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Association of Subjective Cognitive Decline With Progression to Dementia in a Cognitively Unimpaired Multiracial Community Sample

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Abstract

Background and objectives: This prospective study seeks to examine the utility of SCD as a marker of future progression to dementia in a community-based cohort of non-Latinx White, non-Latinx Black and Latinx individuals. Debate surrounds the utility of Subjective Cognitive Decline (SCD), the subjective perception of decline in one's cognition before such impairment is evident in traditional neuropsychological assessments, as an early indicator of impending Alzheimer's disease. Unfortunately, most studies examining SCD have been conducted in non-Latinx White samples and commonly exclude groups of individuals shown to be most vulnerable to dementia.

Methods: Participants were enrolled into this cohort study from the Washington Heights–Inwood Columbia Aging Project (WHICAP) if they were cognitively unimpaired, had baseline

measurement of SCD and self-identified as non-Latinx White, non-Latinx Black or Latinx. SCD was measured as a continuous sum of 10-items assessing cognitive complaints. Competing risk models tested main effects of baseline SCD on progression to dementia. Models were adjusted for age, sex/gender, years of education, medical comorbidity burden, enrollment cohort and baseline memory test performance with death jointly modelled as a function of race/ethnicity.

Results: A total of 4,043 (1,063 non-Latinx White, 1,267 non-Latinx Black and 1,713 Latinx) participants were selected for this study with mean age of 75 years, 67% women and with a mean follow up of 5 years. Higher baseline SCD was associated with increased rates of incident dementia over time in the full sample (HR=1.085, CI=1.047, 1.125, p<.001) as well as within Latinx (HR=1.084, CI=1.039, 1.130, p<.001) and Black individuals (HR=1.099, CI=1.012, 1.194, p=.024).

Discussion: Overall results of this study support SCD as a prodromal marker of dementia in a multiracial community sample, and in Latinx and non-Latinx Black individuals in particular. As models examining the risk of dementia were adjusted for baseline memory test performance, results support the idea that SCD, a subjective reflection of one's own current cognitive functioning, contributes information above and beyond standard memory testing. Current findings highlight the importance of carefully evaluating any memory concerns raised by older adults during routine visits and underscore the potential utility of screening older adults for SCD.

Key words: Subjective cognitive decline (SCD), Dementia, Alzheimer's disease (AD).

Introduction

Subjective cognitive decline (SCD) was defined over a decade ago as the subjective perception of decline in one's cognition before such impairment is evident in traditional neuropsychological assessments [1]. In recent years, SCD has emerged as a potential and valuable marker for a prodromal stage of dementia [2]. Multiple studies show that the presence of SCD can increase risk for future progression to dementia and cognitive decline [3]. Further, Alzheimer's disease (AD) biomarkers, including amyloid-beta (Aβ) and cortical atrophy in AD-related regions, are associated with SCD [4]. However, the utility of SCD as an early marker of AD is debated [5]. Moreover, as with much research in AD and other neurodegenerative diseases, most studies examining SCD have been conducted in non-Latinx White samples. The lack of representativeness in the SCD literature threatens the validity and generalizability of conclusions by commonly excluding groups of individuals shown to be most vulnerable to dementia.

Decades of work have established differences across ethnoracial groups in the diagnostic sensitivity [6,7], clinical manifestations [8] and anatomic correlates [9,10] of cognitive impairment and clinical AD. These differences have been linked to a number of social determinants of health such as quality of education, socioeconomic status, and racial socialization [11]. There is evidence that the predictive utility of SCD for dementia is affected both by task factors (i.e., the characteristics of the tools we use) [12] and person factors (i.e., the characteristics of the individual being evaluated), [13,14] effects which may vary across ethnoracial groups. Previous studies examining SCD in non-Latinx Black individuals have produced conflicting support for SCD as a possible dementia prodrome. Multiple studies in non-Latinx Black older adults have linked SCD to memory function or future decline [15-20]; however, results from at least four studies have

