Specific Features of Subjective Cognitive Decline Predict Faster Conversion to Mild Cognitive Impairment

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Abstract.
Background: Alzheimer's disease (AD) is a silent disorder that needs the earliest possible intervention in order to reduce its high economic and social impact. It has been recently suggested that subjective cognitive decline (SCD) appears at preclinical stages many years before the onset of AD. Therefore, SCD could become an ideal target for early therapeutic intervention.
Objective: The goal of this study was to evaluate the clinical significance of SCD on the conversion from a cognitively healthy stage to a mild cognitive impairment (MCI) in one-year follow-up.
Methods: A total of 608 cognitively intact individuals from the Vallecas Project's cohort, a community-based prospective study to identify early markers of AD, were enrolled in this study. Participants were classified in three groups: i) No Complaints (NCg), ii) Subjects with complaints in one or more cognitive domains (SCDg), and iii) Subjects who, besides complaints, fulfilled the features of SCD Plus proposed by the International Working Group of SCD (SCD-Pg).
Results: Individuals were followed up for a mean of 13.1 months (range 10.7–22.4). During this time, 41 volunteers developed MCI (6.7% of total sample). The conversion rate for SCD-Pg (18.9%) was significantly higher than SCDg (5.6%) and NCg (4.9%).
Conclusion: Specific features associated with SCD may help to identify individuals at high risk of fast conversion to MCI. These results highlight the importance of a close follow-up of subjects with SCD-P and include them in early intervention programs because of their increased risk for the development of MCI.

Keywords: Aging, Alzheimer's disease, cognitive symptoms, dementia, mild cognitive impairment, subjective cognitive decline

INTRODUCTION

Sporadic Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder that begins affecting the brain many years before cognitive impairment is noticeable. According to the National Institute on Aging-Alzheimer Association (NIA-AA) workgroups, there are three different stages of AD's progression over time. First, there is a preclinical phase in which some of the disease hallmarks in the brain have taken place, such as the presence of amyloid plaques, but no objective cognitive impairment is present [1]. A second stage, called prodromal AD or

mild cognitive impairment (MCI) due to AD, involves minor cognitive changes which are noticeable to the patient and/or to others, but are not severe enough to significantly affect everyday activities [2]. Finally, there is a third stage in which the intensity of the cognitive disorder leads to a functional impairment that ends up with a dementia syndrome [3]. The difficulty in pharmacologically altering the progression of AD stages has fostered the growing consensus that therapeutic interventions are more likely to be effective at the earliest possible phase [4]. Currently, treatment efforts between stages 2 and 3 have led to negative results. Thus, the search for early markers of preclinical AD is of paramount importance since disease-modifying therapeutic approaches are being developed for future use in at risk populations [5].

In dominantly inherited AD patients, the studies on pathophysiological changes occurring several years before symptoms onset support the existence of preclinical stages [6]. Biomarkers, based on the analysis of cerebrospinal fluid (CSF) samples or brain imaging [7], have shown evidence of neuropathological features in those preclinical (silent) stages of AD. However, these abnormalities do not seem to be accompanied by a clear cognitive marker. In fact, there is still no full consensus on the clinical significance of possible entities such as subjective cognitive decline (SCD) [8].

SCD refers to a self perception of progressive deterioration of cognitive abilities independently of the objective performance on neuropsychological tests. Since cognitive complaints are heterogeneous and their expression could be affected by various factors (e.g., normal aging, personality traits, depression, drug side effects, neurological disorders, etc.), SCD is not necessarily present in all prodromal cases. Nevertheless, both cross-sectional [9–11] and longitudinal studies [12–14] have provided strong evidence of SCD occurring at preclinical stage of AD. Indeed, the combination of SCD and CSF biomarkers has also proved to be the best predictors of clinical progression from preclinical to prodromal and dementia stages [15]. For all these reasons, during the last decades there has been an increasing interest in the study of SCD as a potential early sign of cognitive decline and future progression to AD [16, 17].

To assess the potential usefulness of SCD for clinical trials, the Subjective Cognitive Decline Initiative (SCD-I) has recently agreed to a common terminology and research procedures to identify individuals with SCD at risk of preclinical AD [18]. The SCD-I aims at knowing whether the self experience of decline in cognition may represent the first symptomatic manifestation of AD. In order to demonstrate that, some common specific features are needed to better establish the profile of SCD. Thus, the SCD-I recommended to collect information regarding features such as settings in which cognitive complaints are expressed, association of SCD with medical help seeking, number of years and age at onset of SCD, subjective decline in memory and non-memory domains, and association of SCD with experience of impairment. In addition, the SCD-I proposed a set of particular features that could be helpful to identify individuals at risk of clinical progression. Those features include a more acute subjective memory decline than any other cognitive domain, onset of complaints within the last 5 years, age at onset over 60 years, worries about SCD, and feeling of worse performance than other people from the same age group. This set of features makes up a more severe form of SCD referred to as SCD Plus. This new category could allow us to explain the transition from a non-symptomatic stage to the first symptomatic manifestation of AD.

