Association of Longitudinal β-Amyloid Accumulation Determined by Positron Emission Tomography With Clinical and Cognitive Decline in Adults With Probable Lewy Body Dementia

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Abstract

**IMPORTANCE** In patients with probable dementia with Lewy bodies (DLB), overlapping Alzheimer disease pathology is frequent and is associated with faster decline and shorter survival. More than half of patients with DLB have elevated β-amyloid levels on carbon-11 labeled Pittsburgh compound B (PiB) positron emission tomography, but the trajectory of longitudinal β-amyloid accumulation and its associations with clinical and cognitive decline in DLB are not known.

**OBJECTIVES** To determine the trajectory of β-amyloid accumulation in patients with probable DBL and to investigate the associations of β-amyloid accumulation with measures of clinical and cognitive decline over time in DLB.

**DESIGN, SETTING, AND PARTICIPANTS** This cohort study included 35 consecutive patients with probable DLB from the Mayo Clinic Alzheimer Disease Research Center and matched them by age, sex, and apolipoprotein e4 status with 140 cognitively unimpaired participants from the population-based Mayo Clinic Study of Aging. Participants were observed from April 2010 to September 2017. Data analysis was conducted from January 2018 to January 2019.

**EXPOSURE** Baseline and follow-up PiB positron emission tomography and comprehensive clinical evaluations.

**MAIN OUTCOMES AND MEASURES** Rate of change in PiB standardized uptake value ratios (SUVRs) by PiB SUVR and time in years; the associations between baseline PiB SUVR, change in PiB SUVR, and change in several measures of clinical and cognitive decline.

**RESULTS** A total of 175 participants were evaluated (35 [20.0%] with probable DLB; mean [SD] age, 69.6 [7.3] years; 16 [45.7%] apolipoprotein e4 carriers; 31 [88.6%] men; and 140 [80.0%] cognitively unimpaired adults; mean [SD] age, 69.7 [7.2] years; 64 [45.7%] apolipoprotein e4 carriers; 124 [88.6%] men). In both groups, the rates of change in PiB SUVR showed an initial acceleration at lower baseline PiB SUVR followed by a deceleration at higher baseline PiB SUVR, thus forming an inverted-U shape. The trajectories of the rates of change in PiB SUVR did not differ between participants with probable DBL and cognitively unimpaired participants in terms of shape (P = .59) or vertical shift (coefficient [SE] 0.007 [0.006]; P = .22). The integral association of cumulative PiB SUVR with time in years showed a sigmoid-shaped functional form in both groups. In participants with probable DBL, higher baseline PiB SUVR and change in PiB SUVR were associated with more rapid clinical decline, as measured by the Clinical Dementia Rating, sum of boxes (baseline PiB SUVR: regression coefficient [SE], 1.90 [0.63]; P = .005; R² = 0.215; change in PiB SUVR, regression coefficient [SE], 16.17 [7.47]; P = .04; R² = 0.124) and the Auditory Verbal Learning Test, delayed
Abstract (continued)

recall (baseline PiB SUVR, regression coefficient [SE], −2.09 [0.95]; \( P = .04; R^2 = 0.182; \) change in PiB SUVR, regression coefficient [SE], −25.05 [10.04]; \( P = .02; R^2 = 0.221 \)).

CONCLUSIONS AND RELEVANCE  In this study, the rate of change in PiB SUVR among participants with probable DLB increased, peaked, and then decreased, which was similar to the trajectory in cognitively unimpaired participants and the Alzheimer disease dementia continuum. Higher baseline PiB SUVR and change in PiB SUVR were associated with more rapid clinical and cognitive decline over time. Measuring the change in PiB SUVR has implications for designing anti-β-amyloid randomized clinical trials for individuals with probable DLB.

Introduction

Dementia with Lewy bodies (DLB) is a common neurodegenerative dementia associated with Lewy body disease pathology. Patients with probable DLB frequently have varying levels of Alzheimer disease (AD) pathology, β-amyloid, and neurofibrillary tangles (NFT), in addition to Lewy body disease pathology.\(^1\)\(^,\)\(^2\) In DLB, concomitant AD pathology has been associated with a faster clinical progression and a shorter survival in autopsy-confirmed cohorts.\(^3\)\(^-\)\(^7\)

Positron emission tomography (PET) imaging with carbon-11 labeled Pittsburgh compound B (PiB) is a well-established biomarker of β-amyloid in vivo.\(^8\)\(^-\)\(^10\) Approximately two-thirds of patients with DLB have elevated PiB uptake on PET.\(^11\) However, the association of a higher PiB uptake with greater clinical or cognitive impairment has been equivocal in DLB cross-sectionally.\(^12\) Longitudinal studies in DLB are needed to understand the trajectory of PiB uptake over time and to determine its association with clinical progression. Monitoring these aspects will be important for identifying the most eligible candidates for emerging targeted treatments and for assessing the response to such treatments.

