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RESEARCH ARTICLE

A short version of the Everyday Cognition scale can predict clinical progression and cognitive decline

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Abstract

BACKGROUND: The Everyday Cognition scale (ECog-39) scores are associated with future cognitive decline. We investigated whether the 12-item ECog (ECog-12), which is being collected in Alzheimer's Disease Neuroimaging Initiative (ADNI)4, can predict progression.

METHODS: Baseline self (PT)- and study partner (SP)-ECog-12 data were extracted from the 39-item version collected in the ADNI. Weibull analysis examined the relationship between baseline ECog-12 and future clinical progression (change in Clinical Dementia Rating Sum of Boxes [CDR-SB] scores and diagnostic conversion).

RESULTS: Higher PT- and SP-ECog-12 scores were associated with faster CDR-SB worsening, with hazard ratios in cognitively unimpaired (CU) 3.34 and 9.61, mild cognitive impairment (MCI) 1.44 and 2.82, and dementia 0.93 and 1.82. They were associated with conversion from CU to MCI 3.01 and 6.24 and MCI to dementia 1.61 and 3.07.

DISCUSSION: SP-ECog-12 provided a higher prognostic value for predicting clinical progression, so this can help identify and monitor patients at risk in research and health-care settings.

KEYWORDS
12-item Everyday Cognition, Alzheimer's disease, dementia, Everyday Cognition scale, mild cognitive impairment

Highlights

- The 12-item Everyday Cognition scale (ECog-12) data obtained from both raters increased diagnostic conversion risk from cognitively unimpaired to mild cognitive impairment (MCI) and from MCI to dementia.
- ECog-12, rated by study partners, was associated with an increased risk of Clinical Dementia Rating Sum of Boxes worsening in all diagnostic groups.
- Our results provide novel information about the specific scoring outputs and rater types (participant vs. study partner) of ECog-12 that can facilitate screening, prioritization, and longitudinal monitoring of the clinical progression of participants in Alzheimer's Disease Neuroimaging Initiative 4 and other Alzheimer's disease clinical studies, clinical trials, and in health-care settings.

1 | BACKGROUND

Identifying older adults at the greatest risk for clinical progression may help prioritize good candidates for appropriate Alzheimer's disease (AD) treatments[1–3] and can be used for screening and longitudinal monitoring in clinical research, clinical trials, and health-care settings. A prior systematic review and meta-analysis revealed that worse scores on cognitive tests, such as lower Mini-Mental State Examination (MMSE) scores and higher Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog) scores, were associated with mild cognitive impairment (MCI) progression.[4] However, these two tests only evaluate cognitive status. Considerable data exists that a person's functional status also predicts future cognitive progression.[5,6] Thus, tools that directly evaluate everyday functional ability may be useful in clinical practice to predict future cognitive decline.

The Everyday Cognition scale (ECog),[7] an instrument to assess subjective change in early functional abilities in older adults, is sensitive for discriminating between cognitively unimpaired (CU) and MCI individuals.[8] The Alzheimer's Disease Neuroimaging Initiative (ADNI) has collected ECog in all phases since ADNI Go. Previous reports demonstrate that the ECog predicts future functional decline[9,10] and cognitive progression from cognitively normal to MCI and from MCI to dementia.[8,11,12] Most previous studies used the original version of ECog, which consists of 39 items (ECog-39). However, a short version of ECog containing only 12 items (ECog-12) was developed to reduce participant (PT) burden, which maintains good psychometric properties.[13] The ECog-12 is being collected in ADNI4, including for those who enroll in the remote, digital cohort, and the in-clinic cohort. For the remote, digital cohort, ECog-12 is being used to identify those with likely cognitive impairment, to prioritize them for referral to in-clinic ADNI, to help achieve ADNI4's enrollment goal of 40% with MCI (see Weiner et al.[14]). Only one cohort study has assessed the predictive ability of ECog-12 for clinical progression and found that subjective cognitive decline, which is indicated by ECog-12 score, is associated with an increased risk of diagnostic conversion from CU to MCI.[15]

The ECog-12 includes versions completed by either a PT or their study partner (SP). ADNI4 is collecting ECog-12 from both PTs and SPs. Prior studies showed that different raters (PT vs. SP) might result in different ECog scores.[15–18] Results from a cross-sectional study supported that PTs who provided better ratings on the ECog scale compared to their SPs had poorer memory test performance and were more likely to have evidence of AD.[16,18] There are limited studies that compare the predictive value of ECog-12 data from patients with data from their SPs.