In the present study, we have assessed the validity of different subtypes of SCD and to determine its association with neuropsychiatric and cognitive performance. Furthermore, we have examined the risk of SCD for objective cognitive decline rather than subjective one. The guidelines of the SCD-I [18] were used in order to analyze whether specific features of SCD were more related to cognitive impairment.

MATERIALS AND METHODS

Subjects participating in this study were part of the Vallecas Project cohort, a community-based prospective study on early detection of AD, recently launched by CIEN Foundation and Queen Sophia Foundation (Madrid, Spain) [19].

Inclusion criteria for the Vallecas Project included community-dwelling individuals from 70 to 85 years of age without dementia or any other mental disorder impeding daily functioning at the beginning of the study. After participants signed proper consent forms, trained neurologists and neuropsychologists conducted structured clinical interviews in order to collect demographic, clinical, and cognitive data. The complete visit was usually carried out within four hours, with convenient breaks.

Baseline and follow-up diagnosis were agreed between neurologists and neuropsychologists at

consensus meetings. Every participant was independently diagnosed according to clinical criteria and taking into account age, gender, cognitive reserve, functional information, and cognitive scores. In all cases, cognitively healthy subjects were given a score of 0 in the global Clinical Dementia Rating (CDR). Criteria from NIA-AA [2] were used to diagnose core MCI.

For the purposes of this study, 608 individuals were enrolled. To be considered eligible for participating in this investigation, subjects had to have been diagnosed as cognitively intact at baseline as well as they had to have completed all questions about subjective complaints. After follow-up, 41 participants progressed to MCI.

Subjective cognitive decline assessment

Questions on cognitive concerns were coded according to the guidelines suggested by SCD-I [18]. Responses to every question were directly provided by the participants since family members were not available in all cases. Cognitive complaints were assessed twice and independently in the Vallecas Project. First, during the neurological interview participants were asked the following nine yes/no-type questions regarding specific cognitive complaints: 1) Are you easily distracted?; 2) Do you get lost in familiar surroundings or have trouble finding your way when driving?; 3) Do you often forget recent information or events?; 4) Do you often forget autobiographically information?; 5) Do you have trouble recognizing objects or faces?; 6) Do you have word-finding difficulties for people's names or common words?; 7) Do you understand simple verbal and written instructions?; 8) Do you have difficulty driving, managing finances or planning daily activities?; 9) Do you have difficulty sequencing movements (e.g., taking the necessary steps to prepare a bath)?

Second, during the neuropsychological interview participants also completed an ordinal scale of cognitive complaints (SCD scale) composed of four items with four points each (ranged 0–3). This SCD scale addressed the following questions: a) How do you perceive your memory in comparison with that of others of your age? (with four response alternatives scoring "3-bad"; "2-somewhat worse"; "1-somewhat better"; "0-excellent"); b) How do you perceive your memory today compared with your young adulthood? ("0-better"; "1-equal"; "2-somewhat worse"; "3-much worse"); c) Do you perceive your memory today is worse than compared with ten years ago? ("0-no"; "1-a little worse"; "2-somewhat worse"; "3-much worse"); d) Do you perceive your memory today is worse than compared with one year ago? ("0-no"; "1-a little worse"; "2-somewhat worse"; "3-much worse"). The sum of these items resulted in a total score of cognitive concerns ranging from 0 to 12 (lower scores meaning fewer complaints). Information concerning age at and years of SCD onset, as well as worries associated with SCD, were also collected in the same neuropsychological interview.

Based on information obtained in both clinical interviews, SCD was operationally defined as the self-rated presence of cognitive deterioration using two criteria: i) a positive response to any yes/no-type complaint question, and ii) scores above 1 on the SCD scale. Therefore, according to both criteria, the sample was classified in three different SCD groups: i) No Complaints group (NCg); ii) Subjective Cognitive Decline group (SCDg), involving some self-reported cognitive complaint; and iii) Subjective Cognitive Decline Plus group (SCD-Pg), when memory and any other cognitive complaint was expressed and all the rest of the main criteria proposed by the SCD-I were fulfilled [18].

