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FEATURED ARTICLE

Clinical meaningfulness of subtle cognitive decline on longitudinal testing in preclinical AD

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Abstract

Introduction: Demonstrating the "clinical meaningfulness" of slowing early cognitive decline in clinically normal (CN) older adults with elevated amyloid-β (Aβ+) is critical for Alzheimer's disease secondary prevention trials and for understanding early cognitive progression.

Methods: Cox regression analyses were used to determine whether 3-year slopes on the preclinical Alzheimer's cognitive composite predicted MCI diagnosis and global Clinical Dementia Rating>0 in 267 Aβ+ CN individuals participating in the Harvard Aging Brain Study, Australian Imaging, Biomarker and Lifestyle Study, and Alzheimer's Disease Neuroimaging Initiative.

Results: Steeper preclinical Alzheimer's cognitive composite decline over 3 years was associated with increased risk for MCI diagnosis and global Clinical Dementia Rating>0 in the following years across all cohorts. Hazard ratios using meta-analytic estimates were 5.47 (95% CI: 3.25–9.18) for MCI diagnosis and 4.49 (95% CI: 2.84–7.09) for Clinical Dementia Rating>0 in those with subtle decline (>−.14 to −.26 preclinical Alzheimer's cognitive composite standard deviations/year) on longitudinal cognitive testing.

Discussion: Early "subtle cognitive decline" among Aβ+ CN on a sensitive cognitive composite demonstrably increases risk for imminent clinical disease progression and functional impairment.

vided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

KEYWORDS

Alzheimer's disease, Amyloid, Clinical meaningfulness, Clinical trials methodology, Outcome research, Preclinical, Secondary prevention

1 | INTRODUCTION

The Alzheimer's disease (AD) continuum involves a protracted asymptomatic phase starting with the accumulation of amyloid β (Aβ) plaques and neurofibrillary tangles, followed by subtle yet increasingly persistent cognitive decline, functional impairment, and ultimately the dementia syndrome.[1] At the symptomatic stages of disease, cognitive and functional decline tend to occur in unison[2] and regulators have historically required co-primary outcomes of cognition and function to ensure the clinical meaningfulness of the cognitive effect on functional progression. Advances in our ability to visualize AD neuropathology *in vivo* have provided the opportunity for early detection during the preclinical phase and have spurred secondary prevention trials to minimize cognitive decline in asymptomatic but at-risk individuals. However, co-primary outcomes are presumed to be challenging for secondary prevention trials because participants lack cognitive or functional impairment at enrollment and are also unlikely to develop significant functional impairment in the timeframes over which such trials are conducted (i.e., 3–5 years).[3,4] Recent regulatory guidance for clinical trials in early AD emphasized the importance of establishing the meaningfulness of clinical outcomes.[3]

In the absence of functional impairment, one means of inferring clinical meaningfulness at the preclinical stage may be to determine whether subtle longitudinal cognitive decline predicts clinical progression beyond the duration of a trial. The recent National Institute of Aging and Alzheimer's Association research framework describes a transitional stage (e.g., "stage 2") along the AD trajectory, in which individuals may exhibit "subtle cognitive decline" on longitudinal cognitive testing as they move from asymptomatic to mildly symptomatic.[5] Quantification of "subtle cognitive decline" remains to be determined. In the same vein, FDA draft guidance offers the possibility of conducting studies long enough to follow individuals over the course of stage 2 until they show functional impairment.[3] However, disease progression is protracted, with a recent study showing that only 20% of stage 1/2 participants progress to MCI/dementia diagnosis after 8 years.[6] Thus, an alternative, more efficient approach is to determine the magnitude of cognitive decline on longitudinal testing that may serve as a proxy for future functional impairment. If a treatment slows this cognitive decline and reduces the likelihood of clinical progression, this would provide evidence for a clinically meaningful therapeutic response. Multiple observational studies have shown that, at the group level, abnormal levels of Aβ (measured with molecular neuroimaging or cerebrospinal fluid) are independently associated with cognitive decline and functional progression[7–9] However, no studies to date have directly quantified the extent of subtle decline measured on longitudinal cognitive testing that is representative of clinically meaningful outcomes (e.g., MCI diagnosis) in biomarker-confirmed asymptomatic AD.[5]

Here, we determine the extent of cognitive decline on longitudinal testing among Aβ+ clinically normal (CN) older adults that predicts risk of subsequent diagnosis of MCI or AD dementia, and separately, progression to a global Clinical Dementia Rating (CDR) score greater than 0 after 3 years. To increase the generalizability of risk estimates in relation to cognitive slopes, data were aggregated from participants enrolled in three independent observational studies. To increase the applicability of results, we used the preclinical Alzheimer's cognitive composite (PACC5), an outcome currently being used in both pharmacological and nonpharmacological secondary prevention trials. We also assessed whether more subtle functional changes on the CDR Sum of Boxes were associated with concurrent cognitive decline before a diagnosis of MCI. Additional analyses in which we further queried these models were conducted within the Harvard Aging Brain Study (HABS) (e.g., reducing the time window of cognitive decline and examining individual cognitive measures).

