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Predicting progression from subjective cognitive decline to dementia using different neuropsychological criteria: A longitudinal study

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HIGHLIGHTS

- Subjective Cognitive Decline (SCD) is a heterogeneous risk stage shaped by neuropsychological criteria for normality.
- Different Jak and Bondi–based criteria define SCD groups with distinct cognitive and functional profiles.
- Less stringent definitions of cognitive normality (Historical and Conservative SCD) were associated with a higher risk of conversion to dementia.
- More stringent definitions (Liberal, Typical or Comprehensive SCD) were associated with lower or non-significant risk.
- The choice of SCD diagnostic criteria is relevant for clinical and research objectives.

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ABSTRACT

Background: Subjective Cognitive Decline (SCD) is considered a risk stage for future cognitive impairment and dementia.
Objective: This study examined whether different neuropsychological criteria for defining cognitive normality influence SCD's ability to predict conversion to dementia.
Methods: Participants from the Cognitive Complaints Cohort were diagnosed according to the Subjective Cognitive Decline Initiative criteria. Normal cognition was defined by the absence of Mild Cognitive Impairment according to five Jak and Bondi criteria. Sociodemographic, clinical, and neuropsychological data were analyzed using descriptive statistics. Bootstrap methods characterized group profiles given overlap between SCD definitions. Kaplan–Meier curves illustrated time to dementia, and a clustered Cox proportional hazards model accounted for overlapping group membership and adjusted for baseline variables.
Results: Among 838 subjects, the five SCD groups showed similar age and sex distributions but differed in education, cognition, and functional status, while subjective complaints and depressive symptoms did not differ meaningfully. Kaplan–Meier curves showed variability in conversion probabilities. At five years, conversion ranged from 3.9% (Liberal) to 25.5% (Conservative); at ten years, from 16.2% to 40.9%. Clustered Cox analysis showed that Conservative and Historical SCD remained associated with higher hazard of conversion after adjustment, whereas Typical and Comprehensive SCD were associated with lower hazard estimates.

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Conclusions: Neuropsychological criteria for cognitive normality define SCD groups with distinct clinical profiles and risks of dementia. Broader definitions identify individuals at higher risk, whereas more stringent definitions capture populations with lower likelihood of decline, highlighting the importance of criterion selection according to clinical and research objectives.

1. Introduction

Subjective Cognitive Decline (SCD) is characterized by a person's self-perceived decrease in cognitive ability compared to previous functioning, despite the absence of objectively measurable cognitive deficits on neuropsychological tests. (Jessen et al., 2014)

SCD is often recognized as the earliest manifestation of various neurocognitive disorders, including Alzheimer's disease, representing an intermediate phase between normal aging and Mild Cognitive Impairment (MCI). (Jessen et al., 2020) However, in clinical practice, complete evaluation of individuals with SCD may prove challenging due to the limited availability of biomarkers, ethical and economic considerations. (Lerch et al., 2024)

There is no universally accepted cutoff for neuropsychological tests to define cognitive impairment or to distinguish between SCD and MCI. (Jessen et al., 2014) This distinction is especially important in memory clinics, where patients with these conditions are often seen, and where the differential diagnosis has significant implications for patient care, particularly regarding prognosis. Despite some inconsistencies related to the clinical setting and diagnostic criteria, the yearly rate of conversion to dementia has been established at 2.3% for SCD (Mitchell et al., 2014) and 16.5% for MCI. (Petersen et al., 2010)

Applying different neuropsychological criteria to define cognitive normality in a large sample of memory clinic patients leads to significant variations not only in the frequency of SCD diagnoses but also in clinical characteristics, including overall cognitive functioning and performance in daily activities. (Pestana et al., 2024)

The presence of SCDplus variables, (Jessen et al., 2014) the diagnostic setting of SCD, (Snitz et al., 2018) and brain atrophy patterns (Lerch et al., 2024) appear to be associated with variations in the risk of progression to dementia. However, to the best of our knowledge, no study has examined how various definitions of cognitive normality employed in SCD diagnosis based on different neuropsychological criteria can influence the risk of progression to dementia.

Given that the neuropsychological thresholds employed in the Jak-Bondi criteria, as delineated in 2009 (Jak et al., 2009), have introduced a more comprehensive framework for diagnosing MCI through the refinement of diagnostic operationalization, it is pertinent to investigate the risk of progression to dementia of patients who have already been diagnosed at baseline with SCD according to these five neuropsychologically based criteria.

Therefore, the primary objective of this study was to compare the prognostic value of various neuropsychological criteria for SCD diagnosis in a large sample of patients from a memory clinic. Specifically, we investigated the ability of each set of SCD criteria to identify individuals who subsequently progressed to dementia during the study period.

