

Mediterranean diet adherence and cognitive function in older, UK adults

Shannon, Oliver M; Stephan, Blossom C M; Granic, Antoneta; Lentjes, Marleen; Hayat, Shabina; Mulligan, Angela; Brayne, Carol; Khaw, Kay-tee; Bundy, Rafe; Aldred, Sarah; Hornberger, Michael; Paddick, Stella-maria; Muniz-tererra, Graciela; Minihane, Anne-marie; Mathers, John C; Siervo, Mario

DOI:
[10.1093/ajcn/nqz114](https://doi.org/10.1093/ajcn/nqz114)

License:
None: All rights reserved

Document Version
Peer reviewed version

Citation for published version (Harvard):
Shannon, OM, Stephan, BCM, Granic, A, Lentjes, M, Hayat, S, Mulligan, A, Brayne, C, Khaw, K, Bundy, R, Aldred, S, Hornberger, M, Paddick, S, Muniz-tererra, G, Minihane, A, Mathers, JC & Siervo, M 2019, 'Mediterranean diet adherence and cognitive function in older, UK adults: The European Prospective Investigation into Cancer and Nutrition-Norfolk (EPIC-Norfolk) Study', *American Journal of Clinical Nutrition*, vol. 110, no. 4, pp. 938-948. <https://doi.org/10.1093/ajcn/nqz114>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:
Checked for eligibility: 16/08/2019

This is a pre-copyedited, author-produced PDF of an article accepted for publication in *American Journal of Clinical Nutrition* following peer review. The version of record Oliver M Shannon, Blossom C M 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 Minihane, John C Mathers, Mario Siervo, Mediterranean diet adherence and cognitive function in older UK adults: the European Prospective Investigation into Cancer and Nutrition–Norfolk (EPIC-Norfolk) Study, *The American Journal of Clinical Nutrition*, is available online at: <https://doi.org/10.1093/ajcn/nqz114>

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

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 Minihane, 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

SOURCES OF SUPPORT

This research was supported by the Alzheimer's Research UK Prevention and Risk Reduction Fund (ARUK-PRRF2017-006). The funders had no role in the study design, data collection, analysis and interpretation, the preparation of the manuscript, or in the decision to submit the article for publication.

RUNNING HEAD

Mediterranean diet adherence and cognitive function

NAMES FOR PUBMED INDEXING

Shannon, Stephan, Granic, Lentjes, Hayat, Mulligan, Brayne, Khaw, Bundy, Aldred, Hornberger, Paddick, Muniz-Tererra, Minihane, Mathers, Siervo

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
4 (MedDiet) is associated with better cognitive function and reduced dementia risk. It is
5 unclear if similar benefits exist in non-Mediterranean regions.

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
10 versus low cardiovascular disease (CVD) risk.

12 **Design**

13 We conducted an analysis in 8009 older individuals with dietary data at Health Check 1
14 (1993-1997) and cognitive function data at Health Check 3 (2006-2011) of the European
15 Prospective Investigation of Cancer, Norfolk (EPIC-Norfolk). Associations were explored
16 between MedDiet adherence and global and domain specific cognitive test scores and risk of
17 poor cognitive performance in the entire cohort, and when stratified according to CVD risk
18 status. Lower scores reflect better performance for tests of global cognition and verbal
19 episodic memory (due to data transformations) and processing speed (indicating faster
20 reaction time), whilst higher scores for other tests reflect better performance.

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
37 of poor cognition in older, UK adults. This evidence underpins the development of
38 interventions to enhance MedDiet adherence, particularly in individuals at higher CVD risk,
39 aiming to reduce the risk of age-related cognitive decline in non-Mediterranean
40 populations.

41

42

43 **KEYWORDS**

44 Mediterranean diet, cognitive function, cognitive decline, dementia risk, cardiovascular
45 health, healthy ageing

46

47

48

49

50

51

52

53 **INTRODUCTION**

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

76 MedDiet adherence and cognitive function with more comprehensive measures of exposure
77 to the MedDiet are warranted.

