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RESEARCH ARTICLE

Amyloid PET predicts longitudinal functional and cognitive trajectories in a heterogeneous cohort

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Abstract

INTRODUCTION: Amyloid positron emission tomography (PET) is increasingly available for diagnosis of Alzheimer's disease (AD); however, its practical implications in heterogenous cohorts are debated.

METHODS: Amyloid PET from 890 National Alzheimer's Coordinating Center participants with up to 10 years post-PET follow up was analyzed. Cox proportional hazards and linear mixed models were used to investigate amyloid burden prediction of etiology and prospective functional status and cognitive decline.

RESULTS: Amyloid positivity was associated with progression from unimpaired to mild cognitive impairment and dementia. Amyloid burden in the unimpaired group was associated with lower initial memory levels and faster decline in memory, language, and global cognition. In the Impaired group, amyloid was associated with lower initial levels and faster decline for memory, language, executive function, and global cognition.

DISCUSSION: Amyloid burden is an important prognostic marker in a clinically heterogeneous cohort. Future work is needed to establish the proportion of decline driven by AD versus non-AD processes in the context of mixed pathology.

KEYWORDS
Alzheimer's disease, amyloid PET, neurodegenerative disease heterogeneity

Highlights

- Our findings highlight the importance of amyloid positron emission tomography (PET) in heterogenous cohorts, including diverse demographics, clinical syndromes, and underlying etiologies.
- The results also provide evidence that higher amyloid levels were linked to functional progression from unimpaired cognition to mild cognitive impairment (MCI) and from MCI to dementia.
- In cognitively unimpaired individuals, higher amyloid burden was associated with poorer memory at baseline and subsequent declines in memory, language, and global cognition.
- Among individuals with cognitive impairment, amyloid burden was associated with worse initial memory, language, executive function, and global cognition, and faster declines over time.

1 | BACKGROUND

Amyloid positron emission tomography (PET) imaging is central to proposed research frameworks that argue for a biological definition of Alzheimer's disease (AD).[1,2] Biological staging frameworks incorporating amyloid (A) and tau (T) using PET or biofluids have been applied to research studying disease progression along the hypothesized AD cascade,[3] differential diagnosis,[4] and early detection,[2] as well as for participant selection in clinical trials.[5] A clinical diagnosis alone is insufficient for many purposes, as 12%–27% of individuals with a clinical presentation consistent with dementia and 40%–60% of individuals with amnestic mild cognitive impairment (MCI) suspected to have AD do not have underlying AD pathology.[6] In addition, AD pathologies often co-exist alongside other neurodegenerative disorders, and these may influence rates of progression.[7,8]

The Alzheimer's Disease Research Center (ADRC) Program comprises more than 35 centers throughout the United States that are focused on human research of AD and AD and related disorders (AD/ADRD). These centers collect longitudinal standardized clinical assessments [the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS)] and obtain high consent rates regarding brain donation (≈60%), and by their natures enroll heterogeneous populations based on the individual centers' principal objectives and location, allowing for a broader and more representative composition.[9]

Notably, the composition of the ADRC program has a broader range of clinical diagnoses and suspected co-etiologies underlying cognitive impairment compared to other widescale imaging studies of AD (such as the Alzheimer's Disease Neuroimaging Initiative [ADNI]),[10] creating a unique opportunity to explore amyloid PET findings in a clinically and demographically heterogeneous cohort. For instance, in addition to recruiting individuals with MCI and dementia thought to be due to AD, ADRCs additionally recruit participants with suspected etiologies of alpha-synucleinopathy disease [Lewy body disease (LBD)/Parkinson's disease (PD)], vascular brain injury (VBI), traumatic brain injury (TBI), and other less common causes of dementia, as well as participants with suspected mixed etiologies and atypical, non-amnestic AD presentations.[2,9] Given the wide range of inclusion criteria used throughout the ADRC program, this resource can help establish whether the amyloid burden is important for informing disease trajectories when examined in the context of clinical heterogeneity and presumed mixed pathologies.

Given that amyloid PET is now offered clinically, is used as a common secondary endpoint in clinical trials, and that sizeable amyloid PET cohorts tend to focus on typical amnestic AD, the primary aim of this study was to examine amyloid PET positivity across clinically defined groups reflecting a range of suspected underlying AD/ADRD etiologies and to understand the predictive value of amyloid PET burden on longitudinal functional and cognitive change in this heterogeneous cohort.

RESEARCH IN CONTEXT

1. **Systematic review**: Amyloid aggregation may be an initiating step in Alzheimer's disease pathogenesis. Amyloid positron emission tomography (PET) is increasingly available for diagnosis. However, its prognostic and practical implications are debated. This study investigates whether amyloid PET burden predicts cognitive and functional decline in a large and heterogenous Alzheimer's Disease Research Center cohort. With up to 10 years of longitudinal follow-up, cognitive performance was assessed using harmonized neuropsychological composite scores.
2. **Interpretation**: Amyloid burden predicted functional progression from unimpaired to mild cognitive impairment and dementia. In the cognitively unimpaired group, higher levels of amyloid were associated with lower cross-sectional memory and subsequent declines in memory, language, and global cognition. In the cognitively impaired group, higher levels of amyloid were associated with worse cross-sectional and longitudinal memory, language, executive function, and global cognition.
3. **Future directions**: Further research is required to determine the extent to which decline is attributable to AD versus non-AD processes within the context of mixed pathology.

2 | METHODS

2.1 | Results of data extraction and processing

Although inclusion and exclusion criteria across ADRCs are site specific and encompass the full spectrum of ADRD, the majority of enrollees with clinical impairment are suspected of having AD. This link: https://naccdata.org/requesting-data/data-summary/uds to the NACC webpage provides updated information about the ADRC cohort. The NACC components have evolved over the years and are described in detail elsewhere.[9,11] All available NACC legacy amyloid PET scans, including all available amyloid tracers, were curated across seven ADRC sites, resulting in a total of 890 unique participants (eFigure 1). When a participant had more than one amyloid PET, the first amyloid PET was included in this study. Clinical data corresponding to these participants were extracted from the publicly available NACC UDS version 3.0 forms ("investigator_nacc60," received on March 7, 2023, from NACC).[11] Clinical variables nearest the amyloid PET scan (and within 1 year prior to the scan) were used to define clinical status at the scan. This clinical visit was re-coded as the baseline UDS visit and treated as time = 0 in longitudinal models (since many participants did not receive their amyloid PET scan close to the time of their initial enrollment into their ADRC). To explore the relationship between amyloid burden and prospective changes in function and cognition, we analyzed the re-coded baseline UDS visit and all subsequent UDS visits for longitudinal analyses. Data preceding the re-coded baseline UDS (i.e., PET visit) were excluded.