2. Methods

2.1. Participants

Participants were selected from our previous cross-sectional study (Pestana et al., 2024) and included all the individuals enrolled in the Cognitive Complaints Cohort (CCC) from 2000 to 2022. The CCC is a clinical cohort of non-demented patients with cognitive complaints, established prospectively at the Faculty of Medicine, University of Lisbon. (Maroco et al., 2011) Its goal is to study patients with cognitive complaints through comprehensive neuropsychological assessments and other biomarkers. The same team of trained neuropsychologists conducts the assessments at each CCC visit, following a standardized protocol. Inclusion criteria for the CCC include (a) presence of cognitive complaints and (b) a detailed neuropsychological assessment. Exclusion criteria are (a) neurological or psychiatric disorders that could cause cognitive deficits; patients with major depression per the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) or with severe depressive symptoms indicated by a score of over 10 on the Geriatric Depression Scale (GDS) short version (Sheikh & Yesavage, 1986), (b) systemic illnesses affecting the brain, (c) history of alcohol or substance abuse or dependence, and (d) dementia as per DSM-IV-TR (American Psychiatric Association, 2000) or a Mini-Mental State Examination (MMSE) score below the Portuguese cutoff point. (Folstein et al., 1975; Guerreiro et al., 1994) More detailed information about the development of the CCC has been published previously. (Maroco et al., 2011; Silva et al., 2012; Silva et al., 2013)

The local Ethics Committee of the Lisbon Academic Medical Centre (CAML) approved this specific study within the CCC. All participants provided informed consent to participate in the CCC. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Examination at the baseline

The examination protocol at the baseline is described in detail in our previous study. (Pestana et al., 2024)In summary, the diagnosis of SCD was conducted in the baseline by operationalizing the criteria proposed by SCD-I (Jessen et al., 2014) (Table 1): (a) Patients have self-experienced persistent decline if they presented to a memory clinic with a complaint of cognitive decline (SCD index criterion), and cognitive complaints were discriminated through clinical records and from the application of the Subjective Memory Complaints Scale (SMC scale) (Blessed et al., 1968; Ginó et al., 2015); (b) normal age, gender, and education-adjusted performance on extensive neuropsychological testing established by the absence of MCI according to the five sets of MCI neuropsychologically based criteria defined by Jak and Bondi in

Table 1
SCD basic criteria according to SCD-I (Jessen et al., 2014) and Jak-Bondi MCI criteria (Jak et al., 2009).

SCD basic criteria	
(a) self-experienced persistent decline in cognitive capacity compared with a previously normal status unrelated to an acute event.	
(b) normal age, gender, and education-adjusted performance on extensive neuropsychological testing according to clinical normative data.	
(c) normal global cognition and performance in activities of daily living.	
(d) absence of MCI or dementia.	
(e) absence of past or present psychiatric or neurologic diseases, medical disorders, substance abuse, or use of medications that might explain the presence of subjective cognitive complaints.	
Jak-Bondi MCI criteria	
Historical criteria	Individuals were classified as MCI if objective memory performance fell >1.5 SD below their age-appropriate norms on the WMS-R LM subtest.
Typical criteria	Individuals were classified as MCI if at least one test within a domain fell >1.5 SD below age-appropriate norms.
Comprehensive criteria	Individuals were classified as MCI if at least two tests within a cognitive domain fell >1 SD below age-appropriate norms.
Liberal criteria	Individuals were classified as MCI if only one test within a cognitive domain fell >1 SD below age-appropriate norms.
Conservative criteria	Individuals were classified as MCI if at least two tests within a cognitive domain fell >1.5 SD below age-appropriate norms.

Abbreviation: SD, standard deviation.

2009 (Jak et al., 2009) (Table 1); (c) normal global cognition defined in this study by a score ≥ 22 for those with 1–11 years of schooling and ≥ 27 for >11 years on the MMSE (Folstein et al., 1975; Guerreiro et al., 1994) and normal performance in activities of daily living defined in this study by a score < 3 on the first part (items 1–8) of the Blessed Dementia Rating Scale (BDRS) (Garcia, 2008; Garcia, 1984); (d) absence of MCI defined according to the Jak and Bondi criteria (Jak et al., 2009) or dementia defined according to DSM-IV-TR (American Psychiatric Association, 2000) criteria; (e) absence of past or present psychiatric or neurologic diseases, medical disorders, substance abuse, or use of medications that might explain the presence of subjective cognitive complaints. It should be noted that patients with Neurodevelopmental Disorders, Schizophrenia Spectrum and Other Psychotic Disorders, Bipolar and Related Disorders, Depressive Disorders, and Obsessive-Compulsive and Related Disorders diagnoses according to DSM-IV-TR (American Psychiatric Association, 2000) criteria were excluded. Significantly, the five different types of SCD considered were defined exclusively by the Jak-Bondi rules applied to criterion b), while the remaining SCD criteria were kept constant across groups, as the remaining four criteria for the diagnosis of SCD remain unchanged. The SCD groups, obtained by the absence of objective cognitive impairment, were designated according to the respective Jak-Bondi criterion, for example, Historical SCD for the absence of Historical MCI, and so on.

