The role of Mediterranean diet in the course of subjective cognitive decline in the elderly population of Greece: results from a prospective cohort study

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Abstract

Very few data are available regarding the association of adherence to the Mediterranean Diet (MeDi) with Subjective Cognitive Decline (SCD) evolution over time. A cohort of 939 cognitively normal individuals reporting self-experienced, persistent cognitive decline not attributed to neurological, psychiatric or medical disorders from the Hellenic Epidemiological Longitudinal Investigation of Aging and Diet (HELIAD study) was followed-up for a mean period of 3·10 years. We defined our SCD score as the number of reported SCD domains (memory, language, visuoperceptual and executive), ranging from 0 to 4. Dietary intake at baseline was assessed through a food frequency questionnaire; adherence to the MeDi pattern was evaluated through the Mediterranean Diet Score (MDS) that ranged from 0 to 55, with higher values indicating greater adherence to the MeDi. The mean SCD score in our cohort increased by 0·20 cognitive domains during follow-up. After adjustment for multiple potential confounders, we showed that an MDS higher by 10 points was associated with a 7 % reduction in the progression of SCD within one year. In terms of food groups, every additional vegetable serving consumption per day was associated with a 2·2 % reduction in SCD progression per year. Our results provide support to the notion that MeDi may have a protective role against the whole continuum of cognitive decline, starting at the first subjective complaints. This finding may strengthen the role of the MeDi as a population-wide, cost-effective preventive strategy targeting the modifiable risk factors for cognitive decline.

Key words: Subjective cognitive decline: Dementia: Greece: Mediterranean diet: Nutrition

Dementia is a global public health issue with substantial personal, societal and fiscal consequences. The burden of dementia worldwide is projected to rise, mainly driven by population growth in low/middle-income countries and increased disease awareness[1]. The search for a cure in the past decades has taught us that the most viable option is to target neurodegenerative processes, like Alzheimer's disease, at as early a stage as possible. However, identifying asymptomatic or oligosymptomatic individuals has proven quite a challenge. Apart from people with a clear-cut family history of dementia, others tend to consider the earliest signs of cognitive decline as normal ageing or attribute them to anxiety. If – at some point – a dementia specialist is consulted, confirming subtle cognitive decline or an early stage of neurodegeneration[2] requires time-consuming neuropsychological testing or expensive/mildly invasive investigations (positron emission tomography/spinal tap). In this context, subjective

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cognitive decline (SCD), a self-reported persistent decline in cognitive capacity, has emerged as a promising surrogate for preclinical dementia[3]. SCD and its potential significance as a marker of future cognitive deterioration has been a subject of debate for long; recent data have confirmed this notion[4], and the development of research diagnostic criteria for SCD[5,6] has rekindled interest in the topic. Even though the risk of SCD progression to overt cognitive decline has been explored[4,7], very little is known about the actual course of SCD severity over time and the parameters influencing it.

Among modifiable risk factors for cognitive decline, diet stands out due to its potential for application of population-wide, cost-effective preventive strategies. Indeed, the association of dietary habits and dementia has been thoroughly researched. The role of diet in the prevention of cognitive decline has been investigated in observational[8,9] and interventional[10–12] studies, and the results are generally in favour of the Mediterranean Diet (MeDi) or other similar plant-based diets[13–17]. There is even limited evidence for the role of dietary factors in the treatment of cognitive decline[18]. As it is known that patients with objective cognitive decline are well downstream the neuropathological cascade of dementia and preventive measures can have a larger effect the earlier they are introduced, the question of the effect of the MeDi on SCD (as a marker of preclinical dementia) is both important and exciting. Published research on this topic is surprisingly scarce; we have identified two randomised, placebo-controlled trials studying the effect of nutrient supplementation on the cognitive function of elderly adults with SCD: one failed to show any beneficial effect after 3 years of *n*-3 PUFA supplementation[19] and the other showed that supplementation with fish oil and/or blueberry improved cognition after 24 weeks[20]. This discrepancy is not unexpected; the effect of each micronutrient is of small magnitude and easily gets diluted in the course of neurodegeneration. Only a combination of beneficial elements in the form of a complete diet[21] for a sufficient amount of time, probably accompanied by an overall 'healthier' lifestyle, might be envisaged to have a measurable and clinically significant outcome. That is why prospective cohort studies on SCD and nutrition, shedding light on real-world habits, might be more useful, especially when they focus on diet as a whole.

Nevertheless, observational data on the effect of dietary patterns on SCD are also very limited. A French study has revealed an inverse association between adherence to the MIND diet[1] and subjective memory complaints in individuals ≥70 years old[22], while another study on a large American cohort showed that adherence to the MeDi[23] was associated with lower odds for SCD years later. It is noteworthy that in the latter publication, which is the only one investigating the MeDi and SCD, the authors have used an extensive and detailed data set to model the association between the average historical MeDi adherence score and the average subjective cognitive function score years later and not the effect of diet on SCD evolution. We therefore decided to use our data from the Hellenic Epidemiological Longitudinal Investigation of Aging and Diet study to explore the association of MeDi adherence with the course of SCD over time in a quantitative manner. We are also

proposing a novel, five-level SCD score based on eighteen items. Cross-sectional data on SCD prevalence and its determinants in our population have been discussed elsewhere[24].