We described clinical characteristics across three diagnostic variables using data from the NACC UDS D1 form: (1) functional status, (2) clinical syndrome, and (3) suspected underlying etiology. Functional status was categorized using the variable "NACCUDSD," which classifies participants into four levels: Normal Cognition, Impairment-Not-MCI, MCI, and Dementia. Due to the small sample size (n = 24), Impairment-Not-MCI was collapsed into the MCI group for analyses. The Impairment-Not-MCI is a heterogenous group that indicates impairment that does not reach the level of dementia. Therefore, the closest group to it is the MCI group.

The clinical syndrome was derived across several variables, including amnestic and non-amnestic (language, attention, executive, visuospatial) single and multi-domain MCI or dementia ("NACCMTCI," "NACCMCIL," "NACCMCIA," "NACCMCIE," "NACCMCIV," "AMNDEM," "NAMDEM"), posterior cortical atrophy ("PCA"), semantic, non-fluent, and logogenic primary progressive aphasias ("NACCPPA," "NACCPPAG," "NACCPPME"), behavioral variant frontotemporal dementia (bvFTD) ("NACCBVFT"), and LBD ("NACCLBDS"). For analysis, the clinical syndromes were categorized into five levels: Unimpaired, amnestic single domain, amnestic multi-domain, non-amnestic single domain, and non-amnestic multidomain.

The suspected underlying etiology was derived from the "NACCETPR" variable, which documents the primary underlying etiology assigned by site clinicians among 30 possible etiologies detailed in (eMethods 1, eTable 1). Individual UDS variables also indicate etiologies that are not a primary cause of impairment but can be present in the Unimpaired group. We re-coded the 30 primary etiologies into seven etiology categories based on similarity and prevalence in the current dataset. These re-coded groups included (1) AD, (2) Vascular brain injury (VBI), (3) Alpha-synucleinopathy, (4) Frontotemporal lobar degeneration (FTLD), (5) Psychiatric, and (6) Other (eMethods 1, eTable 1). Individuals with Parkinson's disease (PD) with normal cognition were excluded from the Unimpaired group when examining longitudinal change in function and cognition, but other etiologies were included (Figure 1). Due to small sample sizes, FTLD and VBI were combined into the "Other" group (for descriptive purposes, these groups are listed separately in Table 1), resulting in five suspected etiology groups (Unimpaired, AD, Alpha-synucleinopathy, Psychiatric, and Other). Pathological data were not considered in this study even if a participant had pathological data. Although the NACC cohort has a high autopsy rate, among the individuals with amyloid PET, very few participants have gone to autopsy.

NACC race and ethnicity variables include Hispanic White, Hispanic Black, Non-Hispanic White, Non-Hispanic Black or African American, Non-Hispanic American Indian or Alaska Native, Non-Hispanic Asian, Hispanic Asian, Non-Hispanic Native Hawaiian or Other Pacific Islander, and Other. Given the small number of participants in many of these groups (Table 1), race and ethnicity were coded into four levels for analysis: Non-Hispanic White, Non-Hispanic Black, Hispanic White, and Other.

2.2 | Functional and neuropsychological data

The Clinical Dementia Rating (CDR) scale was obtained through a semi-structured interview of the participant and study partner and provides a measure of functional and cognitive impairment.[12] The neuropsychological test battery from the UDS of the ADRC program consists of measures of attention, processing speed, executive functioning, episodic memory, and language.[11] The UDS battery has evolved over time from Version 1.0 to 2.0 to 3.0. Across versions, the NACC neuropsychological battery versions include the Montreal Cognitive Assessment (MoCA), the Mini-Mental State Examination (MMSE), logical memory immediate and delayed recall, Craft story immediate and delayed recall, Benson complex figure copy and recall, category fluency, Boston Naming Test, multilingual naming test, letter fluency, repetition, Trails A and B, digit forward and backward, and number span forward and backward. Recent efforts have generated co-calibrated and harmonized composite scores for memory, executive, and language in NACC across the different versions.[13] Outcome measures used in this study were the MoCA, as a measure of global cognition, and harmonized composite memory, executive, and language scores.[13] Available cross-sectional and longitudinal data for each cognitive measure are shown in eFigure 1.

2.3 | PET image processing

An overview of amyloid PET processing steps is described in eMethods 2. Of the 929 total amyloid PET scans available for this analysis, 28 failed quality control and were excluded from the analysis. After additionally excluding longitudinal scans and NACC participants without UDS data, we were left with 890 unique participants with an amyloid PET scan (eFigure 1). Summed PET files were created using data closest to the recommended time window for each ligand [Florbetapir (FBP): 50–70 min post-injection; Florbetaben (FBB): 90–110 min; Pittsburgh compound B (PiB): 50–70 min]. When the optimal time window was unavailable, the closest available data within 10 min of the recommended window was chosen (eTables 2 and 3). The only exception was 93 FBB scans from a single site that were collected on average 27.7 min before the recommended window of 90–110 min post-injection for FBB. Although the acquisition times for this dataset were earlier, they were relatively consistent within this dataset (eTable 2, eMethods 2). Given this within dataset consistency, we did not exclude this FBB dataset but analyzed these data in separate Gaussian mixture modeling (see below).

Summed data were processed with an magnetic resonance imaging (MRI)-free amyloid PET pipeline.[14] Summed late-frame PET data were first linearly co-registered to the Montreal Neurological Institute (MNI)152 T1 template, and then non-linearly normalized to a "universal" amyloid PET template (an average across FBP, FBB, and PIB templates).[14] PET intensities were extracted from a global cortical target region (frontal, parietal, cingulate, and lateral temporal regions), along with the whole cerebellum reference region from the Global Alzheimer's Association Interactive Network (GAAIN) atlas (https://www.gaain.org/), and used to create standardized uptake value ratios (SUVRs) and Centiloid (CL) values. Centiloid values were created for the subset of 797 scans with acquisition times that were within 10 min of the recommended time window (eMethods 3, eTable 4, eFigure 2, eFigure 3, eTable 5).[14]

2.4 | Amyloid positivity

Two approaches were used to quantify amyloid burden. First, the Gaussian mixture model (GMM) was used to classify the amyloid SUVR into two classes in a data-driven manner by computing the probability of being positive across all 890 participants using *mixtools* R package. This approach was run separately within each of the three ligands (eTable 1, eFigure 4). Given the early acquisition start time for one FBB dataset (93 unique participants), a separate GMM was run in that dataset. Across all four GMMs, a two-cluster solution with unequal variance was selected (eFigure 4). Continuous GMM probabilities of belonging to the amyloid positive (A+) cluster and dichotomous amyloid status were used in the subsequent statistical analyses. Dichotomous amyloid positivity was based on a GMM threshold of 50% of belonging to the positive cluster. Second, we additionally performed supplementary analyses using Centiloid values[15] for the 797 participants with scans collected during the recommended acquisition window (demographics