The sociodemographic data were obtained through clinical records. Data on subjective complaints were collected from clinical records and from the SMC scale results. (Blessed et al., 1968; Ginó et al., 2015) Global cognitive functioning was assessed with the Portuguese version of the MMSE (Folstein et al., 1975; Guerreiro et al., 1994). Cognitive performance data (adjusted for age, gender, and education) were collected from the neuropsychological evaluation results using the Battery of Lisbon for the Assessment of Dementia (BLAD) (Yesavage). Two tests from the BLAD, each with a missing data percentage below 10%, were chosen for the five cognitive domains identified by Jak and Bondi in 2009 (Jak et al., 2009). The selected tests (domains) were logical memory with interference and word recall with interference (memory); cancellation task and digit span forward (attention); verbal phonemic fluency and interpretation of proverbs (language); clock-drawing and Raven progressive matrices (visuospatial functioning); digit span backward and motor initiative (executive functioning). Data regarding performance in activities of daily living were collected from the results of the first part of the BDRS that addresses daily life activities. (Garcia, 2008; Garcia, 1984) In terms of neuropsychiatric symptoms, the GDS (Barreto et al., 2008; Figueiredo-Duarte et al., 2021) was used to characterize depressive symptoms, namely its short form (15 items). (Castanho et al., 2016; Sheikh & Yesavage, 1986)

2.3. Re-examination and conversion to dementia

At follow-up, patients were classified as *converter* if they met the DSM-IV-TR (American Psychiatric Association, 2000) criteria for dementia and *non-converter* if they did not meet these criteria. Patients who had not a second assessment were contacted by the assistant neurologist (AdeM) over the phone to get information about their current cognitive status, using the Portuguese version of the Telephone Interview for Cognitive Status (TICS-PT) (Moons et al., 2015), specifically whether they had developed dementia.

2.4. Statistical analysis

The statistical analyses, including multiple imputation, were performed using IBM SPSS Statistics for Windows, Version 28.0.1 (SPSS Inc., an IBM Company, Chicago, IL, USA).

The baseline sociodemographic and clinical data of each SCD diagnostic group were described using descriptive statistics. The neuropsychological assessments were standardized according to the age and education norms for the Portuguese population (Yesavage) and z-scores were calculated. The z-scores of the neuropsychological assessments at the baseline were used to obtain the five different types of SCD determined by the Jak-Bondi rules chosen to define SCD-I criterion b). Missing data were treated according to the principles of the TRIPOD statement. (Haukoos & Newgard, 2007) Considering that the proportion of missing data among the 10 employed neuropsychological tests was <10% and that the predominant absence of values in these variables is assumed to stem from random causes, the multiple imputation methodology (Fishman, 2013; Newgard & Haukoos, 2007) was selected to address these variables.

Recognizing the potential substantive contribution of additional variables to the imputed values, a multiple imputation model was formulated encompassing fourteen variables (ten neuropsychological tests, a metric for global cognitive performance (MMSE), a metric for subjective cognitive complaints (SMC scale), a metric for daily life functioning (first part of the BDRS), and a metric for neuropsychiatric symptoms (third part of the BDRS)). The automatic imputation method was selected in SPSS. After analyzing the data and considering that all fourteen variables were scale-based, SPSS employed the Monte Carlo method for imputation, using linear regression. (Carpenter & Bithell, 2000) Five sets of imputations were generated. The average of the five imputations for neuropsychological test variables was calculated to obtain the final dataset, following a pragmatic approach given the low proportion of missing data in these variables.

It is important to note that the different diagnostic groups of SCD share common patients. Therefore, a direct comparison between these groups was not conducted. Instead, to descriptively explore whether the five SCD criteria might reflect distinct clinical profiles, a bootstrap methodology (Parfenov et al., 2020) was employed to estimate the mean and 95% confidence intervals (CI) for specific parameters of interest, namely age, sex, education, SMC scale (subjective cognitive complaints), MMSE (global cognition), BDRS first part (daily living functioning), and GDS (depressive symptoms), within each of the five SCD diagnostic groups. Bootstrap estimates were interpreted descriptively, given the overlap between SCD groups.

