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Laura A. Rabin
CUNY Brooklyn College

Cuilling Wang
Albert Einstein College of Medicine

Jacqueline A. Mogle
The Pennsylvania State University

Richard B. Lipton
Albert Einstein College of Medicine

Carol A. Derby
Albert Einstein College of Medicine

See next page for additional authors

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Authors

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RESEARCH ARTICLE

An approach to classifying subjective cognitive decline in community-dwelling elders

Laura A. Rabin^{1,2,3} | Cuiling Wang^{3,4} | Jacqueline A. Mogle⁵ | Richard B. Lipton^{3,4,6} | Carol A. Derby^{3,4} | Mindy J. Katz³

¹ Department of Psychology, Brooklyn College, City University of New York (CUNY), Brooklyn, New York, USA

² Department of Psychology, Graduate Center, City University of New York (CUNY), New York, New York, USA

³ Saul R. Korey Department of Neurology, Albert Einstein College of Medicine, Bronx, New York, USA

⁴ Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York, USA

⁵ Edna Bennett Pierce Prevention Research Center, The Pennsylvania State University, University Park, Pennsylvania, USA

⁶ Department of Psychiatry and Behavioral Medicine, Albert Einstein College of Medicine, Bronx, New York, USA

Correspondence

Laura A. Rabin, 2900 Bedford Avenue, Department of Psychology, Brooklyn College, City University of New York (CUNY), Brooklyn, NY 11210, USA.

E-mail: lrabin@brooklyn.cuny.edu

Abstract

Introduction: Subjective cognitive decline (SCD) may be an early symptomatic manifestation of Alzheimer's disease, though published research largely neglects how to classify SCD in community-based studies.

Methods: In neuropsychologically intact Einstein Aging Study participants (n = 1115; mean age = 78; 63% female; 30% non-White), we used Cox models to examine the association between self-perceived cognitive functioning at baseline (using three different approaches) and incident amnesic mild cognitive impairment (aMCI) with covariates of age, sex, education, race/ethnicity, general (objective) cognition, depressive symptoms, and four other SCD-related features.

Results: After a median of 3 years, 198 participants developed aMCI. In models that included all the variables, self-perceived cognitive functioning was consistently associated with incident aMCI as were age, general cognition, and perceived control; apolipoprotein E (APOE) ϵ 4 allele status was significant in one model. We set cut points that optimized the diagnostic accuracy of SCD at various time frames.

Discussion: We provide an approach to SCD classification and discuss implications for cognitive aging studies.

KEYWORDS

Alzheimer's disease, classification, longitudinal study, memory complaints, mild cognitive impairment, subjective cognition, subjective cognitive decline, questionnaire

1 | INTRODUCTION

Some older adults have persistent feelings that aspects of their memory and thinking are becoming worse over time or worse compared to others their age.¹ Consensus groups have sought to provide a common construct for individuals who present with subjective cognitive decline (SCD) in the context of intact performance on neuropsychological tests and preserved daily functioning and independence.¹ The condition of SCD is now recognized by some as a transitional stage in the Alzheimer's disease (AD) pathological continuum,² and possibly an

early symptomatic expression of preclinical AD.^{1,3} Research on SCD⁴ most often focuses on establishing a relation of SCD to specific AD biomarkers⁴⁻²¹ or to validating SCD as a risk condition for mild cognitive impairment (MCI), AD,²¹⁻²⁷ or other diseases that may lead to dementia,^{1,25} with comparatively little attention paid to measurement

* It is important to note that various terms may be used to capture the idea of SCD, such as [subjective] cognitive complaints, [subjective] memory complaints, [subjective] memory concerns, subjective memory impairment, subjective cognitive impairment, and although we adopt the concept of SCD introduced by the Subjective Cognitive Decline Initiative working group [SCD-I] in 2014,¹ studies referenced in this article do not exclusively use that concept or terminology.

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issues including how to classify SCD in diverse research settings.^{28,29}

Studies that treat SCD as a diagnostic group,^{4,8,14,17,19,20,22,26,30,31} as opposed to a continuous variable,^{5,6,9,13,18,32} must determine a threshold for categorizing neuropsychologically intact individuals as having significant self-perceived cognitive decline. The goal is to distinguish between those whose concerns about cognition reach a threshold for significance that may be attributed to underlying neurodegenerative changes consistent with prodromal AD^{1,28} (or other dementia subtypes) from those whose concerns are generally mild and attributed to benign conditions associated with normal aging.³³ Thus, the distinction between SCD and cognitively normal (CN) is made on the basis of subjective cognitive report data, as both groups by definition are unimpaired on standardized objective neurocognitive tests.

To enable comparison of findings across studies it is important to establish, refine, and consistently apply SCD classification criteria.²⁹ However, there is no gold standard instrument or sufficiently validated cut points on measures of self-perceived cognitive functioning for differentiation between CN participants and those with SCD.²⁸ Moreover, there is almost no consistency in how SCD is operationalized in studies that use community- or population-based recruitment methods.[†] Many researchers classify SCD based on a positive response to a single question about perceived difficulty, change, or worry/concern about one's memory or cognition,^{14,20,30,31} while others use cut scores/median split approaches,^{26,36} or other methods.^{4,8,17,19,37} Notably, the rationale or justification for the selected classification approach for SCD is rarely provided.