Using serial PiB PET, prospective studies\(^13\)\(^-\)\(^15\) in cognitively unimpaired (CU) and in cognitively impaired individuals within the AD continuum with a range of baseline PiB standardized uptake value ratios (SUVRs) demonstrated that the rate of change in PiB SUVR is not linear. At lower baseline PiB SUVR, the rate of change in PiB SUVR accelerates and then decelerates at a higher baseline PiB SUVR,\(^13\)\(^-\)\(^15\) thus forming an inverted-U shaped curve as a function of baseline PiB SUVR.\(^13\)\(^,\)\(^15\) Consequentially, cumulative PiB SUVR as a function of time follows a sigmoid-shaped trajectory,\(^13\)\(^,\)\(^15\) reaching a plateau at high baseline PiB SUVR within the AD continuum,\(^13\)\(^,\)\(^15\) with implications for the timing of treatment strategies.

In DLB, the trajectory of the change in PiB SUVR is not known. Nor is it known whether accelerated rates of change in PiB SUVR are associated with faster clinical declines in DLB. In this longitudinal PiB PET cohort study, our objective was to determine the change in PiB SUVR and the cumulative PiB SUVR over time in patients with probable DLB compared with CU adults with similar demographic characteristics. Our second objective was to evaluate the associations of baseline PiB SUVR and change in PiB SUVR with measures of longitudinal clinical and cognitive decline in probable DLB. A final objective was to calculate sample size estimates for a hypothetical randomized clinical trial targeting β-amyloid in DLB.

Methods

Data Source, Study Design, and Population

The probable DLB group included 35 consecutive patients observed through the Mayo Clinic Alzheimer Disease Research Center between April 2010 and September 2017, of whom 32 met
clinical criteria for probable DLB at baseline and developed probable DLB by the first follow up. To compare the trajectory of change in PiB SUVR, we included 140 CU participants observed through the Mayo Clinic Study of Aging, a longitudinal, population-based cohort study. Cognitively unimpaired individuals were matched 4:1 with patients with probable DLB on age, sex, and apolipoprotein (APOE) e4 status; they remained CU throughout the study duration.

**Baseline and Follow-up Visits**

All participants were required to have a baseline PiB PET coupled with a comprehensive clinical evaluation and an identical follow-up within 12 to 15 months for the probable DLB group and within 15 to 30 months for the CU group. Baseline and follow-up visits incorporated a medical history review, informant interview, neurologic examination, neuropsychological assessment, and a series of informant questionnaires. After each visit, a consensus panel, composed of the study nurse, neurologist (B.F.B, J.G.-R., D.S.K., or R.C.P.), and neuropsychologist (T.J.F. or J.A.F.) who evaluated the participant, established the clinical diagnosis after accounting for visual or hearing deficits, education, and prior level of functioning.

**Clinical and Cognitive Measures**

Clinical severity and progression were determined using global cognitive assessments (ie, Mini-Mental State Examination [MMSE] and Dementia Rating Scale [DRS]) and noncognitive functional assessments (Clinical Dementia Rating scale, sum of boxes [CDR-SOB] and motor impairment by Unified Parkinson Disease Rating Scale part III [UPDRS-III]). Neuropsychological evaluations included the Auditory Verbal Learning Test (AVLT) for memory, the Boston Naming Test (BNT) for object naming, the Trail Making Test, part A (TMT-A) for divided attention, and the Rey Complex Figure (RCF) test for visual-perceptual processing.

The study was approved by the Mayo Clinic institutional review board, and informed consent on participation was obtained from every participant or an appropriate surrogate. The study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

**Imaging Study**

Baseline and follow-up PiB PET imaging was performed on PET-computed tomography systems operating in a 3-dimensional mode (GE Medical Systems). Scans consisted of four 5-minute dynamic frames acquired from 40 to 60 minutes after injection of PiB; detailed descriptions have been published elsewhere. For anatomic segmentation and labeling of PiB PET images, 3-dimensional, high-resolution, magnetization-prepared rapid gradient echo T1-weighted magnetic resonance imaging (MRI) scans, performed during the same visit cycle as the PiB PET, were acquired with a 3-T MRI scanner with 1 mm3 resolution (GE Medical Systems). Baseline and follow-up MRI images were automatically segmented and bias corrected using unified segmentation in statistical parametric mapping. We rigidly aligned PET images to MRI images, using statistical parametric mapping 12 (baseline-to-baseline and follow-up-to-follow-up), and MRI segmentations were used to perform 2-class partial volume correction. For consistency, we also performed analyses with no partial volume correction of PiB SUVR. Regions were automatically located using advanced normalization tools with the Mayo Clinic Adult Lifespan Template. For each PiB image, PiB uptake was calculated as the SUVR in a standard composite region consisting of voxels in the parietal, posterior cingulate, precuneus, prefrontal, orbitofrontal, temporal, and anterior cingulate cortices. To maximize the reliability and plausibility of measurements, we used 2 reference regions: 1 for baseline PiB SUVR and 1 for longitudinal change in PiB SUVR. For the baseline PiB SUVR measurement, we used a standard cerebellar crus reference region. To measure the change in PiB SUVR, we used a composite reference region of eroded supratentorial white matter, whole cerebellum, and pons; this technique was developed by our group, has been extensively tested and compared with multiple
alternative approaches, and has been shown to improve reliability and plausibility for serial measurements compared with cross-sectional approaches.\textsuperscript{20}