Experimental methods

Study population, research protocol and covariate assessment

The Hellenic Epidemiological Longitudinal Investigation of Aging and Diet (HELIAD study) is an investigation of the epidemiology of cognitive disorders in the elderly population in Greece, aiming to unravel their interrelation with various demographic, genetic, medical, lifestyle and dietary parameters. The study is conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human participants have been approved by the Institutional Ethics Review Board of the National and Kapodistrian University of Athens and the University of Thessaly. Written informed consent was obtained from all participants. The full cohort consists of 1984 individuals ≥65 years old from urban and suburban sites who have been randomly sampled and invited to participate in the study, so that they can be considered representative of the whole elderly population in Greece. All participants were examined at baseline and then asked to attend a follow-up visit about 3 years after the initial evaluation. The baseline visits occurred between December 2009 and June 2016, while follow-up was conducted between January 2013 and July 2019. Details about study design and methodology have been presented elsewhere[24,25]; only the pillars of our extensive protocol that are related to the present research will be outlined here.

Neurologists, neuropsychologists and dietitians administered all structured questionnaires in face-to-face interviews. The examination had a total duration of approximately 2–2·5 h. Participants provided full medical, neurological and family history and answered questions regarding medication, tobacco and alcohol use, mental, physical, occupational and social activities, sleep and dietary habits, subjective memory or other cognitive complaints, as well as various aspects of everyday function. Changes in the performance of daily activities and self-care habits were measured using the Blessed Dementia Scale[26]. The participants' ability to use the telephone and transportation, to manage their medication and handle their finances independently was assessed using the Lawton Instrumental Activities of Daily Living scale[27]. Several items from the CARE Subjective Memory subscale[28] have also been included to measure functional restrictions in everyday life. Quantification of the staging of dementia was performed using the Clinical Dementia Rating scale[29], which globally assesses six domains of cognitive and functional performance.

Particular focus was placed on identifying potential comorbidities that could affect cognitive performance through screening participants for depression, anxiety and behavioural symptoms, as well as Parkinson's disease, essential tremor and dementia with Lewy Bodies. Participants were screened for depressive symptoms over the past week using the fifteen-item version of the Geriatric Depression Scale (GDS)[30,31]. Anxiety over the past week was quantified using the seven-item

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[1] MIND, Mediterranean-DASH diet intervention for neurodegenerative delay; DASH, Dietary Approaches to Stop Hypertension

Hospital Anxiety and Depression Scale-Anxiety Subscale[32] with a cutoff score of 8[33,34]. We also calculated the Hachinski ischaemia scale score[35], a useful screening tool for vascular dementia. We typically evaluated comorbid conditions using a combined approach, gathering information from self- and/or informant-reported history, current medications and neuroimaging results, where available. Finally, a peripheral blood sample was drawn for basic biochemistry and *APOE (apolipoprotein E)* genotyping. The *APOE* genotype remained unknown for about a third of our sample because of delayed inclusion of this procedure to our protocol and some cases of refusal of venipuncture, so we used a simple approach to estimate genetic predisposition to cognitive decline for the whole sample: subjects were considered genetically predisposed to cognitive decline if they were *APOE-ϵ4* carriers or reported family history of dementia.

Neurological and neuropsychological evaluation and diagnosis

All participants received standard physical and neurological examination, as well as a comprehensive neuropsychological battery, evaluating five cognitive domains in detail (memory (verbal/non-verbal), executive, language, visuospatial and attention-speed), leading to the calculation of a *Z*-score for each test, based on age- and education-standardised normative values of a normal Greek reference population. The average *Z*-score within the tests for each individual cognitive domain determined the subject's domain performance. Subsequently, an overall cognitive *Z*-score was calculated by averaging the above five *Z*-scores. All *Z*-scores were calculated using mean values and SDs from the baseline assessment. A subject was considered to be impaired in a certain cognitive domain when they scored more than 1·5 SD below the age- and education-standardised normative values.

Integration of all the collected data on each participant led to the formation of neurological and psychiatric diagnoses through consensus interdisciplinary meetings including all researchers and main investigators involved in the project, according to the established international criteria. Diagnosis of dementia and its subtypes was based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision[36]. If a participant's score fell below 1·5 SD in at least two cognitive domains, coupled with significant impairment in social/occupational functioning, they received a diagnosis of dementia. Mild cognitive impairment and its subtypes were diagnosed according to the Petersen criteria[37].

Subjective cognitive decline and subjective cognitive decline score

Each research team usually uses their own operationalisation of the SCD definition or an original definition altogether[38]; we chose to adapt the research diagnostic criteria proposed in 2014[5] for use in our data set (Table 1). Complaints relevant to SCD were elicited with the help of a structured list of questions/topics for discussion with the participant (Table 2). Based on our data, subjective decline could be further classified according to the cognitive domain the participant felt they were having problems with, i.e. memory, language, visuoperceptual

and executive function. Corresponding SCD types were memory decline, naming decline, orientation decline and calculation decline, with the latter namely referring to money-handling issues. Participants were considered positive for an SCD type in case of at least one positive answer in the questions of the respective domain. Our overall SCD score was the number of reported SCD domains and thus ranged from 0 to 4.

