Mediterranean diet adherence is associated with reduced subjective cognitive decline in a healthy adult population

Mediterranean diet adherence is associated with reduced subjective cognitive concerns (SCCs) in a healthy adult population

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Abstract:

Importance: Benefits of a Mediterranean diet on loss of cognition have been suggested, but epidemiologic studies have been relatively small and of limited duration.

Objective: To assess prospectively the association between long-term adherence to the Mediterranean dietary pattern to self-reported subjective cognitive concerns.

Design: Prospective observational study

Participants: The Health Professionals' Follow-up Study, a prospective cohort of 51,529 men, 40-75 years of age when enrolled in 1986, of which 27,406 individuals were included in the primary analysis

Exposures: Mediterranean diet score, computed from the mean of 5 food frequency questionnaires, assessed every 4 years through to 2002

Main outcome measures: Self-reported subjective cognitive concerns (SCCs) assessed by a 6-item questionnaire in 2008 and 2012, and validated by association with genetic variants in APOE4.

Results: Using the average of 2008 and 2012 SCC scores, 38.2% of men were considered to have moderate memory scores and 7.4% were considered to have poor memory scores. Specifically, in the multivariate model, having a cumulative MD score in the highest quintile as compared to the lowest quintile was associated with a 40% lower odds of a poor SCC score (Odds Ratio: 0.60, 95% CI: 0.51-0.71) and a 38% lower odds of a moderate SCC score (Odds Ratio: 0.72, 95% CI: 0.66-0.79). The trends for these logistic regression analyses across quintiles of the exposure were significant. A similar pattern was observed in the age-adjusted model.

Conclusions and Relevance: Long-term adherence to the Mediterranean diet pattern was strongly related to lower subjective cognitive concerns. These findings provide

further evidence that healthy dietary patterns may provide an important early intervention to prevent or delay cognitive decline.

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Glossary of Abbreviations

AD Alzheimer's disease

APOE Apolipoprotein E

BMI Body mass index

CVD cardiovascular disease

FFQ Food frequency questionnaire

HPFS Health Profession's Follow-up Study

MCI Mild cognitive impairment

MD Mediterranean diet

METs Metabolic Equivalent of Tasks

MUFA Monounsaturated fatty acid

MV Multivariate

SCC Subjective cognitive concerns

SF Saturated fat

Section I. Introduction

Alzheimer's Disease (AD), the most frequent form of dementia, constitutes a considerable public health challenge given longer life expectancy rates worldwide and the currently lack of treatments that halt or reverse its course (Ferri, 2005). Dementia is characterized by progressive deterioration in multiple domains of cognitive functions that consititute a barrier to daily functioning (APA, 2013). A continuum between early, self-perceived changes in memory, here termed subjective cognitive concerns (SCCs), on one hand and dementia on the other, with intervening clinical manifestations of mild cognitive impairment (MCI) and pre-dementia, has been documented (Petersen et al., 2014). SCCs, changes in memory or thinking reported by cognitively intact older adults, are a good prognostic marker for and predictor of, AD (Gifford et al., 2013).

Given this continuum, the AD pathophysiological process begins with a long pre-clinical phase, which provides a considerable window for preventative interventions. Age and genetic variants confer differential risk of developing AD to individuals (Barberger-Gateau, 2013), but these risk factors are non-modifiable. Modifiable factors that may play a neuroprotective role include physical activity and diet; the latter has recently become the object of much research.

Diets high in specific nutrients such as beta-carotene, Vitamin E (Morris, 2012), Vitamins C and A (Engelhart et al., 2002), flavonoids (Commenges et al., 2000; Schaffer et al., 2012), n-3 polyunsaturated fatty acids (PUFA), (Lopez et al., 2011) have been associated with reduced cognitive decline in some relatively small, observational studies. Accumulating evidence suggests that a combination of dietary factors over time provides most benefit to the brain. Of existing research into the synergistic and cumulative effect of overall dietary patterns on cognitive health, the strongest evidence has accrued on the Mediterranean diet pattern (Knight et al., 2016; Safouris et al., 2015; Knight et al., 2015, Valls-Pedret et al. 2015; Galbete et al. 2015; Trichipolou et al., 2015; Koyama et al., 2015; Tagney et al., 2014; Singh et al., 2014).