**Statistical Analysis**

Demographic, clinical, and cognitive characteristics of participants with probable DBL and CU participants at baseline were summarized using means with SDs or proportions. A log transformation or a square root transformation was performed to normalize the distribution of baseline PIB SUVR, MMSE score, and CDR-SOB score. Continuous variables were compared between probable DBL and CU groups using analysis of variance with a random block design with an added predictor to account for matching. The change in PIB SUVR for probable DBL and CU groups was constructed from partial volume-corrected serial PIB SUVR. Changes in PIB SUVR and in clinical and cognitive measures were annualized. We chose generalized additive models (GAMs) with 95% CIs to model the change in PIB SUVR as a function of baseline PIB SUVR. We used 4-\textit{df} penalized splines in GAMs as our primary analysis to estimate the shapes of change in PIB SUVR vs baseline PIB SUVR for probable DBL and CU groups separately. Subsequently, we tested for a type of interaction between group (probable DBL or CU) and change in PIB SUVR by fitting fixed 4-\textit{df} regression splines (to control the smooths and produce nested models) within each group and then by fitting a 4-\textit{df} regression spline without differentiating the groups. We used an approximate F test from the analysis of deviance table comparing the models to test the interaction. We used GAMs to estimate the cumulative PIB SUVR as a function of time in years in the probable DBL and CU groups; GAMs accounted for matching between the groups. We used linear regression models to determine the association of baseline PIB SUVR and rate of change in PIB SUVR with rate of change in measures of clinical and cognitive decline. We reported results of models without adjustment for any covariates. We investigated regression models, adjusting for combinations of age, sex, education, and APOE e4 carrier status but found that no covariates were statistically significant nor did inclusion of the covariates produce qualitatively different results for PIB SUVR or change in PIB SUVR. Finally, in the probable DBL group, we estimated sample size for a hypothetical anti-β-amyloid clinical trial in patients with probable DBL. Mixed-effect models and the jackknife-based resampling method were used to estimate the sample sizes expressed as mean values with asymptotic confidence intervals. Change in PIB SUVR, CDR-SOB score, DRS score, and MMSE score were used for these calculations, assuming 1-sided tests, 80% power, α = 0.05, and readings at 12, 18, and 24 months of follow-up. Analyses were performed using SAS statistical software version 9.4 (SAS Institute) and R statistical software version 3.1.1 (R Foundation for Statistical Computing) with P < .05 considered statistically significant. All tests were 2-tailed, except for tests for sample size estimates, which were 1-tailed.

**Results**

**Baseline Cohort Characteristics**

Baseline characteristics of participants in the probable DBL and CU groups, matched on age, sex, and APOE e4 status, are listed in Table 1. In total, 175 participants were evaluated. Of these, 35 (20.0%) had probable DBL, with mean (SD) age of 69.6 (7.3) years; 16 (45.7%) were APOE e4 carriers; and 31 (88.6%) were men. A total of 140 CU participants (80.0%) were matched on age (mean [SD] age 69.7 [7.2] years), APOE e4 status (64 [45.7%] carriers), and sex (124 [88.6%] men) to patients with probable DBL. Dementia severity of participants with probable DBL was mild based on MMSE, DRS, and CDR-SOB scores. Mean (SD) baseline PIB SUVR, reported with partial volume correction, was higher among participants with probable DBL than among CU participants (1.58 [0.41] vs 1.36 [0.22]; P < .001; range, 1.17-2.57 vs 1.11-2.36). We obtained similar results on baseline PIB SUVR and findings in this study when we analyzed PIB SUVR data with no partial volume correction (mean [SD] baseline PIB SUVR 1.44 [0.36] vs 1.26 [0.20]; P < .001; range, 1.05-2.23 vs 1.01-2.21). The interval between baseline and follow-up visit was shorter among the probable DBL group than the CU group because of recruitment from 2 sources; therefore, change in PIB SUVR and changes in clinical and cognitive
measures were annualized. Compared with patients with probable DLB who did not carry APOE e4, APOE e4 carriers had higher mean (SD) baseline PiB SUVR (1.40 [0.27] vs 1.79 [0.46]; P = .005) and lower mean (SD) UPDRS-III motor score (11.1 [5.5] vs 6.5 [5.7]; P = .02). In clinical and cognitive measures and frequencies of probable DLB, APOE e4 carriers vs noncarriers did not differ (ie, all P > .05). We did not examine differences in the change in PiB SUVR between participants with probable DLB who were APOE e4 carriers vs noncarriers because of relatively small subgroups.