All cognitively normal individuals not meeting SCD exclusion criteria at baseline who completed their second evaluation comprised our SCD cohort.

Assessment of dietary intake, including adherence to the Mediterranean diet

Dietary intake was evaluated by trained researchers (mainly registered dieticians) through a structured interview using a semi-quantitative food frequency questionnaire (FFQ) that has been validated for the Greek population[39]. Responses were corroborated by another household member, when necessary, and then converted to daily consumption of specific food items and extrapolated into macronutrient intakes. Energy intake was calculated by adding energy intake from macronutrients and alcohol, assuming 4 kcal/g for carbohydrates and proteins, 9 kcal/g for lipids and 7 kcal/g for alcohol. Dietary intake was also clustered into food groups featuring the core foods of the Greek diet[40]. Adherence to the MeDi pattern was evaluated through the Mediterranean diet score (MDS)[41]. This score is based on the weekly consumption of eleven food groups; an individual score for each component is calculated, ranging from 0 to 5. For the consumption of items that are presumed to closely reflect the Mediterranean pattern (i.e. non-refined cereals, fruits, vegetables, legumes, potatoes, fish and olive oil), individuals who reported no consumption were assigned a score of 0, and scores of 1–5 were assigned for rare to daily consumption (for example, weekly consumption in excess of 32 servings of non-refined cereals, >18 servings of potatoes, >22 of fruits, >33 of vegetables, >6 of legumes or fish and daily consumption of olive oil were assigned the maximum score of 5). For the consumption of foods that are presumed to diverge from this diet pattern (i.e. meat and meat products, poultry and full-fat dairy products), participants were assigned scores on a reverse scale (i.e. from 5 when they reported no consumption to 0 when they reported almost daily consumption; for example, over 10 servings of red meat and its products weekly, >10 servings of poultry and >30 servings of full-fat dairy assigned a score of 0, while consumption of ≤1 serving of red meat, ≤3 of poultry and ≤10 of full-fat dairy were assigned 5). For alcohol intake, it was assumed that small amounts of consumption are beneficial, while either high or no consumption may be harmful. Therefore, a score of 5 was assigned for consumption of less than 300 ml of alcohol/d, a score of 0 was assigned for no consumption or for consumption of more than 700 ml/d and scores of 1–4 were assigned for consumption of 600–700, 500–600, 400–500 and 300–400 ml/d, respectively (assumed ethanol concentration: 12 g/100 ml of alcohol). The total MDS ranged from 0 to 55, with higher values indicating greater adherence to the Mediterranean dietary pattern. MDS aims to address one of the limitations of other iterations of MeDi scores, as the frequency of consumption of

Table 1. Criteria for the diagnosis of subjective cognitive decline (SCD) in our research [adapted from Jessen *et al.* A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimer's Dement. 2014 Nov;10(6):844–52]

1. Self-experienced, persistent cognitive decline in comparison with a previously normal status and unrelated to an acute event, elicited during the interview by using specific questions/topics for discussion (please see Table 2)
2. Normal age-, sex- and education-adjusted neuropsychological evaluation
3. Overall categorisation as cognitively normal in the consensus investigators' meeting (absence of mild cognitive impairment or dementia due to Alzheimer's disease or other disorders)

A participant is not considered to have SCD if they report self-experienced cognitive decline that can be explained by

- depression and/or anxiety: when these are considered severe enough to interfere with cognition *plus* GDS ≥ 6 and/or HADS-A ≥ 8 (not individual symptoms that do not reach the threshold of a disorder)
- neurodegeneration without overt dementia (Parkinson's disease, progressive supranuclear palsy, corticobasal syndrome, Huntington's disease, etc.)
- stroke
- traumatic brain injury
- normal pressure hydrocephalus
- obstructive sleep apnoea
- epilepsy
- central nervous system tumour
- alcohol/substance/medication abuse
- psychosis or
- other medical disorders

SCD, subjective cognitive decline; GDS, geriatric depression scale; HADS-A, hospital anxiety and depression scale-anxiety subscale.

Table 2. Questions/topics used to elicit complaints associated with subjective cognitive decline (SCD) and SCD types in our research*

SCD type		Questions/topics
MD	Memory decline	• Do you have any problems with your memory? • Inability to remember a short list of items; for example, in a shopping list • Inability to recall recent events, for example, recent outings, visits of relatives or friends to hospital, etc. • Tendency to dwell in the past • Do you feel you have more problems with memory than most? • Do you have difficulty remembering things you have just read or heard? • Do problems with your memory make it difficult for you to shop? • Do problems with your memory make it difficult for you to get chores done around the house?
ND	Naming decline	• Do you have difficulty remembering the names of people in your family or close friends? (transient mistakes not included) • Do you often have to stop in the middle of saying something because you have difficulty or problems remembering the right word?
OD	Orientation decline	• Inability to find way about indoors • Inability to find way about familiar streets • Inability to interpret surroundings, for example, to recognise whether in hospital or at home; to discriminate between patients, doctors, nurse, relatives, other hospital staff, etc. • Do problems with your memory make it difficult for you to go outside by yourself? • Can you travel independently on public transportation or drive your car?
CD	Calculation decline	• Inability to cope with small sums of money • Do problems with your memory make it difficult for you to keep track of your personal business, like paying bills and handling money? • Can you manage your financial matters independently (budgets, write checks, pay rent, bills and go to bank), collect and keep track of your income?