Objective cognitive assessment

A comprehensive neuropsychological battery was administered to assess all relevant cognitive domains. Overall, six tests were used at baseline: Mini-Mental State Examination (MMSE) [20]; Rey-Osterrieth Complex Figure (ROCF) [21, 22]; Free and Cued Selective Reminding Test (FCSRT) [23–25]; Lexical and Semantic Verbal Fluency [26]; Clock Drawing Test [27]; and Digit Symbol Coding [28]. Moreover, Functional Activities Questionnaire (FAQ) [29] and Clinical Dementia Rating (CDR) [30] complemented the neuropsychological battery.

For statistical purposes, individual indexes of ROCF (i.e., time and score of copy, and immediate and delayed recall) and FCSRT (i.e., total performance within each trial; free and total immediate recall; and free and total delayed recall) were separately assessed.

Neuropsychiatric assessment

The neurological protocol included three questions about self-reported depression (Do you feel sad, lonely and depressed most of the time?), anxiety (Do you feel worried and anxious most of the time?), and apathy (Do you feel a lack of emotion,

motivation or interest in hobbies and previously activities enjoyed?). These three symptoms were collected as dichotomous questions (coded yes/no). In addition, Geriatric Depression Scale (GDS) [31] and State-Trait Anxiety Inventory (STAI) [32] were also administered as part of the neuropsychological battery.

Apolipoprotein E e4 genotyping

APOE gene polymorphism status was studied with total DNA isolated from peripheral blood following standard procedures. Genotyping of *APOE* polymorphisms (rs429358 and rs7412) was performed by Real-Time PCR [33]. *APOE* was coded 1 for the *APOE* e4 carriers, and 0 for non-carriers.

Statistical analyses

We performed a preliminary analysis of demographic, cognitive, and clinical variables at baseline to find out their distribution and possible associations with SCD. Diagnoses at baseline and follow-up, as well as conversion rate to MCI, were relevant variables to study the relationship between SCD groups and cognitive status.

Associations between categorical variables were analyzed with the Pearson's x^2 and Fisher's test when appropriate. In addition, due to differences of sample size groups and that most variables were not adjusted to the parametric assumptions, analysis of variance was based on non-parametric Kruskal-Wallis tests. SCD groups were treated as an independent variable with three levels (NCg, SCDg, and SCD-Pg) whereas demographic, cognitive, and neuropsychiatric data at baseline were used as dependent variables. Although all neuropsychological variables were analyzed, special emphasis in memory tests was made. A multivariate-adjusted Cox proportional hazard regression models was used to study the relationship between SCD groups at baseline and conversion rate to MCI. Time to event was calculated as date of entry into the study to date of MCI diagnosis. Overall, according to the previous analyses, several covariates were adjusted for studying the impact of SCD upon progression to MCI in three consecutive models: a) Model 1: age, gender, and years of education; b) Model 2: Model 1 covariates plus depression, anxiety, and apathy; c) Model 3: Model 2 covariates plus FCSRT free immediate recall, FCSRT free delayed recall, and *APOE*. A final model was calculated by retaining the covariates that met the following two conditions: first, they were found significant in any of the three previous models, and second, the minimum number of them had to explain the most part of conversion rate's variance. These covariates proved to be gender, FCSRT free immediate recall, and *APOE*. All the results were presented as hazard ratio (HR) with a 95% confidence interval (CI).

We used 2-sided significance tests for all analyses, with statistical significance set at p-value <0.05. The proportional hazards assumption was assessed for all variables using the Schoenfeld residuals graphs. Neither violation of assumptions in individual variables nor in the global model was found. All statistical analyses were performed using R version 2.14.2 [34].

RESULTS

Participants were followed up for a mean of 13.1 months (SD 1.3, median 12.9, range 10.7–22.4). During this time, 41 volunteers developed MCI (6.7% of the total sample). Regarding cognitive concerns, 69.6% of participants reported some type of complaint in any of the nine yes/no type questions. As expected, SCD scale showed significant differences between groups, especially when compared NCg and SCD-Pg. In addition, the correlation between the baseline score of the SCD scale and the follow-up SCD score showed a positive correlation ($\rho = 0.66$; $p < 0.001$). This outcome was taken as indicative of an appropriate stability of cognitive concerns.

