

TITLE

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

AUTHORS

Oliver M Shannon, Blossom CM Stephan, Antoneta Granic, Marleen Lentjes, Shabina Hayat, Angela Mulligan, Carol Brayne, Kay-Tee Khaw, Rafe Bundy, Sarah Aldred, Michael Hornberger, Stella-Maria Paddick, Graciela Muniz-Tererra, Anne-Marie Minihihane, John C Mathers, and Mario Siervo

AFFILIATIONS

1. Human Nutrition Research Centre, Institute of Cellular Medicine, Newcastle University, Leech Building, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK (OMS, JCM, MS)
2. Institute of Health and Society and Newcastle University Institute of Ageing, Newcastle University, Biomedical Research Building, Campus of Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK (BCMS, AG)
3. Department of Public Health & Primary Care, University of Cambridge, Worts Causeway, Cambridge, CB1 8RN, UK (ML, SH, AM, CB)
4. School of Medical Sciences and Health, Örebro University, Campus USÖ, 701 82 Örebro, Sweden (ML)
5. Clinical Gerontology Unit, School of Clinical Medicine, University of Cambridge, Cambridge, CB2 2QQ, UK (KTK)
6. Department of Nutrition and Preventive Medicine, Norwich Medical School, University of East Anglia (UEA), Norwich, UK (RB, A-MM)

7. School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, UK (SA)
8. Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK (MH)
9. Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital and Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK (S-MP)
10. Centre for Dementia Prevention, Centre for Clinical, Brain Sciences, University of Edinburgh, Edinburgh, UK (GM-T)
11. School of Life Sciences, The University of Nottingham Medical School, Queen's Medical Centre, Nottingham, NG7 2UH, UK (MS)

CORRESPONDING AUTHOR:

Name: Dr. Oliver Shannon

Mailing address: Room 2.050, William Leech Building, Medical School, Newcastle University, Newcastle-upon-Tyne, NE2 4HH

Telephone number: 0191 208 1140

Email: Oliver.Shannon@Newcastle.ac.uk

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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 Lower scores reflect better performance for tests of global cognition and verbal episodic
19 memory (due to data transformations) and processing speed (indicating faster reaction time),
20 whilst higher scores for other tests reflect better performance.

21

22 **Results**

23 Higher MedDiet adherence defined by the Pyramid MedDiet score was associated with better
24 global cognition ($\beta \pm SE = -0.012 \pm 0.002$; $P < 0.001$), verbal episodic memory ($\beta \pm SE = -$
25 0.009 ± 0.002 ; $P < 0.001$), and simple processing speed ($\beta \pm SE = -0.002 \pm 0.001$; $P = 0.013$). Lower

26 risk of poor verbal episodic memory (OR(95%CI)=0.784 (0.641,0.959); $P=0.018$), complex
27 processing speed (OR(95%CI)=0.739 (0.601,0.907); $P=0.004$), and prospective memory
28 (OR(95%CI)=0.841 (0.724,0.977); $P=0.023$) was also observed for the highest versus lowest
29 Pyramid MedDiet tertiles. The effect of a one-point increase in Pyramid score on global
30 cognitive function was equivalent to 1.7 fewer years of cognitive ageing. MedDiet adherence
31 defined by the MEDAS score (mapped using both binary and continuous scoring) showed
32 similar, albeit less consistent, associations. In stratified analyses, associations were evident in
33 individuals at higher CVD risk only ($P<0.05$).

34

35 **Conclusions**

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

40

41

42 **KEYWORDS**

43 Mediterranean diet, cognitive function, cognitive decline, dementia risk, cardiovascular
44 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 β -
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 HVLIT 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 β -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 10th 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 ≤ 0.5 % of participants for socioeconomic, lifestyle,
221 anthropometric and BP data, ≤ 1.1 % for self-reported medical conditions, ≤ 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 HVLT (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 (β 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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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.