SCD, subjective cognitive decline.
* Participants were considered positive for an SCD type and SCD overall in case of at least one positive answer.

each food group is compared with levels assumed to be consistent or incompatible with the prototypical Mediterranean dietary pattern and not to sample-specific median values.

Statistical analyses

We used descriptive statistics to present demographic, genetic and dietary characteristics, clinical diagnoses, and duration of follow-up of our sample. Continuous variables were reported as mean values, standard deviations and ranges; categorical variables were reported as absolute and relative frequencies. We used Pearson's χ^2 test and *t*-test to compare participants who returned for the second visit with those who were lost to follow-up due to refusal/relocation or being deceased.

We employed models of generalised estimating equations with SCD score as a dependent variable and baseline MDS as the predictor, including the interaction term MDS × time. We adjusted for sex, age, years of education, *APOE-ε4* carriage and follow-up duration (model 1), sex, age, education, genetic predisposition to cognitive decline and follow-up duration (model 2), model 2 + energy intake (kcal/d) (model 3), model 2 + GDS score (model 4) and model 2 + energy intake + GDS score + Hachinski score (model 5). Baseline values were used for age, energy intake, GDS score and Hachinski score. All analyses were performed on the SCD cohort and on the cognitively normal participants at baseline with no exclusion criteria for SCD. The SCD score was treated as a continuous and as an ordinal variable. Both autoregressive and exchangeable correlation structures were tested with no difference in the results.

We then repeated our generalised estimating equation analyses in a model using the baseline daily consumption of each food group as predictors, including the (daily consumption)*time interactions. Studied food groups include milk and yogurt; cheese; cereals and legumes; fruit and juice; vegetables; red meat, poultry and cold cuts; fish; pastries, cakes; sweeteners, regular soft drinks; coffee and tea; alcoholic beverages. Adjustment was performed for sex, age, education, genetic predisposition to cognitive decline and follow-up duration, as well as the aforementioned covariates plus energy intake. Again, baseline values were used for age and energy intake; all analyses were performed on the SCD cohort and on the cognitively normal participants at baseline with no exclusion criteria for SCD. The SCD score was treated as a continuous and as an ordinal variable. Multicollinearity was excluded using a correlation matrix.

The two-sided significance level was set to 0·05. Statistical analyses were performed using the SPSS version 26 package.
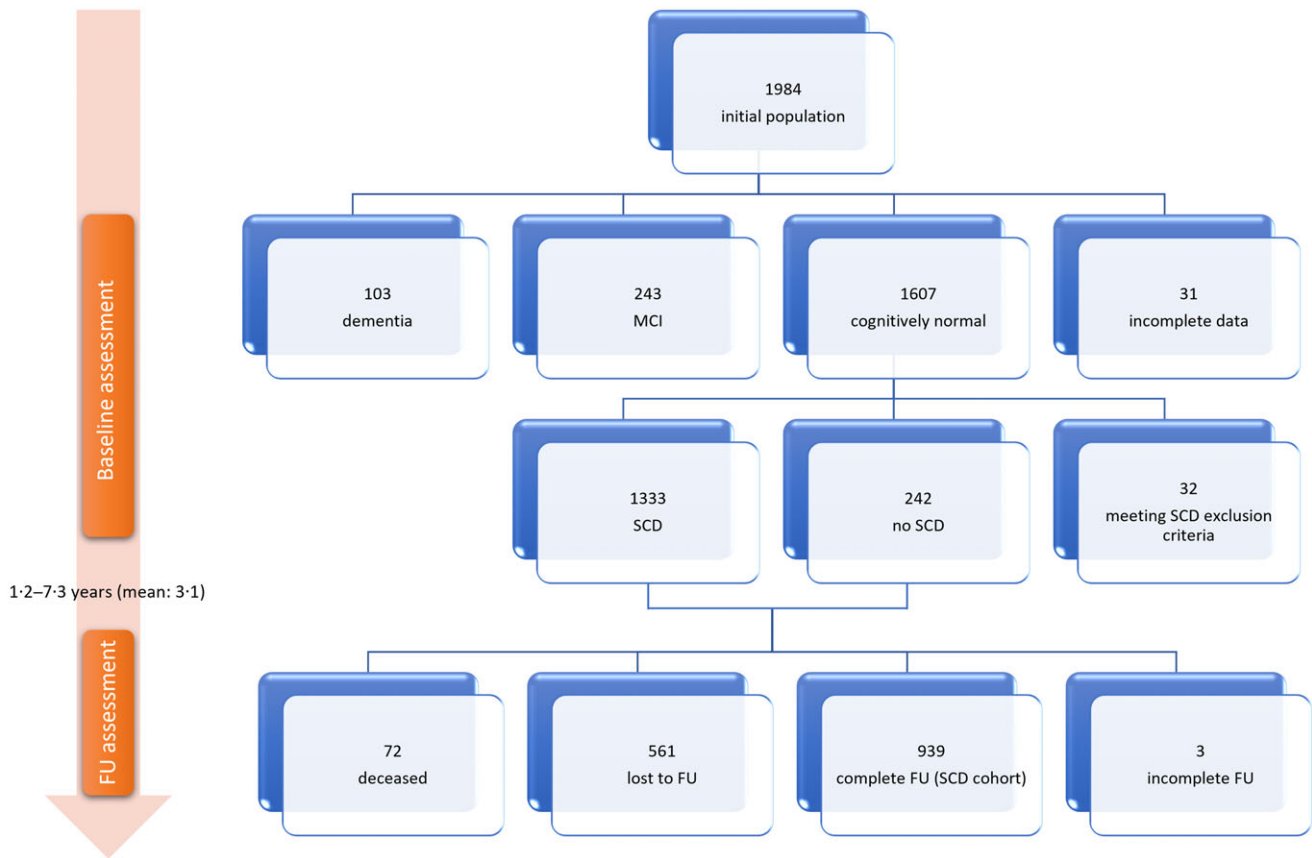
Fig. 1. Study flow chart. SCD, subjective cognitive decline; MCI, mild cognitive impairment; FU, follow-up.

