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Clinical Progression of Baseline Risk States for Mild Cognitive Impairment

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Abstract

Background: This memory-clinic study joins efforts to study earliest clinical signs and symptoms of Alzheimer's disease and related dementias: subjective reports and objective neuropsychological test performance.

Objective: The memory-clinic denoted two clinical "grey zones": 1) subjective cognitive decline (SCD; $n = 107$) with normal objective test scores, and 2) isolated low test scores (ILTS; $n = 74$) without subjective complaints to observe risk for future decline.

Methods: Initial and annual follow-up clinical research evaluations and consensus diagnosis were used to evaluate baseline characteristics and clinical progression over 2.7 years, compared to normal controls (NC; $n = 117$).

Results: The ILTS group was on average older than the NC and SCD groups. They had a higher proportion of people identifying as belonging to a minoritized racial group. The SCD group had significantly more years of education than the ILTS group. Both ILTS and SCD groups had increased risk of progression to mild cognitive impairment. Older age, minoritized racial identity, and baseline cognitive classification were risk factors for progression.

Conclusion: The two baseline risk groups look different from each other, especially with respect to demographic correlates, but both groups predict faster progression than controls, over and above demographic differences. Varied presentations of early risk are important to recognize and may advance cognitive health equity in aging.

Keywords

Cognitive decline; mild cognitive impairment; neurocognitive tests; risk factors

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SUPPLEMENTARY MATERIAL

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INTRODUCTION

In past decades, spurred by increasing dementia burden on individuals and societies, research efforts have focused increasingly on characterizing the earliest clinical signs and symptoms predicting dementia, particularly Alzheimer's disease [1]. Although primary care providers (PCPs) deliver most of the care to older adults at greatest risk for cognitive decline, diagnosis of cognitive syndromes, including mild cognitive impairment (MCI), are most common in specialty settings [2]. This relies on both subjective reports of cognitive change and objective neuropsychological measures [3–5]. Subjective cognitive decline (SCD), defined as self-perceived cognitive changes in the context of normal neuropsychological assessment, has been a focus of research with consensus recommendations [5–7]. However, the converse putative risk state—low neuropsychological test performance in isolation (without subjective cognitive complaints)—is less frequently studied or observed [2, 8]. Several studies from observational research cohorts have investigated isolated (or 'subtle') objectively measured cognitive impairment, finding baseline functional MRI differences in the brain [9]; increased progression to MCI or dementia [10–12]; and increased amyloid-β accumulation and cortical thinning over time [10].

This study sought to investigate two classifications of putative risk for MCI, compared to healthy controls, in an academic memory clinic setting: 1) SCD with normal objective test scores, and 2) lower than expected test scores without subjective complaints (isolated low test scores; ILTS). The first study objective was to evaluate demographic and risk factor differences between baseline groups, and the second was to examine group differences in clinical progression to MCI or dementia.

MATERIALS AND METHODS

Participants

Participants were enrolled in the University of Pittsburgh Alzheimer's Disease Research Center (ADRC) in accordance with procedures approved by the Institutional Review Board. As an academic memory disorders research center funded by the National Institute on Aging, one of currently 33 ADRCs in the U.S., it is also a research registry. People apply to participate for two broad reasons: clinical evaluation or participation in research (or both). Participants may be self-referred, physician-referred, or respond to community outreach efforts either because of concern about possible cognitive decline or as healthy controls. These include targeted recruitment events in under-represented group communities, social/professional contacts, online and print advertisements, and occasional local media features. The present cohort was not systematically enriched other than prioritizing enrollment of applicants from under-represented groups, those likely to participate further in research protocols, and those on the milder end of the cognitive impairment spectrum.

This study analyzed longitudinal data beginning July 1, 2009, when the center implemented the diagnostic category 'low cognitive test performance without subjective complaints,' through December 12, 2019. Center inclusion criteria were English-speaking fluency, minimum 7 years of education, adequate vision and hearing to complete neuropsychological

tests, and a reliable informant. Lifetime history of serious psychiatric illness, age <60 without memory complaints, or recent health conditions or treatments that could affect neuropsychological performance (e.g., electroconvulsive therapy, alcohol or substance use disorder) or life expectancy (some cancers) were excluded. 298 participants satisfied these criteria and did not meet criteria for MCI or dementia at initial evaluation (see below, 'Evaluation and Diagnosis').