Table 1 summarizes the descriptive statistics of the total sample and the three SCD groups at baseline. No differences in age or years of education among groups were found. Nevertheless, there was a trend for significance concerning gender and *APOE* status, being female and e4 carrier more frequent for SCD-Pg than for other groups. SCDg and SCD-Pg reported more depression, anxiety, and apathy compared to NCg. Furthermore, GDS and STAI scores were also significantly lower in NCg. Differences in apathy, GDS, and STAI trait were also found between SCDg and SCD-Pg. Overall, these results highlighted that neuropsychiatric symptoms were more frequent in both SCD groups compared to NCg; and these symptoms were especially marked for SCD-Pg. Regarding cognitive assessment, statistical differences between groups were only found for instrumental activities of everyday (FAQ), verbal episodic memory (FCSRT), and clinical rating (CDR sum of boxes). Interestingly, the SCD-Pg showed the worst cognitive performance, while neuropsychological tests did not significantly

Table 1
Baseline characteristics of the study sample by Subjective Cognitive Decline groups

	Total Sample ($n = 608$)		NCg ($n = 185$)		SCDg ($n = 370$)		SCD-Pg ($n = 53$)		*p*-value	*Post-hoc*
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age (years)	74.14	3.83	74.23	3.96	74.21	3.83	73.32	3.36	0.344	
Education (years)	11.03	6.66	11.00	6.72	11.18	6.73	10.10	5.94	0.530	
Gender	62% Female		64% Female		59% Female		75% Female		0.079	
APOE e4 (%)	17.7		16.5		16.7		29.4		0.074	
FAQ	0.42	0.80	0.22	0.54	0.48	0.86	0.68	0.94	<0.001	b
SCD										
SCD score	5.07	2.00	3.92	1.78	5.46	1.82	6.46	2.00	<0.001	a,b,c
Years of onset	7.30	6.13	6.58	6.86	8.10	6.06	3.28	1.35	<0.001	a,b,c
Age at onset	66.88	7.13	67.90	7.71	66.03	7.15	70.04	3.73	<0.001	c
Neuropsychiatric symptoms										
GDS	1.63	2.22	1.05	1.69	1.75	2.29	2.89	2.75	<0.001	a,b,c
STAI state	14.33	8.73	12.39	8.51	14.65	8.40	18.75	9.89	<0.001	a,b
STAI trait	17.20	9.77	14.16	8.20	17.70	9.97	24.17	9.30	<0.001	a,b,c
Depression (%)	21.2		7.0		26.2		35.8		<0.001	a,b
Anxiety (%)	15.5		4.3		19.2		28.3		<0.001	a,b
Apathy (%)	10.0		1.6		11.9		26.4		<0.001	a,b,c
Cognitive performance										
MMSE	28.61	1.49	28.60	1.63	28.61	1.43	28.57	1.45	0.734	
Clock Drawing Test	9.33	1.12	9.43	0.99	9.31	1.16	9.12	1.27	0.326	
ROCF time of copy	249.09	117.81	247.46	114.83	250.31	120.83	246.19	108.38	0.986	
ROCF copy	30.05	6.67	29.60	7.55	30.24	6.32	30.32	5.78	0.929	
ROCF immediate recall	12.68	6.17	12.82	6.33	12.81	6.14	11.25	5.80	0.186	
ROCF delayed recall	12.51	6.26	12.66	6.35	12.62	6.28	11.25	5.79	0.305	
FCSRT trial 1	12.57	2.65	12.97	2.61	12.52	2.59	11.55	2.98	0.001	b
FCSRT trial 2	13.81	2.16	14.09	1.98	13.81	2.08	12.85	2.90	0.003	b
FCSRT trial 3	14.64	1.70	14.75	1.55	14.69	1.58	13.87	2.57	0.008	
FCSRT free immediate	23.62	6.30	24.69	6.68	23.43	6.05	21.12	5.92	0.002	b
FCSRT total immediate	41.09	5.55	41.81	5.41	41.03	5.52	39.00	5.74	0.002	b
FCSRT free delayed	9.48	2.59	9.93	2.54	9.45	2.54	8.10	2.64	<0.001	b,c
FCSRT total delayed	14.33	1.82	14.46	1.78	14.35	1.81	13.75	1.90	0.018	b
Phonemic Verbal Fluency	36.32	11.60	36.66	12.31	36.11	11.39	36.53	10.73	0.806	
Semantic Verbal Fluency	18.59	4.75	50.85	10.30	48.59	9.17	48.08	9.15	0.079	
Digit Symbol Coding	19.20	7.53	19.93	8.42	18.82	7.17	19.23	6.60	0.413	
CDR sum of boxes	0.11	0.21	0.08	0.19	0.10	0.20	0.23	0.27	<0.001	b
Annual conversion rate to MCI (%)	6.7		4.9		5.6		18.9		0.001	b,c