2 | METHODS

2.1 | Sample characteristics

Participants included individuals from the HABS, the Australian Imaging, Biomarker and Lifestyle Study (AIBL), and the AD Neuroimaging Initiative (ADNI).[10–12] All participants were classified as CN at the baseline using previously reported study-specific criteria.[10–12] Participants were restricted to those with at least two follow-up neuropsychological assessments after baseline (anchored to year of first Aβ PET scan). Primary analyses focused on a subset of participants classified as having high Aβ (Table 1; n = 267). Rates of cognitive and functional decline in the Aβ-negative participants (Aβ−) were computed as a comparison with the Aβ-positive group (Aβ+) (Supplementary Table 1; n = 641).

2.2 | Cognitive outcome: The PACC

Use of both the PACC[13,14] and the PACC5 (PACC + semantic fluency), has previously been described in detail in each of these cohorts.[15] The more sensitive PACC5 is used here but referred to as PACC throughout for clarity.[13] In the HABS, the PACC includes Logical Memory Delayed Recall, the Free and Cued Selective Reminding Test, the Mini–Mental Status Examination (MMSE), the Digit Symbol Substitution Test, and Category Fluency to animals, vegetables, and fruits. The PACC

similarly includes the MMSE and Logical Memory Delayed Recall for the AIBL and ADNI. However, differences in cognitive test batteries across cohorts required substitution with measures assessing the same cognitive process. The PACC has exhibited relative concordance of the baseline and slopes among these cohorts[15] despite differences in measures. The PACC was computed separately in each cohort by averaging the z-transformed scores for each measure derived from cohort-specific sample means and standard deviations. The ADNI and HABS participants completed the PACC annually compared with 18-month intervals in the AIBL.

2.3 | Clinical progression outcomes: Diagnosis of MCI or AD dementia and Clinical Dementia Rating

Measures of clinical disease progression included a diagnosis of MCI or AD dementia as well as a global CDR score and CDR Sum of Boxes. The CDR was included as a disease progression outcome to ensure that the predictive relationship between PACC decline and MCI diagnosis was not driven by overlap in cognitive measures used both in the PACC and in making a study diagnosis of MCI.

In the HABS, the CDR is completed by neuropsychologists and psychiatrists and rated independently from other cognitive testing results. All CDR raters are blinded to participant biomarker status. Quarterly consensus meetings are conducted with 6 or more clinicians as part of a multidisciplinary team. Participants are brought to consensus if they have a global CDR score of 0.5 and/or performance falls 1.5 standard deviations below the sample mean on any individual domain-specific composite score.[16] Diagnoses are determined by clinical consensus after reviewing the CDR, cognitive data, and relevant medications/medical history.

In the AIBL, the CDR is completed by neuropsychologists and is blinded from the other cognitive testing results. Participants are classified as normal or MCI at each visit by consensus of geriatric psychiatrists, behavioral neurologists, and neuropsychologists blinded to Aβ status.[17] MCI subjects met Petersen criteria[18] including subjective and objective cognitive difficulties in the absence of significant functional impairment.

In the ADNI, the CDR rater is ideally not involved with any other cognitive or functional assessments. Rating is not limited to MD/PhD level raters. Participants are diagnosed with MCI on the basis of the presence of a memory complaint, an MMSE score of 24-30 and a global CDR score of 0.5 with a mandatory box score of 0.5 in the memory domain.[19] Diagnosis is made by the site principal investigator or designee and includes review of the larger cognitive test battery, functional measures, and medical issues.