The MD, first described by Keys et al., is characterized by the consumption of non-hydrogenated, unsaturated fats as olive oil (rather than saturated and trans-fats), omega 3-fatty acids from fish and plant sources, and a diet high in fruits, vegetables, nuts and whole grains, with a relatively low consumption of red meat and dairy products (Keys et al., 1986).

Robust evidence from a variety of studies, including clinical trials, prospective cohort studies and basic science experiments on metabolism over the past few decades has documented the cardioprotective effect of the MD pattern (Anand SS et al., 2015; Chiva-Blanch et al. 2014), the data on the potential link between MD and cognitive decline is relatively in its infancy. Preliminary evidence suggests that the MD may contribute to preserve cognition in aging individuals. However, results from existing studies are not fully consistent, resulting in an urgent need to collect rigorous longitudinal data from large, well-characterized cohorts. The PREDIMED randomized-control trial was recently published which provided strong evidence that a vegetable-based Mediterranean diet enhanced with either EVOO or nuts appears to improve cognition compared with a low-fat diet (Martinez-Lapiscina et al., 2013).

The aim of this analysis was therefore to study the association between long-term adherence to the Mediterranean diet and subjective cognitive concerns within a large prospective cohort of male health professionals. Because the participants were all health professionals, they can be assumed to have had a relatively high level of cognitive function as young adults.

Section 2. Student Role

My role in this project was to conceptualize the study design, analyze the data using SAS using existing data available from the Health Professionals Follow-up Study (HPFS) database, tabulate the results and write the manuscript, which is currently being finalized for publication. I supplemented my time with formal training in biostatistics and SAS coursework at the Harvard School of Public Health.

Section 3. Methods

We evaluated the association between adherence to the Mediterranean diet (MD) and subjective cognitive concerns using data from the Health Professionals Follow-up Study (HPFS). The Health Professional's Follow-up Study (HPFS) is a prospective cohort study initiated in 1986 among 51,529 US male health professionals ages 40-75.

Of the 27,406 men in our primary analysis, 15,768 (57.5%) were dentists, 2,056 (7.5%) were pharmacists, 240 (0.88%) were hospital pharmacists, 1,838 (6.7%) were optometrists, 1,100 (4.01%) were osteopathic doctors, 671 (2.5%) were podiatrists and 5,733 (20.9%) were veterinarians. At baseline, participants reported medical diagnoses, medications, height, current weight, ethnicity, and lifestyle factors (including smoking, physical activity and supplement use) and completed a validated semi-quantitative food-frequency questionnaire (FFQ). Most variables are updated every two years and diet information is updated every four years. The validity of the FFQ for measuring individuals' dietary exposures has been documented in the HPFS (Feskanich, 1993; Hu, 1999; Rimm E et al., 1992). The follow-up rate has been approximately 94% at each biennial questionnaire.

Dietary Index: Dietary intake was ascertained by a self-administered mailed food frequency questionnaire (FFQ) that was first administered in 1986 and has been assessed every four years since then. To determine adherence to the Mediterranean diet, we tabulated reported dietary information to compute a Mediterranean diet score (described in full below), computed from dietary information from FFQs from 1986 to 2002.

Diet score: The Mediterranean Diet score (described in full by Trichopoulou et al., 2003), was calculated as 9-point score based on nine indicated components of the Mediterranean diet. The score is computed based on individuals' consumption in comparison to the sex-specific median for that particular food component. For beneficial components traditionally consumed in the Mediterranean diet (vegetables, legumes, fruits and nuts, cereal, ratio of monounsaturated lipids to saturated lipids, and fish), individuals with consumption below the median were assigned a value of 0, and those whose consumption was at or the median were assigned a value of 1. For components presumed to be detrimental (meat, poultry, and dairy products, which are rarely nonfat or low-fat in Greece), individuals whose consumption was below the median were assigned a value of 1, and those whose consumption was at or above the median were assigned a value of 0. For ethanol, a value of 1 was assigned to men who consumed between 10 and 50 grams per day and to women who consumed between 5 and 25 grams per day. Thus, the total Mediterranean-diet score ranged from 0 (minimal adherence to the traditional Mediterranean diet) to 9 (maximal adherence).

Within the HPFS cohort, greater adherence to the MD has predicted lower mortality after prostate cancer diagnosis (Kenfield SA et al., 2014), lower all-cause mortality among individuals with CVD (Lopez-Garcia et al., 2013), lower CVD risk overall (Sotos-Prieto M et al., 2015), less weight gain (Fung et al., 2015), lower risk of type 2 diabetes (de Koning L et al., 2011) and a lower risk of Parkinson's disease (Gao et al., 2007).