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

Characteristic	Mediterranean diet score														
	Overall	MEDAS ¹				<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)	0.002	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	<0.001	50	45	39	<0.001	54	44	36	<0.001		
BMI, kg/m ² (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)	<0.001	25.6 (23.5, 27.9)	25.5 (23.5, 27.8)	25.0 (23.0 – 27.4)	<0.001	25.6 (23.6, 28.0)	25.4 (23.4, 27.8)	25.0 (23.0, 27.4)	<0.001		
Smoking status, % (n=7983)					<0.001				<0.001				<0.001		
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, %					0.001				<0.001				0.007		
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)					<0.001				<0.001				<0.001		
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)	0.046	131 (121, 142)	130 (120, 143)	129 (119, 141)	<0.001	132 (121, 142)	131 (120, 142)	129 (119, 142)	0.001		
Diastolic BP, mmHg (n=7993)	81 (74, 88)	81 (74, 88)	81 (74, 88)	80 (73, 87)	0.010	81 (74, 88)	81 (74, 89)	80 (73, 87)	0.001	81 (74, 88)	81 (74, 88)	80 (73, 87)	0.001		
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)	<0.001	1.3 (1.1, 1.6)	1.4 (1.1, 1.7)	1.5 (1.2, 1.8)	<0.001	1.3 (1.1, 1.6)	1.4 (1.1, 1.7)	1.4 (1.2, 1.8)	<0.001		
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)	0.002	3.9 (3.2, 4.5)	3.8 (3.1, 4.5)	3.7 (3.1, 4.4)	0.001		
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)	<0.001	1.5 (1.0, 2.2)	1.5 (1.0, 2.1)	1.3 (0.9, 1.9)	<0.001	1.5 (1.0, 2.2)	1.4 (1.0, 2.0)	1.4 (0.9, 1.9)	<0.001		

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. ¹For 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	
			β + SE	<i>P</i>	β + SE	<i>P</i>	β + SE	<i>P</i>
SF-EMSE	Global cognition	1	-0.010 ± 0.002	< 0.001	-0.013 ± 0.002	< 0.001	-0.021 ± 0.002	< 0.001
		2	-0.010 ± 0.002	< 0.001	-0.013 ± 0.002	< 0.001	-0.021 ± 0.002	< 0.001
		3	-0.004 ± 0.002	0.019	-0.005 ± 0.002	0.008	-0.012 ± 0.002	< 0.001
		4	-0.004 ± 0.002	0.018	-0.005 ± 0.002	0.008	-0.012 ± 0.002	< 0.001
HVLТ	Retrospective memory (verbal episodic memory)	1	-0.008 ± 0.002	< 0.001	-0.010 ± 0.002	< 0.001	-0.016 ± 0.002	< 0.001
		2	-0.008 ± 0.002	< 0.001	-0.010 ± 0.002	< 0.001	-0.016 ± 0.002	< 0.001
		3	-0.003 ± 0.002	0.147	-0.004 ± 0.002	0.058	-0.009 ± 0.002	< 0.001
		4	-0.003 ± 0.002	0.139	-0.004 ± 0.002	0.054	-0.009 ± 0.002	< 0.001
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	< 0.001
		2	0.065 ± 0.036	0.077	0.083 ± 0.039	0.027	0.137 ± 0.038	< 0.001
		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	0.004
		2	0.042 ± 0.049	0.390	0.093 ± 0.053	0.074	0.138 ± 0.051	0.007
		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	0.004	-0.003 ± 0.001	< 0.001
		2	-0.001 ± 0.001	0.071	-0.002 ± 0.001	0.003	-0.003 ± 0.001	< 0.001
		3	0.000 ± 0.001	0.431	-0.001 ± 0.001	0.082	0.002 ± 0.001	0.014
		4	-0.001 ± 0.001	0.423	-0.001 ± 0.001	0.079	-0.002 ± 0.001	0.013
VST-Complex	Complex processing speed	1	0.000 ± 0.001	0.762	-0.001 ± 0.001	0.078	-0.002 ± 0.001	0.025
		2	0.000 ± 0.001	0.637	-0.001 ± 0.001	0.055	-0.002 ± 0.001	0.014
		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 β -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 ($P < 0.05$).