Results

Sample characteristics

The initial visit of the Hellenic Epidemiological Longitudinal Investigation of Aging and Diet study was attended by 1984 individuals. Subject flow until the follow-up visit is illustrated in Fig. 1. There were 1607 cognitively normal participants after the baseline visit, of which 1333 (67·2 % of the total population) fulfilled criteria for SCD (Table 1), while 242 participants reported no SCD and 32 were excluded from further analysis according to our criteria. Among the 1575 cognitively normal individuals not meeting SCD exclusion criteria at baseline, 72 were deceased and 561 were lost to follow-up (35·6 %), leaving 942 to attend and finally 939 to complete the second evaluation and constitute our SCD cohort. Among the SCD cohort, 628 participants (66·9 %) were diagnosed with SCD on follow-up.

A comparison within the cognitively normal population not fulfilling exclusion criteria for SCD at baseline between those who attended follow-up and those who refused to continue or relocated did not reveal any statistically significant differences in relation to sex ($P = 0.485$), level of educational attainment ($P = 0.390$), APOE-ϵ4 carriage ($P = 0.486$) or MDS ($P = 0.364$), while age was marginally different between the two groups ($P = 0.049$), with younger people more likely to attend follow-up; those with higher initial overall cognitive Z-score were also more likely to return ($P < 0.001$). A comparison within the same

population between those who completed the second visit and those who were deceased at follow-up showed that male sex ($P < 0.001$), older age ($P < 0.001$), lower education ($P = 0.012$) and lower initial overall cognitive Z-score ($P < 0.001$) were associated with increased probability of death, while APOE-ϵ4 carriage ($P = 0.096$) and MDS ($P = 0.069$) remained statistically not significant.

Demographic, genetic and dietary characteristics, as well as neuropsychological results, clinical diagnoses and duration of follow-up of our sample are presented in Table 3. The SCD score for the majority of our sample was 1 for both visits; a mean increase in the score by 0·20 cognitive domains during follow-up was documented. The frequency distribution of the SCD score in the two study visits is shown in Fig. 2 in detail.

Association of nutritional factors and the time course of subjective cognitive decline

Table 4 shows the results of our generalised estimating equation models on the association between the interaction of MDS with time and the SCD score in the SCD cohort. We have found that an MDS higher by ten points was associated with a 7 % reduction in the progression of SCD within 1 year; this result remained statistically significant after adjustment for multiple potential confounders.

Table 3. Demographic, genetic, clinical, neuropsychological and dietary characteristics and duration of follow-up
(Mean values and standard deviation, SCD cohort, *n* 939)

Parameter		Mean value/frequency	SD	Range/%
Sex*	Male	368		39·2 %
	Female	571		60·8 %
Age at baseline (years)†		72·96	4·95	65·03–91·46
Education (years)†		8·30	4·85	0–21
APOE-ε4 alleles* (missing: 34·2 %)	∅	518		83·8 %
	1 or 2	100		16·2 %
Genetic predisposition to cognitive decline*	No	708		75·4 %
	Yes	231		24·6 %
Follow-up diagnosis*	Normal	747		79·6 %
	MCI	158		16·8 %
	Dementia	34		3·6 %
Duration of follow-up (years)†		3·10	0·83	1·17–7·26
GDS score (0–15)†	At baseline	1·87	3·07	0–15
	On follow-up	2·38	3·04	0–15
Overall cognitive *Z*-score†	At baseline	0·0035	0·6902	–3·72–1·37
	On follow-up	–0·2312	0·7862	–4·97–1·16
Hachinski score at baseline (0–13)†		1·18	1·29	0–10
SCD score (*n* of domains, 0–4)†	At baseline	1·17	0·73	0–4
	On follow-up	1·37	0·84	0–4
Energy intake at baseline (kcal/d)†		1999·82	543·69	725·03–4706·79
MDS at baseline (0–55)†		33·64	4·56	18–46
Consumption at baseline (servings/d)†	Milk, yogurt	0·7	0·6	0·0–3·0
	Cheese	1·0	0·7	0·0–6·0
	Cereals, legumes	5·1	2·0	0·0–13·5
	Fruit, juice	2·5	1·6	0·0–10·6
	Vegetables	2·0	1·0	0·0–8·6
	Red meat, poultry, cold cuts and eggs	1·4	0·8	0·0–6·8
	Fish	0·6	0·4	0·0–3·7
	Pastries, cakes	0·4	0·5	0·0–3·1
	Sweeteners, regular soft drinks	1·2	0·8	0·0–4·6
	Coffee, tea	1·5	0·8	0·0–4·0
	Alcoholic beverages	0·4	0·7	0·0–4·2