suggested that SCD is unrelated to actual memory function in this group [21-24]. Negative findings could reflect the cross-sectional nature of these studies, a lack of sensitive cognitive outcome measures [24], or limitations in the SCD instrument [22,24]. Moreover, potential inclusion of individuals with MCI [22-24] could reduce the association between SCD and memory given the degradation in memory awareness that accompanies advancing disease. Indeed, studies have shown that as many as 60% of MCI patients may have impaired awareness of memory loss[25], and thus endorse fewer subjective memory problems than individuals in an earlier stage of disease (i.e., SCD) despite having worse memory performance. Nonetheless, in the study by Jackson and colleagues [21] in which individuals with MCI were carefully excluded, and sensitive measures of cognition and SCD were used, SCD was related to memory in Whites but unrelated to memory in a group of non-Latinx Black individuals matched on age, sex, estimated Verbal IQ, and socioeconomic status. The authors speculated that cultural, health, environmental and lifestyle factors might account for qualitative differences in how each racial group endorsed cognitive concerns, which in turn lead to differences in relationships with objective memory. However, this study was also cross-sectional; longitudinal designs are needed to more definitively establish SCD as a potential risk factor.

With regard to studies in Latinx older adults, evidence for SCD as a clinical precursor of AD is also inconsistent [20,26-30]. Several studies have highlighted the association between SCD and lower cognitive performance [20,28,29]. In a 2021 study by Nakhla and colleagues, SCD was associated with cognition as well as reduced entorhinal thickness and left hippocampal volume [26]. In the latter study, the authors used a 12-item Likert scale to assess SCD as opposed to the 5-item dichotomous measure used in a previous study finding no link between SCD and cognition[27]. Nonetheless, a recent longitudinal study found that SCD predicted later impairment

on the Telephone Interview for Cognitive Status (TICS) in non-Latinx Whites, but not Latinx or Black older adults [30]. The authors speculated that differing trends in cognitive status perception across ethnoracial groups in addition to systemic inequities that may influence their decision to express their concerns may contribute to the varying predictive utility of SCD that they observed.

Taken together, the majority of studies suggest that SCD is associated with cognitive function and/or progression to dementia across ethnoracial groups including non-Latinx White, non-Latinx Black, and Latinx older adults. However, several recent longitudinal studies challenge this idea, and no study has simultaneously examined the utility of SCD across all three ethnoracial groups for predicting conversion to dementia. To more rigorously examine the utility of SCD in diverse cohorts, this study investigates the predictive utility of SCD on progression to dementia in non-Latinx Black, Latinxs and non-Latinx, and Non-Latinx White older adults.

Methods

Participants

Participants were selected for this study from the Washington Heights–Inwood Columbia Aging Project (WHICAP), a community-based, prospective cohort study of cognitive aging and dementia in Northern Manhattan, New York. WHICAP enrollees consist of a diverse sample of Medicare-eligible older adults that reside in the Washington/Hamilton Heights and Inwood area. Participants were enrolled in three primary waves: 1992 (n = 2,338), 1999 (n = 2,183), and 2009 (n = 2,128). WHICAP participants are followed at 18 to 24-month intervals; at each visit they receive a variety of medical, neurological, functional, and neuropsychological measures. Measures are given in either English or Spanish based on the participant's language preference.

This study was approved by the Institutional Review Board (IRB) at Columbia University Irving Medical Center.

For purposes of this study, participants were included if: 1) their primary self-reported race/ethnicity was non-Latinx White, non-Latinx Black or Latinx; 2) they were cognitively unimpaired at baseline (i.e., no dementia or mild cognitive impairment (MCI) [31,32]; and 3) they had subjective cognitive data at their baseline visit. This resulted in a sample of 4,043 individuals.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Institute Review Board (IRB) at Columbia University as a human's subject protocol IRB-AAAO9804. Participants were consented prior testing with a full written consent.

