Mediterranean diet adherence and cognitive function in older, UK adults

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TITLE

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

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RUNNING HEAD

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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

ABSTRACT

Background

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

Objective

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

Design

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

Results

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

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

Conclusions

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

KEYWORDS

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

INTRODUCTION

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

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

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

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

SUBJECTS AND METHODS

Study population and design

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

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

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

Dietary assessment and calculation of Mediterranean diet scores

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

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

Assessment of cognitive function

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

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

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

Assessment of other covariates

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

Statistical analyses

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

Cohort characteristics

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

Mediterranean diet adherence and cognitive function

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

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

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

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

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

Statistical models

A series of statistical models was used to investigate associations between MedDiet adherence and cognitive function or risk of poor cognitive performance. Models were adjusted for a range of covariates measured at the same point as the dietary exposure. Additional covariates were added to the model as we progressed from Model 1 to Model 4 (i.e., basic to maximal adjustment) as follows: Model 1 adjusted for age, sex, body mass index (BMI), waist circumference, marital status, and employment status; Model 2 adjusted additionally 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, triglycerides, smoking status, physical activity status, systolic BP and diastolic BP; Model 3 adjusted additionally for education; and, Model 4 adjusted additionally for *APOE* genotype (presence or absence of the *APOE4 allele*).

Missing data

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

Sensitivity analyses

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

RESULTS

Cohort characteristics

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

INSERT TABLE 1 HERE

Associations between MedDiet adherence and cognitive function

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

INSERT TABLE 2 HERE

Associations between MedDiet adherence and risk of poor cognitive performance

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

INSERT FIGURE 2 HERE

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

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

INSERT FIGURE 2 HERE

Sensitivity analyses

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

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

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

DISCUSSION

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

MedDiet and cognitive function/ risk of poor cognitive performance

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

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

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

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

Strengths and limitations

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

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

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

Conclusions and implications

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

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

This study was designed by BCMS, MS, AMM, and JCM. OS, MS, JCM, AM, ML, RB 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.

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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]				MEDAS Continuous				Pyramid			
		Low = 0 - 2 n=2400	Medium = 3 - 4 n=4198	High = 5 - 10 n=1411	*P*	Low = 1.31 - 4.97 n=2670	Medium = 4.98 - 6.04 n=2670	High = 6.05 - 10.87 n=2669	*P*	Low = 3.47 - 7.53 n=2687	Medium = 7.54 - 8.66 n=2673	High = 8.67-12.93 n=2649	*P*
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,	7.3 (3.3,	6.8 (3.1,	5.8 (2.6,	**<0.001**	7.6 (3.5,	6.8 (3.0,	5.8 (2.6,	**<0.001**	7.7 (3.5,	6.7 (3.0,	6.0 (2.7,	**<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. [1]For the MEDAS score, it was not possible to divide participants into approximately equal sized groups, given a large number of participants achieved the same score. Therefore, participants were split into three groups where all individuals with the same score were categorised together.

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

Outcome	Cognitive domain	Model	MEDAS		MEDAS Continuous		Pyramid	
			β + SE	*P*	β + SE	*P*	β + SE	*P*
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**
HVLT	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); HVLT, 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 HVLT 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), HVLT (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 HVLT (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 ($P < 0.05$).