflict of interest.

438

#### 439 **AUTHOR CONTRIBUTIONS**

440 This study was designed by BCMS, MS, AMM, and JCM. OS, MS, JCM, AM, ML, RB  
441 calculated Mediterranean diet scores. SH, SMP, and MH helped interpret cognitive data. OS  
442 conducted the statistical analysis, with guidance from MS, JCM, AG, BCMS, ML, and GMT.  
443 OS, MS, and JCM drafted the manuscript. All the authors participated in the interpretation of  
444 the results and critical revision of the manuscript, and approved the final version.

**REFERENCES**

1. Bach-Faig A, Berry EM, Lairon D, Reguant J, Trichopoulou A, Dernini S, Medina FX, Battino M, Belahsen R, Miranda G, et al. Mediterranean diet pyramid today. Science and cultural updates. *Public Health Nutr.* 2011;14:2274–84.
2. Trichopoulou A, Martínez-González MA, Tong TY, Forouhi NG, Khandelwal S, Prabhakaran D, Mozaffarian D, de Lorgeril M. Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. *BMC Med.* 2014;12:112.
3. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med.* 2018; 378:e34.
4. Salas-Salvadó J, Bulló M, Babio N, Martínez-González MÁ, Ibarrola-Jurado N, Basora J, Estruch R, Covas MI, Corella D, Arós F, et al. Reduction in the Incidence of Type 2 Diabetes With the Mediterranean Diet: Results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care.* 2011;34:14–9.
5. Toledo E, Salas-Salvadó J, Donat-Vargas C, Buil-Cosiales P, Estruch R, Ros E, Corella D, Fitó M, Hu FB, Arós F, et al. Mediterranean Diet and Invasive Breast Cancer Risk Among Women at High Cardiovascular Risk in the PREDIMED Trial: A Randomized Clinical Trial. *JAMA Intern Med.* 2015;175:1752–60.
6. Schwingshackl L, Schwedhelm C, Galbete C, Hoffmann G. Adherence to Mediterranean Diet and Risk of Cancer: An Updated Systematic Review and Meta-Analysis. *Nutrients.* 2017;9.
7. Scarmeas N, Stern Y, Tang M-X, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. *Ann Neurol.* 2006;59:912–21.

8. Singh B, Parsaik AK, Mielke MM, Erwin PJ, Knopman DS, Petersen RC, Roberts RO. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* . 2014;39:271–82.
9. Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, Julián BS, Sanchez-Tainta A, Ros E, Valls-Pedret C, Martinez-Gonzalez MÁ. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. *J Neurol Neurosurg Psychiatry*. 2013;jnnp-2012-304792.
10. Martínez-Lapiscina EH, Galbete C, Corella D, Toledo E, Buil-Cosiales P, Salas-Salvado J, Ros E, Martinez-Gonzalez MA. Genotype patterns at CLU, CR1, PICALM and APOE, cognition and Mediterranean diet: the PREDIMED-NAVARRA trial. *Genes Nutr*. 2014;9:393.
11. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, Torre R de la, Martínez-González MÁ, Martínez-Lapiscina EH, Fitó M, Pérez-Heras A, Salas-Salvadó J, et al. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. *JAMA Intern Med*. 2015;175:1094–103.
12. Petersson SD, Philippou E. Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review of the Evidence. *Adv Nutr Bethesda Md*. 2016;7:889–904.
13. Ye X, Scott T, Gao X, Maras JE, Bakun PJ, Tucker KL. Mediterranean diet, healthy eating index 2005, and cognitive function in middle-aged and older Puerto Rican adults. *J Acad Nutr Diet*. 2013;113:276-281.e1-3.
14. Tangney CC, Li H, Wang Y, Barnes L, Schneider JA, Bennett DA, Morris MC. Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons. *Neurology*. 2014;83:1410–6.