Evaluation and diagnosis

Initial evaluation included clinical interviews with participant and informant, neuropsychological testing, self-reported race/ethnicity, health history, family history, physical and neurological exams. The Clinical Dementia Rating scale was administered [13]. An interdisciplinary diagnostic consensus panel reviewed available clinical data, including MRI of the brain. The diagnostic process was clinical in nature, not algorithmic; the consensus conference process included consideration of all sources of information, including motivation for evaluation by the ADRC. Presence of clinically significant cognitive complaints was generally supported by concern for memory/cognition as motivation for seeking evaluation by the participant and/or informant. A Clinical Dementia Rating global score of 0.5 was typical for this determination.

The neuropsychological test norms utilized in this study were primarily derived from healthy control participants of the center at their baseline visit, but from an earlier time period relative to the current study. For most tests, the norms were adjusted by two broad age-categories: 75 and younger, and 76 and older. Mild impairment/lower-than-expected test scores on neuropsychological evaluation were both considered to be below −1.0 standard deviation (SD) from age-adjusted normative means, while taking account for educational/occupational background. The SCD group was defined as having subjective complaints with normal cognitive test performance [6], with no more than 1 low score within a domain or 2 low scores across domains. The ILTS group was defined as lower-than-expected test scores, generally, with at least 3 scores below −1.0 SD from age-adjusted normative means, without subjective cognitive complaints (including from informants). Normal controls (NC) had neither low neuropsychological test performance, nor clinically significant cognitive complaints. Both ILTS and NC participants were generally motivated to come to the ADRC primarily to volunteer for research.

APOE genotyping was performed according to previously reported methods [14].

Participants were followed annually with the same evaluation and diagnostic procedures. MCI and dementia diagnoses followed 2011 NIA-AA criteria [3, 15]. MCI was diagnosed when there was participant or informant concern (typically Clinical Dementia Rating of 0.5) or other evidence for change in cognitive abilities (e.g., decline in test scores over repeated assessments); mildly impaired neuropsychological test scores (below −1.0 SD) in at least one cognitive domain (≥2 tests within domain or 3 tests across domains); and independence in daily life [3]. MCI was further subtyped as amnestic, non-amnestic, single domain, and multi-domain [16]. Dementia was diagnosed as follows: cognitive impairment interferes with daily functioning; represents a decline from previous functioning; is not explained

by delirium or major psychiatric disorder; and impairment is in at least two cognitive or behavioral domains.

Neuropsychological testing

The neuropsychological battery assessed memory, attention/concentration, visuo-construction, language, and executive function abilities. Tests were components of the National Alzheimer's Coordinating Center (NACC) Uniform Data Set Version 2 [17] and, starting March 2015, Version 3 [18]. Supplemental tests included a word list learning test [19]; modified Block Design [20, 21]; Stroop color and word test [22]; 15- point scoring of clock drawing [23]; and letter fluency trials [24]. Prior to implementation of NACC Uniform Data Set Version 3 the battery also included a modified Rey-Osterrieth Figure [25] and the Boston Naming Test [26].

Analysis

R 3.6.0 was used to analyze study data. All *p*-values reported are two-tailed. Due to non-normal distributions, Kruskal-Wallis one-way analysis of variance was used to compare groups at baseline, followed by Dunn-Bonferroni pairwise comparisons. For categorical variables the Chi-squared or Fisher's exact tests were adopted for baseline group comparisons followed by pairwise comparisons. Self-reported race/ethnicity other than white was coded as a minoritized racial group. A Bonferroni correction for multiple pair-wise comparisons was applied by comparing *p*-values to a 0.05/3 significance level [27]. The most recent visit was used to calculate duration of follow-up time. The visit date of first occurrence of MCI or dementia diagnosis (without previous MCI diagnosis) was used to calculate time to diagnostic progression. Kaplan-Meier curves [28] were used to depict the probability of progressing to MCI/dementia over time. The two-sided log-rank test was used to compare the three MCI trajectories. Cox proportional hazards models were further used to compare the diagnosis groups while adjusting for risk factors including age, racial identity, education, sex, family history of dementia, and *APOE ε*4 status. The model fitting was evaluated by graphic checks based on estimated cumulative hazards and Cox-Snell residuals.