Data availability

Data are available upon reasonable request to the WHICAP Publications Committee. Data requests should be submitted at cumc.co1.qualtrics.com/jfe/form/SV_6x5rRy14B6vpoqN.

Measures

Demographic and clinical measures

Self-reported race/ethnicity was measured based on the 1990 US Census guidelines. Participants were first asked whether they were Latinx or Latino and then asked to classify themselves racially as Non-Latinx White, Non-Latinx Black, Asian, American Indian, Pacific Islander, or other. Sex/gender was assessed by asking participants if they were male or female;

because it is unknown whether participants answered based on their sex at birth or the gender they identify with, we refer to this variable as 'sex/gender'[33]. Education was defined as the highest level of educational achievement and transformed into the corresponding number of years to obtain a level ranging from 0-20.

A total score of medical burden ranging from 0 to 14 was calculated based on participants' self-reported history of hypertension, diabetes, heart disease, stroke, chronic obstructive pulmonary disease (COPD), thyroid disease, liver disease, renal insufficiency, peptic ulcer disease, peripheral vascular disease, cancer, Parkinson's disease, multiple sclerosis, and essential/familiar tremor [34]. Time to death was coded as years from baseline to time of death. Self-reported depressive symptoms were measured via the Center for Epidemiological Studies-Depression (CES-D) [35] 10-item questionnaire; this score ranges from 0 to 10 with higher scores indicating more depressive symptoms.

Subjective Cognitive Decline

SCD was defined as a continuous sum variable based on the number of cognitive complaints from ten items as defined in eTable 1. Items were drawn from existing questionnaires including the Blessed Dementia Scale, the Comprehensive and Referral Evaluation (CARE) and a WHICAP-specific medical questionnaires [36-38].

Neuropsychological Testing

As part of the parent study, participants underwent a full neuropsychological battery described previously [39,40] that assessed cognitive domains of memory, language, speed/executive function, and visuospatial ability. In the current study, memory performance was included as a covariate. Memory was assessed via the Selective Reminding Test's (SRT) immediate, delayed, and recognition trials [41]. Individual raw scores were converted to z-scores and averaged based on a confirmatory factor analysis approach to obtain a composite memory score [40].

Dementia Diagnosis

Participants received diagnoses of all-cause dementia via consensus case conference based on neurological, neuropsychological, functional, medical, and psychiatric information gathered from self-reports from participants and/or informants, and followed standard research criteria for the all-cause dementia [42].

Statistical Methods

One-way ANOVAs with Tukey post hoc tests and chi-square analyses were conducted to examine demographic and clinical differences across ethnoracial groups. One-way ANCOVA was also conducted to examine differences of SCD endorsement while adjusting for age, sex/gender and education. Fine-Gray competing risk models [43] tested main effects of baseline SCD on progression to dementia as well as the group specific stratified effects of race/ethnicity and SCD. Death was jointly modeled during follow-up as a function of race/ethnicity. Models were adjusted for age, sex/gender, years of education, medical comorbidity burden, enrollment cohort and baseline memory functioning. Due to missing data on the depression scale additional models adjusting for depressive symptoms were conducted in supplementary analyses.

Results

Descriptives

Table 1 summarizes participants' demographic and clinical information. As observed in Table 1, Latinx participants had lower education than Non-Latinx Black participants; both Latinx and non-Latinx Black participants had lower educational attainment than non-Latinx White participants. The medical burden was higher in Latinx participants as compared to non-Latinx Black and non-Latinx White participants, with non-Latinx White individuals having less burden that non-Latinx Black and Latinx participants. Latinx participants also had higher endorsement of depressive symptoms than Non-Latinx Black and non-Latinx Whites participants. No differences emerged in terms of age. There was a larger proportion of women in Latinx and non-Latinx Black participants compared to non-Latinx White participants. The overall endorsement of SCD was different across groups such that Latinx participants reported more complaints than non-Latinx Whites and non-Latinx Black participants. This difference remained after adjusting for education, age and sex/gender. No significant differences were observed between non-Latinx White and non-Latinx Black participants in overall SCD (p>.05). Finally, Latinx participants higher incidence rates of dementia than non-Latinx Black and non-Latinx White participants; non-Latinx Black participants had a higher incidence compared to non-Latinx White participants.