Kaplan–Meier survival analysis was used to illustrate the time-dependent probability of conversion across the five SCD groups, accounting for censored follow-up data. A Cox proportional hazards model was performed, including all SCD definitions simultaneously, together with baseline covariates (age, sex, education, MMSE, and functional status). Robust standard errors were estimated using subject-level clustering to account for the non-independence arising from overlapping group membership. This model estimated the association between each SCD definition and time to dementia conversion, adjusted for baseline variables.

3. Results

The clinical records of patients included in the CCC, between January 1, 2000 and December 31, 2022, were carefully reviewed. By the application of the SCD-I criteria (a), c), d), and e)), 1060 patients were diagnosed with SCD according to at least one of the five different sets of SCD criteria listed above (SCD-I criterion b). 35 patients were excluded, 6 after withdrawing their consent and 29 being excluded due to fulfilment of an exclusion criteria, namely significant psychiatric and non-psychiatric disorders (primarily cancer and major vascular disease) following the initial assessment. In 187 patients, follow-up assessment could not be performed.

The patients who did not undergo follow-up assessments did not differ from those who remained in the study with respect to baseline demographic and clinical characteristics, suggesting that attrition did not introduce substantial bias. As a result, 838 subjects entered this study (Fig. 1).

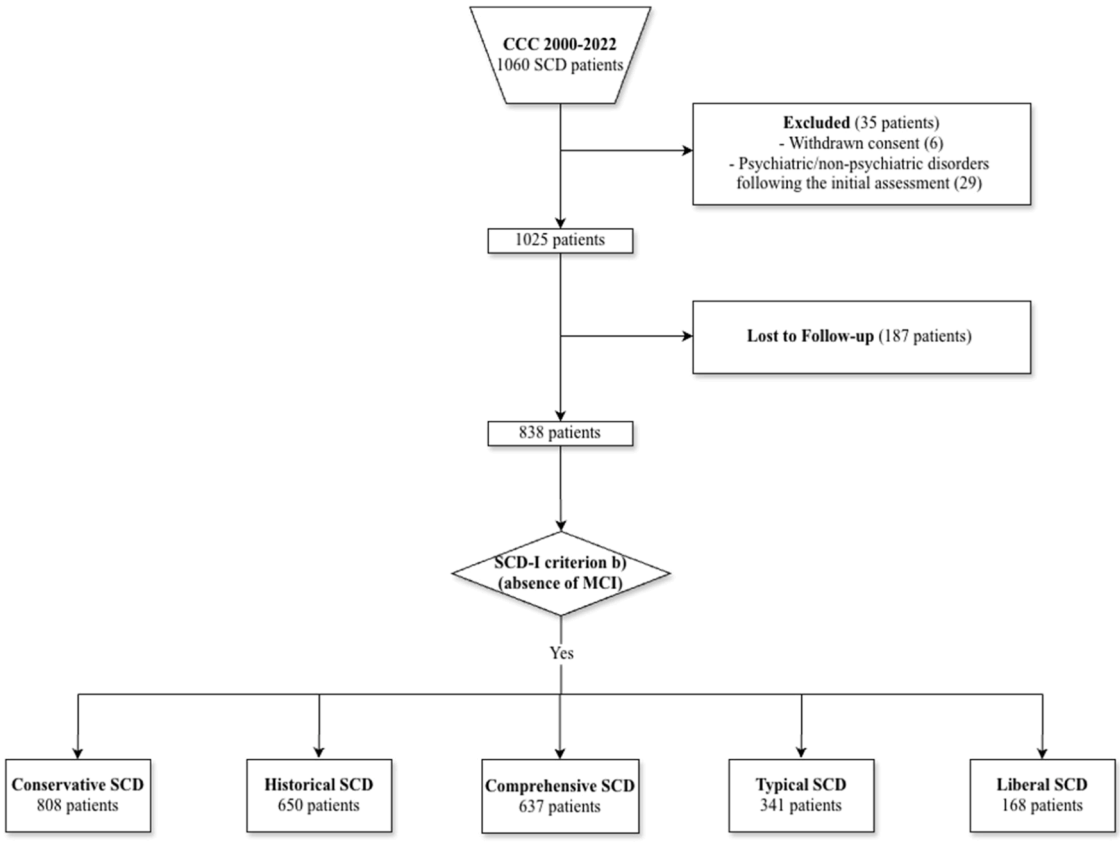


Fig. 1. Patient enrolment, from CCC to SCD-I criteria.

Table 2
Demographic and clinical characteristics of SCD patients diagnosed according to the five different criteria at the baseline and conversion rates to dementia during the follow-up period.