Therefore, this study primarily aimed to evaluate the association between ECog-12 score and risk of clinical progression. In addition to the novel investigation of the relationship between the short-form ECog and clinical progression, our approach extends previous approaches[15] by including PTs who are MCI and dementia at baseline, in addition to CU. We defined clinical progression as either a change in a Clinical Dementia Scale Sum of Boxes (CDR-SB) score or a change in the clinician's assessment of diagnostic conversion.[19] Moreover, we compared the data from self- or SP-report ECog −12 to predict cognitive progression.

2 | METHODS

This was a cohort study aimed to determine the prognostic value of ECog-12 rated by both PTs and SPs in predicting clinical progression defined in the following ways (1) CDR-SB progression and (2) diagnostic conversion.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors conducted a literature review using traditional sources such as PubMed and Scopus. Most Everyday Cognition scale (ECog) studies used the original ECog version, which was cited properly.
2. **Interpretation**: Our study evaluated the ability of self and study partner 12-item ECog (ECog-12) to predict clinical progression defined by Clinical Dementia Rating Sum of Boxes (CDR-SB) worsening and diagnostic conversion. Findings suggested that higher ECog-12 scores are associated with an increased risk of clinical progression. Data obtained from study partners provided a higher prognostic value than that obtained from participants, especially in participants with dementia.
3. **Future directions**: The ECog-12, especially obtained from study partners, has the potential to identify older adults who are at risk for clinical progression. These data can be helpful in both research and clinical care settings. To ensure that the data apply to a broader population, future studies on the value of ECog-12 in the Alzheimer's Disease Neuroimaging Initiative 4 will help validate the results in diverse populations, including different ethnicities and varying levels of education.

2.1 | Subjects and study setting

Data used in this study were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2004 as a public–private partnership led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to validate biomarkers for clinical trials, specifically whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), biofluid-based biomarkers (genetics, cerebrospinal fluid [CSF], plasma), and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

The study included ADNI PTs from ADNI phase GO, 2, and 3 who had available PT and SP report baseline ECog scores and had at least two follow-up data points. At the baseline visit, ADNI site staff clinically diagnosed PTs with CU, MCI, or AD. In brief, the CU PTs had no memory complaints, and the neuropsychological and functional tests showed normal results. For MCI diagnosis, PTs who either self-reported memory complaints or had complaints reported by their SPs exhibited abnormal memory function, scoring below the education-adjusted cutoff on the Logical Memory II subscale from the Wechsler Memory Scale-Revised. However, their cognition and functional performance were preserved enough that they did not meet the criteria for AD. For early AD, PTs either self-reported memory complaints or had complaints reported by their SPs and had abnormal memory function based on scoring below the education-adjusted cutoff. Their clinical profile met the criteria for probable AD by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria. The Clinical Dementia Rating global score was 0.5 or 1. The age range of the PTs was 55 to 90 years. PTs who had major psychiatric and neurological diseases were excluded from the study. The complete inclusion and exclusion criteria can be downloaded from https://adni.loni.usc.edu/methods/documents/.

2.2 | Objectives

The primary objective was to evaluate the association between Ecog-12, which was obtained from self/PTs and SP, and time to clinical progression defined by CDR-SB progression. The secondary objective was to evaluate the association between Ecog-12, which was obtained from self/PTs and SP, and the time to diagnostic conversion.

2.3 | Procedure

During the baseline visit, PTs were required to complete the ECog-39 questionnaire. Their SPs were asked to respond to the same questionnaire. The clinicians evaluated the PTs and diagnosed them as having CU, MCI, or dementia during the same visit. The baseline characteristics were recorded, including age, sex, years of education, marital status, race, and apolipoprotein E (*APOE*) ε4 status.

All PTs were followed up on their cognitive status in clinics every 6 months in the first year of entry, and then they were followed up annually. The study clinician reviewed the PTs' clinical status and gave the PTs a diagnosis during every clinic visit.

2.3.1 | ECog-12

The ECog-12 score used in this study was obtained from the ECog-39 data, which consisted of 39 questions aimed at assessing PTs' everyday functional status. Questionnaires pertain to six specific cognitive domains, including memory, language, visuospatial function, planning, organization, and divided attention. The respondents are required to compare the functional status of PTs in the present to that of the past decade. They could reply to each question by rating scores from 1 to 4, with 1 indicating no change in ability over 10 years, 2 indicating occasionally performed the task worse, 3 indicating consistently performed a little worse on task than 10 years ago, and 4 indicating PTs perform the task much worse than 10 years ago. This questionnaire provides the option "don't know" if the respondent is unsure of a particular answer. The PTs and SPs were asked to complete the ECog-39 separately. Two items per domain were selected from ECog-39 to obtain ECog-12 data, based on a previous study.[13] The questions of ECog-12 are shown in Supplementary Material S1 in supporting information.