Primary analysis: We used a cumulative average of the diet intake from 1986 to 2002 to best represent long-term intake. We stopped updating dietary data in 2002 to minimize effects of altered cognitive function on diet

Outcome: Subjective memory complaints were measured in mailed or online questionnaires administered to the HPFS participants in the years 2008 and 2012. The SCC scores are based on 6 yes/no questions: Do you have more trouble than usual remembering recent events? Do you have more trouble than usual remembering a short list of items, such as a shopping list? Do you have trouble remembering things from one second to the next? Do you have any difficulty in understanding things or following spoken instructions? Do you have more trouble than usual following a group conversation or a plot in a TV program due to your memory? Do you have trouble finding your way around familiar streets?

The SCC outcome was computed as both continuous and categorical variable, which were used in the linear regression and logistic regression models, respectively. The continuous SCC score was an average of the two assessments and ranged between 0-6. This score was also used to categorize participants into one of 3 levels of SCC: “poor subjective memory” (memory score: 3+), “moderate subjective memory” (memory score: 1-2) or “good subjective memory” (memory score: 0). No single, standardized definition of SCC exists (Small, 1999); however, these questions have been used in previous studies of SMC and validated against objective measures of memory loss (Donovan, 2014). Higher SCC score has been shown to be significantly associated with APOE gene status (specifically the e3e4 and e4e4 variants), a known genetic risk factor for Alzheimer’s disease (Carere et al., in preparation). Additionally, SCCs have been associated with the presence of various mid and late-stage biological markers of AD, including amyloid plaques, neurofibrillary tangles and grey matter atrophy (Perrotin A et al., 2012; Saykin AJ et al., 2006 and Wang Y et al., 2012).

Covariates: Covariates were determined at 2002, in keeping with the assessment of diet in the primary analysis. Body mass index (BMI) and physical activity were averaged across multiple assessments over time until 2002, similar to diet. Physical activity was assessed in 1986 and every 2 years thereafter by estimating average energy expended per week (in Metabolic Equivalents of Tasks, METS; Jette, 1990), using information on 10 common leisure-time physical activities. Socio-demographic covariates included the self-reported variables, each updated to 2002, except for where indicated differently: age (continuous, years), smoking history (categorical, in pack-years, quintiles), diabetes (categorical, yes/no), hypertension diagnosis (categorical, yes/no), depression (categorical, defined as use of anti-depressants in the past 2 years, or self-reported physician diagnosis, assessed at 2008) and elevated cholesterol (yes/no). The 1986 questionnaire was considered baseline.

Exclusions: We excluded individuals with a diagnosis of Parkinson's disease at any point until 2002 in our analysis. A history of dementia is not queried on HPFS surveys and therefore was not included as an exclusion factor.

Primary Analysis: Logistic regression models were used to estimate the Odds Ratio (95% confidence intervals) of SCC by five levels of the MD score. Both age-adjusted and multivariate models (accounting for the covariates listed above) were carried out. Comparisons were made between (1) the moderate and good memory group and (2) the poor and good memory group. Trends across the five quintiles of the dietary exposure were computed.

Secondary analyses: To better understand which dietary components of the MD score contributed most importantly to the association seen in our primary analysis, we performed linear regression analyses with the MD score components as independent variables and the continuous SCC score as the dependent variable. A linear regression model of the continuous SCC outcome on the overall dietary score was also conducted for reference.

To evaluate the temporal relation of MD dietary adherence to SCC, and to evaluate the possibility reverse causation, i.e, effects of cognitive change on diet, we examined diet at individual years in relation to SCC. Specifically, we performed a linear regression using a continuous form of the SCC outcome and non-cumulative MD score values at each year the dietary questionnaire was administered (1986, 1990, 1994, 1998, 2002 and 2006). Analyses of cumulative time-points (namely, 1) the mean of 1986 and 1990, 2) the mean of 2002 and 2006 and 3) the mean of all individual time-points were also performed for comparison. To enhance the interpretability of these outputs, the β for the MD score was divided by the β for 1 year of the participants' y of age, yielding the difference in dietary score (out of 9 total units) per unit age that resulted in a corresponding change in the SCC outcome (out of 6 total units). In these analyses, the covariate data closest in time with the dietary assessment was used.