78

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

87

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

94

95 **SUBJECTS AND METHODS**

96 **Study population and design**

97 EPIC is an ongoing, multi-centre prospective cohort study, exploring the relationship
98 between diet and disease across 10 European countries (25). EPIC-Norfolk is one of two UK
99 centres within EPIC. The design and methods of this study have been described
100 comprehensively elsewhere (26). Briefly, EPIC-Norfolk included a baseline health

101 examination (Health Check 1; HC1) of 25,639 men and women aged 40-79 years, recruited
102 from East Anglia in England via general practice registers, between 1993 and 1997.
103 Participants were invited to a follow up assessment (Health Check 2; HC2) between 1998 and
104 2000, which included those tests undertaken at baseline plus further variables such as bone
105 health. Health Check 3 (HC3) was conducted between 2006 and 2011 in 8623 participants
106 (aged 48–92 years at that time), to investigate conditions relevant to ageing, including
107 cognitive function, loss of mobility, and loss of vision (27). Cognitive data were collected for
108 8585 individuals at HC3 (28).

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

118

119 **Dietary assessment and calculation of Mediterranean diet scores**

120 A 130-item, semi-quantitative FFQ, extensively used and validated in previous research (29–
121 31), was used to evaluate the habitual diet of participants over the past year at HC1. Food
122 intake values were calculated from the FFQ data using validated computer programs (32,33),
123 and foods were grouped into relevant categories which were used for the creation of the
124 various MedDiet scores (e.g. total fruit intake or total vegetable intake). Dietary data were
125 energy-adjusted (2000 kcal/d (8.4 MJ/d)) via the residuals method (34) to allow evaluation of

126 diet quality independent of diet quantity (35). Briefly, log transformed dietary variables were
127 used to create residuals with more consistent variance across the levels of total energy intake.
128 Values were back-transformed by adding the residuals to a constant, equivalent to the
129 predicted value for the log of 2000 kcal, and then calculating the antilog. Three MedDiet
130 scores were then calculated as measures of adherence to the MedDiet pattern. These were: i)
131 the MEDAS score (categorical), ii) the MEDAS Continuous score, and iii) the MedDiet
132 pyramid (Pyramid) score. The MEDAS score is a 14-point score used to track MedDiet
133 adherence in the aforementioned PREDIMED RCT (3). As recently validated for use in UK
134 populations (36), the standard MEDAS score was calculated with participants allocated 0 or 1
135 points per food item depending on whether they achieved the cut off for the dietary target.
136 The MEDAS Continuous score was developed as part of the current analysis to provide
137 greater sensitivity. It was calculated using the same dietary targets as the standard MEDAS
138 score but with points allocated on a continuous basis (i.e. between 0 and 1) depending on
139 closeness to the dietary target. The Pyramid score is a 15-point scoring system proposed by
140 the Mediterranean Diet Foundation (1) that was used previously for the EPIC-Norfolk cohort
141 by Tong et al. (35). It is also coded on a continuous basis. Details of the calculations used for
142 each of the MedDiet scores are provided in **Supplementary Tables 1 and 2**.

143

144 **Assessment of cognitive function**

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

- 148 1) **Global cognitive function:** Total score from a shortened version of the Extended
149 Mental State Exam (SF-EMSE; n = 7917).

- 150 2) **Verbal episodic memory:** Total score from the Hopkins Verbal Learning test
151 (HVLТ; n = 7589).
- 152 3) **Non-verbal episodic memory:** The first trial memory score of the Paired Associates
153 Learning Test from the Cambridge Neuropsychological Test Battery (CANTAB-PAL;
154 n = 6970).
- 155 4) **Attention:** Accuracy score (number of targets correctly identified – number missed)
156 from the Letter Cancellation Task, as applied in the Medical Research Council
157 Cognitive Function and Ageing study (MRC-CFAS; n = 7847).
- 158 5) **Simple processing speed:** Mean response time of the Simple Visual Sensitivity Test
159 (VST; n = 6685).
- 160 6) **Complex processing speed and visual deficits contributing to cognitive**
161 **impairment:** Mean response time of the Complex VST (n = 6685).
- 162 7) **Memory:** Pass or fail of the Prospective Memory Test, as also described in the MRC-
163 CFAS (n = 7841).

164

165 **Assessment of other covariates**

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

171

172 **Statistical analyses**

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

175

176 Cohort characteristics

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

180 Mediterranean diet adherence and cognitive function

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

193

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

196 Using the same cognitive data, but now categorised into normal and poor performance,
197 associations between MedDiet adherence and risk of poor cognitive performance were
198 explored via logistic regression. Poor performance on any test was defined as a score below
199 the 10th percentile of the population distribution for each of the cognitive tests (28). Because

200 19% of the population failed the prospective memory task, this was used as the lower cut-
201 point for this outcome.