SCD, subjective cognitive decline; *APOE*, apolipoprotein E gene; GDS, geriatric depression scale; MDS, Mediterranean diet score.
* *n*, %.
† Mean (SD), range.
Continuous variables are reported as mean values, standard deviations and ranges. Categorical variables are presented as frequencies and relative frequencies. Relative frequencies of *APOE-ε4* carriage reflect only participants with known *APOE* status. Subjects were considered genetically predisposed to cognitive decline if they were *APOE-ε4* carriers and/or reported family history of dementia.

Table 5 shows similar models on the association between the interaction of specific food group consumption with time and the SCD score in the SCD cohort. The results reached statistical significance only for vegetables; every additional vegetable serving/d was associated with a 2·2 % reduction in SCD progression/ year. This association remained statistically significant after adjustment for sex, age, education, genetic predisposition to cognitive decline, follow-up duration and energy intake.

The same analyses were performed on the cognitively normal participants at baseline with no exclusion criteria for SCD, irrespective of participation in follow-up (please see in the Supplementary Information), and also with the SCD score treated as an ordinal variable. These extra analyses yielded very similar results (not shown).

Discussion

Using our prospective data set of 939 cognitively normal adults at least 65 years old followed-up for a mean period of 3·10 years, we showed a statistically significant association of MDS with SCD score evolution; specifically, MeDi adherence higher by ten points was associated with a 7 % reduction in the progression of SCD within 1 year. This relationship remained significant after adjustment for multiple potential confounders, including sex, age, education, genetic predisposition to cognitive decline, follow-up duration, GDS score, energy intake and Hachinski score.

The inverse association of MeDi adherence with SCD progression further supports the preventive role of the MeDi against the whole continuum of cognitive impairment. The MeDi has already been shown in a number of studies to exert a protective effect against future mild cognitive impairment/Alzheimer's disease[9,11,13] and overall dementia[15]. Considering the most frequent causes of dementia (neurodegenerative and vascular), our finding can be attributed to the established effect of the MeDi on vascular risk factors: many studies have identified the beneficial role of the MeDi on all-cause and coronary heart disease mortality, stroke prevention, type 2 diabetes, lipid metabolism, blood pressure and body weight control, inflammatory and coagulation processes and brain oxidative stress[41–44]. Several nutrients and non-nutritive compounds that are abundant in the foods of the MeDi, namely long-chain ω-3 fatty acids, polyphenols (including flavonoids), probiotic bacteria, fibre and prebiotic compounds, phytosterols, folic acid and other

Table 4. Association between Mediterranean diet score (MDS) and the time course of subjective cognitive decline (SCD) score in the SCD cohort*

GEE model	Adjustment for:	n	β (MDS × time)	P
1	Sex, age, education, APOE-ε4 carriage and follow-up duration	604	−0·007	0·015**
2	Sex, age, education, genetic predisposition to cognitive decline and follow-up duration	916	−0·007	0·004**
3	Model 2 + energy intake (kcal/d)	911	−0·007	0·005**
4	Model 2 + GDS score	916	−0·007	0·004**
5	Model 2 + energy intake + GDS score + Hachinski score	910	−0·007	0·005**

GEE, generalised estimating equations; APOE, apolipoprotein E gene; GDS, geriatric depression scale.
* The table shows the association between the interaction of MDS with time and the SCD score, after adjustment for potential confounders, using GEE. Participants were considered genetically predisposed to cognitive decline if they were APOE-ε4 carriers or reported family history of dementia. Baseline values were used for age, energy intake, GDS score and Hachinski score. The SCD score was calculated as the number of SCD cognitive domains reported.
** p values denote a statistically significant result ($P < 0.05$).

Table 5. Association of specific food group consumption and the time course of subjective cognitive decline (SCD) score in the SCD cohort*

	Adjustment for sex, age, education, genetic predisposition to cognitive decline and follow-up duration (n 917)		Adjustment for sex, age, education, genetic predisposition to cognitive decline, follow-up duration and energy intake (kcal/d) (n 911)	
	β (intake × time)	P	β (intake × time)	P
Milk, yogurt	0·016	0·352	0·015	0·381
Cheese	−0·001	0·955	0·000	0·988
Cereals, legumes	0·007	0·189	0·006	0·277
Fruit, juice	−0·006	0·395	−0·006	0·392
Vegetables	−0·022	0·023**	−0·022	0·028**
Red meat, poultry, cold cuts and eggs	0·017	0·240	0·016	0·264
Fish	0·041	0·102	0·041	0·103
Pastries, cakes	0·014	0·546	0·019	0·426
Sweeteners, regular soft drinks	−0·003	0·825	−0·003	0·851
Coffee, tea	−0·016	0·245	−0·017	0·206
Alcoholic beverages	−0·026	0·089	−0·024	0·125

GEE, generalised estimating equations; APOE, apolipoprotein E gene.
* The table shows two models exploring the association between the interaction of specific food group consumption with time and the SCD score, after adjustment for potential confounders, using GEE. Participants were considered genetically predisposed to cognitive decline if they were APOE-ε4 carriers or reported family history of dementia. Food consumption was expressed in servings/d. Baseline values were used for age and energy intake. The SCD score was calculated as the number of SCD cognitive domains reported.
** p values denote a statistically significant result ($P < 0.05$).