Secondary analyses: In additional analyses, we stratified our dietary score analysis by age (>53 vs <53 years at baseline), CVD status (defined as having had a myocardial infarction, a coronary artery bypass graft surgery, a stroke or a diagnosis of angina between 1986 and 2002) and depression status (defined the use of anti-depressants in the past 2 years, or self-reported physician diagnosis, assessed at 2008), given the possibility that these covariates could mediate or modify the association of interest., particularly given that CVD and depression underlie the pathophysiology of forms of dementia, namely vascular dementia and pseudo-dementia.

Linear regression models were fitted using PROC GLM and generalized logistic regression models were fitted using PROC LOGISTIC (SAS vs. 9.3; SAS Institute, Cary NC). Statistical significance for all analyses was set at $p < 0.05$.

Section 4. Results

Our study cohort included 27,406 study participants who reported both SCC data and dietary data that comprised the Mediterranean diet score.

The characteristics of study participants at 2002 (the year up to which dietary data were included in our primary analysis) are shown in **Table 1**. Men who had the highest adherence to the MD index were on average, slightly older, tended to be more physically active, had a lower BMI, lower rates of diabetes and depression and had lower rates of significant smoking history (>45 pack-years). They however, tended to have slightly higher rates of cardiovascular disease, hyperlipidemia and hypertension. Physical activity level at baseline was not related to adherence to the MD.

The average number of subjective memory complaints in this cohort was 0.73 ± 1.2 in 2008 and 0.66 ± 1.1 in 2012 (**Table 2**). Among subjective memory complaints, "Do you have much more trouble than usual remembering recent events" was most common, reported by 20.6% and 15.6%, of individuals, respectively, on the 2 surveys. Of the three levels of memory, 54.5% reported 'good' memory, 38.2% reported moderate memory and 7.4% reported poor memory.

In the primary age-adjusted analysis (**Table 3**), higher adherence to the MD diet score was both significantly associated with a lower likelihood of moderate or poor SCC. Adjustment for all potential confounders had had little effect on these associations. Specifically, in the multivariate model, having a cumulative MD score in the highest quintile as compared to the lowest quintile was associated with a 40% lower odds of a poor SCC score (Odds Ratio: 0.60, 95% CI: 0.51-0.71) and a 38% lower odds of a moderate SCC score (Odds Ratio: 0.72, 95% CI: 0.66-0.79). The trends for these logistic regression analyses across quintiles of the exposure were significant. A similar pattern was observed in the age-adjusted model, wherein a cumulative MD score in the highest adherence quintile as compared to the lowest quintile was also associated with a 40% lower odds of a poor SCC score (Odds Ratio: 0.60, 95% CI: 0.51-0.69) and a 38% lower odds of a moderate SCC score (Odds Ratio: 0.72, 95% CI: 0.66-0.78) in the multivariate (MV) model. A sub-analysis was conducted to additionally include professional status as a covariate in the MV model but did not change the results above (results not included in Table 3).

The food groups that comprised the Mediterranean diet score were examined individually and adjusting for potential confounders, vegetables, fruits and nuts, legumes, fish and the ratio of monounsaturated lipids to saturated lipids were significantly associated with a reduced SCC score (**Table 4**). Of these, MF/SF, followed by vegetables, followed by fish consumption, were most strongly associated with a reduced SCC; for instance, an increase of 1 quintile in the ratio of MF to SF produced a drop of 0.12 points in the SCC score (out of 6), an increase of 1 quintile in vegetable consumption produced a drop of 0.05 points in the SCC score while an increase of 1 quintile in fish consumption produced a drop of 0.044 points in the SCC score. Conversely, meat and meat product consumption was significantly associated with an increased SCC score; an increase of 1 quintile in meat consumptions produced an increase of 0.035 points in the SCC score. An additional analysis conducted including all the food groups in a single model confirmed these results, showing that vegetable, fish, legume and MF/SF consumption were independently inversely associated with the outcome, while meat consumption was independently negatively associated with the outcome (results not shown in Table 4).

In stratified analyses (**Table 5**) the association between adherence to MD and reduced SCC was more pronounced among older individuals (greater than 53 years of age at the study's inception) and those with cardiovascular. The MD dietary-SCC association was similar among those with and without depression.

Adherence to the MD at each time point during follow-up was strongly associated with lower SCC score (Table 6). The association was only slightly stronger in more recent years, and the strongest inverse association was with the average of all dietary assessments.