2.4 | PET data acquisition and analysis

Both the HABS and AIBL use the ^{11}C-Pittsburgh Compound-B (PiB) Aβ-PET tracer, whereas the ADNI uses the ^{18}F-AV45 (florbetapir) Aβ-PET tracer. The PET acquisition parameters for each study have been published previously.[11,12,20–22] In brief, the ADNI and AIBL's PET acquisition time was 50–70 minutes after injection (http://adni.loni.usc.edu/), whereas for the HABS, PiB-PET data were collected 40–60 minutes after injection. Cerebellar gray matter was used as the reference region across studies. The HABS used a distribution value ratio, whereas the ADNI and AIBL used standardized uptake value ratios. We used previously published study-specific regional summary measures and cutoffs to classify individuals as Aβ+. Cutoffs included were as follows: HABS, >1.2 distribution value ratio;[22] AIBL, >1.40 standardized uptake value ratio,[12] ADNI, >1.11 standardized uptake value ratio.[21]

RESEARCH IN CONTEXT

1. Systematic review: The extant literature was reviewed using traditional methods. Multiple observational studies have shown that abnormal amyloid-β (Aβ) among asymptomatic older adults is associated with 1) cognitive decline and 2) functional progression longitudinally. However, the predictive relationship between very subtle cognitive decline and imminent clinical disease progression (i.e., diagnosis of MCI, Clinical Dementia Rating>0) in asymptomatic Aβ+ individuals is unclear.
2. Interpretation: Results across three large observational cohorts of asymptomatic Aβ+ older adults indicate that subtle 3-year cognitive decline (>−0.14 to −0.25 standard deviations) on the preclinical Alzheimer's cognitive composite was associated with a 5.47 increase in hazards for MCI diagnosis and a 4.49 increase in hazard for Clinical Dementia Rating>0.
3. Future directions: These findings have important implications for the design and interpretation of results of secondary prevention trials and for interpreting the meaningfulness of subtle cognitive decline in an Aβ+ unimpaired older adult to their risk for Alzheimer's disease progression.

2.5 | Statistical analyses

Statistical analyses were completed using R version 3.5.0 (packages: survival, ggsurvfit and lme4, pROC, metafor). Differences in demographics across cohorts and Aβ+/− groups within cohort were examined using a series of one-way ANOVAs for continuous variables and χ^2 tests for dichotomous variables.

Ordinary least-squares regression was used to derive individual PACC slopes and intercepts for each participant by cohort over a three-year period (Fig. 1). Computation of slopes was restricted to the first 3 years after Aβ PET scans to correspond with the average length of a clinical trial. For studies with annual follow-up (HABS/ADNI), 4 time points were used in contrast with 3 time points in the AIBL (18-month

TABLE 1 Baseline demographic characteristics of Aβ+ clinically normal participants by cohort

Variable	HABS	AIBL	ADNI	Significance testing (F, χ^2)	*P*
N	73	84	110		
Age, mean, sd	74.80 (6.09)	74.96 (6.92)	76.16 (6.15)	2.78	.065
Female sex, %	61	45*	64	6.93	.031
Education, mean, sd	16.15 (2.93)	13.51 (2.42)*	16.05 (1.10)	14.11	<.0001
MMSE score, median, IQR	29 (28–30)	29 (27–30)	29 (28–30)	0.08	.924
PACC, mean, sd	0.02 (0.68)	−0.14 (0.64)	−0.09 (0.60)	0.48	.620
Overall Follow-up, mean, sd, range	4.35 (1.55) [1.0–6.71]	4.89 (1.28)* [2.77–6.98]	3.96 (1.01)* [1.96–5.24]	12.94	<.0001
Progressors to MCI at year 3+, %	20 (12/58)	26 (12/45)	32 (19/59)	1.16	.560
Progressors to CDR>0 at year 3+, %	23 (10/44)	31 (14/45)	39 (23/59)	1.62	.444

NOTE. Means and standard deviations reported unless otherwise noted.
Abbreviations: HABS, Harvard Aging Brain Study; AIBL, Australian Biomarker and Lifestyle Study; ADNI, Alzheimer's Disease Neuroimaging Initiative; MMSE, Mini–Mental State Examination; PACC, preclinical Alzheimer's cognitive composite (5-component); MCI, mild cognitive impairment; sd, standard deviation; CDR, Clinical Dementia Rating; IQR, inter-quartile range.
*Indicates the cohort which was significantly different from the others using Tukey post-hoc comparisons.