APOE, apolipoprotein E; CDR, Clinical Dementia Rating; FAQ, Functional Activities Questionnaire; FCSRT, Free and Cued Selective Reminding Test; GDS, Geriatric Depression Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NCg, No Complaints group; ROCF, Rey-Osterrieth Complex Figure; SCD, subjective cognitive decline; SCDg, Subjective Cognitive Decline group; SCD-Pg, Subjective Cognitive Decline Plus group; SD, standard deviation; STAI, State-Trait Anxiety Inventory. *Post-hoc* analyses: a = NCg versus SCDg; b = NCg versus SCD-Pg; c = SCDg versus SCD-Pg.

differ between NCg and SCDg. Finally, conversion rate to MCI was significant especially high for SCD-Pg (18.9%) compared to NCg (4.9%) and SCDg (5.6%).

A specific analysis between SCD-Pg converters ($n = 10$; 19%) and SDC-Pg non-converters ($n = 43$; 81%) was developed with the aim of finding out what variables could directly influence upon the diagnosis of MCI. In this case, due to the small sample size, a robust bootstraping procedure was carried out along with the standard non-parametric analysis (Table 2). Significant differences were found in SCD scale, where converters reported more concerns than non-converters. Surprisingly, no differences were found in neuropsychiatric symptoms, neither depression nor anxiety questionnaires. Among cognitive variables, several indexes of FCSRT (trial 2, and free immediate and delayed recall) differed between groups. Figure 1 shows the magnitude of the differences between non-converters and converters through three types of variables: subjective cognitive complaints, objective cognitive performance and psychiatric variables. All these results suggested that subjective and objective cognitive variables, but not psychiatric ones, were actually involved in conversion from SCD-Pg to MCI.

In unadjusted Cox proportional hazard regression models, SCDg had about a 32% increased risk of progression to MCI compared to NCg, whereas the increased risk for SCD-Pg was about 360%. Kaplan-

Table 2
Baseline comparisons between SCD-Pg non-converters and SCD-Pg converters

	Non Converters ($n = 43$)		Converters ($n = 10$)		p-value
	Mean	SD	Mean	SD	
Age (years)	73.05	3.27	74.50	3.66	0.230
Education (years)	9.89	5.76	11.00	6.96	0.608
Gender	77% Female		70% Female		0.692
APOE e4 (%)	24.39		50.00		0.173
FAQ	0.60	0.95	1.00	0.82	0.088
SCD					
SCD score	6.19	1.68	8.00	3.06	0.033
Years of onset	3.23	1.34	3.50	1.43	0.568
Age at onset	69.81	3.65	71.00	4.11	0.356
Neuropsychiatric symptoms					
GDS	2.65	2.68	3.90	2.96	0.146
STAI state	18.09	9.56	21.60	11.29	0.466
STAI trait	23.53	9.52	26.90	8.20	0.339
Depression (%)	32.56		50.00		0.465
Anxiety (%)	23.26		50.00		0.123
Apathy (%)	25.58		30.00		0.999
Cognitive performance					
MMSE	28.65	1.41	28.20	1.62	0.443
Clock Drawing Test	9.28	1.11	8.45	1.71	0.152
ROCF time of copy	257.63	108.30	197.00	99.11	0.053
ROCF copy	30.35	5.63	30.20	6.70	0.732
ROCF immediate recall	11.43	5.70	10.50	6.44	0.439
ROCF delayed recall	11.69	5.80	9.40	5.66	0.165
FCSRT trial 1	11.84	2.57	10.30	4.27	0.448
FCSRT trial 2	13.42	2.00	10.40	4.65	0.038
FCSRT trial 3	14.28	1.65	12.10	4.61	0.068
FCSRT free immediate	21.95	5.70	17.11	5.56	0.040
FCSRT total immediate	39.53	5.42	36.44	6.84	0.303
FCSRT free delayed	8.42	2.63	6.56	2.19	0.045
FCSRT total delayed	13.91	1.97	13.00	1.32	0.080
Phonemic Verbal Fluency	36.05	10.81	38.60	10.68	0.517
Semantic Verbal Fluency	49.16	9.02	43.40	8.59	0.106
Digit Symbol Coding	19.21	6.35	19.30	7.97	0.847
CDR sum of boxes	0.198	0.27	0.35	0.24	0.080

APOE, apolipoprotein E; CDR, Clinical Dementia Rating; FAQ, Functional Activities Questionnaire; FCSRT, Free and Cued Selective Reminding Test; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; ROCF, Rey-Osterrieth Complex Figure; SCD, Subjective Cognitive Decline; SD, standard deviation; STAI, State-Trait Anxiety Inventory.