Section 5. Discussion, Limitations and Suggestions for Future Work

In this large sample of older male health professionals, we found a robust and consistent relationship between a Mediterranean diet pattern, as measured by the MD score, and subjective cognitive concerns during subsequent follow-up. In breaking down the dietary components of these three scores, we found the strongest inverse relationships potentially explaining the aforementioned association between the consumption of vegetables, fish and MUFA/SF, and reduced SCC, and a positive relationship between meat consumption and increased SCC.

Importantly, cereals (which included both refined and unrefined grains) were not shown to have a statistically significant association with the SCC outcome; it would be useful to conduct further analyses separating out refined and unrefined grains to assess whether each independently have an association with SCC. In the MD score, nuts and fruits are also included in the same category, but contain quite different nutrients and amounts of sugar; therefore, further analyses separating out these two components would be instructive.

Our overall findings that MD dietary pattern is associated with reduced SCC are largely consistent with the literature and significantly bolster past research given this sample represents, to our knowledge, the largest sample of men in which such an association has been demonstrated. Adherence to the MD has been associated with reduced rates of cognitive decline or AD in a number of observational studies (Feart et al., 2009; Feart et. al, 2013; Gu et al., 2010; Kesse-Guyot et al., 2013; Psaltopolou et al., 2008; Roberts et al., 2010; Samieri et al., 2013a; Samieri et al. 2013b; Scarmeas et al., 2006; Scarmeas at al., 2009; Tagney et al., 2011; Tagney et al., 2014; Tsivgoulis et al., 2013; Gardener et al., 2014; Koyama et al., 2015; Trichopoulou et al., 2015; Burgener, 2008, Wengreen et al., 2013; Zbeida et al., 2014), in two recent systematic reviews (Singh et al., 2014; Lourida et al., 2013) and five randomized-control trials (Martinez-Lapiscina et al., 2013a, Santoro et al., 2013a. Knight, 2015; Hardman et al., 2015; Valls-Pedret et al., 2015). But a handful of negative results among smaller cohorts have also been published (Vercambre, 2012; Cherbuin et al., 2012; Samieri et al., 2013b and Crighton, 2013). In the study by Crighton and colleagues, a higher pattern of adherence to the MD was not related to cognitive function, but was associated with other cognitive outcomes including reduced anxiety, depression and perceived stress, suggesting a nevertheless existent link between the gut and brain.

Our findings regarding individual dietary components and SCC risk also support previous research, which is scant, but documents links between vegetable consumption and improved cognition (Morris et al., 2006; Kang et al., 2005; Barberger-Gateau et al., 2007; Hughes et al., 2010; Ritchie et al., 2010, Nooyens et al., 2011), fish consumption and improved cognition (Morris et al., 2005a; Barberger-Gateau at al. 2007; Fotuhi et al., 2009; van Gelder et al., 2007), MUFA intake and lower rates of cognitive decline (Naqvi et al., 2011; Vercambre et al., 2010; Solfrizzi et al., 2009) and nut consumption and improved cognition (O'Brien et al., 2014, Nooyens et al., 2011),

The association between fish consumption and SCC could be partially mediated through the association between omega-3-fatty acids and SCC—one in line with past research (Lopez et al., 2011; Johnson et al. 2006; Beydoun at al., 2008), including randomized-control trails (RCTs) and meta-analyses showing improved cognition with omega-3 fatty acid supplementation (Strike et al., 2015; Zhang et al., 2016).

Our analysis also adds to research that has been conflicting or limited. For instance, our study also shows an inverse relationship between fruit consumption and SCC. One recent systematic review (Lamport et al., 2014) noted that research on the link between fruit consumption and SCC is lacking. Additionally, no studies have specifically analyzed the associations between MUFA/SF consumption and cognitive outcomes, to our knowledge.

Our study is also in contrast to some null results found in the literature. For instance, one study showed no association between vegetable consumption and cognitive functioning (Peneau et al., 2011), and a third (Nooyens et al., 2011) showed no association between fruits, legumes or vegetables and cognitive function. It is possible that these smaller-scale studies did not achieve the statistical power to detect the effects evident in our larger cohort study. Additionally, some of the variability in published results may stem from the fact that specific vegetables and fruits—and the nutrient contained therein—may be associated with improved SCC, rather than overall fruit and vegetable consumption per se. Indeed, in the Nooyens study, nuts, cabbage and root vegetables in particular were associated with improved cognition, while overall food categories were not. Further research is needed to elucidate the specific fruits and vegetables that yield the most consistent and robust improvements in cognitive health as well as the nutrients that underlie these effects.