When deciding how to classify SCD in research settings, it is instructive to consider features thought to increase the likelihood of preclinical AD in those with SCD (ie, sometimes referred to as "SCD-plus").¹ These include: subjective decline specific to memory, onset of SCD within the last 5 years, age at onset of SCD ≥ 60 years, expression of concerns (worries) associated with SCD, feeling of worse cognitive performance compared to others of the same age group, confirmation of cognitive decline by an informant, presence of the apolipoprotein E (APOE) $\epsilon 4$ allele, and biomarker evidence of AD. The SCD-plus concept, which is subject to ongoing expansion, refinement, and validation,³³ may be a low-cost enrichment strategy for preclinical AD in secondary prevention trials.³⁸

In the current study, we established a method for classifying SCD in participants from the Einstein Aging Study (EAS) who were neuropsychologically intact at baseline. Our classification approach optimized predictive validity for incident amnesic MCI (aMCI), often thought to be a precursor of AD.³⁹ In participants who were neuropsychologically intact at baseline, we examined the association of self-perceived cognitive functioning, as described in the Methods section, with the incidence of aMCI, controlling for relevant covariates. The aMCI defi-

RESEARCH IN CONTEXT

1. **Systematic review:** Despite a proliferation of publications on various aspects of subjective cognitive decline (SCD), the critical issue of how to optimize classification, particularly in community-based studies, has received almost no attention. The authors carried out an extensive PubMed search for literature on approaches to classification of SCD in neuropsychologically intact older adults.
2. **Interpretation:** We showed that subjective cognitive function scores (and relevant covariates) were associated with incident amnesic mild cognitive impairment (aMCI) and could be used to classify SCD in a manner that optimizes the early detection of aMCI.
3. **Future directions:** Future research should investigate whether the current classification approach can be applied successfully in other studies and whether it produces a diagnosis that is stable and predicts important clinical and cognitive outcomes. In addition, alternative methods should be developed and compared, and at a minimum all future research on SCD should report the specific classification approach and rationale for its use.

inition used was consistent and had significant overlap with the criteria for clinical cognitive staging in the absence of biomarkers, put forth by the National Institute on Aging-Alzheimer's Association Research Framework.² Next, we determined whether the four available SCD-plus (and other related) features added to the predictive ability. Finally, using information derived from the predictive models, we evaluated the discriminative ability of self-perceived cognitive functioning (alone and in combination with other variables) for incident aMCI after various follow-up periods from baseline to determine optimal cut scores for defining SCD.

2 | METHODS

2.1 | Participants

Participants were drawn from the EAS, a longitudinal community-based study that includes a demographically diverse cohort from the Bronx, NY. As described elsewhere,⁴⁰ participants were recruited through systematic sampling from Medicare or voter registration lists. Individuals were mailed introductory letters and then screened by telephone. Those who met preliminary eligibility criteria were invited for further in-person screening. Participants were aged 70 years or older, non-institutionalized, ambulatory, and English speaking. Exclusion criteria included severe audiovisual or physical impairments or active psychiatric symptomatology, which interfered with the ability to complete assessments. The study was approved by the

[†] For clinical/help-seeking SCD samples, which recruit from memory clinics and/or local physicians, there is greater consistency in approach, with SCD typically defined by spontaneous expression of cognitive concerns by patients and/or informants, or by virtue of having been referred for cognitive evaluation in the first place.^{10,12,15,16,34,35} Notably, individuals with SCD from memory clinics settings may be at greater risk for progressive cognitive decline than those from community settings.^{25,26,37}

local institutional review board and participants provided written informed consent at baseline assessment. In-person assessments were conducted annually and included neurological and neuropsychological examinations, and ascertainment of demographics, medical history, activities of daily living, and self-perceived cognitive functioning. Informant reports regarding cognition and function were available for $\approx 51\%$ of participants. APOE $\epsilon 4$ allele status was available for 48% of participants. Participants eligible for this analysis were enrolled between October 1993 and June 2016; were free of all MCI, AD, and other dementias at baseline; and had at least one annual follow-up.

2.2 | Neuropsychological assessment and participant classification

Participants underwent neuropsychological testing at baseline and follow-up visits.⁴⁰ The battery included the picture version of the Free and Cued Selective Reminding Test with Immediate Recall (FCSRT);⁴¹ the Wechsler Memory Scale-Revised Logical Memory I subtest (WMS-R-LMI);⁴² Trail-Making Test Parts A and B;⁴³ Digit Symbol, Block Design, and Digit Span subtests of the Wechsler Adult Intelligence Scale—Revised;⁴⁴ F-A-S Letter Fluency Test;⁴⁵ Boston Naming Test;⁴⁶ and Category Fluency.⁴⁷ Data derived from these tests were used to classify participants as aMCI, non-aMCI (naMCI), and dementia.

Dementia diagnoses were assigned at a consensus case conference attended by a neurologist and neuropsychologist applying Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR) criteria.⁴⁸ aMCI diagnoses were assigned to non-demented participants who presented with objective memory impairment as measured by a score of less than or equal to 24 on free recall (possible range: 0 to 48) from the FCSRT or 1.5 or greater standard deviations below age-corrected normative mean scores on WMS-R-LMI. Additionally, participants were required to endorse at least one item from among specific Consortium to Establish a Registry for Alzheimer's Disease (CERAD) clinical history self-reported memory items (Table 1) or one item from among specific informant reported memory items (Table 1), and have no functional impairment on the Lawton Brody Instrumental Activities of Daily Living scale. The aMCI group included both single (memory impairment only) and multiple domain (deficits in memory and at least one additional cognitive domain) subtypes. We did not include participants with non-amnesic subtypes of MCI at baseline. CN did not meet criteria for dementia or any MCI subtype.

2.3 | Self-perceived cognitive functioning

We used 22 items derived from three questionnaires administered at each visit (Table 1): 17 items from the CERAD clinical history questionnaire; a yes/no/don't know rating scale of current functioning in several cognitive domains;⁴⁹ four items from the EAS Health Self-Assessment (HSA)⁵⁰ that inquire about current memory problems and changes

in memory compared to 1 and 10 years prior to the assessment (ordinal data with 3 to 4 response options); and one dichotomous item from the short form of the Geriatric Depression Scale (GDS),⁵¹ which inquires whether participants feel they have "more memory problems than most." The EAS also includes items that assess informant perceptions of participants' cognition: 21 items from the CERAD (informant form), a yes/no/don't know rating scale of current cognitive functioning.