Meier plots showed clear differences in risk by SCD-Pg after 14 months of follow-up (Fig. 2). On the other hand, adjusted Cox regression models were also conducted to control the influence of sociodemographic, neuropsychiatric, neuropsychological, and genetic variables upon SCD and its association with conversion to MCI. As shown in Table 3, after adjustment for all fitted models SCDg did not display differences compared to NCg. However, SCD-Pg showed a significant high risk of MCI, especially in Model 1 when control was only made for age, gender, and education (HR 5.44, 95% CI = 2.16–13.75). Additional adjustment for depression, anxiety, and apathy (Model 2) yielded similar results for SCD-Pg. Finally, additional adjustment for both free immediate and delayed memory, as well as *APOE* genotyping (Model 3), only marginally decreased the HR values for SCD-Pg. Hence, as expected, memory performance (HR 0.83; 95% CI 0.76–0.91; p-value <0.001) was the most significant predictor of progression to MCI, in such a manner that the lower the memory score, the higher the risk to convert to MCI.

In order to confirm these outcomes, we conducted a more parsimonious final model controlling for gender, FCSRT free immediate recall, and *APOE* as covariates. The reason for considering these three covariates and no others was because only those ones proved to be significant in their respective models. As a result, in our final model, the multivariate adjusted HRs in participants who reported SCD-P were 4.17 (95% CI: 1.52–11.43) compared to NCg, while SCDg did not differ from NCg. The value of the determination coefficient was 0.13, almost the same as Model 3 with 9 covariates. This small value could indicate

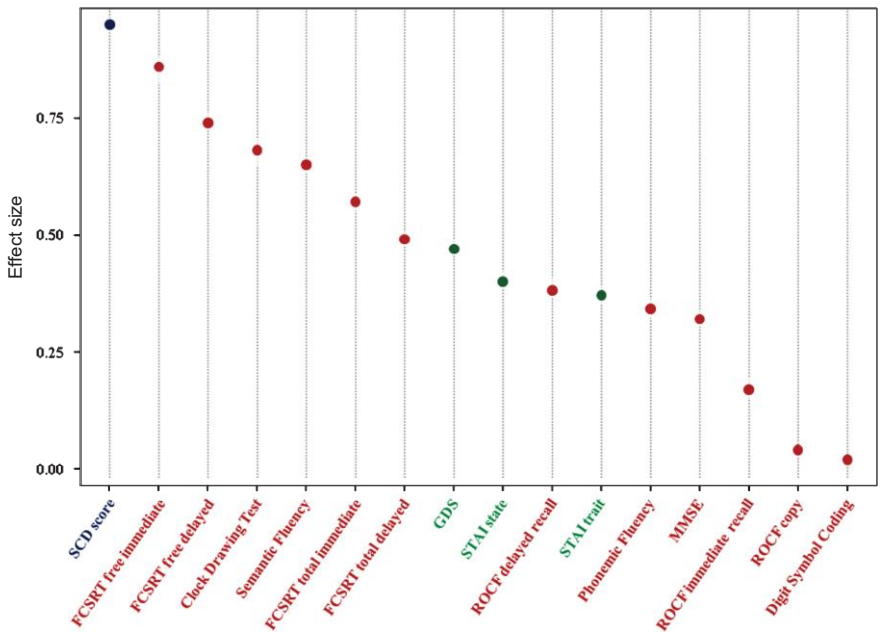

Fig. 1. Effect size of individual variables at baseline on conversion from SCD Plus to MCI. This graphic represents the effect size of the individual variables at baseline on the profiles of SCD-Pg non-converters and SCD-Pg converters. Variables are clustered in three categories: i) subjective cognitive complaints (blue), ii) objective cognitive performance (red), and iii) psychiatric symptoms (green). As shown, SCD score had the largest effect size (Cohen's d = 0.94) among groups followed by cognitive performance variables, especially free recall of verbal information. Magnitude of depression and anxiety scores resulted less important to discriminate SCD-P subjects at risk of conversion to MCI. FCSRT, Free and Cued Selective Reminding Test; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; ROCF, Rey-Osterrieth Complex Figure; SCD, subjective cognitive decline; STAI, State-Trait Anxiety Inventory.