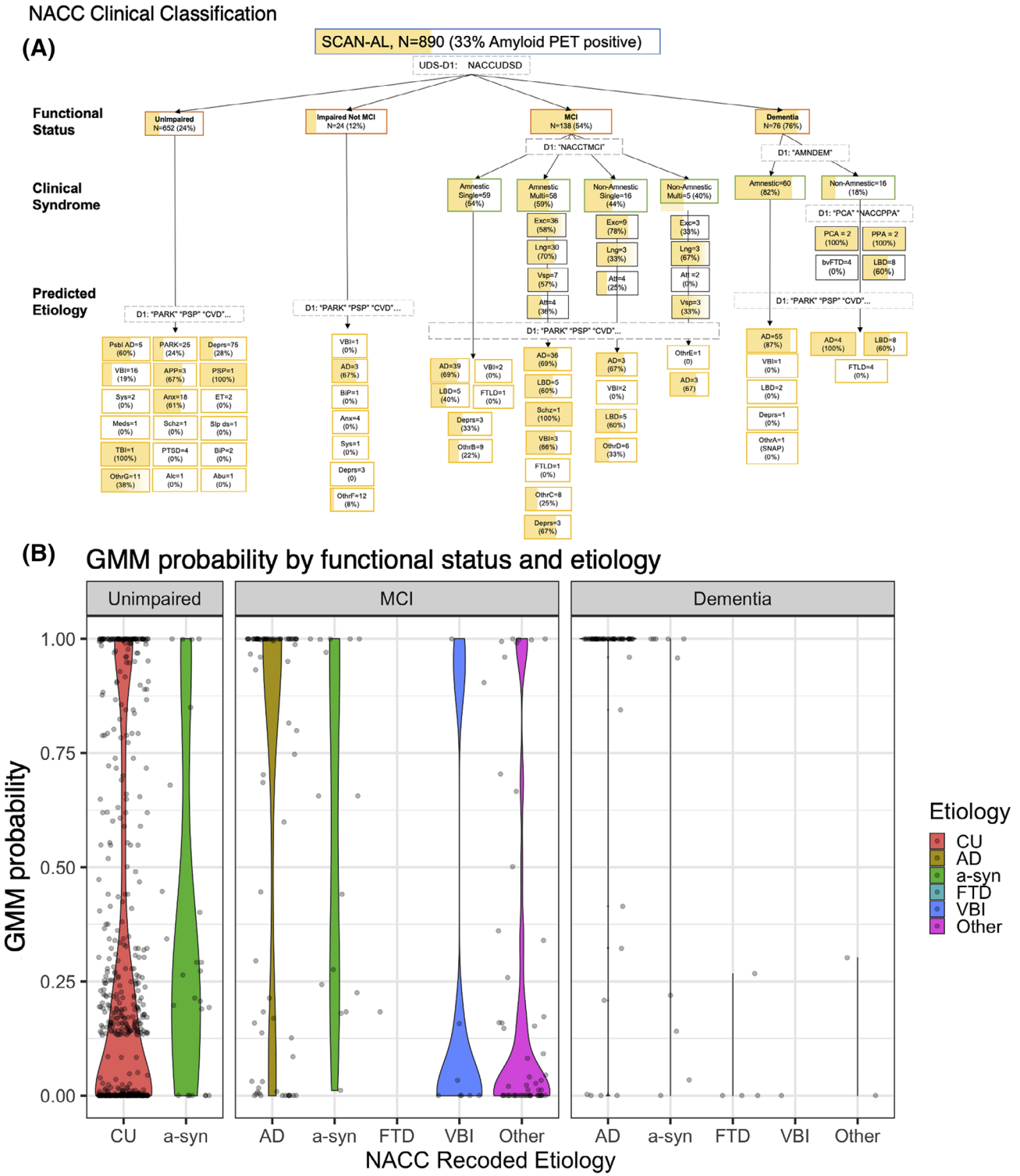

FIGURE 1 Clinical heterogeneity and amyloid burden. (A) Flowchart depicting three diagnostic levels include (functional status, clinical syndrome, and suspected etiology). All the variables are extracted from the NACC Unified Dataset (UDS) D1 form. Dashed boxes indicate the name of the specific NACC variable used. The number of participants and percent of amyloid positivity is included for each variable (the shaded portion of the box reflects the percent of amyloid positivity). In the suspected etiology boxes, numbers indicate the number of participants with a certain etiology. (B) Amyloid burden is quantified with Gaussian Mixture Model (GMM) probablities and plotted against clinical groups. Abu, Drug abuse; AD, Alzheimer's disease; Alc, Alcohol abuse; Anx, anxiety; APP, amyloid precursor protein genetic mutation; BiP, bipolar disorder; CVD, cerebrovascular disease; Deprs, depression; ET, essential tremor; FTD, frontotemporal dementia; LBD, Lewy body dementia; MCI, mild cognitive impairment; Meds, medication side effects; PARK, Parkinson's disease; PSP, progressive supranuclear palsy; PTSD, posttraumatic stress disorder; Schz, schizophrenia; Slp ds, sleep-related disease; Sys, systemic disorder; TBI, traumatic brain injury; VBI, vascular brain injury; Othr A-G are detailed in eMethods 1.

TABLE 1 Participant characteristics.

	Unimpaired		Mild cognitive impairment						Dementia					
	N = 651		*N* = 163						*N* = 76					
	CU	a-syn	AD	a-syn	Psy	VBI	FTD	Other	AD	a-syn	Psy	VBI	FTD	Other
N, (count)	626	25	84	15	16	9	1	38	59	10	1	1	4	1
Age, years (SD)	71.4 (6)	71.6 (5)	73.5 (8)	69.8 (9)	68 (7)	73.0 (7)	66	76 (9)	72.2 (9)	67 (8)	44	90	62 (3)	70
Female sex, *N*	422	9	44	2	13	4	0	21	29	2	1	0	3	1
Education mean (SD)	16.2 (2)	16.6 (2)	15.9 (3)	16.9 (2.34)	15.9 (4)	15 (2)	20	15.3 (3)	15.7 (3)	16.8 (3)	12	23	15 (3)	12
Reported disease duration prior to PET (in years) Mean (SD)			5.0 (3.24)	4.7 (4.6)	3.8 (2.9)	4.6 (3.2)	9.5	4.4 (4.1)	6.5 (2.4)	5.2 (3.2)		11.2	6.8 (3.7)	2.3
Follow up post PET (in years) mean (SD, range)	2.1 (2.3, 0-9.8)	2.3 (1.9, 0-8.9)	2.0 (2.3, 0-9.9)	3 (1.5, 0-3)	1.2 (1.3, 0-4.0)	1.7 (1.6, 0-4.8)	1.2	2.5 (1.6, 0-5)	2.6 (2.4, 0-11)	0.8 (0.9, 0-39)	1.6 (2.3, 0-3.3)	3.2,	1.9 (0.1, 1.8-2.1)	2.1
Amyloid status, *N*														
Negative	478	19	26	7	12	7	1	32	7	4	1	1	4	1
Positive	148	6	58	8	4	2	0	6	52	6	0	0	0	0
APOE*, *N														
ε4 negative	271	20	30	12	8	8	1	33	25	5	1	1	1	0
ε4 positive	143	5	48	3	8	1	0	4	33	5	0	0	2	1
Missing	212	0	6	0	0	0	0	1	1	5	0	0	2	1
Ethnicity/race, *N*														
Hispanic White	54	0	19	2	6	5	0	19	16	0	1	0	0	1
Non-Hispanic White	500	23	54	13	8	2	1	19	39	10	0	1	4	0
Non-Hispanic Black	50	0	9	0	2	0	0	0	1	0	0	0	0	0
Non-Hispanic Asian	11	2	1	0	0	0	0	0	1	0	0	0	0	0
Non-Hispanic NAIAN	9	0	1	0	0	0	0	0	0	0	0	0	0	0
Non-Hispanic NNHPI	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Non-Hispanic Other	2	0	0	0	0	1	0	0	2	0	0	0	0	0