	Historical SCD	Typical SCD	Comprehensive SCD	Liberal SCD	Conservative SCD
N (838)	650 (77.6%)	341	637	168	808
Mean (SD)		(40.7%)	(76.0%)	(20.0%%)	(96.4%)
Sociodemographic Data					
Sex M	38.2%	38.4%	37.4%	38.1%	37.5%
F	61.9%	61.6%	62.6%	61.9%	62.5%
Age at the baseline	67.4 (9.5)	66.5 (9.6)	67.7 (9.2)	66.8 (9.1)	68.1 (9.3)
Education, years	10.8 (4.6)	10.9 (4.8)	10.4 (4.7)	11.4 (4.6)	10.1 (4.8)
Memory Complaints					
SMC scale	10.3 (3.8)	10.2 (3.6)	10.1 (3.7)	10.3 (3.6)	10.0 (3.9)
Global Cognition					
MMSE	27.4 (1.9)	27.8 (1.8)	27.3 (2.1)	28.1 (1.6)	26.9 (2.2)
Activities of Daily Living					
BDRS 1st Part	0.7 (0.7)	0.5 (0.7)	0.7 (0.7)	0.3 (0.6)	0.8 (0.8)
Depressive Symptoms					
GDS	5.0 (3.1)	4.6 (3.0)	4.7 (3.1)	4.0 (3.0)	4.6 (3.1)
Follow-up time (years)					
Mean (SD), years	5.0 (3.7)	5.8 (3.9)	5.0 (3.7)	6.2 (3.9)	4.7 (3.6)
Conversion to dementia					
Converters	22.5%	15.8%	21.7%	10.1%	25.9%

Abbreviations: BDRS, Blessed Dementia Rating Scale; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; SD, standard deviation; SMC, Subjective Memory Complaints.

3.1. Demographic variables

The sociodemographic data of SCD patients diagnosed based on the five criteria are shown in Table 2.

Across all SCD diagnostic groups, nearly two-thirds of the subjects were women. Age remained consistent across the SCD diagnostic groups, with mean ages ranging from 66.5 years (Typical SCD) to 68.1 years (Conservative SCD). The average educational levels ranged from 10.1 years (Conservative SCD) to 11.4 years (Liberal SCD).

We performed a bootstrap analysis to descriptively explore whether the SCD patients diagnosed according to the five criteria might reflect distinct clinical profiles. The bootstrap analysis did not indicate meaningful differences in age or sex among the SCD groups. However, differences in educational level were observed, with lower values in the

Fig. 2. Bootstrap Analysis.
* denotes a group whose 95% CI does not overlap with at least one other group's CI.
Abbreviations: BDRS, Blessed Dementia Rating Scale; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; SMC, Subjective Memory Complaints.

Conservative SCD group compared with the Liberal group (Fig. 2).

3.2. Clinical variables

Regarding memory complaints, the SMC scale scores ranged from 10.0 (Conservative SCD) to 10.3 (Liberal and Historical SCD) (Table 2). The bootstrap analysis did not suggest meaningful differences between the SCD groups (Fig. 2 and Table S1).

In terms of overall cognitive functioning, the MMSE score ranged from 26.9 (Conservative SCD) to 28.1 (Liberal SCD). The Liberal SCD group showed higher global cognitive performance compared with the Historical, Comprehensive, and Conservative groups. The Conservative SCD group showed lower performance than the remaining groups, except for the Comprehensive group.

Regarding performance in activities of daily living, the BDRS first part score ranged from 0.3 (Liberal SCD) to 0.8 (Conservative SCD). The Liberal SCD group demonstrated better functional performance than the Historical, Comprehensive, and Conservative groups.

Lastly, concerning depressive symptoms, GDS score ranged between 4.0 (Liberal SCD) and 5.0 (Historical SCD). No meaningful differences

were observed between groups.

3.3. Follow-up time

The average follow-up time ranged from 4.7 (Conservative SCD) to 6.2 years (Liberal SCD) across the groups (Table 2).