Responses to items probing self-perceived cognitive functioning were recoded, as needed, such that higher values consistently indicated greater level of cognitive concern/impairment. Table 1 presents the items, their respective cognitive domains, and scoring.[‡] A *subjective cognitive function* score defined as the sum of responses to all 22 items tapping self-perceived cognitive functioning was used as the primary summary measure of SCD (possible range: 2 to 28). An *adjusted subjective cognitive function* score that excluded the five items used for aMCI diagnosis was used as an alternative summary measure of SCD (possible range: 2 to 23). Where applicable, don't know response options, which were infrequent (ie, <5% and 8% of responses for self- and informant items, respectively), were handled as missing data. Approximately 35% of participants did not have complete data for all the subjective cognitive function items (see note in Table 2).

2.4 | Covariates

Covariates were selected based on previously reported associations with SCD.^{28,29} Sociodemographic variables included age (years; continuous), sex (male, female; dichotomous), educational attainment (years; continuous), and ethnicity (White; Black; other; categorical). Depressive symptoms were assessed with the 15-item self-report GDS, using an adjusted score that did not include the one cognitive item. A comorbidity illness scale was the sum (range 0 to 10) of the number of self-reports of arthritis, angina, depression, diabetes, chronic obstructive pulmonary disease, hypertension, myocardial infarcts, heart failure, Parkinson's disease, and stroke.⁵³ The Blessed Information-Memory-Concentration Test (BIMC, possible range: 0 to 33), was not used to classify aMCI, but we did adjust for it in models assessing aMCI as an outcome; higher scores indicated worse general cognitive status.

2.5 | Additional variables of interest

For selected study analyses, we also included data related to SCD-plus criteria. The four SCD-plus features assessed were APOE $\epsilon 4$ allele status (dichotomized as $\epsilon 4$ -carrier or $\epsilon 4$ -non carrier), informant report of cognitive function (*subjective cognitive function informant score* based on the sum of CERAD binary items, possible range: 0 to 21 or 0 to 16

[‡] Cognitive domains were previously assigned as part of a descriptive analysis of 640 cognitive self-report items that included the EAS measures/items.⁵² For each item, we designated a primary cognitive domain from one of the following: *memory; attention/working memory/processing speed; language; executive function; basic calculation and arithmetic; orientation; general cognitive ability; and visuospatial skills.*

TABLE 1 Items and response options probing self- and informant-perceived cognitive functioning

Measure and source	Cognitive domain	Item stem	Response options/(score)
CERAD, self-1 ^a	Memory	Do you have difficulty remembering things that happened recently?	Yes (1)/No (0)/Don't Know
CERAD, self-2 ^a	Memory	Do you forget conversations that occurred a few days or hours earlier?	Yes (1)/No (0)/Don't Know
CERAD, self-3 ^a	Memory	Do you seem to ask the same questions repeatedly?	Yes (1)/No (0)/Don't Know
CERAD, self-4 ^a	Memory	Do you forget to turn off the stove?	Yes (1)/No (0)/Don't Know
CERAD, self-5	Memory	Do you forget approaching holidays, days to attend religious services, income tax dates, etc.?	Yes (1)/No (0)/Don't Know
CERAD, self-6	Memory	Do you have trouble remembering short lists for shopping, etc.?	Yes (1)/No (0)/Don't Know
CERAD, self-7	Language	Do you have trouble finding words in carrying on a conversation?	Yes (1)/No (0)/Don't Know
CERAD, self-8	Language	Is it sometimes difficult for others to understand what you are talking about?	Yes (1)/No (0)/Don't Know
CERAD, self-9	Language	Do you have difficulties relating to or understanding T.V. shows or newspaper articles?	Yes (1)/No (0)/Don't Know
CERAD, self-10	Visuospatial	Do you have trouble finding the bedroom or bathroom at home or in other familiar houses (friends or relatives)?	Yes (1)/No (0)/Don't Know
CERAD, self-11	Visuospatial	Do you get lost in familiar surroundings, such as local neighborhood or shopping malls?	Yes (1)/No (0)/Don't Know
CERAD, self-12	Calculation	Do you have difficulty handling small sums of money?	Yes (1)/No (0)/Don't Know
CERAD, self-13	Orientation	Do you have trouble remembering the day or the month?	Yes (1)/No (0)/Don't Know
CERAD, self-14	Executive function	Do you have difficulty operating simple household appliances (eg, T.V., lawnmower or vacuum cleaner)?	Yes (1)/No (0)/Don't Know
CERAD, self-15	Executive function	Do you have difficulty performing simple household tasks (eg, making a cup of coffee, setting the table)?	Yes (1)/No (0)/Don't Know
CERAD, self-16	Executive function	Do you show problems in judgement such as responding inappropriately to a salesman at the door?	Yes (1)/No (0)/Don't Know
CERAD, self-17	General cognitive ability	Do you have any other cognitive problems?	Yes (1)/No (0)/Don't Know
HSA, self-1	Memory	In the past year, how often did you have trouble remembering things?	Frequently (3)/Sometimes (2)/Rarely (1)/Never (0)
HSA, self-2	Memory	Compared to 1 year ago, do you have trouble remembering things?	More often (3)/Less Often (1)/About the Same (2)
HSA, self-3	Memory	Compared to 10 years ago, do you have trouble remembering things?	More often (3)/Less Often (1)/About the Same (2)
HSA, self-4	Memory	Has your memory change caused any serious problems (eg, forgetting to turn off the stove, getting lost, misplacing valuables)?	Yes (1)/No (0)/Don't Know
GDS, self ^a	Memory	Do you feel that you have more problems with memory than most?	Yes (1)/No (0)
CERAD, informant-1 ^a	Memory	Does he/she have difficulty remembering things that happened recently?	Yes (1)/No (0)/Don't Know
CERAD, informant-2 ^a	Memory	Does he/she forget conversations that occurred a few days or hours earlier?	Yes (1)/No (0)/Don't Know
CERAD, informant-3 ^a	Memory	Does he/she seem to ask the same questions repeatedly?	Yes (1)/No (0)/Don't Know
CERAD, informant-4 ^a	Memory	Does he/she forget to turn off the stove?	Yes (1)/No (0)/Don't Know
CERAD, informant-5	Memory	Does he/she forget approaching holidays, days to attend religious services, income tax dates, etc.?	Yes (1)/No (0)/Don't Know
CERAD, informant-6	Memory	Does he/she have difficulty remembering short lists for shopping, etc.?	Yes (1)/No (0)/Don't Know