Sensitivity and *post-hoc* analyses included a) evaluating the stability of MCI diagnosis over subsequent follow-up visits; b) running the Cox proportional hazards model in white participants only; and c) and running the model with a combined SCD and ILTS group.

RESULTS

Of the $n = 298$ participants, $n = 117$ were classified as NC, $n = 107$ as SCD, and $n = 74$ as ILTS at baseline (Table 1). The ILTS group was on average older than the NC ($p < 0.01$) and SCD groups ($p < 0.01$). They had a higher proportion of people identifying as belonging to a minoritized racial group (ps < 0.01), including 'Black or African-American' ($n = 57$; 19% of total sample), 'Asian' ($n = 3$; 1%), 'Native Hawaiian or other Pacific Islander' ($n = 1$; 0.3%), and 'Other' ($n = 1$; 0.3%). The ILTS group had significantly fewer years of education than the SCD group ($p < 0.01$). All other pairwise comparisons did not show significant differences. Effect sizes were generally small to moderate except

for minoritized racial group with a relatively large effect size [29] (https://imaging.mrc-cbu.cam.ac.uk/statswiki/FAQ/effectSize).

Participants were followed annually to a maximum 9.3 years; however, 83 participants did not return for follow-up, and thus are not included in the longitudinal analyses. Participants without follow-up were significantly younger (mean 65.7 versus 68.0 years) and had a higher proportion identifying as a minoritized racial group (34.9% versus 15.3%). There were no differences in education, proportion of women, family history of MCI/dementia, or *APOE ε*4 allele. The proportions of participants not returning for follow-up were 0.26, 0.23, and 0.36 in the NC, SCD, and ILTS groups, respectively, which did not differ between groups ($p = 0.14$). The mean (SD) follow-up durations were 2.8 (2.4), 3.0 (2.6), and 2.0 (2.1) years for the NC, SCD, and ILTS groups, respectively, with significant difference among groups (Table 1). During the time observed, participants progressed as follows: In the NC group, 4 (3%) progressed to amnestic MCI, 1 (1%) to non-amnestic MCI, and 1 (1%) to dementia. In the SCD group, 14 (13%) progressed to amnestic and 3 (3%) to non-amnestic MCI. In the ILTS group, 10 (14%) progressed to amnestic and 3 (4%) to non-amnestic MCI.

As shown in Fig. 1, the ILTS group progressed to MCI the fastest, followed by the SCD and then NC groups. The log-rank test indicated significant differences in MCI progression probabilities between the NC and SCD groups (Z12 = 2.47, $p = 0.01$), and significant differences between NC and ILTS groups (Z13 = 4.18 and $p < 0.001$). However, the SCD and ILTS groups did not differ significantly from each other (Z23 = 1.49 and $p = 0.14$).

Table 2 presents Cox proportional hazards model results for prediction of incident MCI. Older age, minoritized racial identity, and baseline diagnostic group (reference = NC) were significant risk factors. Both SCD and ILTS groups were significantly different from the NC group, with comparable effect size (HR = 4.62, $p < 0.01$ SCD versus NC; HR = 4.80, $p < 0.01$ ILTS versus NC). As the ILTS group was older and had a higher proportion of people identifying as a minoritized race, MCI risk between the ILTS and SCD groups were not different (HR = 1.04, $p = 0.91$) after controlling for age, minoritized racial identity, education, and sex.

In a *post-hoc* analysis evaluating the subsequent stability of MCI: of the $n = 36$ cases of incident MCI/dementia, 6 had no further follow-up (median number of visits = 2, range 0–9). Of those with further follow-up visits after incident MCI, 63% remained MCI ($n = 14$) or progressed to dementia ($n = 5$), while the remaining reverted to NC ($n = 2$), SCD ($n = 7$) or ILTS ($n = 2$).

In sensitivity analyses to probe robustness of the primary Cox model results, we found that restricting the model to white participants only ($n = 215$) (Supplementary Table 1), significant predictors of incident MCI/dementia were age, SCD classification (NC as reference) and ILTS classification (NC as reference). Sex, education, family history and *APOE ε*4 were not significant predictors. In the model combining SCD and ILTS (Supplementary Table 2), age, minoritized racial/ethnic identity and the combined SCD + ILTS baseline group (NC as reference) were significant, while sex, education, family history, and *APOE ε*4 were not significant.