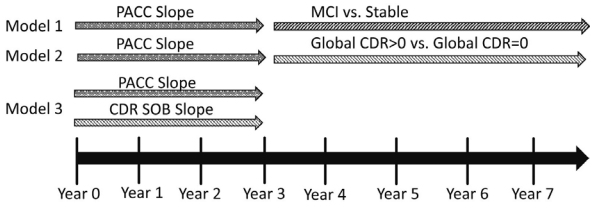

FIGURE 1 Schematic of study analyses. Note. Models 1 and 2 examine the predictive relationship between subtle decline measured on longitudinal cognitive testing (PACC slope) among normal older adults and subsequent clinical disease progression to either a diagnosis of MCI (model 1) or a global CDR>0 (model 2). Model 3 examines the relationship between concurrent subtle cognitive decline and clinical disease progression (slope of CDR SOB—Sum of Boxes score). Abbreviations: PACC, preclinical Alzheimer's cognitive composite (5-component); CDR, Clinical Dementia Rating.

follow-up period). To determine the extent to which PACC declined over 3 years in the Aβ+ individuals, a linear mixed effects model controlling for age (centered at 75 years), sex (female), and education (centered at 16 years) was utilized for each cohort. Using the HABS as an example, we also computed 1- and 2-year slopes to determine whether cognitive decline over a shorter duration could predict functional progression.

Given our interest in simulating AD secondary prevention trials, some of which are specifically recruiting older adults with elevated Aβ,[23] primary analyses were completed in only those individuals with elevated Aβ. Cox proportional hazards models were used to separately estimate the effect of PACC slope from the baseline to year 3 on the risk for clinical progression to MCI/AD dementia at or after year 3. Analyses were controlled for the baseline PACC performance, age, sex, and education to account for demographic differences both within and between cohorts (model 1; Fig. 1). The equivalent analysis was completed substituting diagnosis with global CDR score >0 (model 2). In models 1 and 2, we restricted our data set to those who progressed at or after year 3 such that the event of interest (i.e., MCI diagnosis or CDR>0) did not precede the measurement of cognitive slope. A summary meta-analysis estimate was calculated for models 1 and 2 using the rma function to fit a meta-analytic fixed-effect model from cohort model estimates and confidence intervals. Receiver operating curve analysis was used to identify the sensitivity and specificity of PACC slope cutpoints to MCI diagnosis. Finally, we were interested in whether subtle cognitive decline was simultaneously associated with an increase in subtle functional changes. To answer this question, we examined whether PACC slope was associated with evidence for concurrent subtle functional changes before MCI by examining the correlation of PACC slope with slope of CDR Sum of Boxes over 3 years (model 3).

Using the HABS as an example, we explored whether individual PACC tests were significant predictors of MCI using Cox proportional hazards models in line with models 1 and 2 aforementioned.

All analyses were two-sided and significance was set at $P < .05$.

3 | RESULTS

3.1 | Demographic characteristics

Among the Aβ+ participants, there were no differences across cohorts for age or baseline cognition (Table 1). The AIBL participants had a lower proportion of females and lower education compared with the HABS and ADNI. Among Aβ+ subjects, mean follow-up in the AIBL was longer compared with the HABS ($P = .022$) and ADNI ($P < .001$). These cohort-differences were comparable when including Aβ− participants (Supplementary Table 1).

3.2 | Cognitive decline by Aβ+ status and cohort

Over a 3-year period, Aβ+ participants declined on the PACC in the HABS ($P < .0001$), ADNI ($P = .0001$) and AIBL ($P = .008$)

TABLE 2 Model 1: Cox regression analyses showing progression to MCI among Aβ+

Progressors to MCI/Stable	HR (95% CI)	Estimate (se)	P
HABS, n = 58, events = 12			
PACC slope*	**0.009 (0.001–0.682)**	**−2.13 (2.22)**	**.033**
PACC intercept	0.867 (0.265–2.836)	−0.24 (0.60)	.814
Age	1.036 (0.898–1.194)	0.48 (0.07)	.631
Sex	0.076 (0.009–0.652)	−2.35 (1.10)	.019
Education	0.917 (0.679–1.240)	−0.56 (0.15)	.575
AIBL, n = 45, events = 12			
PACC slope*	**0.000 (0.000–0.021)**	**−3.71 (2.20)**	**.000**
PACC intercept*	**0.034 (0.004–0.288)**	**−3.11 (1.08)**	**.001**
Age	0.850 (0.727–0.994)	−2.03 (0.08)	.042
Sex	0.857 (0.102–7.241)	−0.141 (1.08)	.887
Education	0.680 (0.483–1.081)	−1.628 (0.24)	.103
ADNI, n = 59, events = 19			
PACC slope*	**0.143 (0.022–0.911)**	**−2.06 (0.94)**	**.039**
PACC intercept	0.498 (0.246–1.007)	−1.94 (0.35)	.052
Age	1.073 (0.984–1.170)	1.60 (0.04)	.110
Sex	0.753 (0.229–2.476)	−0.47 (0.61)	.641
Education	0.957 (0.773–1.185)	−0.40 (0.10)	.687

Abbreviations: HABS, Harvard Aging Brain Study; AIBL, Australian Biomarker and Lifestyle Study; ADNI, Alzheimer's Disease Neuroimaging Initiative; PACC, preclinical Alzheimer's cognitive composite-5; HR, hazard's ratio; se, standard error; MCI, mild cognitive impairment; CI, confidence interval.
*and bold text indicate significant variables.