In this study, the ECog-12 was calculated using both continuous average score and categorized grouping based on item-level response. We calculated the average ECog-12 score by dividing the sum of the

total score by the number of items answered for the continuous system. Items with no response or "don't know" option were excluded. Scoring ranged from 1 to 4. For the categorized grouping, the PTs would be defined as having any consistent subjective cognitive decline (any consistent SCD) in case any item of ECog-12 was rated at least 3.[15]

2.4 | Clinical progression

To define clinical progression in this study, we used two definitions, including CDR-SB progression and diagnostic conversion.

2.4.1 | For CDR-SB progression

For CDR-SB progression, a previous study[19] showed that even small changes in CDR-SB scores can indicate significant clinical progression that notably impacts the well-being of the PT and/or their partner. The criteria for CDR-SB progression are shown as follows:

1. MCI and normal cognitive patient: the CDR-SB score worsens by ≥ 1 point from the baseline at any of the subsequent visits.
2. Dementia patient: the CDR-SB score worsens by ≥ 2 points from the baseline at any of the subsequent visits.

2.4.2 | For diagnostic conversion

1. PTs were diagnosed as having CU at baseline visits, and their diagnosis was changed to MCI or dementia at the subsequent visits.
2. PTs who were diagnosed as MCI at baseline visit but at subsequent visits meeting the criteria for dementia.

3 | STATISTICAL ANALYSIS

We used descriptive statistics to describe the demographic and clinical characteristics of the PTs divided based on progression by CDR-SB criteria and presented the results as percentage, mean, and standard deviation (SD). If the data distribution was not normal, median and interquartile range (IQR) were used. Characteristics between groups were compared using chi-squared, one-way analysis of variance (ANOVA), or Kruskal–Wallis ANOVA. A Weibull time-to-event regression model was used to test associations between ECog-12 and disease progression, which were defined by both CDR-SB progression and diagnostic conversion. The results were shown as hazard ratios and included 95% confidence intervals (CIs). For the survival analysis, we included all the duration times from the ADNI cohort data.

4 | RESULTS

4.1 | PTs

A total of 1322 PTs had baseline self- and study-partner ECog data and baseline and at least two data time points for CDR data. The median follow-up time was 1197 days (IQR 725, 1849). During the baseline visit, 40.6% of the PTs were diagnosed as CU, 46.2% as having MCI, and 13.2% as having dementia. Among 1322 PTs, 487 (36%) had clinical progression based on CDR-SB worsening criteria.

For characteristics based on diagnostic conversion, a total of 1112 PTs had baseline ECog-12 data and had at least two data time points for clinical diagnosis data. At the baseline visit, out of 1112 PTs, 510 were CU, while 602 had MCI. Out of the total PTs, 234 (21%) were defined as having diagnostic conversion, including 76 CU PTs who progressed to MCI and 158 MCI who progressed to dementia. Table 1 shows a comparison of baseline characteristics between PT groups divided based on both CDR-SB progression and diagnostic conversion.

4.2 | Association between ECog-12 score and CDR-SB progression

4.2.1 | Average ECog-12 score

According to univariate analysis, higher (worse) ECog-12 scores from self/PTs were associated with an increased risk of CDR-SB worsening in total PTs with hazard ratios 2.1 (95% CI: 1.83–2.41, p value: < 0.001). In subgroup analyses in CU and MCI PTs, higher self/PTs reported ECog-12 scores were also associated with increased risk of CDR-SB worsening with hazard ratios 3.53 (95% CI: 2.22–5.62, p value: < 0.001) and 1.3 (95% CI: 1.08–1.58, p value: 0.006), respectively. Conversely, higher ECog was associated with slower CDR-SB progression in dementia PTs, but the result was not statistically significant, with a hazard ratio of 0.88 (0.61–1.26, p value: 0.48). Higher ECog-12 from the SPs was associated with increased risk of CDR-SB progression in all PT groups, including CU, MCI, dementia, and total PTs with hazard ratios 8.86 (95% CI: 5.45–14.39, p value: < 0.001), 2.78 (95% CI: 2.36–3.28, p value: < 0.001), 1.45 (95% CI: 1.07–1.97, p value: 0.017), and 3.41 (95% CI: 3.05–3.82, p value: < 0.001), respectively. Additionally, we evaluated the risk of progression, adjusting for covariates, and the results are shown in Tables 2 and 3.