(Continues)

TABLE 1 (Continued)

Measure and source	Cognitive domain	Item stem	Response options/(score)
CERAD, informant-7 ^a	Memory	Do you believe he/she has a problem with memory?	Yes (1)/No (0)/Don't Know
CERAD, informant-8	Language	Does he/she have trouble finding words in carrying on a normal conversation?	Yes (1)/No (0)/Don't Know
CERAD, informant-9	Language	Is it sometimes difficult for others to understand what he/she is talking about?	Yes (1)/No (0)/Don't Know
CERAD, informant-10	Language	Does he/she have difficulties relating to or understanding TV. shows or newspaper articles?	Yes (1)/No (0)/Don't Know
CERAD, informant-11	Language	Do you believe he/she has a problem with language?	Yes (1)/No (0)/Don't Know
CERAD, informant-12	Visuospatial	Does he/she have trouble finding the bedroom or bathroom at home or in other familiar houses (friends or relatives)?	Yes (1)/No (0)/Don't Know
CERAD, informant-13	Visuospatial	Does he/she get lost in familiar surroundings, such as local neighborhood or shopping malls?	Yes (1)/No (0)/Don't Know
CERAD, informant-14	Orientation	Does he/she have trouble remembering the day or the month?	Yes (1)/No (0)/Don't Know
CERAD, informant-15	Orientation	Do you believe he/she is disoriented for time or place?	Yes (1)/No (0)/Don't Know
CERAD, informant-16	Calculation	Does he/she have difficulty handling small sums of money?	Yes (1)/No (0)/Don't Know
CERAD, informant-17	Executive function	Does he/she have difficulty operating simple household appliances (eg, TV., lawnmower or vacuum cleaner)?	Yes (1)/No (0)/Don't Know
CERAD, informant-18	Executive function	Does he/she have difficulty performing simple household tasks (eg, making a cup of coffee, setting the table)?	Yes (1)/No (0)/Don't Know
CERAD, informant-19	Executive function	Does he/she show problems in judgement such as responding inappropriately to a salesman at the door?	Yes (1)/No (0)/Don't Know
CERAD, informant-20	Executive function	Do you believe he/she has problems with judgement or problem solving?	Yes (1)/No (0)/Don't Know
CERAD, informant-21	General cognitive ability	Does he/she have any other cognitive problems?	Yes (1)/No (0)/Don't Know

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease clinical history; HSA, Einstein Aging Study Health Self-Assessment; GDS, Geriatric Depression Scale, short form.

^aDenotes an item not used for the adjusted self- or informant subjective cognitive function scores.

for the *adjusted subjective cognitive function informant score*), and one HSA item that taps into worry over health (ie, Has your overall health caused you a great deal of worry/some worry/hardly any worry/or no worry at all?). Although this item does not inquire specifically about worry related to cognition, we felt it captured something similar to the SCD-plus criterion of concerns (worries) associated with SCD, in the context of this cognitive aging study. We also included a related item from the HSA (ie, How much control do you think you have over your future health?; great deal/some/very little/none at all), in light of research showing associations between perceived control and various aspects of physical, emotional, and cognitive well-being, particularly in older age.⁵⁴

2.6 | Data analysis

Baseline characteristics were summarized with descriptive statistics for the whole sample and stratified by aMCI status at follow-up, and compared using chi-square tests, t-tests, or nonparametric Wilcoxon test if appropriate. Cox proportional hazards models were used to

examine associations between the subjective cognitive function score and other variables of interest on risk of incident aMCI. Participants who developed dementia without developing aMCI were censored at their time of dementia diagnosis. The proportional hazards assumptions were examined using methods based on scaled Schoenfeld residuals and were satisfied.⁵⁵ Time-dependent receiver operating characteristic (ROC) analyses^{56,57} using the inverse probability of censoring approach⁵⁸ were used to examine the discriminative ability of subjective cognitive function score and other variables on incidence of aMCI within specified time periods. With the exception of the CERAD and GDS items noted in Table 1, the self- and informant subjective cognitive items used in our analyses were independent from those considered when diagnosing aMCI.

To deal with missing data for self- and informant subjective cognitive items (including "don't know" responses discussed above), APOE $\epsilon 4$ allele status, and GDS, we applied the multiple imputation (MI) approach,⁵⁹ which consists of imputation, analysis, and pooling. MI uses all available data, thus increasing statistical power and preventing bias. By comparison, the commonly used convenient method of complete case analysis, in which records with missing data are simply

TABLE 2 Baseline descriptive characteristics of whole sample and amnesic mild cognitive impairment (aMCI) status at follow-up

	Whole sample	no aMCI	aMCI	<i>P</i> ^a
Mean (SD) or percentage	n = 1115	n = 917	n = 198	
Age, years at baseline	78.33 (5.17)	78.02 (5.08)	79.80 (5.34)	<.0001
Education (years)	13.79 (3.46)	13.81 (3.49)	13.70 (3.37)	.527
Sex, % female	63%	63%	61%	.485
Ethnicity: % White	70%	69%	69%	.833
% Black	25%	25%	26%	
% Other	5%	6%	5%	
Adjusted GDS score (max = 14)	2.05 (2.14) ^a	2.03 (2.13)	2.17 (2.18)	.329
APOE ε4 allele status, carrier	21% ^b	20%	37%	.092
Medical index (max = 10)	1.82 (1.23)	1.83 (1.23)	1.78 (1.25)	.566
BIMC score (max = 33)	2.07 (2.03)	1.98 (2.01)	2.49 (2.09)	.0002
Subjective cognitive function score (max = 28)	7.11 (2.01) ^c	7.00 (1.96)	7.80 (2.13)	<.0001
Subjective cognition function informant score (max = 21)	1.06 (1.72) ^d	0.95 (1.61)	1.61 (2.11)	.001

Note: Sample sizes before imputation: ^an = 921; ^bn = 693; ^cn = 726; ^dn = 475.