(Supplementary Table 2). A different pattern was observed among the Aβ− group, which showed improved performance (practice effect) over the same period in the HABS (P = .002) and stability in PACC performance for the AIBL and ADNI (Supplementary Table 2).

3.3 | Clinical progression by Aβ+ status and cohort

The proportion of Aβ+ participants who progressed to MCI at year 3 and thereafter was 20% in the HABS, 26% in the AIBL, and 32% in the ADNI (Table 2), which was systematically higher than MCI progression rates observed in Aβ− (Supplementary Table 1).

3.4 | Cognitive decline and subsequent clinical disease progression

3.4.1 | Progression to MCI/dementia (model 1)

Four participants in the HABS (6%), 3 in the AIBL (4%), and 12 in the ADNI (7%) were excluded from the Cox regression analysis because they progressed to MCI before study year 3. Mean time to a diagnosis of MCI/dementia in Aβ+ CN individuals including those who progressed before year 3 was 3.82 (1.85) years (HABS), 4.25 (1.90) years (AIBL), and 2.89 (1.62) years (ADNI). Follow-up time did not differ between those who progressed to MCI versus those who remained stable in the HABS (P = .799) or AIBL (.891); however, stable participants exhibited longer follow-up compared with MCI progressors in the ADNI (P < .01).

Results showed that steeper PACC decline was a significant predictor of MCI diagnosis across all 3 cohorts (Table 2). This remained true when controlling for baseline PACC performance, which was also a significant predictor of disease progression in the AIBL with a trend on the bounds of significance in the ADNI (Table 2). Additional predictors of MCI in Aβ+ CN were female sex (HABS) and age (AIBL).

To better visualize and interpret the risk of MCI diagnosis for a given cognitive slope, Cox regression analyses were recomputed using PACC dichotomized into "decliner" versus "stable" groups using the sample-specific Aβ+ slope. For those whose slope was in the lowest tertile (−0.16 in the HABS, −0.14 in the AIBL, and −0.26 in the ADNI), hazard for MCI diagnosis increased by a factor of 9.11 in the HABS, 6.73 in the AIBL, and 4.23 in the ADNI (Fig. 2). Combining these estimates across cohorts using meta-analytic techniques showed that overall hazard for MCI diagnosis was 5.47 (95% CI: 3.25–9.18). Sensitivity and specificity of different PACC slope cutpoints to MCI diagnosis are provided in Supplementary Table 4. As an example, a PACC slope < −0.16 in the HABS is associated with 99.80% sensitivity and 58.80% specificity to MCI diagnosis, a PACC slope < −0.14 in the AIBL is associated with 99.79% sensitivity and 75.00% specificity, and a PACC slope < −0.26 in the ADNI is associated with 99.83% sensitivity and 68.40% specificity to MCI diagnosis.

3.4.2 | Progression to CDR>0 (model 2)

Mean time to a CDR>0 in Aβ+ CN individuals, including those who progressed before year 3, was 2.84 (1.53) years (HABS), 4.13 (1.9) years (AIBL), and 2.59 (1.51) years (ADNI). Recapitulating results observed in model 1, steeper PACC decline was a significant predictor of CDR>0 across all 3 cohorts (Table 3). Using the same groupings for PACC "decliner" versus "stable" groups as aforementioned, hazard for CDR>0 was 7.13 (95% CI: 1.07–47.20, P = .041) in the HABS, 5.08 (95% CI: 1.43–18.18, P = .011) in the AIBL, and 3.78 (95% CI: 1.53–9.35, P = .004) in the ADNI. Combining these estimates across cohorts using meta-analytic techniques showed that overall hazard for CDR>0 was 4.49 (95% CI: 2.84–7.09).