DISCUSSION

This study examined two baseline risk states for cognitive decline within a “clinical gray zone,” neither clearly meeting criteria for normal cognition or MCI: 1) subjective cognitive complaints with normal neuropsychological test performance (SCD), and 2) lower-than-expected test performance without subjective cognitive complaints (ILTS). The ILTS group was older on average and had a higher proportion of racially minoritized groups (45% versus19% of controls). The SCD group had more years of education than the ILTS group. Both SCD and ILTS groups showed increased risk for clinical progression to MCI compared to NC, adjusting for significant risk/protective factors. In sum, MCI baseline risk states look different from each other, especially with respect to demographic correlates; however, both risk states predict faster progression than control participants, over and above demographic differences.

Few studies have directly compared these two presentations of cognitive decline risk states on clinical outcomes. Similar classifications, methods and findings were reported in a Florida ADRC research cohort [11]. One salient difference was that the ‘pre-MCI-NP’ category was restricted to memory test impairment, whereas in the present study, ILTS also included low scores on non-memory tests. Other studies focusing on objectively measured, often termed “subtle,” test impairment not meeting MCI diagnostic thresholds, have reported associated increased amyloid-β accumulation and cortical thinning over time, prospectively [10], and increased risk for cognitive decline in newly diagnosed Parkinson’s disease [12]. Papp et al. [30] measured subtle longitudinal decline on test performance over three years in clinically normal older adults with elevated amyloid-β and found steeper decline increased risk for progression to MCI. The present study adds support to the literature indicating lower-than-expected cognitive test scores, without meeting MCI criteria, confer risk for future clinical progression, and to about the same degree as SCD.

Age, education, and minoritized status were key demographic group differences between SCD and ILTS. A sizeable literature documents increased risk of SCD for clinical progression and presence of Alzheimer’s disease biomarkers [31]. However, evidence also suggests Black research participants are less likely to endorse subjective memory complaints [32, 33], and perhaps other minoritized racial/ethnic groups, as well [34, 35]. There is a critical need to widen consideration of how early risk factors for cognitive decline manifest in different research, clinical, and community settings. Achieving greater representation of minoritized races and ethnicities in Alzheimer’s disease and related dementias research studies should continue to be a high priority [36, 37], as is engaging minoritized older adults in clinical screening and follow-up [2]. As normative data and cut- offs for neuropsychological tests directly affect specificity and sensitivity of MCI or dementia diagnosis, validation of diagnostic tools and criteria needs to be established with adequate inclusion of under-represented groups [38].

Important limitations of this study include the relatively small sample size, small number of incident MCI/dementia cases, and follow-up duration of 2.7 years on average. Although we followed some participants up to 9.3 years, there was a significant proportion with no follow-up, and overall limited power to better understand selection bias or investigate

informative interactions, such as effects of minoritized status and other demographic factors by baseline diagnosis. The ILTS group had the shortest mean follow-up of 2.0 years; this suggests the effect of baseline ILTS on progression risk is likely underestimated, since people with cognitive disorders are over-represented in loss to follow-up [39]. Baseline diagnostic definitions were not independent of the outcome; however, we believe the diagnostic consensus process, involving a large inter-disciplinary group of clinical investigators, and a gold standard in dementia research, mitigates the risk of frank diagnostic bias. Some minoritized racial groups were too small to analyze separately. Results may not generalize well outside an academic memory disorders research center, where participants receive diagnostic feedback. The neuropsychological test norms were derived from samples which were not well representative of minoritized people, which was one of the key rationales for establishing the ILTS classification, in an attempt to avoid being overly punitive (i.e., an MCI diagnosis) as a result of non-representative norms. Finally, inclusion of biomarkers may well change prediction results. As Alzheimer's disease and related dementias biomarkers become more available and clinically meaningful, their nexus with early clinical signs and symptoms should be investigated for potential application in clinical settings.