Highlighted rows indicate statistically significant variables; this applies to subsequent tables.

Abbreviations: APOE, apolipoprotein E; BIMC, Blessed Information-Memory-Concentration test; GDS, Geriatric Depression Scale, short form; SD, standard deviation.

deleted, is based on the stronger assumption that data are missing completely at random (MCAR) and is less efficient due to loss of information. For imputation, we adopted the fully conditional specification, also known as imputation by chained equation method, to impute the missing data using logistic regression models for binary and categorical variables, and linear regression models for continuous variables. All variables used in the primary models were included in the imputation. The fully conditional specification method is flexible and can handle mixed continuous and categorical variables with an arbitrary missing data pattern. This step is repeated M times to generate M complete data sets. For analysis, we performed the aforementioned analyses using Cox models and time-dependent ROC analyses for each of the M complete data sets. In the pooling step, the M sets of parameter estimates were combined to appropriately reflect the uncertainty associated with the imputed values. We set M = 20.

In our primary analysis, we used the subjective cognitive function score as the primary measure. The association of this score with risk of aMCI was evaluated using Cox models, adjusting for covariates (Model 1a); we then added SCD-plus (and related) variables (Model 1b) to evaluate whether these variables further contributed to risk of aMCI and whether the association of SCD with aMCI persisted in presence of these variables. In a second approach, we examined all 22 items probing self-perceived cognitive functioning separately, in association with aMCI, adjusting for covariates (Table 1). Items that were significantly associated with aMCI were then simultaneously evaluated in a Cox model adjusting for covariates (Model 2a), and then further adjusted for SCD-plus and related features (Model 2b). To evaluate the impact of the potential circularity in the subjective cognitive function score caused by items used for aMCI diagnosis, we replaced the total score based on 22 items with the adjusted

score (described above). The adjusted subjective cognitive function score was examined in association with aMCI, adjusting for covariates (Model 3a); we then further added available SCD-plus and related features, including the adjusted subjective cognitive function informant score.

Time-dependent ROC analysis was performed and area under the ROC curve (AUC) for developing aMCI within specified time periods (3, 5, 7 years) were reported. The optimal cut points for SCD score and for the combination of SCD and covariates were determined based on the Youden index. Study analyses were carried out using SAS 9.4 (https://www.sas.com/en_us/software/sas9.html) and R,⁶⁰ with an α value of 0.05 used to determine statistical significance.

3 | RESULTS

3.1 | Sample characteristics

Our final sample included 1115 participants. At baseline (Table 2), participant age ranged from 70 to 97 (mean = 78.3 ± 5.2) years, the sample was 62.8% female, and participants averaged 13.8 ± 3.5 years of education. Subjective cognitive function score ranged from 3 to 19 (mean = 7.1 ± 2.0). The sample was 70% White, 25% Black, and 5% other. A total of 198 participants developed aMCI during a median of 3 years of follow-up (Q1 = 1.9, Q3 = 6.2, maximum 20). Those who developed aMCI were significantly older at baseline (by ≈ 1 year), had higher BIMC scores (approximately half a point), and their informants endorsed a greater level of perceived cognitive decline. The groups did not differ by sex, education, race/ethnicity, depressive symptoms, medical index, or APOE ε4 allele status.

TABLE 3 Cox proportional hazard models assessing subjective cognitive function score on incident aMCI (adjusting for covariates) and with SCD-plus variables

Variable	Model 1a			Model 1b		
	Hazard ratio	95% C.I.	P	Hazard ratio	95% C.I.	P
Baseline age (years)	1.10	1.07-1.13	<.0001	1.10	1.07-1.13	<.0001
Education (years)	1.01	0.97-1.06	.5990	1.01	0.97-1.06	.5889
Female	0.81	0.60-1.09	.1631	0.80	0.58-1.09	.1501
Race-Black	0.98	0.69-1.38	.8877	0.99	0.70-1.41	.9586
Race-other	0.90	0.45-1.80	.7658	0.88	0.44-1.76	.7116
Adjusted GDS score	1.03	0.95-1.11	.4876	1.02	0.94-1.10	.6994
Medical index	1.02	0.89-1.16	.7854	0.90	0.90-1.17	.7291
BIMC score	1.16	1.08-1.25	<.0001	1.15	1.07-1.24	.0002
Subjective cognitive function score (1-point increase)	1.14	1.07-1.21	<.0001	1.11	1.04-1.19	.0039
Subjective cognitive function informant score				1.10	0.98-1.25	.1167
APOE ε4 allele status				1.50	0.99-2.29	.0559
HSA worry				0.95	0.79-1.13	.5343
HSA control				1.25	1.04-1.50	.0159

Note: For the race covariate, non-Hispanic White was the reference group.

Abbreviations: aMCI, amnesic mild cognitive impairment; APOE, apolipoprotein E; BIMC, Blessed Information-Memory-Concentration test; HSA, Einstein Aging Study Health Self-Assessment; SCD, subjective cognitive decline.

3.2 | Effect of subjective cognition on incident aMCI

Table 3 (Model 1a) revealed that age, BIMC score, and subjective cognitive function score all had significant effects, with a 1-point increase in subjective cognitive function score increasing the risk of incident aMCI by 14% ($P < .0001$). We also reran Model 1a on the subset of 720 participants with complete subjective cognitive function data (105 incident aMCI cases), with the same pattern of results (Table S1 in supporting information). We fit additional models to account for the four SCD-plus and related features. In Model 1b, the association of subjective cognitive function score with incident aMCI persisted (hazard ratio [HR] = 1.11, $P = .0039$), as did higher BIMC score ($P = .0002$); control over future health also showed a significant effect (HR = 1.25 per one level of lower perceived control, $P = .0159$), and APOE ε4 allele positive status showed increased risk but marginal significance (HR = 1.50, $P = .056$).