3.4.3 | Concurrent cognitive decline and functional progression (model 3)

We also examined whether subtle cognitive decline was associated with a concurrent increase in functional symptoms before an MCI diagnosis. Across all cohorts, steeper PACC slope was associated with increased Sum of Boxes scores on the CDR (HABS: r = −.612, P < .01; AIBL: r = −.439, P < .01; ADNI: r = −.374, P < .01) over the same

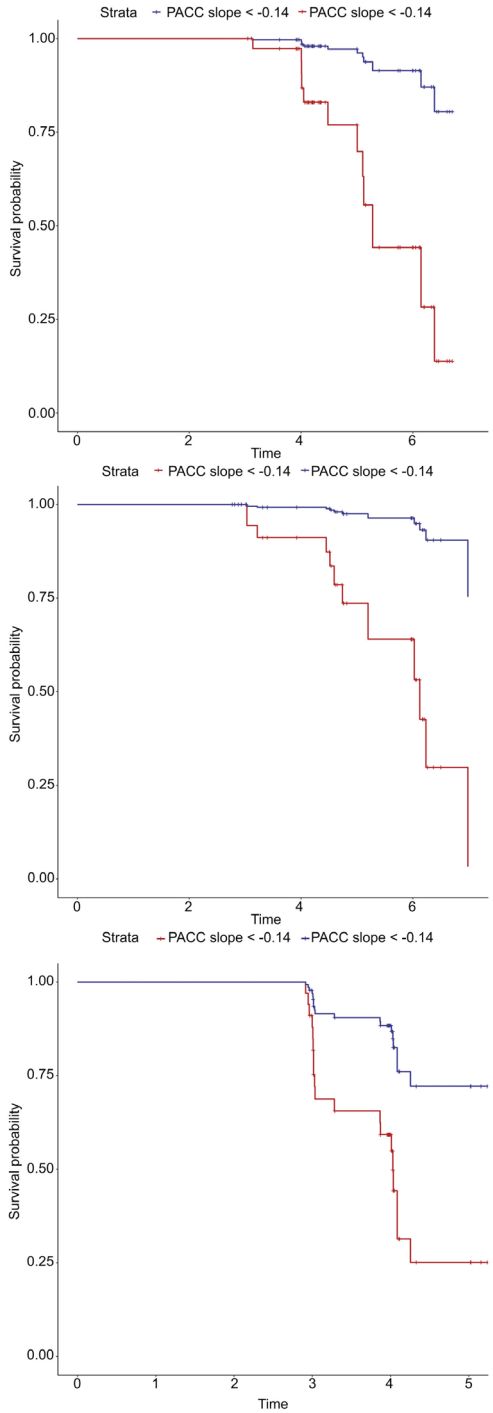

FIGURE 2 Hazard ratio for MCI diagnosis in PACC decliners: visualization of model results. Note. Kaplan–Meier curves showing the relative risk of MCI diagnosis among initially clinically normal but Aβ+ older adults with steeper (red) versus more stable (blue) PACC slopes in the preceding 3 years. PACC slope is dichotomized into steep versus stable groups using the bottom tertile. HABS hazard ratio = 9.11 (95% CI: 1.37–60.51) $P < .001$, AIBL hazard ratio = 6.73 (95% CI: 1.57–29.41) $P = .010$, ADNI hazard ratio = 4.23 (95% CI: 1.5–12.04) $P = .006$. Abbreviations: Aβ, amyloid-β; HABS, Harvard Aging Brain Study; AIBL, Australian Biomarker and Lifestyle Study; ADNI, Alzheimer's Disease Neuroimaging Initiative; PACC, preclinical Alzheimer's cognitive composite-5; MCI, mild cognitive impairment; CI, confidence interval.

TABLE 3 Model 2: Cox regression analyses showing progression to global CDR>0 among Aβ+

CDR progression; global CDR>0 versus global CDR = 0	HR (95% CI)	Estimate (se)	*P*
HABS, n = 44, events = 10			
PACC5 slope*	**0.003 (0.000–0.454)**	**−5.62 (2.47)**	**.023**
PACC5 intercept	0.797 (0.241–2.833)	−0.23(0.65)	.726
Age	0.926 (0.802–1.069)	−0.08 (0.07)	.296
Sex	0.289 (0.053–1.589)	−1.24 (0.87)	.154
Education	0.973 (0.716–1.321)	−0.03 (0.16)	.859
AIBL, n = 45, events = 14			
PACC5 slope*	**0.000 (0.000–0.014)**	**−8.45 (2.14)**	**.000**
PACC5 intercept*	**0.020 (0.002–0.175)**	**−3.88 (1.09)**	**.000**
Age	0.855 (0.740–0.989)	−0.16 (0.07)	.035
Sex	0.268 (0.043–1.666)	−1.32 (0.93)	.158
Education	0.753 (0.525–1.081)	−0.28 (0.18)	.125
ADNI, n = 59, events = 23			
PACC5 slope*	**0.064 (0.011–0.386)**	**−2.75 (0.92)**	**.003**
PACC5 intercept*	**0.360 (0.181–0.717)**	**−1.02 (0.35)**	**.004**
Age	0.976 (0.894–1.066)	−0.02 (0.04)	.592
Sex	0.454 (0.156–1.325)	−0.79 (0.55)	.149
Education	1.070 (0.862–1.329)	0.07 (0.11)	.539