15. Gardener SL, Rainey-Smith SR, Barnes MB, Sohrabi HR, Weinborn M, Lim YY, Harrington K, Taddei K, Gu Y, Rembach A, et al. Dietary patterns and cognitive decline in an Australian study of ageing. *Mol Psychiatry*. 2015;20:860–6.
16. Vercambre M-N, Grodstein F, Berr C, Kang JH. Mediterranean Diet and Cognitive Decline in Women with Cardiovascular Disease or Risk Factors. *J Acad Nutr Diet*. 2012;112:816–23.
17. Samieri C, Grodstein F, Rosner BA, Kang JH, Cook NR, Manson JE, Buring JE, Willett WC, Okereke OI. Mediterranean diet and cognitive function in older age. *Epidemiol Camb Mass*. 2013;24:490–9.
18. Titova OE, Ax E, Brooks SJ, Sjögren P, Cederholm T, Kilander L, Kullberg J, Larsson E-M, Johansson L, Ahlström H, et al. Mediterranean diet habits in older individuals: associations with cognitive functioning and brain volumes. *Exp Gerontol*. 2013;48:1443–8.
19. Corley J, Starr JM, McNeill G, Deary IJ. Do dietary patterns influence cognitive function in old age? *Int Psychogeriatr*. 2013;25:1393–407.
20. Luciano M, Corley J, Cox SR, Valdés Hernández MC, Craig LCA, Dickie DA, Karama S, McNeill GM, Bastin ME, Wardlaw JM, et al. Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. *Neurology*. 2017;88:449–55.
21. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR, Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology*. 2001;56:42–8.
22. Raz N, Rodrigue KM, Acker JD. Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. *Behav Neurosci*. 2003;117:1169–80.

23. DeBette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, Wolf PA, DeCarli C. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*. 2011;77:461–8.
24. Parletta N, Milte CM, Meyer BJ. Nutritional modulation of cognitive function and mental health. *J Nutr Biochem*. 2013;24:725–43.
25. Riboli E. Nutrition and cancer: background and rationale of the European Prospective Investigation into Cancer and Nutrition (EPIC). *Ann Oncol*. 1992;3:783–91.
26. Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A, Wareham N. EPIC-Norfolk: study design and characteristics of the cohort. *European Prospective Investigation of Cancer. Br J Cancer*. 1999;80 Suppl 1:95–103.
27. Hayat SA, Luben R, Keevil VL, Moore S, Dalzell N, Bhaniani A, Khawaja AP, Foster P, Brayne C, Wareham NJ, et al. Cohort Profile: A prospective cohort study of objective physical and cognitive capability and visual health in an ageing population of men and women in Norfolk (EPIC-Norfolk 3). *Int J Epidemiol*. 2014;43:1063–72.
28. Hayat SA, Luben R, Dalzell N, Moore S, Anuj S, Matthews FE, Wareham N, Brayne C, Khaw K-T. Cross Sectional Associations between Socio-Demographic Factors and Cognitive Performance in an Older British Population: The European Investigation of Cancer in Norfolk (EPIC-Norfolk) Study. *PLoS One*. 2016;11:e0166779.
29. Bingham SA, Gill C, Welch A, Cassidy A, Runswick SA, Oakes S, Lubin R, Thurnham DI, Key TJ, Roe L, et al. Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *Int J Epidemiol*. 1997;26 Suppl 1:S137-151.
30. Bingham SA, Welch AA, McTaggart A, Mulligan AA, Runswick SA, Luben R, Oakes S, Khaw KT, Wareham N, Day NE. Nutritional methods in the European Prospective Investigation of Cancer in Norfolk. *Public Health Nutr*. 2001;4:847–58.

31. McKeown NM, Day NE, Welch AA, Runswick SA, Luben RN, Mulligan AA, McTaggart A, Bingham SA. Use of biological markers to validate self-reported dietary intake in a random sample of the European Prospective Investigation into Cancer United Kingdom Norfolk cohort. *Am J Clin Nutr.* 2001;74:188–96.
32. Welch AA, Luben R, Khaw KT, Bingham SA. The CAFE computer program for nutritional analysis of the EPIC-Norfolk food frequency questionnaire and identification of extreme nutrient values. *J Hum Nutr Diet.* 2005;18:99–116.
33. Mulligan AA, Luben RN, Bhaniani A, Parry-Smith DJ, O'Connor L, Khawaja AP, Forouhi NG, Khaw K-T. A new tool for converting food frequency questionnaire data into nutrient and food group values: FETA research methods and availability. *BMJ Open.* 2014;4:e004503.
34. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr.* 1997;65:1220S–1228S.
35. Tong TYN, Wareham NJ, Khaw K-T, Imamura F, Forouhi NG. Prospective association of the Mediterranean diet with cardiovascular disease incidence and mortality and its population impact in a non-Mediterranean population: the EPIC-Norfolk study. *BMC Med.* 2016;14:135.
36. Papadaki A, Johnson L, Toumpakari Z, England C, Rai M, Toms S, Penfold C, Zazpe I, Martínez-González MA, Feder G. Validation of the English Version of the 14-Item Mediterranean Diet Adherence Screener of the PREDIMED Study, in People at High Cardiovascular Risk in the UK. *Nutrients.* 2018;10.
37. Hayat SA, Luben R, Moore S, Dalzell N, Bhaniani A, Anuj S, Matthews FE, Wareham N, Khaw K-T, Brayne C. Cognitive function in a general population of men and women: a cross sectional study in the European Investigation of Cancer–Norfolk cohort (EPIC-Norfolk). *BMC Geriatr.* 2014;14:142.

38. Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, Day NE. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Public Health Nutr.* 2003;6:407–13.
39. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, Brindle P. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ.* 2008;336:1475–82.
40. Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake: basal metabolic rate. A practical guide to its calculation, use and limitations. *Int J Obes Relat Metab Disord J Int Assoc Study Obes.* 2000;24:1119–30.
41. Deary IJ, Corley J, Gow AJ, Harris SE, Houlihan LM, Marioni RE, Penke L, Rafnsson SB, Starr JM. Age-associated cognitive decline. *Br Med Bull.* 2009;92:135–52.
42. Anastasiou CA, Yannakoulia M, Kontogianni MD, Kosmidis MH, Mamalaki E, Dardiotis E, Hadjigeorgiou G, Sakka P, Tsapanou A, Lykou A, et al. Mediterranean Lifestyle in Relation to Cognitive Health: Results from the HELIAD Study. *Nutrients.* 2018;10:1557.
43. Lewis F, Karlsberg Schaffer, S, Sussex, J, O'Neill, P, Cockcroft, L. The Trajectory of Dementia in the UK – Making a Difference. *Off Health Econ.* 2014;
44. Mena M-P, Sacanella E, Vazquez-Agell M, Morales M, Fitó M, Escoda R, Serrano-Martínez M, Salas-Salvadó J, Benages N, Casas R, et al. Inhibition of circulating immune cell activation: a molecular antiinflammatory effect of the Mediterranean diet. *Am J Clin Nutr.* 2009;89:248–56.
45. Rodríguez-Rejón AI, Castro-Quezada I, Ruano-Rodríguez C, Ruiz-López MD, Sánchez-Villegas A, Toledo E, Artacho R, Estruch R, Salas-Salvadó J, Covas MI, et al. Effect of a Mediterranean Diet Intervention on Dietary Glycemic Load and Dietary Glycemic Index: The PREDIMED Study. *J Nutr Metab.* 2014: doi: 10.1155/2014/985373.

46. Medina-Remón A, Tresserra-Rimbau A, Pons A, Tur JA, Martorell M, Ros E, Buil-Cosiales P, Sacanella E, Covas MI, Corella D, et al. Effects of total dietary polyphenols on plasma nitric oxide and blood pressure in a high cardiovascular risk cohort. The PREDIMED randomized trial. *Nutr Metab Cardiovasc Dis.* 2015;25:60–7.
47. Shannon OM, Stephan BCM, Minihane A-M, Mathers JC, Siervo M. Nitric oxide boosting effects of the Mediterranean diet: A potential mechanism of action. *J Gerontol A Biol Sci Med Sci.* 2018; doi: 10.1093/gerona/gly087.
48. Lentjes MAH. The balance between food and dietary supplements in the general population. *Proc Nutr Soc.* 2018; doi: 10.1017/S0029665118002525.
49. Deary IJ, Johnson W. Intelligence and education: causal perceptions drive analytic processes and therefore conclusions. *Int J Epidemiol.* 2010;39:1362–9.