In summary, this study found comparably heightened risk for progression to MCI from both baseline SCD and ILTS. Different presentations of early risk are associated with minoritized group identification and are likely important to advancing cognitive health equity in aging. Both should be considered and included in Alzheimer's disease and related dementias prevention trials and investigated further in observational studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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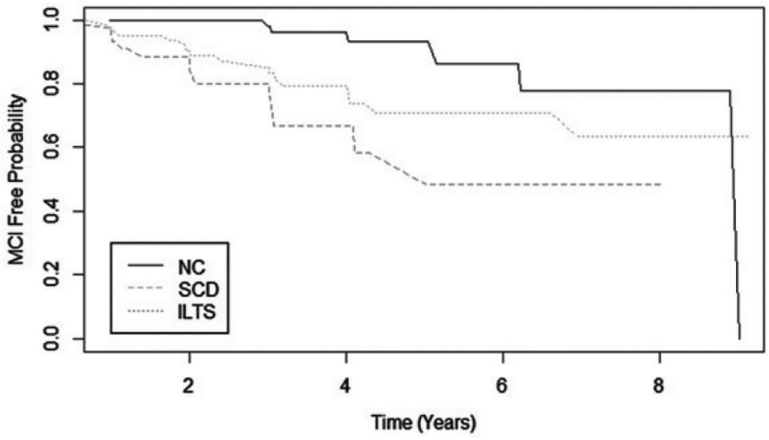

Fig. 1.

Probability of incident MCI/dementia among baseline risk groups. Risk of progression to MCI/dementia over follow-up time, by baseline diagnostic group. NC, normal controls; SCD, subjective cognitive decline; ILTS, isolated low test scores.

Table 1

Baseline characteristics by risk group

	NC N=117 Mean (SD)	SCD N = 107 Mean (SD)	ILTS N = 74 Mean (SD)	Pairwise Comparison Adjusted *p*-values		Test	*p*	Effect Size*
Age (y)	65.3 (12.9)	66.4 (7.2)	71.3 (7.2)	NC versus SCD	0.49	*Kruskal H* (2) = 18.7	<0.001	0.06
				NC versus ILTS	<0.01			
				SCD versus ILTS	<0.01			
Education (y)	16.3 (2.4)	16.7 (2.5)	15.4 (2.6)	NC versus SCD	0.14	*Kruskal H* (2) = 10.9	<0.01	0.03
				NC versus ILTS	0.04			
				SCD versus ILTS	<0.01			
Females, N (%)	89 (83.2%)	69 (64.5%)	47 (63.5%)	NC versus SCD	0.06	χ^2 (2) = 4.8	0.09	0.12
				NC versus ILTS	0.06			
				SCD versus ILTS	0.89			
Minoritized Racial Identity, N (%)	22 (18.8%)	7 (6.5%)	33 (44.6%)	NC versus SCD	<0.01	χ^2 (2) = 38.8	<0.001	0.36
				NC versus ILTS	<0.001			
				SCD versus ILTS	<0.001			
Family History MCI/Dementia, N (%)	64 (54.7%)	62 (57.9%)	39 (52.7%)	NC versus SCD	0.63	χ^2 (2) = 0.52	0.77	0.04
				NC versus ILTS	0.79			
				SCD versus ILTS	0.49			
APOE ε4, N (%)	33 (28.2%)	35 (32.7%)	16(21.6%)	NC versus SCD	0.46	χ^2 (2) = 2.65	0.27	0.09
				NC versus ILTS	0.31			
				SCD versus ILTS	0.10			
Time Observed (y)	2.8 (2.4)	3.0 (2.6)	2.0 (2.1)	NC versus SCD	0.59	*Kruskal H* (2) = 8.6	0.001	0.02
				NC versus ILTS	0.02			
				SCD versus ILTS	<0.01			

* η^2 for continuous data; Cramer's V for categorical data. NC, normal controls; SCD, subjective cognitive decline; ILTS, isolated low test scores.

Table 2

Cox proportional hazards model (HR: hazard ratio) predicting incident MCI/dementia in full longitudinal sample ($n = 215$)

Variables	HR	Z test	*p*	95% CI HR
Female sex	1.07	0.18	0.86	(0.49, 2.36)
Education	0.90	−1.51	0.13	(0.79,1.03)
Age	1.08	2.99	<0.01	(1.03, 1.14)
Minoritized Racial Identity, N (%)	3.13	2.56	0.01	(1.30, 7.51)
SCD (reference = NC)	4.62	3.09	<0.01	(1.75,12.23)
ILTS (reference = NC)	4.80	2.97	<0.01	(1.70,13.58)
Family History of MCI/Dementia	1.53	1.22	0.22	(0.77, 3.02)
*APOE ε*4	0.97	−0.08	0.93	(0.47, 2.01)

NC, normal controls; SCD, subjective cognitive decline; ILTS, isolated low test scores.