4.2.2 | Categorization of ECog-12

The results for the categorical ECog scoring were similar to results using the average ECog score as a continuous measure; the results are shown in Supplementary Materials S2 and S3 in supporting information.

4.3 | Association between ECog-12 scale and diagnostic conversion

4.3.1 | Average ECog-12 score

Higher average self-report ECog-12 were associated with increased risk of diagnostic conversion from CU to MCI and from MCI to demen-

TABLE 1 Baseline characteristics of PTs divided groups based on CDR-SB progression and diagnostic conversion.

	CDR progression									Diagnostic conversion					
	CU			MCI			Dementia			CU			MCI		
Baseline Dx Characteristics	Non-progress $N = 447$	Progress $N = 90$	p	non-progress $N = 295$	Progress $N = 316$	p	Non-progress $N = 93$	Progress $N = 81$	p	Non-progress $N = 434$	Progress $N = 76$	p	Non-progress $N = 444$	Progress $N = 158$	p
Age; median (IQR)	70 (67, 76)	72 (69, 77)	0.004	71 (65, 76)	74 (68, 78)	<0.001	74 (69, 79)	76 (71, 80)	0.14	70 (67, 76)	73 (70, 79)	<0.001	72 (66, 72)	74 (69, 78)	0.011
Male; *n* (%)	176 (39)	42 (47)	0.2	157 (53)	187 (59)	0.14	54 (58)	53 (65)	0.3	174 (40)	40 (53)	0.041	249 (56)	89 (56)	>0.9
Edu years; median (IQR)	17 (16, 18)	16 (14, 18)	0.2	16 (15, 18)	16 (14, 18)	0.06	16 (14, 18)	16 (14, 18)	0.4	17 (16, 18)	16 (14, 18)	0.2	16 (14, 18)	16 (14, 18)	0.5
Married; *n* (%)	313 (70)	67 (74)	0.4	221 (75)	249 (79)	0.3	81 (87)	72 (89)	0.7	311 (72)	56 (74)	0.7	339 (76)	122 (77)	0.8
White; *n* (%)	377 (84)	85 (94)	0.01	265 (90)	303 (96)	0.003	84 (90)	73 (90)	>0.9	384 (88)	66 (87)	0.7	407 (92)	152 (96)	0.057
APOE ε4; *n* (%)			0.4			0.001			0.15			0.4			<0.001
Negative	290 (69)	55 (62)		162 (61)	140 (46)		21 (24)	29 (37)		289 (68)	48 (64)		244 (59)	53 (35)	
Positive 1 allele	119 (28)	31 (35)		85 (32)	124 (41)		46 (53)	31 (40)		121 (29)	23 (31)		133 (32)	76 (50)	
Positive 2 allele	13 (3.1)	3 (3.4)		19 (7.1)	39 (13)		19 (22)	18 (23)		12 (2.8)	4 (5.3)		34 (8.3)	24 (16)	
Baseline CDR-SB scores; median (IQR)	0 (0, 0)	0 (0, 0)		1 (0.5, 2)	1.5 (1, 2)	<0.001	4.5 (3.5, 5)	4.5 (3, 5)	0.9	0 (0, 0)	0 (0, 0)		1 (0.5, 1.5)	2 (1.5, 2.5)	<0.001
Surv time days; median (IQR)	1461 (754, 1991)	1454 (690, 2064)	0.15	1141 (693, 1832)	591 (346, 1098)	<0.001	371 (346, 386)	367 (196, 503)	0.6	1464 (777, 2035)	905 (690, 1949)	0.008	1226 (727, 1851)	749 (384, 1454)	<0.001
Average ECog-12 PT; median (IQR)	1.25 (1.08, 1.42)	1.42 (1.18, 1.75)	<0.001	1.58 (1.33, 2)	1.67 (1.42, 2.08)	0.072	1.75 (1.45, 2.25)	1.75 (1.5, 2.25)	0.6	1.25 (1.08, 1.49)	1.42(1.25, 1.75)	<0.001	1.67 (1.33, 2)	1.71 (1.42, 2.09)	0.1
Average ECog-12 SP; median (IQR)	1.08 (1, 1.25)	1.25 (1.02, 1.49)	<0.001	1.42 (1.17, 1.75)	1.8 (1.42, 2.29)	<0.001	2.67 (2.09, 3.17)	2.83 (2.42, 3.33)	0.07	1.08 (1, 1.25)	1.22 (1, 1.42)	<0.001	1.5 (1.17, 1.92)	1.91 (1.55, 2.57)	<0.001
"Any consistent SCD" categorization of ECog-12 for PT response; *n* (%)	139 (31)	47 (52)	<0.001	202 (68)	237 (75)	0.07	71 (76)	61 (75)	0.9	138 (32)	36 (47)	0.008	308 (69)	123 (78)	0.042
"Any consistent SCD" categorization of ECog-12 for SP response; *n* (%)	43 (9.7)	33 (37)	<0.001	148 (50)	233 (74)	<0.001	87 (94)	78 (96)	0.5	48 (11)	24 (32)	<0.001	245 (55)	132 (84)	<0.001