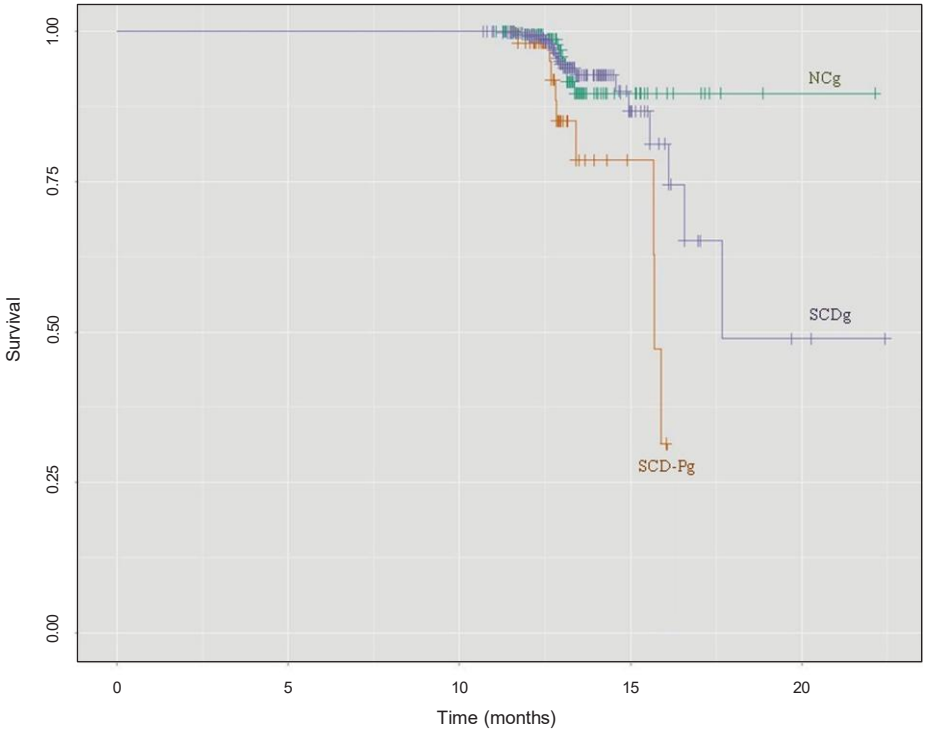

Fig. 2. Kaplan-Meier survival curves for unadjusted rates of MCI by SCD groups. SCD-Pg shows the highest risk of conversion to MCI.

Table 3
Cox proportional hazard regression models of conversion rate to MCI with additional adjustment for potential mediators

	HR (95% CI)		
Adjustment Model	NCg	SCDg	SCD-Pg
Model 1	1 [Reference]	1.30 (0.60–2.82)	5.44 (2.16–13.75)***
Model 2	1 [Reference]	0.10 (0.49–2.48)	4.40 (1.65–11.72)**
Model 3	1 [Reference]	0.89 (0.35–2.22)	2.92 (0.96–8.86)
Final Model	1 [Reference]	1.17 (0.52–2.65)	4.17 (1.52–11.43)**

Model 1: adjusted for age, gender and education (years). $R^2 = 0.04$
Model 2: adjusted for Model 1 covariates and depression, anxiety and apathy. $R^2 = 0.05$
Model 3: adjusted for Model 2 covariates and FCSRT free immediate, FCSRT free delayed and *APOE*. $R^2 = 0.14$
Final Model: adjusted for sex, FCSRT free immediate and *APOE*. $R^2 = 0.13$

CI, confidence interval; FCSRT, Free and Cued Selective Reminding Test; HR, hazard ratio; NCg, Non Complaint group; SCDg, Subjective Cognitive Decline group; SCD-Pg, Subjective Cognitive Decline Plus group. $^{**}p < 0.01$; $^{***}p < 0.001$.

that other variables apart from SCD account for the rate of conversion to MCI.

DISCUSSION

The role of the clinical significance of SCD in the transition from a cognitively intact stage to MCI has been analyzed in a cohort that was followed-up approximately for 13 months. According to the guidelines proposed by the SCD-I [18], subjects were classified depending on their cognitive concerns. Thus, 69.6% of the sample reported some type of complaint, what is slightly higher than the common prevalence of SCD in the general population [35], but consistent with this age group [36, 37]. Finally, based on self-reported complaints, three different groups of SCD were established (NCg, SCDg, and SCD-Pg).

Although no statistical differences were found with regard to gender and *APOE*, a trend for significance was obtained between groups. Indeed, female gender and e4 carrier were more associated with SCD-Pg than the two other groups. Since both features have been proved to increase the risk of AD [38], cognitive complaints could be somehow related to them. This relationship might occur at preclinical stages, before anosognosia and objective impairment appear. Nevertheless, to isolate the role of SCD as early sign of progression to MCI, gender and *APOE* were controlled in further analysis.