202

203 Given the well documented associations between poor cardiovascular health and cognitive
204 impairment (21–23), we performed stratified analyses which tested the hypothesis that the
205 effects of MedDiet adherence on risk of poor cognitive performance differed by CVD risk
206 group. Lower and higher CVD risk was defined as below and above the median QRISK2
207 score (which is indicative CVD risk in the next 10 years (39)). Results are presented as odds
208 ratios (OR) with 95% confidence intervals.

209

210 **Statistical models**

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

223

224 **Missing data**

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

231 **Sensitivity analyses**

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

246

247 **RESULTS**

248 **Cohort characteristics**

249 Baseline participant characteristics are in **Table 1**, with additional details also provided in
250 **Supplementary Table 3**. Participants with high adherence to the MedDiet were less likely
251 to be smokers, and more likely to be female, unmarried, more physically active, and have a
252 higher education status compared with individuals with low MedDiet adherence. In addition,
253 individuals with a high MedDiet adherence were more likely to have lower BMI, waist
254 circumference, systolic and diastolic BP, triglyceride concentrations, and QRISK2 score, and
255 higher HDL-cholesterol concentrations, compared with individuals with low MedDiet
256 adherence (all $P < 0.05$).

257

258 ****INSERT TABLE 1 HERE****

259

260 **Associations between MedDiet adherence and cognitive function**

261 Associations between MedDiet adherence and cognitive performance are shown in **Table 2**.
262 In the maximally adjusted linear regression models (model 4), higher MedDiet adherence, as
263 characterised by all three MedDiet scores, was associated with significantly better
264 performance on the SF-EMSE (global cognition; MEDAS: $\beta \pm SE = -0.004 \pm 0.002$, $P =$
265 0.018 ; MEDAS Continuous: $\beta \pm SE = -0.005 \pm 0.002$, $P = 0.008$; Pyramid: $\beta \pm SE = -0.012 \pm$
266 0.002 , $P < 0.001$). Higher adherence to the MedDiet (assessed using the Pyramid score) was
267 also associated with significantly better performance on the HVLIT (verbal episodic memory;
268 $\beta \pm SE = -0.009 \pm 0.002$, $P < 0.001$) and VST-Simple (simple processing speed; $\beta \pm SE = -$
269 0.002 ± 0.001 , $P = 0.013$). To put this into perspective, the effects of a one point increase in
270 MedDiet score (maximum 14-15 points) on SF-EMSE performance, a measure of global
271 cognition, was equivalent to 0.57, 0.71, and 1.7 fewer years of ageing for the MEDAS,
272 MEDAS Continuous, and Pyramid scores, respectively (β value for age in maximally
273 adjusted models was 0.007, $P < 0.001$).

274

275 ****INSERT TABLE 2 HERE****

276

277 **Associations between MedDiet adherence and risk of poor cognitive performance**

278 Associations between MedDiet adherence and risk of poor cognitive performance are
279 presented in **Figure 1** and **Supplementary Table 4**. In maximally adjusted models (model
280 4), high compared with low MedDiet adherence as defined by the MEDAS Continuous score
281 was associated with reduced risk of poor cognitive performance on the SF-EMSE (global
282 cognition; OR (95% CI) = 0.828 (0.696, 0.985), $P = 0.033$) and HVLT (verbal episodic
283 memory; OR (95% CI) = 0.797 (0.653, 0.973), $P = 0.026$). Higher MedDiet adherence
284 defined by the Pyramid score was associated with a lower risk of poor performance in the
285 HVLT (OR (95% CI) = 0.784 (0.641, 0.959), $P = 0.018$), VST-Complex (OR (95% CI) =
286 0.739 (0.601, 0.907), $P = 0.004$), and Prospective memory task (Prospective memory; OR
287 (95% CI) = 0.841 (0.724, 0.977), $P = 0.023$). Moderate MedDiet adherence defined by the
288 MEDAS Continuous score and the Pyramid score was also associated with a lower risk of
289 poor performance on the VST-Complex task (complex processing speed; MEDAS
290 Continuous: OR (95% CI) = 0.803 (0.660, 0.977), $P = 0.029$; Pyramid: OR (95% CI) = 0.820
291 (0.675, 0.995), $P = 0.045$).