**Table 1** Participant characteristics at baseline (HC1) of the EPIC-Norfolk study according to Mediterranean diet adherence score

Characteristic	Mediterranean diet score														
	Overall	MEDAS <sup>1</sup>				<i>P</i>	MEDAS Continuous				<i>P</i>	Pyramid			<i>P</i>
		Low = 0 - 2 n=2400	Medium = 3 - 4 n=4198	High = 5 - 10 n=1411	Low = 1.31 - 4.97 n=2670		Medium = 4.98 - 6.04 n=2670	High = 6.05 - 10.87 n=2669	Low = 3.47 - 7.53 n=2687	Medium = 7.54 - 8.66 n=2673		High = 8.67-12.93 n=2649			
Age, Years	55.0 (49.4, 61.7)	54.5 (49.1, 61.6)	55.3 (49.5, 61.9)	54.7 (49.5, 61.2)	0.131	55.5 (49.5, 62.4)	55.0 (49.3, 61.6)	54.5 (49.2 – 61.0)	<b>0.002</b>	54.9 (49.4, 61.7)	55.4 (49.5, 61.8)	54.9 (49.3, 61.5)	0.439		
Sex, % males	44	51	44	34	<b>&lt;0.001</b>	50	45	39	<b>&lt;0.001</b>	54	44	36	<b>&lt;0.001</b>		
BMI, kg/m <sup>2</sup> (n=7989)	25.4 (23.3, 27.7)	25.5 (23.4, 28.0)	25.4 (23.4, 27.7)	24.9 (23.0, 27.2)	<b>&lt;0.001</b>	25.6 (23.5, 27.9)	25.5 (23.5, 27.8)	25.0 (23.0 – 27.4)	<b>&lt;0.001</b>	25.6 (23.6, 28.0)	25.4 (23.4, 27.8)	25.0 (23.0, 27.4)	<b>&lt;0.001</b>		
Smoking status, % (n=7983)					<b>&lt;0.001</b>				<b>&lt;0.001</b>				<b>&lt;0.001</b>		
Current	9	11	8	6		11	8	7		12	8	6			
Former	39	37	40	40		37	39	41		39	39	39			
Never	52	51	53	54		52	54	52		49	53	55			
Physical activity level, %					<b>0.001</b>				<b>&lt;0.001</b>				<b>0.007</b>		
Inactive	22	24	22	17		24	23	18		24	23	18			
Moderately inactive	30	29	30	32		29	30	31		28	31	32			
Moderately active	26	26	25	27		27	24	26		26	24	27			
Active	23	21	23	25		21	23	25		22	23	23			
Education status (n=8012)					<b>&lt;0.001</b>				<b>&lt;0.001</b>				<b>&lt;0.001</b>		
No education	26	30	26	19		33	26	20		34	26	18			
O-levels	12	12	12	11		12	13	11		12	12	12			
A-levels	44	44	44	46		43	44	46		43	46	44			
Degree	18	14	18	24		13	17	23		11	17	25			
Systolic BP, mmHg (n=7993)	130 (120, 142)	130 (121, 142)	131 (120, 143)	129 (119, 141)	<b>0.046</b>	131 (121, 142)	130 (120, 143)	129 (119, 141)	<b>&lt;0.001</b>	132 (121, 142)	131 (120, 142)	129 (119, 142)	<b>0.001</b>		
Diastolic BP, mmHg (n=7993)	81 (74, 88)	81 (74, 88)	81 (74, 88)	80 (73, 87)	<b>0.010</b>	81 (74, 88)	81 (74, 89)	80 (73, 87)	<b>0.001</b>	81 (74, 88)	81 (74, 88)	80 (73, 87)	<b>0.001</b>		
HDL cholesterol, mM (n=7419)	1.4 (1.1, 1.7)	1.3 (1.1, 1.6)	1.4 (1.1, 1.7)	1.5 (1.2, 1.8)	<b>&lt;0.001</b>	1.3 (1.1, 1.6)	1.4 (1.1, 1.7)	1.5 (1.2, 1.8)	<b>&lt;0.001</b>	1.3 (1.1, 1.6)	1.4 (1.1, 1.7)	1.4 (1.2, 1.8)	<b>&lt;0.001</b>		
LDL cholesterol, mM (n=7419)	3.8 (3.1, 4.5)	3.8 (3.2, 4.5)	3.8 (3.1, 4.5)	3.7 (3.1, 4.4)	0.123	3.8 (3.2, 4.5)	3.8 (3.2, 4.5)	3.7 (3.1, 4.4)	<b>0.002</b>	3.9 (3.2, 4.5)	3.8 (3.1, 4.5)	3.7 (3.1, 4.4)	<b>0.001</b>		
Total triglycerides, mM (n=7592)	1.4 (1.0, 2.1)	1.5 (1.0, 2.2)	1.4 (1.0, 2.0)	1.3 (0.9, 1.9)	<b>&lt;0.001</b>	1.5 (1.0, 2.2)	1.5 (1.0, 2.1)	1.3 (0.9, 1.9)	<b>&lt;0.001</b>	1.5 (1.0, 2.2)	1.4 (1.0, 2.0)	1.4 (0.9, 1.9)	<b>&lt;0.001</b>		