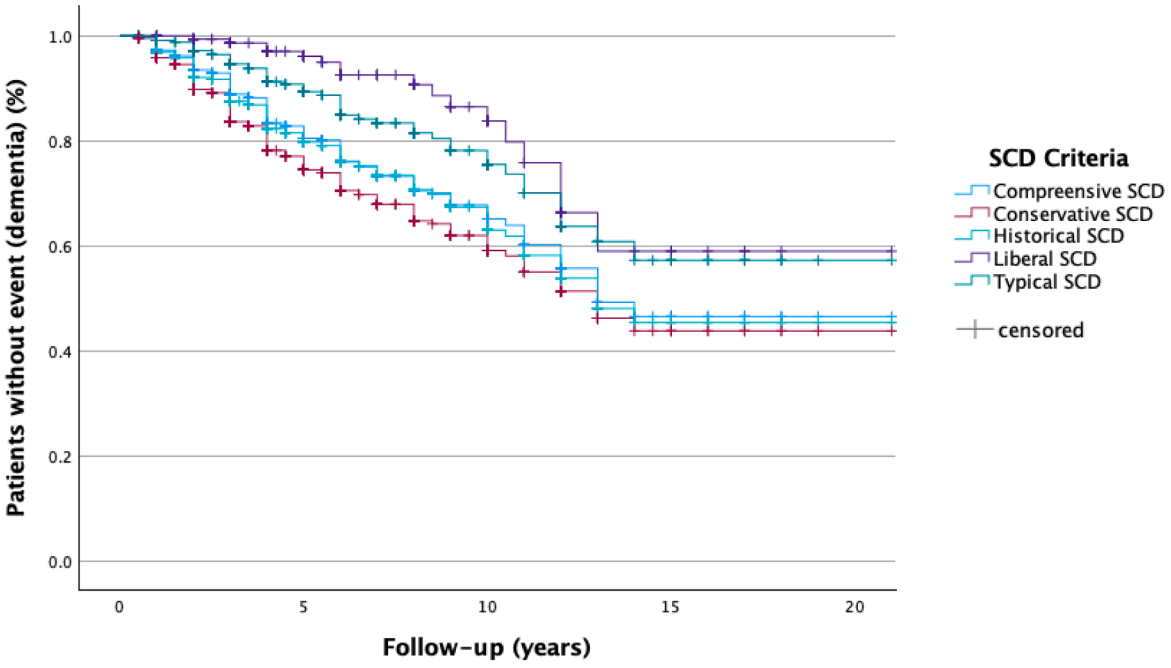
3.4. Conversion to dementia

Regarding conversion to dementia, the highest proportion was observed in the Conservative group (25.9%), followed by the Historical (22.5%) and Comprehensive (21.7%) groups. The Typical group had a lower conversion rate (15.8%), and the Liberal group showed the lowest rate (10.1%).

3.5. Kaplan-Meier analysis

According to the Kaplan-Meier curves, the probability of conversion to dementia varied across SCD definitions (Fig. 3 and Table 3).

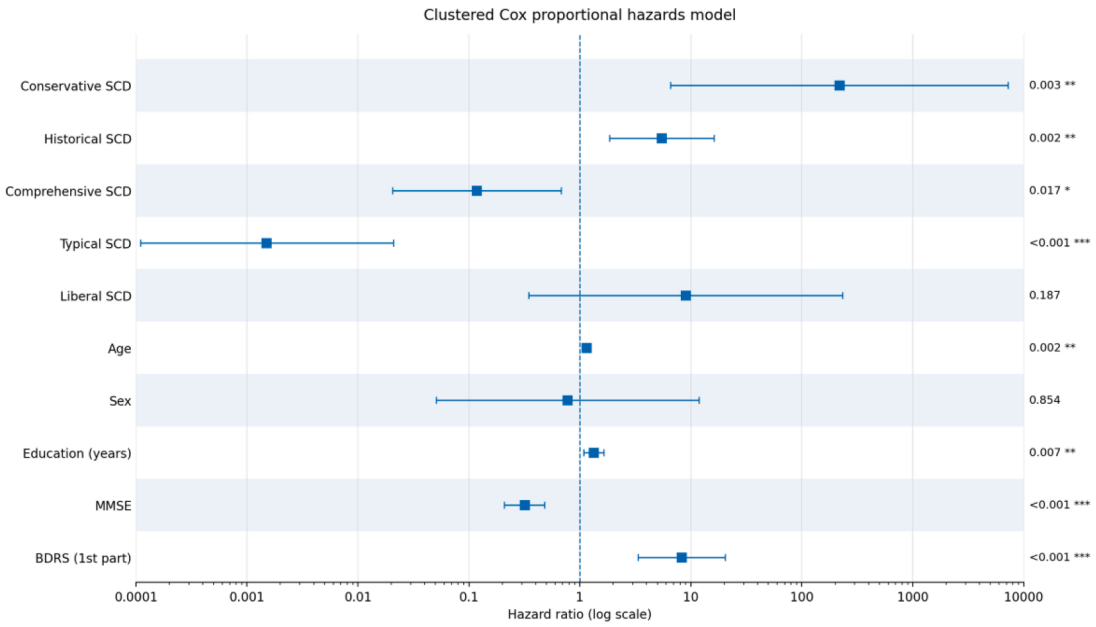
At 5 years, the probability of conversion to dementia ranged from 3.9% in the Liberal SCD group to 25.5% in the Conservative SCD group. By 10 years, it ranged from 16.2% (Liberal SCD) to 40.9% (Conservative SCD).