Table S2 in supporting information displays the 22 items and their individual associations with incident aMCI after adjusting for covariates, with six memory items showing statistical significance (see highlighted rows). Table S3 in supporting information displays baseline descriptive characteristics for variables used in Models 2 and 3. Table 4 (Model 2a) revealed similar findings to Model 1a—with age, BIMC score, and one individual subjective memory item (HSA self-1: “In the past year, how often did you have trouble remembering things?”) having significant effects. In Model 2b, the association of the one memory item continued to be significant, as did age and BIMC score; control

over future health showed a significant effect, and APOE ε4 allele status showed a marginally significant effect. As shown in Table 5 (Models 3a, 3b), when we examined subjective cognitive function using adjusted scores, the pattern of findings was similar; however, in this model APOE ε4 allele status reached statistical significance, $P = .0214$.

3.3 | Diagnostic accuracy of SCD for incident aMCI

Given the combined results of earlier models, we focused on the subjective cognitive function score only, and the AUCs obtained from time-dependent ROC analysis for cumulative aMCI status. AUCs were: 0.62 (standard error [SE] = 0.03, confidence interval [CI]: 0.56 to 0.68) at 3 years, 0.60 (SE = 0.05, CI: 0.59 to 0.80) at 5 years, and 0.61 (SE = 0.03, CI: 0.55 to 0.68) at 7 years. The optimal cut-off values C for subjective cognitive function score based on Youden's index, in which values greater than C are considered positive, were 6, 6, and 7 at 3, 5, and 7 years, with sensitivities of 0.57, 0.55, and 0.47, and specificities of 0.66, 0.61, and 0.71, respectively. Optimal cuts for the combination of the subjective cognitive function score and covariates and SCD-plus features, as well as in combination with age (as the only significant covariate from these models), are reported in the supporting information. Kaplan Meier survival curves for SCD and CN groups (defined by subjective cognitive function score ≤ 6 and >6) from observed data are presented in Figure 1. Risk of aMCI was more than doubled (HR = 2.22, CI: 1.54 to 3.19, $P < .0001$) among SCD versus CN.

TABLE 4 Cox proportional hazard models assessing individual subjective cognitive function items on incident aMCI (adjusting for covariates) and with SCD-plus variables

Variable	Model 2a			Model 2b		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Baseline age (years)	1.10	1.07–1.13	<.0001	1.10	1.07–1.13	<.0001
Education (years)	1.01	0.97–1.05	.7015	1.01	0.97–1.06	.6432
Female	0.80	0.59–1.09	.1525	0.80	0.58–1.10	.1649
Race-Black	1.01	0.72–1.44	.9408	1.03	0.72–1.47	.8904
Race-Other	0.90	0.45–1.81	.7707	0.89	0.44–1.80	.7542
Adjusted GDS score	1.03	0.95–1.11	.5447	1.02	0.93–1.10	.7274
Medical index	1.02	0.89–1.16	.8246	1.02	0.89–1.16	.8187
BIMC score	1.15	1.07–1.23	.0001	1.14	1.06–1.23	.0008
CERAD, self-1	1.20	0.74–1.94	.4620	1.21	0.74–1.97	.4521
CERAD, self-6	1.36	0.84–2.21	.2167	1.16	0.68–1.98	.5976
HSA, self-1	1.47	1.10–1.98	.0107	1.42	1.05–1.91	.0212
HSA, self-3	1.29	0.93–1.79	.1277	1.27	0.92–1.76	.1488
HSA, self-4	1.23	0.81–1.86	.3320	1.31	0.86–1.98	.2103
GDS, self	1.43	0.86–2.38	0.1736	1.39	0.82–2.38	.2233
Subjective cognitive function informant score				1.10	0.96–1.24	.1905
APOE ϵ 4 allele status				1.45	0.949–2.24	.0942
HSA worry				0.91	0.77–1.10	.5343
HSA control				1.26	1.05–1.50	.0159

Note: For the race covariate, non-Hispanic White was the reference group.

Abbreviations: aMCI, amnesic mild cognitive impairment; APOE, apolipoprotein E; BIMC, Blessed Information-Memory-Concentration test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease clinical history; CI, confidence interval; GDS, Geriatric Depression Scale, short form; HSA, Einstein Aging Study Health Self-Assessment; SCD, subjective cognitive decline.

TABLE 5 Cox proportional hazard models assessing adjusted subjective cognitive function score on incident aMCI (adjusting for covariates) and with SCD-plus variables

Variable	Model 3a			Model 3b		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Baseline age (years)	1.09	1.07–1.13	<.0001	1.10	1.07–1.13	<.0001
Education (years)	1.01	0.97–1.06	.5253	1.01	0.97–1.06	.5232
Female	0.81	0.60–1.09	.1698	0.79	0.58–1.08	.1418
Race-Black	0.98	0.69–1.39	.9061	0.98	0.68–1.40	.8938
Race-other	0.88	0.44–1.76	.7181	0.85	0.42–1.72	.6539
Adjusted GDS score	1.03	0.95–1.10	.4908	1.01	0.94–1.10	.7457
Medical index	1.03	0.91–1.18	.6419	1.03	0.90–1.18	.06755
BIMC score	1.16	1.08–1.25	<.0001	1.15	1.07–1.23	.0002
Adjusted subjective cognitive function score (1-point increase)	1.19	1.08–1.30	<.0004	1.16	1.06–1.27	.0014
Adjusted subjective cognitive function informant score				1.16	0.96–1.41	.1210
APOE ϵ 4 allele status				1.59	1.07–2.37	.0214
HSA worry				0.96	0.81–1.14	.6538
HSA control				1.22	1.03–1.45	.0233

Note: For the race covariate, non-Hispanic White was the reference group.

Abbreviations: aMCI, amnesic mild cognitive impairment; APOE, apolipoprotein E; BIMC, Blessed Information-Memory-Concentration test; CI, confidence interval; GDS, Geriatric Depression Scale, short form; HSA, Einstein Aging Study Health Self-Assessment; SCD, subjective cognitive decline.