Nevertheless, It is important to note that the MD diet score overall shows a stronger inverse association with SCC as compared to its component dietary groups. This corroborates accumulating evidence that, while particular nutrients may be driving these associations to a greater degree than others, a balanced diet, containing the optimal combination of various foods and nutrients, ultimately has the greatest potential to benefit cognitive health (Kesse Goyot et al., 2012).

Our study also finds that the association between adherence to the MD and SCC is more pronounced among older individuals and among those with cardiovascular disease (CVD). These findings also warrant corroboration and further investigation. One possible explanation of the former result is that elderly individuals are more apt to report and experience SCC; therefore, we are able to better detect this association among an older sub-group. An alternative hypothesis that the dietary effects of MD adherence take time to accumulate and improve cognitive outcomes, conferring a higher rate of association between this exposure and outcome among older individuals. A third is that the elderly stand more to benefit from improving their diet; studies have shown that the gut microbial diversity declines with age, one of the main causes of which is dietary composition (Claesson et al., 2012). This hypothesis touches on the fascinating and yet nascent field of the microbiome-gut brain axis, a schematic proposed by Collins et al. 2012, and beginning to yield promising therapeutic results in the cognitive world.

Our second finding, that the diet-SCC association is stronger among those with CVD than among those without CVD, may speak to the pathophysiologic mechanisms that mediate the diet-cognition link, and yet remain to be fully eludicated. Indeed, systemic inflammation and oxidative stress is considered one of the primary mechanisms underlying age-related cognitive decline (Griffin et al., 2013) and multiple studies show that particular foods promote the regulation of oxidative stress (Stevenson and Hurst, 2007; Letenneur et al. 2007). The impact of diet on these pathways may be more effective in a cardiovascularly impaired host, where inflammation may be additionally high for disease-related reasons. The MD has also been demonstrated in a variety of studied to improve CVD outcomes (Sleiman, 2015); it is possible there is an overlap between the mechanisms through which MD adherence is associated with improved CVD and those mediating the MD-cognitive health link. In other words, it is possible that hosts with CVD have more potential to benefit from MD adherence due to the potential collateral effects of MD diet adherence in these individuals.

However, these results must be interpreted in the context of their much lower statistical power given they were sub-group analyses and given that we did not pursue analyses establishing that these differences were statistically significant. Nonetheless, they provide interesting inroads into potential future research questions.

Lastly, our individual time-point analyses show that reverse causation is not at play in our results given the non-significance of the slightly larger inverse associations between diet-SCC reported in the years closer to the time of SCC documentation. This trend, while non-significant, lends corroboration to the finding in our stratified analysis that the diet-SCC association may be more robust among older individuals, given the cohort ages as the year of FFQ increases.

Strengths of the current study include its large size, longitudinal follow-up (affording multiple dietary assessments over time to reduce errors and variability in the data and repeated measurements of subjective cognition), comprehensive dietary intake data (allowing us to stratify by different food groups and construct three dietary scores) and information on a variety of other demographic and health-related parameters, allowing us to adjust for many potential confounders.

However, limitations of the study remain. For instance, our questionnaire data relies on self-reports for all data, which could be flawed. However, given that data was collected prospectively, the misreporting of data should be random and not contribute to any systematic biases. Furthermore, we were able to minimize such random variation by averaging dietary intake across multiple time points for our primary analysis. Additionally, our sample was limited to mostly Caucasian healthcare professionals (nurses and other health professionals, respectively, in the two cohorts), both participating in employment requiring a relatively high cognitive demand, hailing from high socio-economic status groups and having a relatively high knowledge of disease and health, limiting its generalizability. Additionally, while our focus was on subjective cognitive concerns, which has been well-validated in previous studies to correlate with more objective measures of memory loss (Samieri et al., 2014), our analysis did not take into account any objective outcome metrics.

Section 6. Conclusion

There is a robust positive association between adherence to the Mediterranean diet pattern, as measured by the Mediterranean diet score, and reduction in later subjective cognitive concerns. Dietary patterns resembling the Mediterranean Diet may constitute an important early intervention to prevent or delay cognitive decline.