B vitamins, and antioxidants, are hypothesised to have neuroprotective properties and modulate beta amyloid aggregation and tau hyperphosphorylation[44]. Given that a proportion of individuals with SCD will progress to overt cognitive impairment, incorporation of the elements of the MeDi in the daily dietary pattern could be advocated as part of the lifestyle counselling for this population[3].

SCD is gaining acceptance as a surrogate for preclinical dementia. Although it has been shown that individuals with SCD are at risk of objective cognitive decline[4,7], very little is known about the trajectory over time of a quantitative measure of SCD severity and of the factors affecting it. This is, in part, due to the relative scarcity of quantitative SCD metrics. In our operationalisation of SCD (Tables 1 and 2), we used eighteen questions spanning four cognitive functions (memory, naming, orientation and calculations). Due to the lack of objective measures for SCD, as its definition suggests, we must rely on the individuals' metacognitive ability, which might already be compromised in some members of our elderly SCD cohort. Reiteration of similar topics in our question set is a way to capture more data with our queries, but at the same time construction of a global score based on the sum of all positive answers may suffer from lower validity in terms of reflecting the progression of SCD *severity* over time. Therefore, we opted to grade our SCD score

by domain: any number of positive answers in the questions for a given domain scored one point, yielding an SCD score of 0 to 4, changes to which might be more representative of substantial differences. So, if a participant reported SCD in one cognitive domain at baseline and two during follow-up, it would be relatively safe to assume that this spread of SCD into adjacent cognitive abilities was a sign of deterioration. The validity of this concept is further strengthened by the inverse association of our SCD score with the overall cognitive Z-score in our population[24]. As anticipated, the mean SCD score in our cohort worsened slightly by 0·20 cognitive domains during the mean 3·10 years of follow-up; such slow evolution is to be expected, given the long-term trajectory of neurodegenerative processes[2].

Because of the subjective nature of SCD and its sole reliance on self-reporting, it is essential to mitigate potential confounding. The construct of SCD has been criticised as heavily dependent on concomitant depression, anxiety and personality traits pertaining to neuroticism, fear of dementia and excessive self-monitoring[3,45]. Comparison of SCD scores in the same person through prospective monitoring mostly negates any personality effect, while persistence of the association with MDS after adjustment for the baseline affective state further corroborates our findings.
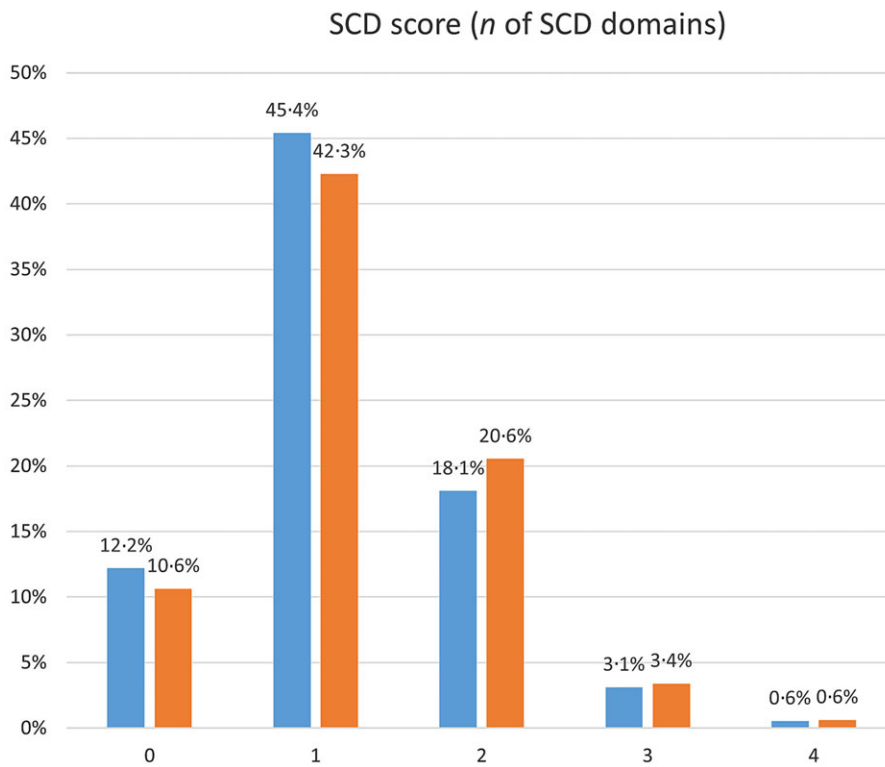
Fig. 2. Frequency distribution of the SCD score in the two study visits. SCD, subjective cognitive decline. ▮, Baseline; ▮, follow-up.