Abbreviations: HABS, Harvard Aging Brain Study; AIBL, Australian Biomarker and Lifestyle Study; ADNI, Alzheimer's Disease Neuroimaging Initiative; PACC, preclinical Alzheimer's cognitive composite-5; HR, hazard's ratio; se, standard error; MCI, mild cognitive impairment; CI, confidence interval.

*and bold text indicate significant variables.

3-year period (Fig. 3). However, 65% of individuals showed no change (slope = 0) on CDR-Sum of Boxes over 3 years.

3.5 | Further analysis of the association between cognition and MCI diagnosis in the HABS

Testing the limits of model 1 within the HABS, PACC slope was not a significant predictor of MCI when restricted to either 2- ($P = .399$) or 1-year ($P = .906$) follow-up (Supplementary Table 3). Returning to 3-year slopes, the slope of each PACC component (including MMSE, Digit Symbol Substitution Test, Free and Cued Selective Reminding Test, Logical Memory Delayed Recall, and Category Fluency) was a significant predictor of MCI diagnosis at or after 3 years when examined independently (Supplementary Table 3).

4 | DISCUSSION

Results across three large observational cohorts indicate that rates of disease progression among initially normal older adults are systematically higher in Aβ+ compared with Aβ− and range from 20 to

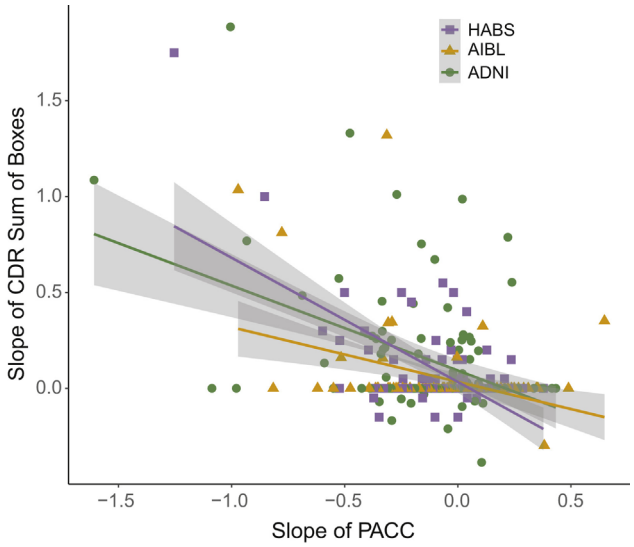

FIGURE 3 Concurrent subtle cognitive decline and increasing functional impairment over 3 years in Aβ+ CN individuals. Note. Correlation between 3-year cognitive slopes and 3-year CDR Sum of Boxes among initially clinically normal but Aβ+ older adults. The correlation between PACC and CDR slope is r = −0.612 ($P < .001$), r = −0.439, ($P < .001$), and r = −0.374, ($P < .001$) in the HABS, AIBL, and ADNI, respectively. Abbreviations: Aβ, amyloid-β; CN, clinically normal; CDR, Clinical Dementia Rating; HABS, Harvard Aging Brain Study; AIBL, Australian Biomarker and Lifestyle Study; ADNI, Alzheimer's Disease Neuroimaging Initiative; PACC, preclinical Alzheimer's cognitive composite-5; MCI, mild cognitive impairment; CI, confidence interval.

32% of Aβ+ progressing to MCI or 23 to 39% progressing to global CDR score>0. Subtle cognitive decline (between −0.14 and −0.26 standard deviations per year on a multidomain cognitive composite) among these Aβ+ older adults is associated with an approximately 5-fold greater risk of subsequent clinical disease progression (i.e., MCI diagnosis or global CDR score>0). These findings provide strong evidence for the meaningfulness of subtle cognitive decline in the context of biomarker-defined preclinical AD.