QRISK2 score (n=7953)	6.8 (3.0, 14.0)	7.3 (3.3, 14.8)	6.8 (3.1, 14.1)	5.8 (2.6, 12.6)	<0.001	7.6 (3.5, 15.5)	6.8 (3.0, 13.9)	5.8 (2.6, 12.7)	<0.001	7.7 (3.5, 15.4)	6.7 (3.0, 13.8)	6.0 (2.7, 12.6)	<0.001
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Participant characteristics were compared between low, medium and high Mediterranean diet adherence groups for each score using the Kruskal-Wallis test for ordered and non-normally distributed continuous variables and the chi squared test for nominal variables. Data are presented as median (IQR) for non-normally distributed continuous data and % for nominal/ categorical data. Where measurements were not obtained in the full set of 8009 participants, the exact number of participants for the variable is stated in brackets under the variable name. <sup>1</sup>For the MEDAS score, it was not possible to divide participants into approximately equal sized groups, given a large number of participants achieved the same score. Therefore, participants were split into three groups where all individuals with the same score were categorised together.

**Table 2** Mediterranean diet adherence and cognitive function in the EPIC-Norfolk study

Outcome	Cognitive domain	Model	MEDAS		MEDAS Continuous		Pyramid	
			$\beta$ + SE	<i>P</i>	$\beta$ + SE	<i>P</i>	$\beta$ + SE	<i>P</i>
SF-EMSE	Global cognition	1	-0.010 ± 0.002	<b>&lt;0.001</b>	-0.013 ± 0.002	<b>&lt;0.001</b>	-0.021 ± 0.002	<b>&lt;0.001</b>
		2	-0.010 ± 0.002	<b>&lt;0.001</b>	-0.013 ± 0.002	<b>&lt;0.001</b>	-0.021 ± 0.002	<b>&lt;0.001</b>
		3	-0.004 ± 0.002	<b>0.019</b>	-0.005 ± 0.002	<b>0.008</b>	-0.012 ± 0.002	<b>&lt;0.001</b>
		4	-0.004 ± 0.002	<b>0.018</b>	-0.005 ± 0.002	<b>0.008</b>	-0.012 ± 0.002	<b>&lt;0.001</b>
HVLТ	Retrospective memory (verbal episodic memory)	1	-0.008 ± 0.002	<b>&lt;0.001</b>	-0.010 ± 0.002	<b>&lt;0.001</b>	-0.016 ± 0.002	<b>&lt;0.001</b>
		2	-0.008 ± 0.002	<b>&lt;0.001</b>	-0.010 ± 0.002	<b>&lt;0.001</b>	-0.016 ± 0.002	<b>&lt;0.001</b>
		3	-0.003 ± 0.002	0.147	-0.004 ± 0.002	0.058	-0.009 ± 0.002	<b>&lt;0.001</b>
		4	-0.003 ± 0.002	0.139	-0.004 ± 0.002	0.054	-0.009 ± 0.002	<b>&lt;0.001</b>
CANTAB-PAL	Retrospective memory (non-verbal episodic memory)	1	0.061 ± 0.036	0.096	0.085 ± 0.039	0.029	0.134 ± 0.037	<b>&lt;0.001</b>
		2	0.065 ± 0.036	0.077	0.083 ± 0.039	0.027	0.137 ± 0.038	<b>&lt;0.001</b>
		3	0.002 ± 0.036	0.967	0.007 ± 0.039	0.859	0.041 ± 0.038	0.279
		4	0.002 ± 0.036	0.952	0.008 ± 0.039	0.842	0.042 ± 0.038	0.266
Letter Cancellation	Attention	1	0.038 ± 0.049	0.442	0.091 ± 0.053	0.084	0.146 ± 0.050	<b>0.004</b>
		2	0.042 ± 0.049	0.390	0.093 ± 0.053	0.074	0.138 ± 0.051	<b>0.007</b>
		3	-0.013 ± 0.049	0.795	0.024 ± 0.053	0.652	0.055 ± 0.052	0.282
		4	-0.012 ± 0.049	0.801	0.024 ± 0.053	0.647	0.056 ± 0.052	0.276
VST-Simple	Simple processing speed	1	-0.001 ± 0.001	0.082	-0.002 ± 0.001	<b>0.004</b>	-0.003 ± 0.001	<b>&lt;0.001</b>
		2	-0.001 ± 0.001	0.071	-0.002 ± 0.001	<b>0.003</b>	-0.003 ± 0.001	<b>&lt;0.001</b>
		3	0.000 ± 0.001	0.431	-0.001 ± 0.001	0.082	0.002 ± 0.001	<b>0.014</b>
		4	-0.001 ± 0.001	0.423	-0.001 ± 0.001	0.079	-0.002 ± 0.001	<b>0.013</b>
VST-Complex	Complex processing speed	1	0.000 ± 0.001	0.762	-0.001 ± 0.001	0.078	-0.002 ± 0.001	<b>0.025</b>
		2	0.000 ± 0.001	0.637	-0.001 ± 0.001	0.055	-0.002 ± 0.001	<b>0.014</b>
		3	0.000 ± 0.001	0.947	-0.001 ± 0.001	0.145	-0.001 ± 0.001	0.058
		4	0.000 ± 0.001	0.939	-0.001 ± 0.001	0.141	-0.001 ± 0.001	0.056