Trying to elucidate the effect of individual food group consumption on SCD evolution, we employed similar models using food group intake as predictors. The results reached statistical significance only in the case of vegetable intake; every additional vegetable serving/d was associated with a 2·2 % reduction in SCD progression within a year. A similar result has already been published regarding subjective cognitive function[46], and also in many studies on dementia prevention, and can be attributed to the high vitamin, antioxidant, flavonoid and fibre content of vegetables, as well as their low energy density[15,47]. B vitamins are essential parts of cell energy production and reduce homocysteine levels; polyphenols can modulate the circadian rhythm and together with carotenoids and certain essential minerals found in vegetables may enhance the brain's defense against oxidative stress. Moreover, higher intake of fibre increases the diversity of gut microbiota, potentially exerting neuroprotective and anti-inflammatory effects through the gut-brain axis[48].

Literature regarding the effects of vegetable consumption on disease prevention *in general* is not consistent; stronger evidence exists for a probable protective effect on cardiovascular disease and age-related cataract, with further possible evidence of decreased risk for stroke and depression[47]. Given the established role of cerebrovascular disease in brain ageing, one could hypothesise that the potential protective effect of vegetables on cognitive decline might also be attributable to the beneficial effect of their consumption on cardiovascular health. Considering all the aforementioned data, the small effect size for vegetable consumption in our study and the lack of statistical significance for other food groups may appear

counter-intuitive at first, but the impact of diet as a whole surpasses the sum of effects of its components, as has been noted previously in the literature[9]. Potential explanations include the inevitably limited role of each single nutrient in the multi-faceted synthesis of the neuronal milieu, the integration within a complete dietary regimen of non-nutritional (lifestyle etc.) factors that are difficult to isolate[9] and a possible lack of statistical power.

SCD prevalence in our population is high (67·2 % at baseline and 66·9 % on follow-up), but that is to be expected, as reported values in the literature range from 9·0 to 58·1 %[49] and according to the COSMIC collaboration from 6·1 to 52·7 %[50]. There is lack of standardisation, as well as great heterogeneity in definitions, ethnicities, ages and clinical settings in studies worldwide. According to our research on SCD prevalence, 84·2 % of the cognitively normal population ≥65 years old reported subjective decline in at least one cognitive domain[24]. We believe that our structured interview seeking cognitive complaints helps elicit more positive answers than just asking open-ended questions: inquiring about specific items may prompt the subject to search their daily experiences and result in more accurate reporting and, thus, a higher prevalence rate[28,38]. Therefore, we do not attribute high SCD prevalence to sample selection bias.

Among the limitations of the present study, it should be noted that we evaluated dietary intake only through a self-reported tool, a validated FFQ, without the added value of blood biomarkers that may have indicated adherence to at least some of the components of the MeDi more objectively. Concerns have been raised in the literature regarding retrospective assessment

of dietary habits in the elderly population, but it has not been shown irrefutably that cognitively healthy older adults provide less valid self-reports[51,52] (our population may have expressed subjective cognitive complaints, but they were all considered normal in their objective evaluation). In any case, questionnaire administration by trained researchers (mainly dietitians) and cross-reference of responses by another household member – when present – served as extra levels of response validity, while it should also be noted that the validation study of the FFQ included participants up to 82 years old[39,53]. Moreover, our clinical evaluation was not complemented by routine neuroimaging or cerebrospinal fluid biomarker collection, and APOE genotyping was not performed in a third of our sample; despite that, we believe our detailed and thorough clinical and neuropsychological protocol followed by consensus interdisciplinary team meetings integrating all collected data ensured a high level of diagnostic accuracy. Lastly, 35·6 % of the cognitively normal population not fulfilling SCD exclusion criteria at baseline were lost to follow-up, which, although unfortunate, is not uncommon in studies of this kind and in similar populations[54]. It should be noted here that participant selection was random, and invitations to enroll and attend the follow-up visit were made by phone call, with multiple attempts when needed. Comparison of those who attended the second visit and those who were lost to follow-up did not reveal significant differences, except for an age and cognitive score discrepancy. Among those who missed follow-up because of death, there was a preponderance of men, older and less educated individuals, as well as those with lower cognitive performance, as expected.

Conversely, a strength of our research is that, to our knowledge, it is the first one trying to elucidate the complex interplay in time between MeDi adherence and SCD evolution in an elderly population. Because of our methodology, we consider our sample to be representative and our diagnoses to be fairly accurate. Our subjects have been given a comprehensive neurological and neuropsychological evaluation and have answered a meticulously designed FFQ. As SCD operationalisation and development of relevant metrics is still a matter of active research in the scientific community, another small contribution of our work is the creation of a quantitative SCD score that funnels data from eighteen questions into four potential domains and the proposition of its use as a method of longitudinal assessment of SCD severity over time.

In conclusion, based on the prospective follow-up of a cohort of people at least 65 years old in Greece, we have found that MeDi adherence higher by ten points was associated with a 7 % reduction in the progression of SCD within 1 year, and every additional vegetable serving/d was associated with a 2·2 % reduction in SCD progression/year. Our results provide support to the notion that MeDi has a protective role against the whole continuum of cognitive decline, starting at the first subjective complaints. Replication of this finding, especially for individual food groups, and further clarification of the underlying mechanisms may strengthen the role of the MeDi as a cost-effective and easily implemented preventive strategy targeting the modifiable risk factors for cognitive decline.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114521005109

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