Section 7. Acknowledgements

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Tables and Figures

Table 1. Demographic Characteristics of Individuals who completed Subjective Memory Concerns questions in the Health Professionals Follow-up Study (HPFS) by quintiles of adherence to the Mediterranean Diet, as quantified by the Mediterranean Diet Score

	Mediterranean Diet Score				
	Q1 (n=5,392)	Q2 (n=5,418)	Q3 (n=5,664)	Q4 (n=5,330)	Q5 (n=5,602)
Age at study baseline, 1986*	49.1	50.6	51.2	51.9	52.7
Diabetes diagnosis, %	7.1	7.4	7.5	7.4	6.6
BMI	27.0	26.7	26.4	26.1	25.6
CVD diagnosis, %	11.1	14.4	15.6	17.2	20.1
High blood pressure diagnosis at or before 2002, %	38.7	41.3	41.5	43.1	43.0
Elevated cholesterol diagnosis at or before 2002, %	46.2	49.5	51.9	53.6	55.9
45+ pack-years smoking history, %	7.9	5.9	5.1	4.3	3.8
Total physical activity level (Mets/week)**	49.1	25.7	27.8	30.5	35.1
Depression diagnosis or anti-depressant use at 2008, %	8.1	7.5	6.8	6.2	6.0

Notes: Values are means (SD) or percentages and are standardized to the age distribution of the study population; Values of polytomous variables may not sum to 100% due to rounding
*Value is not age adjusted

Table 2. Frequency of Subjective Memory Complaints among participants in HPFS		
Survey Year	2008 (N=25,352)	2012 (N=22,218)
Survey Items, n (%)		
Do you have much more trouble than usual remembering recent events?	5,497 (20.6%)	4,268 (15.6%)
Do you have more trouble than usual remembering a short list of items, such as a shopping list?	6,477 (23.6%)	5,031 (18.4%)
Do you have trouble remembering things from one second to the next?	3,176 (11.6%)	2,406 (8.8%)
Do you have any difficulty in understanding things or following spoken instructions?	1,770 (6.5%)	1,455 (5.3%)
Do you have more trouble than usual following a group conversation or a plot in a TV program due to your memory?	1,343 (4.9%)	1,255 (4.6%)
Do you have trouble finding your way around familiar streets?	295 (1.1%)	321 (1.2%)
Subjective Memory Complaints Score, Mean ± SD	0.73 (1.2)	0.66 (1.1)
Subjective Memory Complaints Score, N = 27,406 (%)		
Good subjective memory (Score=0)	14,901 (54.4%)	
Moderate subjective memory (Score=1-2)	10,468 (38.2%)	
Poor subjective memory (Score=3+)	2,037 (7.4%)	

Table 3. Odds Ratio (and 95% confidence intervals) for Subjective Cognitive Concerns (poorest memory compared to most intact memory) according to quintile of the Mediterranean Diet Score

	Quintile of Intake					
	1	2	3	4	5	Trend (p-value)
Mediterranean Diet Score						
N	5,392	5,418	5,664	5,330	5,602	
Good memory(reference) (cases)	2,896 (53.7%)	2,868 (52.9%)	3,067 (54.2%)	2,890 (54.2%)	3,180 (56.8%)	
Moderate memory cases	2093 (38.8%)	2108 (38.9%)	2204 (38.9%)	2055 (38.6%)	2,008 (35.8%)	
Poor memory cases	403 (7.5%)	442 (8.2%)	393 (6.9%)	385 (7.2%)	5,233 (93.4%)	
Moderate vs. Good						
Age-adjusted OR (95% CI)	1	0.94 (0.87-1.02)	0.89 (0.82-0.96)	0.85 (0.78-0.92)	0.72 (0.66-0.78)	$p < 0.05$
Multivariate OR (95% CI)	1	0.93 (0.86-1.02)	0.90 (0.82-0.97)	0.87 (0.80-0.95)	0.72 (0.66-0.79)	$p < 0.05$
Poor vs. Good						
Age-adjusted OR (95% CI)	1	0.92 (0.79-1.07)	0.71 (0.62-0.82)	0.67 (0.58-0.79)	0.60 (0.51-0.69)	$p < 0.05$
Multivariate OR (95% CI)	1	0.93 (0.80-1.09)	0.71 (0.61-0.84)	0.70 (0.60-0.82)	0.60 (0.51-0.71)	$p < 0.05$

Notes: Covariates included in the MV model include the following: age (at baseline, continuous, years), smoking history (in pack-years, quintiles), diabetes (yes/no), hypertension diagnosis (yes/no), depression (defined as use of anti-depressants or self-reported physician-diagnosed, measured at 2008), elevated cholesterol (yes/no), physical activity level (cumulative average from 1986-2002, tertiles) and BMI (cumulative average from 1986-2002, quartiles).