292

293 ****INSERT FIGURE 2 HERE****

294

295 When participants were grouped by CVD risk (below and above the median QRISK2 score;
296 **Figure 2; Supplementary Table 5**), no associations between MedDiet adherence and risk of
297 poor cognitive performance in individuals with low CVD risk emerged. However, in
298 individuals at high CVD risk, MedDiet adherence as defined by the MEDAS Continuous

299 score was associated with lower risk of poor HVLТ performance (verbal episodic memory;
300 OR (95% CI) = 0.756 (0.596, 0.958), $P = 0.021$). Additionally, in high CVD risk individuals,
301 moderate MedDiet adherence defined by the MEDAS Continuous score was associated with
302 lower risk of poor VST-Complex performance (complex processing speed; OR (95% CI) =
303 0.728 (0.565, 0.939), $P = 0.015$). Both moderate and high MedDiet adherence defined by the
304 Pyramid score were associated with lower risk of poor VST-Complex performance in
305 individuals with high CVD risk (Moderate: OR (95% CI) = 0.707 (0.551, 0.908), $P = 0.007$;
306 High: OR (95% CI) = 0.667 (0.551, 0.871), $P = 0.003$).

307

308 ****INSERT FIGURE 2 HERE****

309

310 **Sensitivity analyses**

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

320

321 In analyses where diet scores were derived after sequential removal of individual MedDiet
322 components, the significant positive associations with cognition remained reasonably stable
323 (**Supplementary Table 8 and 9**), except for the removal of wine or fruit from the MEDAS

324 score and wine from the MEDAS Continuous score, after which associations with SF-EMSE
325 performance were no longer present ($P > 0.05$; global cognition). When potential under- and
326 over-reporters were excluded from the analysis according to the Goldberg cut offs, higher
327 MedDiet adherence defined by the Pyramid score remained significantly associated with
328 better SF-EMSE (global cognition), HVLT (verbal episodic memory), and VST-Simple
329 (simple processing speed) performance, and was additionally significantly associated with
330 higher VST-Complex (complex processing speed) performance. Higher MedDiet adherence
331 defined by the MEDAS continuous score was now significantly associated with higher HVLT
332 performance, but associations with SF-EMSE performance were no longer significant.
333 Associations between the MEDAS and SF-EMSE performance were no longer significant
334 (**Supplementary Table 10**). When we included an interaction term in the model for
335 MedDiet * CVD risk category, we found the MedDiet was more effective in individuals with
336 high versus low CVD risk at reducing the risk of poor cognitive performance
337 (**Supplementary Table 11**), confirming the results from our stratified analyses. Finally,
338 when we compared cohort characteristics between participants with and without complete
339 cognitive testing data, we found that participants who completed all cognitive tests were
340 overall significantly younger, more physically active, had a higher educational attainment,
341 and lower systolic BP and QRISK2 score (all $P < 0.05$; **Supplementary table 12**).

342

343 **DISCUSSION**

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

349

350 MedDiet and cognitive function/ risk of poor cognitive performance

351 This is the first, large-scale prospective study exploring associations between an *a priori*
352 defined MedDiet and cognitive function/poor cognitive performance in a UK population. We
353 found that higher MedDiet adherence defined by one or more MedDiet scores was associated
354 with better global cognition, verbal episodic memory, and simple processing speed, together
355 with a lower risk of poor global cognition, verbal episodic memory, complex processing
356 speed, and prospective memory. To put this into perspective, compared with the effects of
357 age, which is the strongest determinant of cognitive decline (41), a 3 point increase in
358 Pyramid score is equivalent to ~ 5 fewer years of ageing on global cognitive function. These
359 findings are consistent with a recent study conducted in Greece by Anastasiou et al. (42), who
360 reported that higher adherence to the Mediterranean lifestyle (encompassing the MedDiet
361 plus physical activity, sleep, and daily activities) reduced risk of low global cognitive
362 function equivalent to 2.7 fewer years of ageing. Delaying the onset of dementia by two- or
363 five-years would reduce UK dementia prevalence by 19% and 33% by 2050, and result in
364 much lower prevalence of severe dementia (43).

365

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

374 versus prospective) and follow up duration, and participant groups (e.g. divergent age
375 profiles, healthy versus non-healthy cohorts).