Note: p values represent differences between diagnostic groups based on the Kruskal–Wallis rank-sum test for continuous variables or the chi-square test for categorical variables. p values < 0.05 indicate significant differences.
Abbreviations: *APOE*, apolipoprotein E; CDR-SB, Clinical Dementia Rating Sum of Boxes; CU, cognitively unimpaired; Dx, diagnosis; ECog-12, 12-item Everyday Cognition scale; Edu, education; IQR, interquartile range; MCI, mild cognitive impairment; PT, self/participant; SCD, subjective cognitive decline; SP, study partner; Surv, survival.

TABLE 2 Association between an average ECog-12 from self-PTs and CDR-SB progression.

	CU ($n = 511$)		MCI ($n = 566$)		Dementia ($n = 164$)		Total ($n = 1237$)	
	HRs (95% CI)	*p* value	HRs (95% CI)	*p* value	HRs (95% CI)	*p* value	HRs (95% CI)	*p* value
ECog-12 self-PT	3.34 (2.04–5.46)	<0.001	1.44 (1.18–1.75)	<0.001	0.93 (0.63–1.37)	0.72	1.44 (1.23–1.69)	<0.001
Age	1.04 (1.001–1.08)	0.068	1.05 (1.03–1.07)	<0.001	0.99 (0.96–1.03)	0.81	1.04 (1.03–1.06)	<0.001
Male sex	1.22 (0.78–1.91)	0.542	1.14 (0.89–1.48)	0.302	1.17 (0.71–1.91)	0.54	1.16 (0.95–1.42)	0.14
Education years	0.94 (0.87–1.02)	0.261	0.94 (0.9–0.99)	0.009	0.97 (0.88–1.06)	0.49	0.94 (0.9–0.97)	<0.001
APOE ε4								
1 allele	1.24 (0.78–1.95)	0.255	1.75 (1.37–2.23)	<0.001	0.88 (0.52–1.5)	0.64	1.52 (1.24–1.85)	<0.001
2 alleles	2.31 (0.69–7.68)	0.664	2.55 (1.77–3.66)	<0.001	0.86 (0.43–1.71)	0.67	2.13 (1.58–2.87)	<0.001
White	2.12 (0.77–5.79)	0.124	2.12 (1.15–3.88)	0.016	0.65 (0.29–1.45)	0.31	1.68 (1.1–2.59)	0.018
Married	0.88 (0.53–1.48)	0.374	1.25 (0.93–1.67)	0.132	1.29 (0.56–3.01)	0.55	1.31 (1.04–1.66)	0.024
Baseline dx.								
MCI							3.47 (2.71–4.46)	<0.001
Dementia							6.17 (4.35–8.76)	<0.001

Abbreviations: *APOE*, apolipoprotein E; Baseline dx., baseline diagnosis; CDR-SB, Clinical Dementia Rating Sum of Boxes; CI, confidence interval; CU, cognitively unimpaired; ECog-12, 12-item Everyday Cognition scale; HR, hazard ratio; MCI, mild cognitive impairment.

TABLE 3 Association between an average ECog-12 from SPs and CDR-SB progression.