SF-EMSE, Short Form Extended Mini Mental State Exam (n = 7917); HVLТ, Hopkins Verbal Learning Test (n = 7589); CANTAB-PAL, Paired Associates Learning Test from the Cambridge Automated Neuropsychological Test Battery (n = 6970); Letter cancellation (n = 7847); VST-Simple, Visual Sensitivity Test, simple version (n = 6685); VST-Complex, Visual Sensitivity Test, complex version (n = 6685). Associations were explored via linear regression. Model 1 was adjusted for age, sex, BMI, waist circumference, marital status, and employment status. Model 2 was additionally adjusted for self-reported medical conditions (heart attack, stroke, arrhythmia, diabetes, depression, and other psychological illness), self-reported medication (BP lowering, lipid lowering, steroids, diabetes medication), HDL and LDL cholesterol, total triglycerides, smoking status, physical activity status, systolic and diastolic BP. Model 3 was additionally adjusted for education. Model 4 was additionally adjusted for *APOE E4* genotype. Scores for the SF-EMSE and HVLТ were negatively skewed, and therefore log and reverse score transformed variables were derived. Lower transformed scores on these tests reflect better cognitive performance (i.e. greater original scores). VST-Simple and VST-complex scores were log transformed (log10), whilst untransformed variables were used for the CANTAB-PAL and Letter Cancellation Task. Results are presented as  $\beta$ -coefficients and standard errors (SE).



## FIGURE LEGENDS

**Figure 1** Mediterranean diet adherence and risk of poor cognitive performance across the SF-EMSE (A; n = 7917), HVLТ (B; n = 7589), VST-Complex (C; n = 6685), and Prospective Memory (D; n = 7841) tasks in the EPIC-Norfolk study. Poor performance was defined as a score in the bottom 10 % of the population distribution for each test. Results are expressed as odds ratios plus 95 % confidence intervals for poor cognitive performance with medium and high compared with the lowest tertile of Mediterranean diet adherence (dashed line). Associations were explored via logistic regression. \* represents a significantly lower risk of poor cognitive performance compared with the lowest tertile of Mediterranean diet adherence ( $P < 0.05$ ).

**Figure 2** Mediterranean diet adherence and risk of poor cognitive performance in individuals with low (shaded area) and high CVD risk across the HVLТ (A; high risk n = 3685, low risk n = 3847) and VST-Complex (B; high risk n = 3207, low risk n = 3424) tasks in the EPIC-Norfolk study. Participants were stratified into low and high risk groups for analysis by the median QRISK2 score. Poor performance was defined as a score in the bottom 10 % of the population distribution for each test. Results are expressed as odds ratios plus 95 % confidence intervals for poor cognitive performance with medium and high compared with the lowest tertile of Mediterranean diet adherence (dashed line). Associations were explored via logistic regression. \* represents a significantly lower risk of poor cognitive performance compared with the lowest tertile of Mediterranean diet adherence in the same CVD risk category ( $P < 0.05$ ).