	Number at risk			
	5 years	10 years	15 years	20 years
Historical SCD	286	77	15	2
Typical SCD	187	58	14	1
Comprehensive SCD	287	77	15	2
Liberal SCD	106	32	7	1
Conservative SCD	332	86	16	2

	Cumulative probability of conversion to dementia			
	5 years	10 years	15 years	20 years
Historical SCD	20.2%	37.0%	54.6%	54.6%
Typical SCD	10.7%	24.5%	42.8%	42.8%
Comprehensive SCD	19.5%	34.9%	53.5%	53.5%
Liberal SCD	3.9%	16.2%	41.0%	41.0%
Conservative SCD	25.5%	40.9%	56.2%	56.2%

Fig. 3. Kaplan-Meier analysis for Dementia-Free Survival.



Predictor	β	Robust SE	z-value	p-value	HR	95% CI	
Conservative SCD	5.381	1.788	3.010	0.003*	217.314	6.539	7221.987
Liberal SCD	2.192	1.662	1.319	0.187	8.952	0.345	232.420
Typical SCD	-6.495	1.337	-4.859	0.000*	0.002	0.000	0.021
Comprehensive SCD	-2.138	0.893	-2.393	0.017*	0.118	0.020	0.679
Historical SCD	1.700	0.552	3.082	0.002*	5.475	1.857	16.143
Age	0.140	0.045	3.140	0.002*	1.151	1.054	1.256
Sex	-0.256	1.391	-0.184	0.854	0.774	0.051	11.834
Education	0.287	0.107	2.686	0.007*	1.332	1.081	1.643
MMSE	-1.147	0.214	-5.353	0.000*	0.317	0.209	0.483
BDRS (1st part)	2.110	0.460	4.586	0.000*	8.250	3.348	20.330

Fig. 4. Clustered Cox proportional hazards model for conversion to dementia across SCD definitions.
All SCD definitions were entered simultaneously in a Cox proportional hazards model.
The model was adjusted for age, sex, education, MMSE, and functional status (BDRS, 1st part), with robust standard errors estimated using subject-level clustering to account for overlapping group membership.
Abbreviations: HR: hazard ratio; CI: confidence interval; MMSE: Mini-Mental State Examination; BDRS: Blessed Dementia Rating Scale. Statistically significant ($p < 0.05$) is marked with *.

3.6. Cox proportional hazards analysis

Based on Cox proportional hazards analysis (Fig. 4), the associations were estimated while accounting for overlapping group membership using subject-level clustering. Conservative and Historical SCD showed a higher risk of progressing to dementia, while Typical and Comprehensive SCD were linked to a lower risk. The Liberal SCD definition did not have a significant connection to conversion. These associations should be interpreted as conditional on the other variables included in the model and do not imply direct comparisons between SCD definitions or absolute differences in risk. Increased age, higher education, and poorer functional status were linked to greater risk, whereas higher MMSE scores correlated with a lower risk. Sex did not influence the likelihood of conversion.

4. Discussion

4.1. Principal findings

This study demonstrates that applying various neuropsychological criteria to define normal cognition in the diagnosis of SCD identifies patient groups with distinct clinical and prognostic profiles. While the groups were similar in terms of age, sex, and subjective cognitive complaints, they differed in education, global cognition, daily functioning, and the risk of developing dementia.

4.2. Comparison with other studies

In line with prior cross-sectional research within the Cognitive Complaints Cohort (CCC), this longitudinal study confirms that neuropsychological definitions of normality significantly affect clinical characteristics of people with subjective cognitive complaints. The present investigation contributes additional insights into their longitudinal profiles.

The Jak and Bondi Liberal criteria for MCI diagnosis include many patients with only very mild cognitive changes within this diagnosis, while those who fall outside and are classified as having SCD are cognitively very well preserved. Therefore, the Liberal SCD group consists of individuals with higher educational levels, better overall cognition, preserved daily functioning, and the lowest risk of dementia. In contrast, the Jak and Bondi Conservative criteria, by applying stricter thresholds for cognitive normality, diagnose patients with MCI having substantial deficits, thus leaving out a SCD group that includes patients with lower educational levels, reduced cognitive performance, greater functional impairment, and the highest likelihood of progressing to dementia.