Potential differences between groups were analyzed using neuropsychiatric and cognitive variables. Symptoms of depression, anxiety, and apathy were strongly associated with SCD, and they were able to identify the NCg from the rest of SCD groups. This finding has been highlighted in a large number of studies [39–41], suggesting that complaints correlate more closely to depression and anxiety than cognitive performance; thus, they could play a mediating role between mood and cognitive status [42]. However, our results did not support the fact that the combination of SCD and specific psychiatric symptoms increased the risk of conversion to MCI. Indeed, according to the Cox regression Model 2, psychiatric covariates neither resulted significant nor provided additional information to SCD. Perhaps, the explanation of these outcomes has to do with the fact that SCD would begin to decline the cognitive status some years before that of psychiatric symptoms. This explanation is somehow consistent with the literature since while depression and anxiety are mainly suggested to be risk factors for dementia in prodromal AD [43–45], SCD is proposed to be an early sign of MCI in preclinical stages [46, 47]. Otherwise, although cognitive measures were related to SCD in a lesser degree than neuropsychiatric variables as expected [36, 48, 49], low memory performance at baseline allowed to better differentiate SCD-Pg. In addition, and most importantly, controlling for depression, anxiety and apathy, episodic memory performance was associated with a faster rate of MCI conversion in individuals with SCD Plus.

In line with previous studies that have found an increased risk of AD in healthy subjects who reported SCD seven years earlier [12–14], our annual conversion rate to MCI for subjects with SCD Plus at baseline was almost 20%. This outcome was significant and differed from SCDg, which displayed a conversion rate of 5.6%. Indeed, while the HR obtained for SCDg were similar to other studies [50, 51], and it did not significantly differ from NCg, individuals who reported SCD Plus had a higher risk of developing MCI (HR = 4.17) compared to those subjects without complaints. In addition, the inclusion of gender, memory performance, and *APOE* genotyping in the survival analyses did not decrease the predictive power of the SCD-Pg.

Taking into account that the follow-up period covered less than two years, these results indicate that some particular features associated with cognitive complaints (i.e., onset of complaints within the last 5 years, age at onset over 60 years, worries associated with complaints, and feeling of worse performance than other people from the same age group) may identify those individuals at high risk of fast conversion to MCI. These findings have paramount implications for clinical settings. For instance, cognitive training programs should be implemented in subjects meeting all features of SCD Plus proposed by SCD-I [18].

Regarding the weaknesses of the present study, it is recognized that the short follow-up could be seen as an important limitation. Nevertheless, we consider that the elapsed time is enough to examine the main objective of this paper, that is, to seek for the minimum time required for conversion to MCI in healthy subjects who report SCD. Our outcomes suggest the existence of different rates of conversion to MCI that depend on the features of SCD. Thus, SCD-Pg seems to exhibit a larger and faster risk of MCI. Given that the Vallecas Project is still in progress, the association between SCD and MCI shall be analyzed in next visits to explore deeply our present results. In addition, since the SCD data were collected in a volunteer sample of elderly people, generalization of results should be treated with caution.

Although biomarkers have a clear value for diagnosis of early AD, we should not look down on the complementarity that behavioral markers hold for the disorder. Age-dependent neuropsychological and cognitive assessment has provided evidence that a decline in speed of information processing, executive function (working memory, task switching, inhibitory function), and reasoning goes along with normal aging. Longitudinal studies assessing cognitive function prior to dementia have also steadily shown a gradual cognitive decline in episodic memory as well as non-memory domains up to a decade before dementia onset. Interestingly, the preclinical path suggests a long and slow rate of presymptomatic changes as well as a period of acceleration of performance decline that may begin several years before MCI onset. However, current neuropsychological tests do not seem to be sensitive enough to discriminate SCD converters and non-converters which lead to the necessity of developing more sensitive tools for these preclinical stages of the disease.

Self-report of subtle cognitive decline, even in the absence of significant objective impairment on testing, may predict future decline in older individuals. Subjects who report SCD Plus might need special attention in terms of an early cognitive or pharmacological intervention. Thus, combining biomarkers with measures sensitive to detect very subtle cognitive decline in longitudinal studies of older individuals could be extremely useful in coming years. For instance, it will be needed to prove whether individuals at preclinical stage with subjective complaints and positive biomarkers have a major risk of AD progression. If so, since at this preclinical phase the brain is supposed to be recoverable, the effectiveness of new clinical trials with AD modifying therapies should be examined.

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