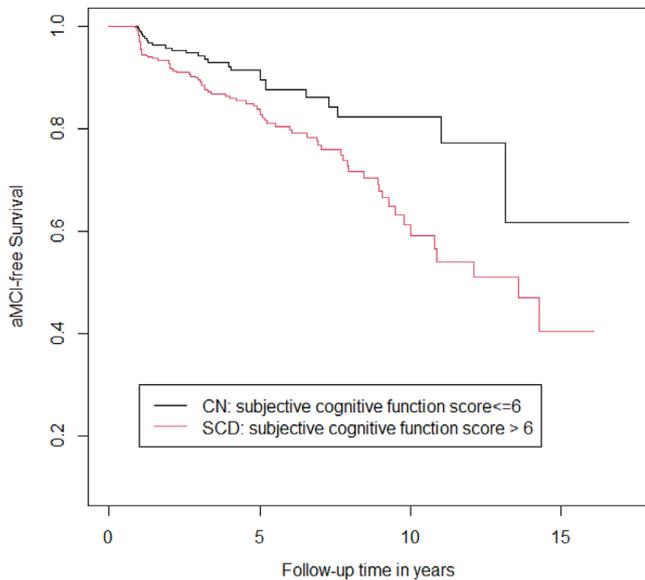


FIGURE 1 Kaplan-Meier survival curve by subjective cognitive function score (cut score 6) obtained from the observed data ($n = 726$)

4 | DISCUSSION

The field of cognitive aging is focused on earlier, and more efficient, identification of individuals free of objective cognitive impairment who are most at-risk for future decline. Self-perceived cognitive functioning is a noninvasive, easy to use method that, in some cases, is a marker of risk for future aMCI, AD, or other dementias.²⁵ Understanding that SCD could be among the first clinically observable signs of AD, and in some cases is not a “benign” CN state,^{1,28,33} it is important to determine how to classify SCD in cognitive aging studies. Using longitudinal data up to 20 years of follow-up, we were able to identify a group of neuropsychologically intact, community-dwelling EAS participants at increased risk of incident aMCI using baseline endorsement of self-perceived decline in cognitive functioning and other variables. We then used this information to establish cut-off scores for SCD for predicting aMCI over specified follow-up intervals.

We began with the premise that SCD is not the same as CN and that it is important to identify the level of self-perceived cognitive decline at baseline that best distinguishes those at risk for future aMCI. We used three approaches to handling the items probing self-perceived cognitive functioning that we had available: (1) a total score for all items, (2) individual items that showed significant associations with incident aMCI, or (3) a total score that excluded items used to classify aMCI. In our primary approach, which used the sum of all 22 items probing self-perceived cognitive functioning, results indicated that a 1-point increase in subjective cognitive function score was associated with a 14% higher risk of aMCI, after controlling for relevant demographic, mood, objective cognitive, and medical covariates.

When additional variables were added, the subjective cognitive function score remained significantly associated with risk of aMCI. This pattern was observed for the other two approaches. Notably, in the approach that used individual items, adjusting for demographics, of

the six items with statistically significant associations with aMCI all related to memory (Table S1). This offers support for the idea that self-perceived decline in memory, rather than in other cognitive domains, may increase the likelihood of preclinical AD in those with SCD (an SCD-plus feature). When additional variables were added, one memory item continued to show statistical significance (HSA, self-1, Table 1). This item, which inquired about trouble remembering things in the past year, was previously found to be among the most commonly used self-report items in cognitive aging studies,⁵² and likely merits inclusion in future assessments.

Most of the other SCD plus features that we had available did not make a statistically significant impact on the incidence of aMCI. Specifically, subjective cognitive function informant score, worry about health, and perception of worse memory than others, were not significant. The GDS item that asks whether an individual feels he/she has “more problems with memory than most” was associated with aMCI in the model that only adjusted for demographics—but did not retain significance in the full model. This item, though widely used in the field, has mixed support for its utility—and may be more valid for capturing self-perceived memory difficulty in those with MCI than in cognitively unimpaired older adults.⁶¹ APOE $\epsilon 4$ allele status showed marginal or statistical significance in all models. As APOE $\epsilon 4$ is an important genetic risk factor for AD, and may be associated with the prospective risk of cognitive decline in SCD,^{62–64} it may be worth incorporating APOE data into SCD classification. However, it is notable that our approach works even in the absence of APOE, which may be preferable in clinical and research settings where genetic data are not readily available.

The perceived control over future health item was included in our analyses because of research suggesting a relation between the belief that future events are under one’s own control and successful cognitive aging.^{54,65} This item made a statistically significant impact on the incidence of aMCI in all models. There are various reasons why higher perceived control may be related to better cognition including that such a mindset increases the motivation to adopt healthy behaviors and engage in strategies that could help maintain cognitive efficiency and prevent decline.⁶⁵ Also, in neuropsychologically intact older adults, subtle cognitive changes could lead to both lower levels of perceived control and a tendency to express concern about cognition, which together could result in expending less effort to overcome age-related challenges. Future research should investigate the role of perceived control in the classification and course of SCD, using items that inquire about control related to specific cognitive outcomes. Such an item may even be included on future assessments of self-perceived cognitive functioning.

Based on the association of SCD with incident aMCI, we obtained cut points for baseline subjective cognitive function score related to developing aMCI within 3, 5, and 7 years, which optimally balanced sensitivity and specificity. We also provided optimal cut points using the combination of SCD and other study variables based on their joint effect on incident aMCI (see supporting information). The AUC results were not as high as we might have hoped. However, we are not proposing to use SCD as a diagnostic tool for aMCI/AD. Instead, we seek to identify a group of individuals more likely to convert to

these conditions and, in this regard, we found statistically significant associations for SCD in terms of prediction of incident aMCI that persisted after adjusting for covariates and plus factors. In future clinical applications, we can imagine that SCD might be assessed as a first step, using a self-administered questionnaire. Those who screen positive might be offered neurocognitive or other assessments as a prelude to definitive diagnosis. Additionally, given only modest improvement in accuracy when we accounted for all statistically significant covariates, for ease and simplicity, it may be advisable to set cut-off scores for SCD using just the most relevant and/or readily available variables—that is, self-perceived cognitive functioning alone or in combination with age (in light of research suggesting that cognitive concerns may reflect different underlying changes in the young-old versus oldest-old).^{9,38} In future research we will investigate the viability of our classification approach through careful study and longitudinal follow-up of our SCD group. Among other things, we hope to identify specific characteristics that discriminate between those with SCD due to benign conditions and those in the earliest stages of neurodegenerative cognitive decline.