Our cumulative rate of conversion to dementia ranged from 10.1% to 25.9%, depending on the SCD diagnostic criteria, with average follow-up periods between 4.7 and 6.2 years. This rate seems higher than what is reported in the literature, where a systematic review of SCD studies found a pooled cumulative conversion rate to dementia of 7.23%, with a similar average follow-up of 5.27 years. (Cummings, 2025) It is plausible that our cohort, representing patients from a memory clinic, includes a higher proportion of individuals with underlying neurodegenerative diseases. However, differences in diagnostic criteria may also contribute to this variability. The Kaplan–Meier analysis illustrated differences in the probability of developing dementia across SCD definitions. These patterns were consistent with the results of the Cox proportional hazards analysis, supporting the presence of heterogeneous prognostic profiles across criteria. At 10 years, over one-third of patients with Conservative, Historical, or Comprehensive SCD have a chance of progressing to dementia, compared to about one-quarter in the Typical SCD group and one-sixth in the Liberal SCD group. In this context, the Cox analysis further indicated that Conservative and Historical SCD definitions were independently associated with an increased risk of conversion, whereas Typical and Comprehensive definitions were associated with a reduced risk. The Liberal definition was not significantly associated with conversion, which may reflect its selection of individuals with more preserved cognitive and functional profiles. The magnitude of some hazard ratio estimates should be interpreted with caution, as substantial overlap between SCD definitions may introduce collinearity and lead to imprecise estimates with wide confidence intervals, although the direction of the associations remains informative.

Thus, clinically, these findings suggest that different operational definitions of SCD may serve distinct purposes. Broader definitions of cognitive normality (e.g., Conservative or Historical SCD), by allowing patients with suboptimal cognitive performance into SCD diagnosis, were associated with a higher risk of conversion and may be more informative for identifying individuals at increased risk of progression, whereas more stringent definitions (e.g., Liberal, Typical or Comprehensive SCD), by limiting SCD diagnosis to better performing patients, were associated with lower risk and may be more appropriate for identifying individuals with a lower likelihood of decline. This pattern may partly reflect baseline selection effects, particularly for the Liberal definition, whose association with conversion was attenuated after adjustment for baseline variables. Accordingly, the choice of diagnostic criterion may depend on the clinical or research objective, whether to identify higher-risk individuals for closer monitoring or to reassure those at lower risk.

We call attention to the fact that the distinction between SCD and MCI, or in other words, how cognitive normality is defined, may have implications for patient selection in emerging disease-modifying therapies for Alzheimer's disease, which are currently approved for individuals with MCI or mild dementia. (Cummings, 2025) Given the heterogeneity in neuropsychological criteria and global cognitive thresholds used across clinical trials (Van Dyck et al., 2023; Pharmacy Benefits Management, 2024) , our findings suggest that different operational definitions of cognitive normality may identify populations with distinct baseline characteristics and risks of progression. This variability may influence the composition of trial samples and, consequently, observed treatment effects. These considerations are exploratory and should be interpreted with caution, but they highlight the importance of transparent and standardized criteria when defining target populations.

4.3. Strengths and limitations

Limitations of this study include potential attrition bias, during the follow-up period, even though patients lost to follow-up were similar to those who remained. Additionally, as a single-center study conducted at a specialized memory clinic, likely enriched for individuals at higher risk of neurodegenerative disease, the findings may not fully generalize to other settings, namely to community-based populations. Furthermore, the different SCD groups substantially overlapped and, therefore, should not be interpreted as independent populations. However, the use of complementary analytical approaches, including survival analysis and clustered Cox modeling, enabled a more robust assessment of prognostic patterns despite overlapping group membership. The absence of biomarker data limits the ability to determine whether the observed differences reflect underlying Alzheimer's disease pathology or differences in baseline clinical severity. Finally, dementia diagnosis was based on DSM-IV-TR criteria without differentiation by etiology, which limits conclusions regarding disease-specific progression.

On the other hand, the study has several strengths. Its large sample size and extended follow-up provide robust characterization of conversion trajectories over time. The prospective design and well-characterized cohort ensured standardized and consistent neuropsychological assessments, reducing diagnostic variability. Importantly, applying five established neuropsychological criteria within the same cohort enabled a direct, systematic comparison of how different operational definitions of cognitive normality influence both clinical profiles and longitudinal outcomes.

4.4. Conclusions

Using different neuropsychological criteria to define cognitive normality identifies groups with distinct clinical and prognostic features, reflected in both baseline profiles and longitudinal risk of dementia. Broader definitions (e.g., Conservative or Historical) tend to identify individuals at higher risk of progression, whereas more stringent definitions (e.g., Liberal, Typical, or Comprehensive) capture populations with a lower likelihood of decline. Accordingly, the choice of diagnostic criteria may depend on the clinical or research objectives, including risk stratification, patient counselling, and the selection of individuals for monitoring or therapeutic interventions.

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Pedro Câmara Pestana: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Sandra Cardoso:** Methodology, Formal analysis, Data curation. **Manuela Guerreiro:** Writing – review & editing, Data curation. **Frank Jessen:** Writing – review & editing. **Frederico Simões do Couto:** Writing – review & editing, Supervision, Methodology, Conceptualization. **João Marôco:** Writing – review & editing, Formal analysis. **Alexandre de Mendonça:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

Dr. Câmara Pestana reports no potential conflicts of interest;
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Supplementary materials

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