Table 4. Linear regression of the dietary components (in quintiles) of the MD Diet Score on Subjective Memory Complaints score

Dietary component	β (Standard Error) p-value
Vegetables (g/day)	-0.05 (0.005) $p < 0.05$
Fruit and nuts (g/day)	-0.035 (0.005) $p < 0.05$
Legumes (g/day)	-0.025 (0.005) $p < 0.05$
Cereals, including bread and potatoes (g/day)	-0.003 (0.005) $p = 0.57$
Fish (g/day)	-0.044 (0.005) $p < 0.05$
Meat and meat products (g/day)	0.035 (0.005) $p < 0.05$
Ratio of monounsaturated lipids to saturated lipids	-0.12 (0.005) $p < 0.05$
Milk and dairy products (g/day)	0.01 (0.005) $p = 0.025$
Alcohol (g/day)	-0.0004 (0.005) $p = 0.94$
Overall Score	-0.046 (0.005) $p < 0.05$

Abbreviations: MD = Mediterranean Diet
Notes: The vegetable group includes potatoes, fruit group includes nuts, grain group includes all grains and meat group includes all meats and meat products excluding fish or chicken;
Covariates included in the multivariate model include the following: age (at baseline, continuous, years), smoking history (in pack-years, quintiles), diabetes (yes/no), hypertension diagnosis (yes/no), depression (defined as use of anti-depressants or self-reported physician-diagnosed, measured at 2008), elevated cholesterol (yes/no), physical activity level (cumulative average from 1986-2002, tertiles) and BMI (cumulative average from 1986-2002, quartiles).

Table 5. Parameter (and Standard Errors) for Subjective cognitive concerns according to the MD Diet Score, stratified by age, depression status and CVD status

Stratification, β (Standard Error) p-value	
Age	
<53 years (N1: 16,888/27,406) (N2: 16,546/26,808)	-0.03 (0.005) $p < 0.05$
>53 years (N1: 10,518/27,406) (N2: 10,262/26,808)	-0.05 (0.01) $p < 0.05$
Depression status	
With depression (N1: 1,895/27,406) (N2: 1,847/26,808)	-0.05 (0.02) $p = 0.08$
Without depression (N1: 25,511/27,406) (N2: 24,961/26,808)	-0.05 (0.005) $p < 0.05$
CVD status	
With CVD (N1: 4,301/27,406) (N2: 4,199/26,808)	-0.06 (0.01) $p < 0.05$
Without CVD (N1: 23,105/27,406) (N2: 22,609/26,808)	-0.04 (0.005) $p < 0.05$

Abbreviations: CVD = cardiovascular disease
Notes: Covariates included in the multivariate model include the following: age (at baseline, continuous, years), smoking history (in pack-years, quintiles), diabetes (yes/no), hypertension diagnosis (yes/no), depression (defined as use of anti-depressants or self-reported physician-diagnosed, measured at 2008), elevated cholesterol (yes/no), physical activity level (cumulative average from 1986-2002, tertiles) and BMI (cumulative average from 1986-2002, quartiles).
Age, depression and CVD status, respectively, were removed in the models computed in the age, depression and CVD stratification analyses.

Table 6. Linear regressions output for age-equivalent non-cumulative MD Diet Score at each year of FFQ (1986, 1990, 1994, 1998, 2002, 2006) on SCC score (β and SE values multiplied by 10)

Year of Intake	β (Standard Error)
1986	-7.02 (-0.958)
1990	-7.43 (-1.00)
1994	-8.38 (-1.00)
1998	-8.41 (-0.991)
2002	-8.04 (-0.901)
2006	-8.35 (-0.932)
Mean (86-90)	-8.08 (-0.992)
Mean (02-06)	-8.60 (-0.945)
Mean (86-06)	-9.54 (-0.102)

Abbreviations: MD = Mediterranean Diet
Notes: The last three rows of the table refer to linear regression outputs where the years of intake were a mean of those listed;
SCD was treated as a continuous variable and as the mean of that in the 2008 and 2012 questionnaires;
To divide standard errors, the following formula was used: A*SQRT((DB/B)^2+(DC/C)^2), where:
B= parameter estimate for dietary exposure, C=parameter estimate for age, A = B/C, DB=standard error for parameter estimate of dietary exposure and DC=standard error for parameter estimate for age