[INSERT TABLE 1 HERE]

SCD predicting progression to dementia

Table 2 includes estimates of the overall effect of SCD on incident dementia in the whole sample. Higher baseline SCD was related to greater likelihood of progression to dementia such that at any given time and additional one point on the 10-point SCD scale is associated with an 8.5% higher risk of having dementia, roughly comparable to the effect of two years of aging. Similarly, being a woman and being Latinx increased the risk of conversion to dementia. Higher memory performance as well and higher educational attainment were associated with a reduced in risk of dementia (see Table 2 and Figure).

[INSERT TABLE 2 HERE]

Table 3 includes estimates of SCD by ethnoracial groups on incident dementia. SCD increased the risk of conversion to dementia in Latinx and non-Latinx Black participants but not

in White participants although effect size and CI were comparable across groups (Figure). Finally, models included in Tables 2 and 3 were then adjusted for depressive symptoms included in eTables 2 and 3. The overall effect of SCD on dementia remained significant in the whole sample and in Latinx participants. The effect within non-Latinx Black participants was similar but lost its significance at the margin (p = .077, see eTable 3).

[INSERT TABLE 3 HERE]

[INSERT FIGURE 1 HERE]

Discussion

This study examined whether SCD is a marker of dementia risk in a community- based multiethnic and multiracial sample. Latinx participants endorsed higher levels of SCD, and also

had the greatest likelihood of progressing to dementia as compared to non-Latinx Black and non-Latinx White participants. Overall results of this study support SCD as a preclinical marker of dementia in the full sample, and in Latinx and non-Latinx Black individuals in particular. Whilst the association between baseline SCD and future progression to dementia was not statistically significant in non-Latinx White participants, the effect size and confidence intervals were comparable to the other racial and ethnic groups. Models examining the risk of dementia were also adjusted for baseline memory test performance supporting the idea that SCD, a subjective reflection of one's own current cognitive functioning, contributes information above and beyond a clinical neuropsychological assessment of memory. Models examining the risk of dementia were also adjusted for baseline memory test performance supporting the idea that SCD, a subjective reflection of one's own current cognitive functioning, contributes information above and beyond a clinical neuropsychological assessment of memory. Perhaps as would be expected, objective memory as measured via a composite score representing immediate recall, delayed recall, and recognition memory on a rigorous list learning test, exhibited a stronger effect than SCD on progression to dementia. The difference in the magnitude of the unstandardized effect partially reflects scaling differences in the two scores. When examining the standardized coefficients, the difference in the effect sizes is reduced. Nonetheless, memory function remains a stronger predictor of progression to dementia than SCD in this model. The deterioration of episodic memory in early AD is well known [44]; indeed, episodic memory testing is a core feature of MCI assessments [45]. The additional contributory value of SCD for progression to dementia is important because SCD screening is far more practical than episodic memory testing in frontline settings. Moreover, the independent predictive value of SCD reinforces the idea that older adults' cognitive complaints might capture subtle weaknesses not yet detectable on clinical memory

testing. Indeed, emerging studies show that SCD maps onto several sensitive cognitive tasks when clinical neuropsychological performance is within standard limits [12].

Results from this study are in line with some [18,26,28] but not all studies [21,22,24,27,30] examining the association of SCD with dementia or cognitive functioning. Literature examining SCD in diverse populations is emerging, and there is no 'gold standard' approach. Methodologies across studies vary widely, but some potential limitations of the studies with inconclusive results include exclusion of participants of Latinx descent; use of cognitive screeners as outcomes; and inclusion of patients with MCI, possibly including patients with disturbances of self-awareness (i.e., anosognosia). Moreover, the majority of inconclusive studies were cross-sectional, a design which may exacerbate possible confounders such as differential thresholds for defining cognitive impairment, variable cognitive presentations, cultural thresholds for reporting SCD [46], in addition to differences in psychological factors such as depression [47,48]. The current study addresses some of these concerns by using a longitudinal approach, simultaneously examining all three groups, and utilizing a clinical consensus diagnosis to define incident dementia, a robust definition of future decline.