Amyloid status determined using a 50% GMM probability cutoff.

Abbreviations: AD, Alzheimer's disease; a-syn, alpha synucleinopathy; CU, cognitively unimpaired; FTD, frontotemporal dementia; MCI, mild cognitive impairment; N, number of participants, NAIAN, non-Hispanic American Indian or Alaska Native; non-Hispanic Native Hawaiian or Other Pacific Islander; Psy, psychiatric disease; SD, standard deviation; Tox/Metb, toxic metabolic; VBI, vascular brain injury. Mean and SD listed for continuous variables.

of this cohort is represented eTable 4). SUVRs were converted to centiloids using ligand and pipeline-specific conversion equations derived from the paired PIB-FBB and PIB-FBP datasets downloaded from the GAAIN project (eTables 4 and5).

All primary analyses were based on the amyloid positivity status and continuous burden probability values determined by GMM, which incorporated all 890 participants. Dichotomous amyloid groups were based on a GMM threshold 50% of belonging to the positive cluster. Supplementary analyses leveraged amyloid positivity status and burden variables defined by Centiloids for the subset of 797 participants (eMethods 3, eTable 5).[14,16]

2.5 | Statistical analysis

Statistical analyses were completed in R version 4.1.0. Statistical differences in the frequency of categorical variables across groups, such as sex and apolipoprotein E (*APOE*) genotype, were performed with a chi-square test. Means of demographic measures were compared across groups with the analysis of variance (ANOVA).

Separate logistic regression models were run with functional status (three levels), clinical syndrome (five levels), or etiology (five levels) as a predictor of amyloid positivity (eMethod 4). Each model was adjusted for age, sex, education, and race/ethnicity. We also reran the models additionally adjusting for disease duration at the time of amyloid PET based on the participant-reported first symptoms. Cox regression models (R package *survival*) were used to investigate longitudinal functional progression in functional diagnosis after PET imaging (Unimpaired to MCI, Unimpaired to Dementia, and MCI to Dementia) or global CDR (CDR = 0 to CDR = 0.5, CDR = 0 to CDR = 1 or higher, CDR = 0.5 to CDR = 1 or higher) adjusting for age, sex, education, and race/ethnicity (e.g., (Time, Unimpaired-to-Dementia) ~ Age + Sex + Education + Race/Ethnicity + Amyloid GMM probability). The "Time" term reflects time from the clinical visit closest to amyloid PET, but not preceding the PET scan by more than a year. For individuals who progressed from Unimpaired to MCI or from MCI to Dementia, follow-up time was calculated as the interval from the clinical visit closest to amyloid PET. For individuals who did not progress, follow-up time was the interval from the clinical visit closest to amyloid PET to either death or the record censor date of January 14, 2022.

Linear mixed-effects models (R package *lmer*)[17] were used to investigate longitudinal trajectories of global cognition (MoCA), memory, executive functioning, and language composite scores adjusting for age, sex, education, and race/ethnicity (e.g., Memory-composite ~ Age*Time + Sex*Time + Education*Time + Race/Ethnicity*Time + Amyloid GMM-Probability*Time + (~ Time | Participant)). Models were run separately for the Impaired group (MCI, Impaired-not-MCI, Dementia) and the Unimpaired group. Time was defined as the time since re-coded baseline (visit closest to the amyloid PET scan).

Amyloid GMM probabilities and Centiloid values were modeled as continuous variables for both the survival and linear mixed-effects model analyses. Dichotomous amyloid status was used for visualization purposes only.

3 | RESULTS

3.1 | Clinical characteristics and patterns of amyloid-positivity

Of the 890 unique ADRC participants with amyloid PET imaging data in this study, the median clinical follow-up was 2.2 years, interquartile range (IQR) = 3.3 years, with a maximum follow-up of 10 years. Six hundred fifty-one participants were Unimpaired, and 239 were Impaired (139 MCI, 76 dementia, and 24 cognitively impaired not-MCI participants) at baseline (Table 1 and Figure 1). Six hundred twenty-four of the participants (68%) had longitudinal clinical visits for over 1 year after their amyloid PET scan, 504 participants (55%) for over 2 years, 312 participants (34%) for over 3 years, 130 participants (14%) for over 5 years, and only 11 participants (1%) were followed for over 9 years post PET. Heterogeneity in clinical presentations was high, and suspected etiologies are highlighted in Table 1 and Figure 1 (see also eTable 4, eFigure 5).

Whereas 25% of the Impaired group had an amnestic-only impairment, 50% had amnestic multidomain, 21% had non-amnestic single domain, and 8.8% had non-amnestic multidomain impairment. One hundred fifty-two participants (23%) in the Unimpaired group had a non-contributing diagnostic etiology (most common were depression, anxiety, and vascular brain injury) (Figure 1). Furthermore, 68 participants (29%) had a secondary suspected etiology listed (data not shown).

Among the 651 participants who were cognitively Unimpaired, 25 had PD. The rate of A+ was 24% in the Unimpaired group without PD (N = 148/626) as well as in the Unimpaired group with PD (N = 6/25). Of 239 Impaired participants, 60% (N = 143) were diagnosed clinically with AD as the primary driver of their impairment. Of this clinical AD group, 58/84 (69%) with MCI and 52/59 with dementia (88%) were A+. Of the remaining 96 Impaired that were suspected of having etiologies other than AD pathology driving their impairment, 27% were A+ (N = 26). Fifty-six percent of impaired participants with alpha-synuclein pathology as their primary suspected driver of cognitive impairment were A+ (N = 14/25).