376

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

392

393 **Strengths and limitations**

394 Study strengths include the large sample size and the comprehensive assessment of cognitive
395 function using a range of previously validated tests which cover multiple different domains
396 that are affected during the early stages of cognitive decline prior to dementia onset.
397 Moreover, we used a prospective design in which dietary measures were obtained
398 approximately 13 years before the cognitive assessments were made thus reducing the risk of

399 reverse causality. A further strength of this study is that we used two previously published,
400 robustly defined measures of exposure to the MedDiet. In addition, we created a novel
401 derivative of the MEDAS score where we coded intake of foods continuously rather than on a
402 binary basis, which was more sensitive at quantifying individual diet quality and showed
403 stronger links with cognitive outcomes. However, although dietary data were derived from a
404 validated FFQ, this instrument may not provide sufficient detail about the consumption of
405 some foods key to the MedDiet pattern, such as the type and intake of olive oil, consumption
406 of sofrito, and the type of nuts consumed (12). Moreover, the scales we used to evaluate
407 MedDiet adherence do not account for intake of supplements, which may contain several
408 nutrients key to this dietary pattern (e.g. omega-3, 50% of which is obtained from
409 supplements in the UK (48)). Furthermore, for our primary analysis, dietary intake was
410 assessed between 1993-1997, whilst cognitive function was assessed 13 to 18 years later, and
411 it is possible that participants may have altered their diet during this follow up period.
412 Likewise, given cognitive function was only measured at one time point, we were unable to
413 explore associations between MedDiet adherence and cognitive trajectories. In addition,
414 despite adjusting for multiple covariates, our results may have been influenced by
415 unmeasured variables. For example, we did not measure participant IQ, which influences
416 both cognitive performance and dietary choices (19), but we included education as a
417 covariate which, typically, shows good correlation with IQ (49). Finally, it is possible that
418 there is a degree of selection bias in this study, which may limit the generalisability of our
419 findings to the wider population. Indeed, participants with poorer cognition may have decided
420 not to/ were unable to take part in data collection at HC3. Alternatively, these individuals
421 may have only completed a sub-set of tests at this phase. In this regard, it is noteworthy that
422 participants with incomplete cognitive data showed generally poorer health than those who
423 completed all tests. It is difficult to speculate how this may have influenced our results, and

424 future research is warranted to explore the impact of the MedDiet on cognition in different
425 cohorts.

426

427 **Conclusions and implications**

428 This study provides evidence that higher MedDiet adherence is associated with better
429 cognitive function and lower risk of poor cognitive performance in a UK population. In
430 addition, we demonstrated that the MedDiet is particularly associated with lower risk of poor
431 cognitive performance in individuals with higher CVD risk. These results have implications
432 for the development of dietary recommendations to facilitate healthy cognitive ageing. In
433 addition, the findings suggests that individuals with higher CVD risk are a key population
434 group for future RCTs testing lifestyle modifications to improve cognition during ageing.

435

436 **ACKNOWLEDGEMENTS**

437 The authors would like to express their gratitude to the participants, General Practitioners and
438 staff of the EPIC-Norfolk study team. Finally, we would like to thank Alzheimer's Research
439 UK for funding this research under the project 'Diet, physical activity and dementia risk in
440 UK adults: Epidemiology and MedEx feasibility study'.

441

442

443 **CONFLICT OF INTEREST STATEMENT**

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

445

446 **AUTHOR CONTRIBUTIONS**

447 This study was designed by BCMS, MS, AMM, and JCM. OS, MS, JCM, AM, ML, RB
448 calculated Mediterranean diet scores. SH, SMP, and MH helped interpret cognitive data. OS

449 conducted the statistical analysis, with guidance from MS, JCM, AG, BCMS, ML, and GMT.
450 OS, MS, and JCM drafted the manuscript. All the authors participated in the interpretation of
451 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 ¹			P	MEDAS Continuous			P	Pyramid			P
		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	6.8 (3.0, 10.6)	7.3 (3.3, 11.3)	6.8 (3.1, 10.5)	5.8 (2.6, 9.0)	<0.001	7.6 (3.5, 11.7)	6.8 (3.0, 10.6)	5.8 (2.6, 9.0)	<0.001	7.7 (3.5, 11.9)	6.7 (3.0, 10.4)	6.0 (2.7, 9.3)	<0.001

(n=7953)	14.0)	14.8)	14.1)	12.6)	15.5)	13.9)	12.7)	15.4)	13.8)	12.6)
----------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------

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 ($P < 0.05$).