Socioeconomic disparities are a critical consideration in understanding mechanisms which may underlie potential differences in SCD and/or its association with cognition across ethnoracial groups. In the current study, the Latinx group had lower education and higher SCD than non-Latinx White or Black older adults. When adjusting for education, which may partially address differences in SES, SCD remained higher in the Latinx group. Nonetheless, there is no clear moderating effect of race on the association between SCD and dementia. In other words, SCD appears to put all ethnoracial groups at a similar risk for dementia. It is certainly possible that differences in SES could have main effects on both SCD and dementia, as well as a

moderating effect on the association between these two variables. Future studies will need to address this question directly.

From a public health standpoint, current findings highlight the importance of carefully evaluating any memory concerns raised by older adults during routine, primary care visits, and underscore the potential utility of screening older adults for SCD. Delayed diagnoses of cognitive impairment in older adults are multifactorial, in part reflecting the belief that memory loss is a normal part of aging [49]. SCD screening is highly practical: it is fast, easy, non-invasive, inexpensive and adaptable to any setting. As plasma-based biomarkers of AD become increasingly accessible and widespread practice across in primary and specialized medical care facilities, it will be critical to interpret values in conjunction with cognitive symptoms [50].

The current study also has several limitations. First, the different ethnoracial groups were treated as monolithic groups when in fact each group is very heterogenous, with individuals representing many different backgrounds. It is thus important for future research to examine these topics with greater attention to this diversity. Second, whilst this study adjusted for depressive symptoms in supplementary models, missing data on the depression scale reduced the number of participants included in these models, limiting the comparison of results. Second, the SCD measurement was primarily focused on memory complaints and did not comprehensively cover cognitive domains. Further, this study did not consider language of testing and cultural factors, which, as indicated above, could act as potential confounders. Future studies should examine the effects of language, cultural and psychological factors on SCD as a function of race and ethnicity to fully optimize this measurement's utility. Finally, there is limited understanding of the pathology that drives SCD and the extent to which such pathology differs across

ethnoracial groups. Efforts are needed to elucidate the potential neural pathways through which SCD manifests across these groups.

Appendix 1: Contributing Authors

Name	Location	Contribution
Silvia Chapman, PhD	Columbia University, New York	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Miguel Arce Rentería, PhD	Columbia University, New York	Design and conceptualization of study. Revised the manuscript for intellectual content
Jordan D. Dworkin, PhD	Columbia University, New York	Analyzed the data; revised the manuscript for intellectual content
Stella Garriga, BS	Columbia University, New York	Revised the manuscript for intellectual content and contributed significantly to revisions
Megan S Barker, PhD	Columbia University, New York	Revised the manuscript for intellectual content
Justina Avila-Reiger, PhD	Columbia University, New York	Revised the manuscript for intellectual content
Christopher Gonzalez, MS	Columbia University, New	Revised the manuscript for intellectual content

	York	
Jillian L Joyce, MS	Columbia University, New York	;Revised the manuscript for intellectual content
Jet M J Vonk, PhD	Columbia University, New York	Revised the manuscript for intellectual content
Elizabeth Soto, BS	Columbia University, New York	Revised the manuscript for intellectual content
Jennifer J Manly, PhD	Columbia University, New York	Revised the manuscript for intellectual content
Adam M Brickman, PhD	Columbia University, New York	Revised the manuscript for intellectual content
Richard P. Mayeux, PhD	Columbia University, New York	Revised the manuscript for intellectual content
Stephanie Cosentino, PhD	Columbia University, New York	Design and conceptualized study; Interpreted the data; revised the manuscript for intellectual content