	CU ($n = 508$)		MCI ($n = 565$)		Dementia ($n = 164$)		Total ($n = 1237$)	
	HRs (95% CI)	*p* value	HRs (95% CI)	*p* value	HRs (95% CI)	*p* value	HRs (95% CI)	*p* value
ECog-12 SPs	9.61 (5.72–16.15)	<0.001	2.82 (2.36–3.36)	<0.001	1.82 (1.3–2.57)	0.0004	2.8 (2.39–3.27)	<0.001
Age	1.04 (1.001–1.08)	0.044	1.05 (1.03–1.07)	<0.001	0.99 (0.96–1.03)	0.642	1.04 (1.03–1.05)	<0.001
Male sex	1.21 (0.77–1.91)	0.404	1.11 (0.86–1.44)	0.406	1.46 (0.87–2.46)	0.152	1.2 (0.98–1.46)	0.0821
Education years	0.94 (0.87–1.02)	0.159	0.96 (0.92–1.01)	0.098	0.98 (0.89–1.08)	0.698	0.95 (0.92–0.99)	0.0079
APOE ε4								
1 allele	1.28 (0.82–2.01)	0.281	1.63 (1.27–2.08)	<0.001	0.72 (0.42–1.24)	0.238	1.42 (1.16–1.73)	<0.001
2 alleles	2.73 (0.84–8.93)	0.096	2.3 (1.59–3.33)	<0.001	0.7 (0.35–1.38)	0.302	1.95 (1.44–2.64)	<0.001
White	2.1 (0.77–5.75)	0.151	2.02 (1.1–3.7)	0.023	0.47 (0.2–1.11)	0.079	1.55 (1.01–2.38)	0.0468
Married	0.86 (0.51–1.41)	0.521	1.15 (0.85–1.54)	0.367	1.41 (0.61–3.27)	0.422	1.2 (0.95–1.52)	0.1346
Baseline dx.								
MCI							2.45 (1.89–3.18)	<0.001
Dementia							1.66 (1.09–2.52)	<0.018

Abbreviations: *APOE*, apolipoprotein E; Baseline dx., baseline diagnosis; CDR-SB, Clinical Dementia Rating Sum of Boxes; CI, confidence interval; CU, cognitively unimpaired; ECog-12, 12-item Everyday Cognition scale; HRs, hazard ratios; MCI, mild cognitive impairment; PT, participant; SP, study partner.

tia with hazard ratios 3.4 (95% CI: 2.03–5.68, *p* value: < 0.001) and 1.5 (95% CI: 1.15–1.95, *p* value: 0.0027), respectively. Moreover, higher ECog-12 scores from SPs were associated with increased risk of diagnostic conversion from CU to MCI and from MCI to dementia with hazard ratios 5.64 (95% CI: 3.19–9.97, *p* value: < 0.001) and 3.19 (95% CI: 2.57–3.95, *p* value: < 0.001), respectively. Additionally, we evaluated the risk of progression with covariates adjustment; the results are shown in Tables 4 and 5. After adjusting for covariates, higher average ECog-12 scores from self/PTs and SPs increased the risk of diagnostic conversion in CU and MCI PTs.

4.3.2 | Categorization of ECog-12

The association between any consistent SCD categorization of ECog-12 and diagnostic conversion was conducted. The results for the

TABLE 4 Association between continuous average ECog-12 from self-PTs and diagnostic conversion.

	CU ($n = 497$)		MCI ($n = 560$)		Total ($n = 1058$)	
	HRs (95% CI)	*p* value	HRs (95% CI)	*p* value	HRs (95% CI)	*p* value
ECog-12 self/PT	3.01(1.72–5.29)	<0.001	1.61(1.23–2.1)	<0.001	1.72 (1.36–2.19)	<0.001
Age	1.09(1.05–1.14)	<0.001	1.06 (1.03–1.08)	<0.001	1.06 (1.04–1.08)	<0.001
Male sex	1.29(0.79–2.09)	0.32	0.87 (0.61–1.24)	0.439	1.04 (0.78–1.39)	0.781
Education years	0.91(0.83-1)	0.054	0.98 (0.92-1.04)	0.48	0.95 (0.91-1.0)	0.073
*APOE ε*4						
1 allele	1.24(0.74–2.07)	0.412	3.01 (2.1–4.31)	<0.001	2.18 (1.64–2.89)	<0.001
2 alleles	1.84(0.65–5.22)	0.251	4.07 (2.47–6.73)	<0.001	3.28 (2.13–5.05)	<0.001
White	0.47(0.23–0.96)	0.037	2.3 (0.94–5.63)	0.071	1.11 (0.64–1.91)	0.707
Married	1.27(0.74–2.2)	0.384	1.44 (0.96–2.16)	0.078	1.32 (0.95–1.82)	0.093
Baseline dx.					–	–
MCI					1.43 (1.06–1.93)	0.021

Abbreviations: *APOE*, apolipoprotein E; Baseline dx., baseline diagnosis; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; CI, confidence interval; CU, cognitively unimpaired; ECog-12, 12-item Everyday Cognition scale; HRs, hazard ratios; MCI, mild cognitive impairment; PT, participant.