Logistic regression model adjusting for age, sex, education, and race/ethnicity, with amyloid status as an outcome measure and functional status as a predictor, showed that compared to Unimpaired, higher proportions of people with MCI (odds ratio [OR] = 2.99, 95% confidence interval [CI] = 2.0–4.4, $p < 0.001$) and dementia (OR = 12.5, CI = 7.0–23.4 $p < 0.001$) were amyloid positive (Table 2). Similarly, all clinical syndromes had higher proportions who were amyloid positive compared to Unimpaired. Specifically, amnestic multi-domain (OR = 9.07, CI = 5.7–14.8, $p < 0.001$), non-amnestic multi-domain [OR = 4.3, CI = 1.74–11.1, $p = 0.002$), amnestic single-domain (OR = 3.82, CI = 2.2–6.8, $p < 0.001$), and non-amnestic single domain (OR = 2.95, CI = 1.0–8.4, $p = 0.042$) all had higher proportions of amyloid-positivity compared to Unimpaired. A similar adjusted logistic regression model with re-coded etiology as an outcome measure found that suspected AD (OR = 11.38, CI = 7.2–18.1, $p < 0.001$) as well as alpha-synucleinopathy (OR = 2.18, CI = 1.15–4.06, $p = 0.015$)

TABLE 2 Results of logistic regression models examining the association with amyloid status.

	Model 1 - Functional Status			Model 2 - Clinical Syndrome			Model 3 - Etiology		
Predictors	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*
Age, years	**1.06**	**1.03–1.08**	**<0.001**	**1.05**	**1.03–1.08**	**<0.001**	**1.05**	**1.03–1.08**	**<0.001**
Sex, male	1.1	0.80–1.51	0.563	1.03	0.74–1.43	0.843	1.11	0.79–1.54	0.541
Education, years	0.98	0.93–1.04	0.573	0.98	0.93–1.04	0.449	0.98	0.92–1.03	0.461
Non-Hispanic Black	0.68	0.34–1.27	0.242	0.56	0.28–1.08	0.095	0.51	0.24–1.00	0.063
Hispanic White	0.67	0.41–0.07	0.101	**0.57**	**0.34–0.92**	**0.025**	0.80	0.47–1.31	0.418
Race/Eth Other	**0.3**	**0.09–0.80**	**0.026**	**0.33**	**0.10–0.86**	**0.036**	**0.27**	**0.08–0.74**	**0.022**
Functional status									
MCI	**2.99**	**2.03-4.42**	**<0.001**						
Dementia	**12.54**	**7.04–23.39**	**<0.001**						
Clinical syndrome									
Amnestic single				**3.82**	**2.16–6.79**	**<0.001**			
Amnestic multi				**9.07**	**5.69–14.81**	**<0.001**			
Non-amnestic single				**2.95**	**1.00–8.41**	**0.042**			
Non-amnestic multi				**4.32**	**1.74–11.11**	**0.002**			
Predicted etiology									
Alzheimer's disease							**11.30**	**7.23–18.13**	**<0.001**
Alpha- synucleinopathies							**2.17**	**1.15–4.06**	**0.015**
Psychiatric							1.36	0.37–4.10	0.611
Other							0.45	0.16–1.07	0.055

Note: Effects of race/ethnicity are contrasted to the non-Hispanic White group across all models. Effects of functional status (Model 1), clinical syndrome (Model 2), and predicted etiology (Model 3) are contrasted to the Unimpaired group.
Bold Significant *p* value < 0.05.

were associated with higher proportions of amyloid positivity compared to Unimpaired. The Psychiatric and Other groups did not have higher proportions with amyloid positivity.

3.2 | Amyloid burden predicts longitudinal functional and cognitive decline

Greater amyloid burden was associated with a higher risk of progression from Unimpaired to MCI (RR = 3.3, 95% CI = 1.7–6.4, $p = 0.001$), Unimpaired to dementia (Relative Risk (RR) = 17.1, 95% Confidence Interval = 2.9–101.1, $p = 0.002$), and from MCI to dementia (RR = 6.81, 95% CI = 2.6–17.5, $p = 0.001$). We found similar results when examining global CDR progression (Figure 2A, eResults 1, eTable 6, eTable 7, eFigure 6). Based on the clinical diagnosis, in the cognitively unimpaired participants who have high amyloid burden, 50% progression to MCI in 7 years. In addition, in the MCI participants who have high amyloid burden, 50% progressed to dementia in 4 years. Similar progression rates were observed when using global CDR as an outcome (Figure 2A). Figure 2A also includes the number of censored participants.

In the Unimpaired group, higher amyloid burden was associated with worse cross-sectional ($\beta = -0.12$, CI = −0.23 to −0.01, $p = 0.028$) and longitudinal ($\beta = -0.04$, CI = −0.08 to −0.00, $p = 0.027$) memory composite scores. Higher amyloid burden was associated with longitudinal decline in language ($\beta = -0.04$, CI = −0.07 to −0.01, $p = 0.009$) and MoCA ($\beta = -0.35$, CI = −0.57 to −0.14, $p = 0.002$) scores. There were no significant associations with cross-sectional language, cross-sectional executive function scores, or longitudinal executive function scores (Figure 2B, Table 3). In the Impaired group, amyloid PET burden was associated with cross-sectional memory ($\beta = -0.93$, CI = −1.17 to −0.70, $p < 0.001$), language ($\beta = -0.34$, CI = −0.52 to −0.15), $p < 0.001$), executive function ($\beta = -0.34$, CI = −0.56 to −0.11, $p = 0.004$), and MoCA ($\beta = -5.21$, CI = −6.95 to −3.47, $p < 0.001$), as well as longitudinal memory ($\beta = -0.18$, CI = −0.24 to −0.12, $p < 0.001$), language ($\beta = -0.08$, CI = -0.13 to −0.03, $p = 0.002$), executive function ($\beta = -0.19$, CI = −0.25 to −0.13, $p < 0.001$), and MoCA ($\beta = -1.05$, CI = −1.61 to −0.49, $p < 0.001$) (Figure 2B, Table 3). Similar results were found when repeating analyses with Centiloid values instead of GMM probabilities (eTable 8, eTable 9, eFigure 7). The models adjusted for disease duration show consistent results and are shown in Supplementary Materials (eTable 10 and eTable 11).