Our results provide general parameters for the expected degree of subtle decline measured on longitudinal cognitive testing that is representative of "transitional cognitive decline" in stage 2 of the revised National Institute of Aging and Alzheimer's Association criteria.[5] We corroborate findings from multiple reports showing that among initially CN older adults, abnormal Aβ is associated with both cognitive decline[7,9] and functional progression.[24] In contrast with previous work, we examined the predictive utility of longitudinal cognition for imminent clinical disease progression. Furthermore, we focused on CN individuals with biomarker-defined AD (Aβ+).

Criteria for cognitive impairment in MCI is defined as 1.5 standard deviations below normative data,[18] and previous studies have shown that the correlation between cognition and function is strongest as the disease progresses.[25] However, we show the extent to which quite subtle cognitive decline (as small as −0.14 to −0.26 standard deviations annually) among initially asymptomatic Aβ+ individuals is associated with imminent clinical disease progression, that is, a 5-fold increase in hazard for MCI diagnosis. These findings support the notion that AD treatment effectiveness in secondary prevention may be inferred by examining subtle decline measured on longitudinal cognitive testing alone. Recent FDA draft guidance for industry similarly raises this possibility suggesting it will "consider strongly justified arguments that a persuasive effect on sensitive measures of neuropsychological performance may provide adequate support for a marketing approval".[3] The persuasiveness of the clinical meaningfulness of cognitive performance would likewise be enhanced with evidence for a large magnitude of effect and a large breadth of effect. Although the magnitude of cognitive decline was relatively subtle, its predictive utility was robust, evident on two separate markers of disease progression (i.e., CDR>0 and MCI diagnosis), and persisting across three cohorts despite differences in methodology (including differences in PACC tests, follow-up duration, and diagnostic procedures) and relatively small sample sizes of Aβ+ individuals with extended follow-up.

Interestingly, baseline PACC performance was not a significant predictor of either MCI or CDR 0.5 in the HABS and while baseline cognition did contribute some explanatory variance in the ADNI and AIBL, subtle decline measured on longitudinal cognitive testing remained the best predictor of clinical disease progression. This suggests that risk for imminent clinical progression is not solely driven by those further along the trajectory at study initiation as evidenced by lower cognition at study outset, but by those who are subtly declining over time. The scope of subtle cognitive decline's pervasive relationship with clinical disease progression was further revealed by the HABS results showing that decline on each individual task predicted MCI diagnosis independently. Furthermore, there was also evidence that a more subtle increase in functional symptoms (i.e., slope of CDR-Sum of Boxes) was moderately correlated with concurrent PACC decline, but this was driven by a subset (only 35% showed change on the CDR-Sum of Boxes). This last finding raises the possibility that traditional co-primary outcomes of cognition and function may be appropriate when targeting those in the latest stages of preclinical AD.

Finally, the reported link between an individual's own cognitive concerns (rather than those of an informant) and AD biomarkers in asymptomatic individuals[26] suggests that there may be additive utility in examining trajectories of cognitive complaints alongside cognitive decline to predict risk for clinical progression.[27] This may also be extended to measures of mild neurobehavioral changes[28–30] as well as potentially novel measures of health outcomes developed in coordination with patient and caregivers to better identify what is of value from an individual's perspective (e.g., driving, perceived competence, etc).

4.1 | Limitations

Although we pooled data across 3 large observational cohorts, our sample is insufficient to set standards for predicting risk of clinical progression at the individual level for a given slope, age, sex, or genetic profile. In addition, there may be some circularity in using

cognitive slopes to predict MCI diagnosis, which in most cases involves a review of cognitive performance to make this diagnosis. However, our identical finding of 3-year PACC decline on subsequent global CDR progression (which is rated independently of cognitive testing) allays concerns regarding circularity and reinforces the robustness of the pattern. Finally, disappointing results from clinical trials testing anti-Aβ therapies at the symptomatic stages of AD certainly raise the question of the relevance of Aβ accumulation to tau spreading, neurodegeneration, and cognitive decline. Our results remain agnostic as to whether Aβ is a relevant target for intervention or whether both anti-Aβ and anti-tau therapies in addition to mitigation of other contributing factors may be required at even earlier stages of disease to fully prevent cognitive decline.

5 | CONCLUSIONS

Neuropsychological measures, on face value, do not reflect the everyday cognitive skills needed to function independently; rarely are people faced with matching digits and symbols in daily life or learning unrelated lists of words. However, subtle decline measured on longitudinal cognitive testing was predictive of subsequent MCI diagnosis, which is certainly a meaningful outcome. We may infer that subtle decline measured on longitudinal cognitive testing alone, particularly in the setting of biological markers for a neurodegenerative disease, may serve as a proxy for movement along the AD disease trajectory in future secondary prevention trials.

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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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