TABLE 5 Association between an average ECog-12 from SPs and diagnostic conversion.

	CU ($n = 494$)		MCI ($n = 560$)		Total ($n = 1054$)	
	HRs (95% CI)	*p* value	HRs (95% CI)	*p* value	HRs (95% CI)	*p* value
ECog-12 SPs	6.24(3.37–11.54)	<0.001	3.07 (2.45–3.85)	<0.001	3.21 (2.6–3.96)	<0.001
Age	1.1(1.06–1.14)	<0.001	1.06 (1.04–1.09)	<0.001	1.07 (1.05–1.09)	<0.001
Male sex	1.21(0.74–1.96)	0.46	0.76 (0.53–1.09)	0.14	0.96 (0.72–1.28)	0.78
Education years	0.89(0.81–0.98)	0.022	1.002 (0.94–1.07)	0.956	0.97 (0.92–1.02)	0.28
*APOE ε*4			–			–
1 allele	1.26(0.76–2.11)	0.377	2.93 (2.04–4.2)	<0.001	2.13 (1.6–2.83)	<0.001
2 alleles	3.4(1.2–9.66)	0.023	3.52 (2.06–6)	<0.001	2.91 (1.85–4.57)	<0.001
White	0.43(0.21–0.88)	0.019	2.16 (0.88–5.31)	0.093	1.01 (0.59–1.74)	0.97
Married	1.0001(0.58–1.72)	0.99	1.42 (0.93–2.16)	0.104	1.24 (0.89–1.73)	0.2
Baseline dx.					–	–
MCI					0.9 (0.65–1.25)	0.52

Abbreviations: *APOE*, apolipoprotein E; Baseline dx., baseline diagnosis; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; CI, confidence interval; CU, cognitively unimpaired; ECog-12, 12-item Everyday Cognition scale; HRs, hazard ratios; MCI, mild cognitive impairment; SP, study partner.

categorical ECog scoring were similar to results using the average ECog score as a continuous measure, and the results are shown in Supplementary Materials S4 and S5 in supporting information.

5 | DISCUSSION

Based on the current study, the key findings are as follows: (1) Two self-report ECog-12 scoring outputs (average score and categorical score based on item-level responses) were associated with increased risk of CDR-SB worsening in both CU and MCI PTs. However, self-report ECog-12 did not show any association with CDR-SB worsening in people diagnosed with dementia. (2) ECog-12 rated by SPs was associated with a significantly increased risk of CDR-SB worsening in all diagnostic groups. (3) Average SP-report ECog-12 score showed the lowest hazard ratios for association with worsening CDR-SB in dementia compared to CU and MCI PTs, but "any consistent SCD" categorized ECog-12 by SPs provided higher HRs in dementia PTs compared to CU and MCI PTs. (4) ECog-12 data obtained from both raters increased diagnostic conversion risk from CU to MCI and from MCI to dementia. (5) The ECog-12 assessments completed by PTs indicated a higher risk of progression from CU to MCI compared to the risk of progression from MCI to dementia. Taken together, these results support the use of the ECog-12 for identifying older adults at risk for cognitive decline and clinical progression in ADNI4 and other studies. Our results provide novel information about the specific scoring outputs and rater type (PT vs. SP) of ECog-12 that should be used to facilitate screening, prioritization, and longitudinal

monitoring of PTs for AD clinical studies, clinical trials, and in health-care settings.

For predicting the decline of CDR-SB, our study demonstrated subjective cognitive decline defined by the continuous average ECog-12 scale could predict future clinical decline defined by CDR-SB progression. However, results obtained from the SPs, which provided higher HRs in all PT groups, had a greater power to predict CDR progression. Among CU and MCI PTs, the average ECog-12 from self/PTs was significantly associated with CDR-SB scores worsening, but in the dementia PTs, the average ECog-12 rated by self/PTs could not significantly predict progression (Table 2). The average Ecog-12 rating from SPs was found to significantly increase the risk of CDR-SB progression in all diagnostic groups.