Strengths of the current study included a large, racially/ethnically diverse sample with a long follow-up period. We faced several challenges, however, in classifying SCD in EAS participants. Although we wanted to use AD as an outcome (in addition to aMCI), we were unable to do so given the relatively limited number of incident cases in our sample ($n = 71$) and the many factors being examined, despite many years of follow-up data. Additionally, we did not have biomarker evidence of AD. We consider this to be a limitation, but also recognize that research that focuses on clinical features of cognition has a place in the field and may be more inclusive of research participants globally. Given significant missing data in key variables, we applied MI, which yields valid results under the assumption that data are missing at random (MAR), that is, the missing data process can depend on the observed, but not the unobserved, data. When we reran our primary analysis (Table S1) among those with complete subjective cognitive function data, findings were unchanged. However, this reanalysis did not account for the high level of missingness for APOE and informant report data, which may have influenced the lack of statistically significant effects for these variables, despite our attempts to recover these data using MI. The MAR assumption is not testable without further information. In the future we will consider using a sensitivity analysis to explore the potential impact when data are not missing at random (MNAR). Finally, future studies would benefit from the assessment of SCD in the context of a broader set of psychological, physical, or behavioral characteristics (eg, anxiety, specific personality traits, medical help seeking, quality of life, stress, frailty) to determine their separate and joint predictive value for subsequent MCI. Although the concept of SCD was developed within a research context, increasing numbers of individuals with self-perceived cognitive decline are seeking medical help and advice. Future research should determine the optimal SCD assessment approach for clinical settings. In addition, clinicians should be made aware of the potential significance of cognitive concerns in the context of various neurocognitive, psychological, and medical conditions.

In sum, we used available data and relevant covariates to classify SCD in a manner that optimized the diagnostic accuracy for incident aMCI. Based on our experience, we offer the following considerations:

1. Because we were focused on SCD related to the prodromal/pre-MCI stage of AD, we did not consider progression to naMCI, though research indicates that SCD constitutes a heterogeneous population that in many cases remains stable or progresses to non-AD etiologies.²⁵ Researchers may need to use different items or classification approaches to capture SCD that precedes non-AD dementias. Also, cut-off scores for SCD derived in the current study likely will not generalize to studies that use other subjective cognitive items or to memory clinic samples. It is important to continue with efforts to pool international data to create a common SCD metric that can be shared across diverse studies and settings.^{28,66}
2. Although we had access to a sufficient number of items probing self-perceived cognitive functioning that tapped multiple domains using various response types and temporal referents, available items had certain content and psychometric limitations, and some of the items were used in the diagnosis of aMCI, which could result in a circularity issue. While there is currently no consensus on “best” items to capture SCD related to preclinical AD, overall our results suggest that various approaches to handling subjective cognitive data may yield similar results. This is positive news, as it is unlikely that international aging studies will be able to arrive at a consensus on a single set of items, though research efforts should continue to refine measures and identify items with strong content and psychometric properties. In addition, although all individual items with associations to aMCI were related to memory, the scores used in models 1 and 3 included items tapping other cognitive domains, and all three models were roughly comparable in terms of diagnostic accuracy for the time periods considered. Thus, results align with the suggestion to include items that capture a diversity of cognitive domains and other relevant features of older adults' experiences—in a way that mirrors the heterogeneity of the SCD diagnosis itself.^{28,29,52,67} Also, results suggest that a simple summed total of all available subjective cognitive items might offer a practical and simple method for handling these data.
3. Although we incorporated four SCD-plus features into our analysis (eg, concerns about memory rather than other domains, APOE $\epsilon 4$ allele, feeling of worse performance than peers, confirmation by an informant), we did not have data for other features (eg, onset within the past 5 years, onset at 60 years or older). Also, we had to approximate features such as worry about overall health instead of worry about memory, which may not capture the essence of the concern/worry that associates with an increased likelihood of future AD.²² We have since added this (and other) promising items into the EAS battery, and we recommend continued research into the evolving SCD-plus concept, including determining whether specific features merit incorporation into the assessment and classification process itself.

4. The field has not yet arrived at a consensus for what constitutes “significant” or “meaningful” concern about cognition.²⁸ In the current study, we chose to focus on how subjective cognitive data and other relevant variables impact subsequent cognitive impairment/aMCI, and we set cut points based on optimization of the diagnostic performance using time-dependent ROC analysis. We acknowledge that using other outcomes or approaches to “SCD positivity” (eg, median split, 1 or 1.5 SD above the mean among cognitively healthy individuals), may have resulted in our characterizing a different phenotype of SCD. Future research should endeavor to explore various classification approaches using large/multisite samples with the overall goal of producing an SCD diagnosis that is stable and that predicts important clinical and cognitive outcomes.
5. Finally, the incorporation of SCD measures into clinical and research assessments is grounded in the idea that older individuals may be sensitive to modest, initial declines that are meaningful. This assessment approach is useful in cross-sectional research, where neuropsychological tests are unable to capture change in performance within the individual,¹ and in longitudinal research in which self-perceived cognitive decline is often prognostic of future cognitive impairment.^{21–27} However, researchers almost never provide a justification for the instruments used, methods used to score subjective cognitive function data, or classification approach for SCD. If the field is to advance, it is essential that researchers report their methods as well as the rationale for their assessment and classification choices. Without such information, it is impossible to compare findings across studies and refine the construct, including distinguishing subgroups of individuals with SCD who are likely on the AD/dementia trajectory, for enrichment of cohorts. Also, in clinical trial research, classification reporting is essential for understanding which interventions succeed and under which conditions.

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CONFLICTS OF INTEREST

The authors report no competing interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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