4 | DISCUSSION

Elevated amyloid PET burden has been shown to predict longitudinal trajectories in multiple independent cohorts focused on AD and normal aging.[18–21] However, most longitudinal amyloid PET studies

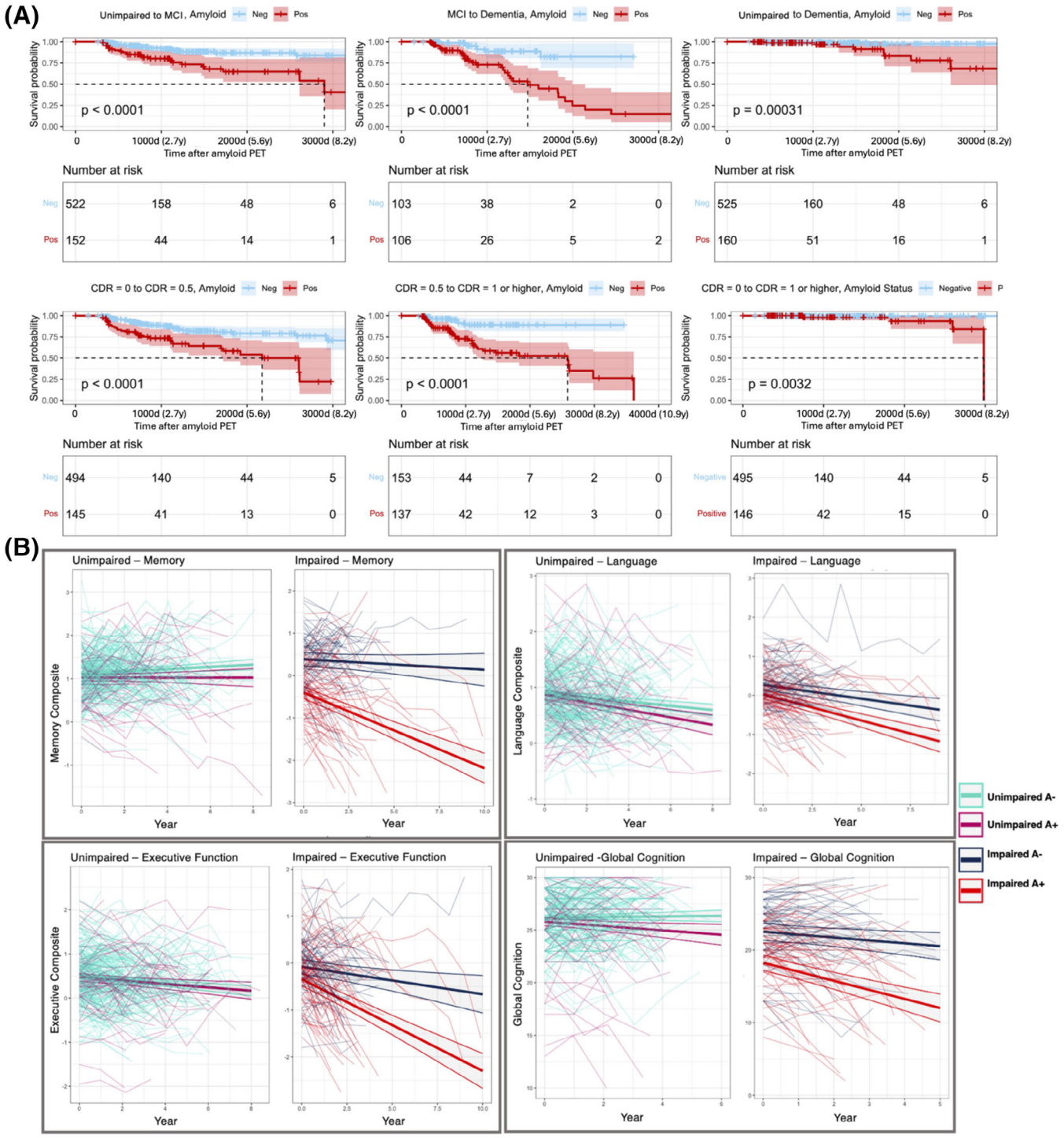

FIGURE 2 Amyloid PET association with prospective functional and cognitive measures. (A) Survival plots and (B) longitudinal cognitive decline by dichotomous GMM status (50% cutoff, dichotomous amyloid status is used for visualization purposes only). A–, amyloid negative; A+, amyloid positive; CDR: Clinical Dementia Rating; d, day; MCI, Mild Cognitive Impairment; Neg, negative; pos, positive; y, year.

focus on amnestic AD and involve selection criteria that exclude common co-morbidities, raising concerns about generalizability.[7,22] Here, we investigated the effects of amyloid PET on longitudinal cognitive and functional performance in a large, clinically heterogeneous dataset that included a greater range of suspected etiologies than typical PET cohorts. Our main findings were that rates of amyloid positivity vary across clinically defined groups and that the presence of elevated amyloid PET burden is an important predictor of future clinical progression and cognitive decline. These results provide support for the utility of amyloid PET in predicting trajectories of decline in a clinically heterogeneous cohort across the clinical spectrum of neurodegenerative disease.

TABLE 3 Results of linear mixed effect models examining associations of amyloid Gaussian mixture model (GMM) probabilities with prospective cognitive decline.