For predicting diagnostic conversion, the continuous average ECog-12 score obtained from the SPs showed an increased risk of diagnostic conversion from CU to MCI and from MCI to dementia, with higher hazard ratios (adjusted hazard ratios: 6.24 and 3.07, respectively) than the average ECog-12 obtained from the PTs themselves (adjusted hazard ratios: 3.01, 1.61, respectively). Self-reported ECog-12 did not accurately predict diagnostic conversion or CDR-SB score deterioration in PTs with dementia. This is likely due to the loss of awareness about one's own cognitive and functional ability in dementia (anosognosia), which has previously been shown to limit the accuracy of subjective reports of decline in individuals with dementia.[20,21] Another contributing factor may be that cognitively impaired patients deny their impairment because loss of independence is a stigma for them.[22] These results were similar to the results from a prior study that used the original 39-item ECog.[11] The prior study revealed that ECog-39 from self/PTs and SPs was associated with diagnostic conversion from CU to MCI, but the ECog-39 from self/PTs was not associated with conversion from MCI to dementia. Nevertheless, the short version of the ECog scale rated by self/PTs may be better than the self-reported original version at predicting diagnostic conversion because an increasing score of self-reported ECog-12 is associated with conversion from MCI to dementia.

Considering a continuous average ECog-12 rated by self/PTs, increasing scores showed a greater risk of diagnostic conversion from CU to MCI than from MCI to dementia. Furthermore, PTs with CU showed the highest adjusted HRs for continuous average ECog-12 and CDR-SB progression, whereas the MCI PTs provided lower hazard ratio, and the association was insignificant for dementia PTs. These can be explained by the fact that healthy individuals still have a good memory and enough insight to compare their current and prior functions, so their answers to the questionnaire might be very reliable. While MCI PTs have some degree of cognitive impairment, such as a memory problem, they might not remember every detail of their functioning, and self-reporting ECog-12 would be the least reliable when PTs have dementia.

In terms of the relative value of two different ECog scoring outputs (continuous averaged score and categorical ECog score), we found that both the averaged and categorized scoring systems of ECog-12 produced similar results. The categorical SP-report ECog score identifying those with consistent SCD in any domain showed a higher associative risk for diagnostic conversion than consistent SCD from self-report ECog score. Any consistent SCD categorized by ECog-12 from self and SP was associated with conversion from CU to MCI with adjusted hazard ratio 1.81 (p value of 0.01) and 2.88 (p value < 0.001) and from MCI to dementia 1.6 (p value 0.02) and 4.17 (p value < 0.001), respectively. These results were consistent with the results of the previous longitudinal study by van Harten et al., which reported any consistent SCD defined by informant/SP-based ECog-12 was associated with an increased risk of progression to MCI.[15] The current study extends these findings. Our results found that any consistent SCD ECog-12 predicted not only the incidence of MCI but also the incidence of dementia. Moreover, it was a prognostic risk for a meaningful minimally cognitive progression. This is very useful because the categorized grouping of ECog-12 is very simple. In case there is not much time in real practice, this is a convenient tool to evaluate which patients are at risk for progression.

There are several limitations in this study. First, the ECog-12 scale in this study was derived from the original version of ECog.[7] Therefore, the ECog-12, derived from the updated version of ECog (ECog-II),[23] should be evaluated in further study. Second, we evaluated and showed the results from the baseline ECog-12, so that further studies may evaluate the association between longitudinal ECog-12 and the risk of clinical progression. Third, the ADNI sample lacks ethnocultural and educational diversity, which may limit the generalizability and external validity of the results. ADNI4 aims to enroll at least 50% of new PTs from underrepresented populations.[24] Therefore, future studies of the value of ECog-12 in ADNI4 will enable us to validate the results in diverse populations.

In conclusion, our results support the ability of a short subjective decline measure, ECog-12, to identify those at risk for clinical progression. Because these patients may be candidates for AD-modifying medication, ECog-12 could be used to prioritize which patients would benefit most from therapeutic intervention. Moreover, the ECog-12 could be used for future clinical applications in health-care settings, such as routine check-ups of older adults. Data obtained from SPs provided a higher prognostic value than those rated by self/PTs, especially in PTs with dementia. This finding highlights the importance of obtaining data on everyday function from SPs of older adults with cognitive impairment in addition to information from the individuals themselves.

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CONSENT STATEMENT

This is a secondary analysis of data provided by the Alzheimer's Disease Neuroimaging Initiative (ADNI), a multicenter study. Each study site got approval for the ADNI protocol from its local institutional review board. All participants have given written informed consent.

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SUPPORTING INFORMATION

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

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