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Table 1. Demographic and clinical information of participants by ethnoracial group

Demographics and clinical information									
	Non-Latinx White		*Non-Latinx Black*		*Latinx*		*Total*		
	Mean (SD) *or* % (n)	Sample range	Mean (SD) *or* % (n)	Sample range	Mean (SD) *or* % (n)	Sample range	Mean (SD) *or* % (n)	Sample range	Statistics
Age	75.32 (6.53)	59.84, 99.64	75.19 (6.53)	61.96, 101.78	75.40 (6.31)	63.04, 101.95	75.32 (6.44)	59.84, 101.95	(F(2,4040) = 0.418, p =.659)
Sex/gender (% women)[b,c]	59.8% (636)	-	69.5 % (881)	-	68.5% (1173)	-	66.5% (2690)	-	(χ^2(2, n = 4043) = 29.48, p <.001)
Education[a,b,c]	14.17 (3.62)	0, 20	11.99 (3.70)[a]	0, 20	7.39 (4.41)[a]	0, 20	10.62 (4.92)	0, 20	(F(2,4040) = 1051.61, p <.001)
Medical Burden[a,b,c]	1.81 (1.55)	0, 10	2.12 (1.56)	0, 10	2.13 (1.60)	0, 10	2.12 (1.60)	0, 10	(F(2,4040) = 32.19, p <.001)
Cohort[a,b,c]									
1992 Cohort	19.0% (202)	-	24.1% (305)	-	23.0% (394)	-	22.3% (901)	-	(χ^2(4, n = 4043) = 84.36, p <.001)
1999 Cohort	45.0% (478)		39.3% (498)		29.4% (503)		36.6% (1479)		

2009 Cohort	36.0% (383)		36.6% (464)		47.6% (816)		41.1% (1663)		
Subjective Cognitive Decline Sum[a,b]	1.73 (2.04)	0, 9	1.87 (2.14)	0, 9	2.31 (2.67)	0, 10	2.02 (2.36)	0, 10	(F(2,4040) = 23.87, p <.001)*
Incident Dementia[a,b,c]	4.8% (51)	-	9.6% (121)	-	17.5% (299)	-	11.6% (471)	-	(χ^2(2, n = 4043) = 110.00, p <.001)
Years in study[c]	4.92 (4.40)	0, 22.51	4.34 (4.14)	0, 25.65	4.90 (4.62)	0.00, 25.10	4.75 (4.42)	0, 25.65	(F(2,4040) = 7.81, p <.001)
CES-D depression scale[a,b] (n = 3133)	1.43 (1.75)	0, 10	1.33 (1.73)	0, 10	1.99 (2.25)	0, 10	1.63 (1.98)	0,10	(F(2,3130) = 37.60, p <.001)

Note. [a] = significantly different between Latinx individuals and Non-Latinx Black individuals; [b]= significantly different between Latinx and Non-Latinx White individuals. [c]=significantly different between Non-Latinx Black and Non-Latinx White individuals. *Results remained after adjusting for age, education and sex/gender (F(5,4037)=19.11, p <.001).

Table 2. Competing risks model of baseline SCD as a predictor of dementia in whole sample

	Dementia (Hazard Ratio)		
Predictors	*Estimates*	*CI*	*p*
SCD main effect			**<.001**
- Per unit	**1.085**	**1.047, 1.125**	
increase	**1.213**	**1.114, 1.322**	
- Per SD			
increase			
Baseline memory			**<.001**
- Per unit	**0.404**	**0.347, 0.469**	
increase	**0.545**	**0.492, 0.603**	
- Per SD			
increase			
Age	**1.043**	**1.028, 1.058**	**<.001**
Education	**0.936**	**0.911, 0.962**	**<.001**
Sex/gender	**1.39**	**1.127, 1.715**	**0.002**
Latinx ethnicity	**1.71**	**1.207, 2.423**	**0.003**

Non-Latinx Black race	1.368	0.972, 1.924	0.072
Burden	0.943	0.882, 1.01	0.093
Cohort - 1999	1.076	0.843, 1.373	0.560
Cohort - 2009	1.156	0.876, 1.526	0.300

Note. Significant main effects bolded.