	MEM Unimpaired			LAN Unimpaired			EXF Unimpaired			MoCA Unimpaired		
	betas	CI	p	betas	CI	p	betas	CI	p	betas	CI	p
Age	**−0.03**	**(−0.03 to −0.02)**	**<0.001**	−0.02	(−0.03 to −0.01)	<0.001	−0.03	(−0.03 to −0.02)	<0.001	**−0.1**	**(−0.13 to −0.07)**	**<0.001**
Time in years	**0.28**	**(0.11–0.46)**	**0.002**	−0.06	(−0.20–0.08)	0.366	0.06	(−0.09–0.21)	0.441	**1.15**	**(0.13–2.16)**	**0.026**
Sex	0.03	(−0.09–0.16)	0.593	0.13	(−0.00–0.26)	0.054	**0.15**	**(0.02–0.29)**	**0.025**	−0.29	(−0.91–0.32)	0.354
Education	**0.04**	**(0.03–0.06)**	**<0.001**	**0.04**	**(0.03–0.06)**	**<0.001**	**0.07**	**(0.05–0.09)**	**<0.001**	**0.35**	**(0.28–0.42)**	**<0.001**
Non-Hispanic Black	−0.14	(−0.29–0.02)	0.083	**−0.3**	**(−0.45 to −0.14)**	**<0.001**	**−0.39**	**(−0.55 to −0.23)**	**<0.001**	**−1.66**	**(−2.38 to −0.93)**	**<0.001**
Hispanic White	**−0.19**	**(−0.34 to −0.04)**	**0.014**	**−0.37**	**(−0.52 to −0.21)**	**<0.001**	**−0.38**	**(−0.54 to −0.22)**	**<0.001**	**−1.75**	**(−2.50 to −1.00)**	**<0.001**
Non-Hispanic Other	−0.05	(−0.29–0.19)	0.697	**−0.26**	**(−0.50 to −0.02)**	**0.032**	**−0.25**	**(−0.49–0.00)**	**0.05**	−1.01	(−2.09–0.07)	0.066
GMM Probability	**−0.12**	**(−0.23 to −0.01)**	**0.028**	−0.06	(−0.17–0.05)	0.298	−0.04	(−0.15–0.08)	0.528	−0.5	(−1.01–0.01)	0.056
Age × Time (year)	**0**	**(−0.01 to −0.00)**	**0.002**	0	(−0.00–0.00)	0.705	0	(−0.00–0.00)	0.069	−0.01	(−0.03–0.00)	0.073
Sex × Time (year)	**−0.04**	**(−0.07 to −0.01)**	**0.009**	−0.02	(−0.05–0.00)	0.061	−0.02	(−0.05–0.01)	0.116	0.06	(−0.14–0.26)	0.571
Education × Time years	0	(−0.00–0.01)	0.339	0	(−0.00–0.00)	0.68	0	(−0.00–0.01)	0.125	−0.01	(−0.04–0.02)	0.537
Black × Time (year)	−0.03	(−0.09–0.03)	0.355	0.01	(−0.04–0.05)	0.76	−0.02	(−0.07–0.03)	0.494	−0.12	(−0.43–0.19)	0.456
Hispanic × Time (year)	**−0.08**	**(−0.13 to −0.03)**	**0.001**	−0.01	(−0.05–0.02)	0.47	**−0.08**	**(−0.12 to −0.04)**	**<0.001**	−0.25	(−0.54–0.04)	0.09
Other × Time (year)	−0.05	(−0.14–0.04)	0.251	0.05	(−0.02–0.12)	0.151	−0.04	(−0.11–0.04)	0.331	**−0.66**	**(−1.14 to −0.19)**	**0.006**
GMM Probability × Time (year)	**−0.04**	**(−0.08 to −0.00)**	**0.027**	**−0.04**	**(−0.07 to −0.01)**	**0.009**	0	(−0.03–0.03)	0.99	**−0.35**	**(−0.57 to −0.14)**	**0.002**
	MEM Impaired			**LAN Impaired**			**EXF Impaired**			**MOCA Impaired**		
	betas	CI	p	betas	CI	p	betas	CI	p	betas	CI	p
Age	0	(−0.01–0.01)	0.941	**−0.02**	**(−0.03–-0.00)**	**0.005**	0	(−0.02–0.01)	0.695	0	(−0.11–0.10)	0.99
Time in years	**0.32**	**(0.03–0.62)**	**0.032**	−0.01	(−0.26–0.25)	0.965	0.24	(−0.07–0.54)	0.13	0.34	(−2.67–3.35)	0.825
Sex	−0.27	(−0.79–0.26)	0.316	−0.09	(−0.50–0.32)	0.681	0	(−0.51–0.50)	0.987	0.27	(−3.44–3.99)	0.885
Education	0.02	(−0.01–0.06)	0.186	0.01	(−0.02–0.04)	0.454	**0.06**	**(0.03–0.10)**	**<0.001**	**0.34**	**(0.08–0.60)**	**0.012**
Non-Hispanic Black	0.09	(−0.44–0.62)	0.74	0.02	(−0.40–0.43)	0.941	0.09	(−0.43–0.60)	0.736	1.45	(−2.38–5.27)	0.458
Hispanic White	−0.04	(−0.29–0.20)	0.723	−0.13	(−0.33–0.07)	0.192	−0.14	(−0.38–0.10)	0.25	−0.36	(−2.18–1.46)	0.695
Non-Hispanic Other	−0.31	(−0.97–0.35)	0.358	**−0.57**	**(−1.09 to −0.05)**	**0.032**	−0.25	(−0.89–0.39)	0.449	−2.9	(−7.66–1.86)	0.232
GMM Probability	**−0.93**	**(−1.17 to −0.70)**	**<0.001**	**−0.34**	**(−0.52 to −0.15)**	**<0.001**	**−0.34**	**(−0.56 to −0.11)**	**0.004**	**−5.21**	**(−6.95 to −3.47)**	**<0.001**
Age × Time (year)	**−0.01**	**(−0.01 to −0.00)**	**0.001**	0	(−0.00–0.00)	0.395	0	(−0.01–0.00)	0.192	0	(−0.04–0.03)	0.863
Sex × Time (year)	−0.13	(−0.33–0.08)	0.22	**−0.24**	**(−0.41 to −0.07)**	**0.005**	−0.22	(−0.45–0.01)	0.057	0.71	(−0.24–1.65)	0.143
Education × Time (year)	0	(−0.01–0.01)	0.531	0	(−0.01–0.01)	0.63	−0.01	(−0.02–0.00)	0.293	−0.04	(−0.13–0.05)	0.371
Black × Time (year)	0.1	(−0.11–0.31)	0.349	0.04	(−0.13–0.22)	0.618	0.04	(−0.18–0.26)	0.727	1.19	(−0.37–2.75)	0.134
Hispanic × Time (year)	0.02	(−0.05–0.08)	0.555	0.03	(−0.03–0.08)	0.342	−0.05	(−0.12–0.02)	0.145	0.46	(−0.15–1.06)	0.138
Other × Time (year)	0.07	(−0.19–0.32)	0.613	0.08	(−0.13–0.28)	0.48	−0.13	(−0.39–0.13)	0.326	−0.22	(−1.93–1.48)	0.799
GMM Probability × Time (year)	**−0.18**	**(−0.24 to −0.12)**	**<0.001**	**−0.08**	**(−0.13 to −0.03)**	**0.002**	**−0.19**	**(−0.25 to −0.13)**	**<0.001**	**−1.05**	**(−1.61 to −0.49)**	**<0.001**

Abbreviations: EXF, executive function composite score; LAN, language composite score; MEM, memory composite score; MoCA, Montreal Cognitive Assessment.
Bold Significant p value < 0.05.

The current dataset combined amyloid PET across seven ADRCs. There are over 30 National Institutes of Health (NIH)–funded ADRCs across the United States, with each site focusing on different aspects of ADRD. Although amyloid PET data were collected across these sites without a uniform standardized acquisition protocol, most protocols were similar and followed recommended timing acquisition windows for each of the three amyloid PET ligands represented.[23] To combine these data across sites and ligands, all data were processed locally with an MRI-Free pipeline developed by Landau et al.,[14] and GMMs were applied to extracted SUVRs to provide a probability of belonging to either the amyloid-positive or amyloid-negative cluster. These probabilities enable data from different ligands to be placed on a similar scale and additionally allow for a probability distribution when global values are in the ambiguous range.[24] Although there are current efforts to collect and analyze standardized amyloid PET acquisitions throughout the ADRC network (the "SCAN" initiative),[16] our work analyzing this older mixed protocol "legacy" data is an initial attempt to leverage pre-existing amyloid PET and link these data to the extensive clinical data already available through the NACC.