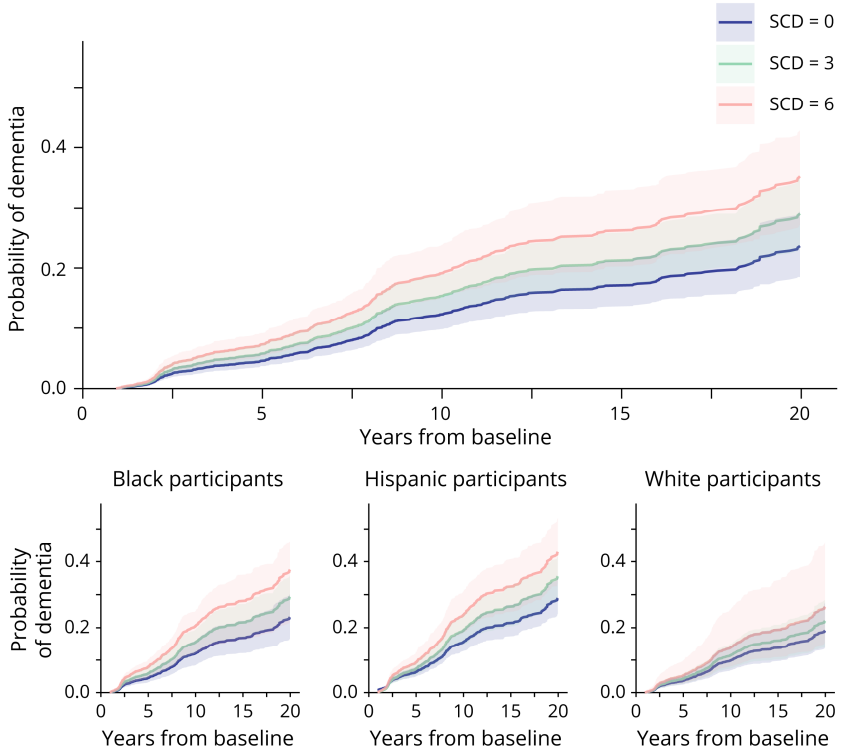
Table 3. Model including interactions terms for SCD and ethnoracial group

	Dementia (Hazard Ratio)		
Predictors	*Estimates*	*CI*	*p*
SCD*White race			.360
- Per unit increase	1.063	0.933, 1.212	
- Per SD increase	1.156	0.848, 1.576	
SCD*Non-Latinx Black race			**.024**
	1.099	**1.012, 1.194**	
- Per unit increase	**1.251**	**1.029, 1.520**	
- Per SD increase			
SCD*Latinx ethnicity			**<.001**
- Per unit increase	**1.084**	**1.039, 1.130**	
- Per SD increase	**1.210**	**1.096, 1.336**	
Baseline memory			**<.001**
- Per unit increase	**0.403**	**0.347, 0.469**	
- Per SD increase	**0.544**	**0.492, 0.603**	
Age	**1.043**	**1.028, 1.058**	**<.001**
Education	**0.936**	**0.910, 0.962**	**<.001**
Sex/gender	**1.388**	**1.125, 1.713**	**.002**

Latinx race	**1.647**	**1.048, 2.587**	**.030**
Non-Latinx Black race	1.277	0.803, 2.030	.300
Burden	0.944	0.882, 1.010	.094
Cohort - 1999	1.077	0.844, 1.374	.550
Cohort - 2009	1.157	0.877, 1.526	.300

Note. Significant main and interaction effects bolded.

Figure 1. Dementia risk by baseline SCD in the whole sample and by ethnoracial group.



Association of Subjective Cognitive Decline With Progression to Dementia in a Cognitively Unimpaired Multiracial Community Sample

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