A unique feature of the ADRC program is heterogeneity in clinical presentations. Clinical heterogeneity poses a significant challenge in the accurate diagnosis of neurodegenerative diseases, particularly in cases of non-amnestic AD, where symptoms may overlap with other conditions.[4] We found that both amnestic and non-amnestic clinical syndromes were associated with higher rates of amyloid positivity, consistent with other studies showing that AD processes can result in different profiles of cognitive impairment[25–28] and underscoring the importance of amyloid PET as a valuable tool for differential diagnosis among impaired individuals.[29,30] Odd ratios were highest for amnestic multidomain followed by non-amnestic multidomain, amnestic single domain, and non-amnestic single domain, suggesting that amyloid positivity is higher when multiple cognitive domains are impacted and is higher for amnestic than non-amnestic presentations. Moreover, amyloid PET facilitates the identification of elevated amyloid burden in the context of other primary etiologies, such as alpha-synucleinopathies, vascular disease, or hippocampal sclerosis, which can further inform treatment strategies and prognosis.[31] Thus, the utility of amyloid PET extends beyond mere diagnostic confirmation, playing a crucial role in personalized medicine. Consistent with previous studies focused on the AD spectrum,[32–34] we also found heterogeneity in amyloid burden in individuals with a clinical presentation consistent with AD. We found that 54% of the MCI participants who were thought to have an AD underlying etiology and 76% of individuals with dementia thought to be due to AD were amyloid positive. In addition, amyloid positivity in alpha-synucleinopathy followed previously reported literature,[35,36] as 56% of LBD had comorbid AD pathology. Twenty-three percent of the Unimpaired individuals were amyloid positive, similar to the reported 24% prevalence in the Amyloid Biomarker Study,[37] which included data from 85 cohorts not included in this study (average age = 69.1, SD = 9.8) and higher than the 17% amyloid prevalence reported in the Mayo Clinic Study of Aging (average age = 71.3, SD = 9.9).[38] The proportion of MCI participants who were amyloid positive in this study is similar to 57% in the Amyloid Biomarker Study and higher than in the Mayo Clinic Study of Aging.[37,38] The proportion of the Dementia participants who were amyloid positive in this study is lower than 86% in the Amyloid Biomarker Study.[37] This lower percentage of positivity in the Dementia group is consistent with a greater range of suspected etiologies included throughout ADRCs. Overall, the current analysis is in line with previous work highlighting a high degree of mismatch between clinically suspected AD and amyloid positivity. Furthermore, despite a greater degree of co-morbid medical conditions in our Unimpaired group (such as psychiatric conditions), our rates of amyloid positivity were like other studies that would typically exclude these conditions.

Our study is consistent with previous work showing that amyloid positivity is associated with future longitudinal cognitive decline; even though few made it to over 9 years and only 14% to over 5 years following PET, the sample showed significant predictive value for amyloid status on future cognitive and functional decline, with divergence in the curves beginning around 4 years of follow-up for models predicting conversion from unimpaired to MCI, and slightly earlier for MCI to dementia. This is consistent with the time course noted in previous studies examining clinical progression.[33,34,39–41] These studies show that even with small sample sizes, significant differences were seen within 3 years. Our findings support that, in amyloid-negative individuals, there is a low risk of progression to dementia in the next 10 years. However, among amyloid-positive individuals, there is 50% progress from Unimpaired to MCI after 7 years and from MCI to Dementia after 4–6 years. This finding is important because of the greater degree of clinical heterogeneity in our dataset, which may suggest a greater burden of co-pathologies and other contributors to decline beyond amyloid. The finding that amyloid positivity is an important predictor of clinical progression in the context of clinical heterogeneity highlights the importance of the AD pathway among individuals who may have co-pathologies. The heterogeneity in amyloid PET status underscores the importance of biological staging. However, scalable tools, like plasma p-tau217, should be integrated into datasets to provide key phenotyping information.

This study's strengths include using a large-scale, multicenter, clinically heterogeneous dataset to understand the impact of amyloid positivity on future progression. Although participants from the ADRC represent convenience samples and not population data given recruitment biases, the clinical heterogeneity present across ADRCs is more reflective of the full scope of AD and related disorders than AD cohorts that more narrowly focus on amnestic presentations or normal aging cohorts that exclude common co-morbid conditions. Participants observed in the ADRCs are representative of individuals who visit memory clinics due to a combination of subjective cognitive complaints, objective cognitive impairments, or a family history of neurodegenerative diseases. However, they do not represent the broader community. This study has several limitations: the inclusion criteria for the ADRCs vary among sites, and the number of events in the Unimpaired to Dementia survival analysis was low. Because amyloid PET was collected using site-specific acquisition protocols, we expect a greater degree of noise in the resulting amyloid PET variables than in other research studies. Although we have shown that amyloid burden is

an important predictor of decline in a clinically heterogeneous cohort, more data are needed to probe specific subgroups. The integration of amyloid PET during the diagnostic consensus process is unclear across sites and likely has evolved over time. For instance, some sites may use amyloid PET while determining participant diagnoses, whereas others may remain blinded. Thus, there is a potential circularity in relating amyloid positivity to clinical diagnosis. However, we found similar rates of amyloid positivity in clinical groups suspected of having underlying AD as reported previously in the literature. In addition, it remains unclear what proportion of participants in each ADRC received a PET scan and what factors influenced the decision to administer one. Variables such as age, education, race/ethnicity, geographic location (rural vs urban), and distance from the PET center may have played a role, potentially affecting the representativeness of the results. Another limitation is the focus on amyloid PET. Given the lack of availability of tau PET and other non-AD biomarkers, we did not examine these biomarkers. Future work in the ADRC program should simultaneously integrate markers capturing the major etiologies associated with dementia as these biomarkers become available. The cohort includes a high percentage of highly educated participants, thereby reducing the generalizability. Future work is needed to understand whether amyloid PET predicts progression in more diverse cohorts.[42,43] Although we did not base the diagnosis on pathology data, some diagnoses like argyrophilic grain disease, were found in the "Other" section. We assume this was a diagnosis of exclusion based on clinical suspicion. Further work is needed to understand the impact of amyloid PET in autopsy cohorts.

Given that large amyloid PET cohorts tend to focus on typical amnestic AD, the ADRC program provides a unique opportunity to explore the impact of AD biomarkers like amyloid PET in the context of clinical heterogeneity. Our findings highlight that amyloid positivity and clinical diagnosis are often misaligned, and that amyloid status is an important predictor of future decline in a clinically heterogenous cohort.

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CONFLICT OF INTEREST STATEMENT

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