Trajectories of Change in PiB SUVR
Change in PiB SUVR by baseline PiB SUVR did not differ between the probable DLB and CU groups (Figure 1A); the regression-based smooth curves for rate of change in PiB SUVR did not differ between DLB and CU (P = .59). Moreover, we observed no difference in the shape (vertical shift) of

| Table 1. Participants’ Baseline Characteristics |
|-----------------------------------------------|
| Characteristic                      | Mean (SD) | Patients With Probable DLB (n = 35) | P Valuea |
|-----------------------------------------------|
| Men, No. (%)                       | 124 (88.6) | 31 (88.6) | >.99 |
| Age, y                             | 69.7 (7.2) | 69.6 (7.3) | .68 |
| APOE e4 carrier, No. (%)           | 64 (45.7) | 16 (45.7) | >.99 |
| Education, y                       | 15.3 (2.4) | 15.7 (2.9) | .44 |
| Interscan interval, y              | 2.4 (1.0) | 1.2 (0.4) | <.001 |
| PiB SUVR                           |           |           |      |
| Baseline, mean (SD) [range]        | 1.36 (0.22) [1.11-2.36] | 1.58 (0.41) [1.17-2.57] | <.001b |
| Slope, baseline to follow-up       | 0.016 (0.024) | 0.020 (0.037) | .45 |
| CDR-SOB score                     | 0.0 (0.2) | 3.4 (1.8) | <.001b |
| MMSE score                        | 28.5 (1.1) | 24.3 (4.7) | <.001b |
| UPDRS-III motor score              | 0.4 (1.2) | 9.1 (6.0) | <.001 |
| AVLT, delayed recall score         | 8.2 (2.9) | 3.2 (3.4) | <.001 |
| TMT-A score                       | 33.6 (9.0) | 69.0 (38.4) | <.001 |
| BNT score                         | NA | 25.3 (4.7) | NA |
| RCF copy, total score              | NA | 17.9 (10.5) | NA |
| DRS score                         | 128.6 (8.9) | 128.6 (8.9) | NA |
| Visual hallucination, No. (%)      | NA | 17 (50.0) | NA |
| Fluctuations, No. (%)              | NA | 22 (64.7) | NA |
| Parkinsonism, No. (%)              | NA | 29 (85.3) | NA |
| RBD, No. (%)                       | NA | 33 (97.1) | NA |
| Cognitive impairment, y            | NA | 5.58 (3.32) | NA |

Abbreviations: APOE, apolipoprotein; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; CDR-SOB, Clinical Dementia Rating Scale, sum of boxes; CU, cognitively unimpaired; DLB, dementia with Lewy bodies; DRS, Dementia Rating Scale; MMSE, Mini-Mental State Examination; PiB SUVR, carbon-11 labeled Pittsburgh compound B, standardized uptake value ratio; RCF, Rey Complex Figure; RBD, REM Sleep Behavior Disorder; TMT-A, Trail Making Test, part A; UPDRS-III, Unified Parkinson Disease Rating Scale, part III.

a P values for differences between groups came from an analysis of variance using a random block design with an added predictor for the matching ID.

b Either a log transformation or square root transformation was performed to normalize the distribution.

c Data missing for 1 CU participant.

d Data missing for 1 CU participant and 1 participant with probable DLB.

e Data missing for 1 CU participant and 6 participants with probable DLB.

f Data missing for 1 CU participant and 2 participants with probable DLB.

g Data missing for 5 participants with probable DLB.

h Data missing for 6 participants with probable DLB.

i Data missing for 1 participant with probable DLB.

j A total of 25 of 34 patients (73.5%) with probable DLB had probable RBD confirmed by polysomnography; 8 (23.5%) had possible RBD confirmed by Mayo Clinic Sleep Questionnaire18; and 1 (2.9%) did not have RBD.
trajectories between the probable DLB and CU groups (regression spline model, approximate $P = .07$; penalized spline model, coefficient [SE] 0.007 [0.006]; $P = .22$) (Figure 1A). The association between change in PiB SUVR and baseline PiB SUVR was nonlinear (test of linearity, $P < .001$) in both PDLB and CU groups. In both probable DLB and CU groups, change in PiB SUVR accelerated at lower baseline PiB SUVR, peaked at a PiB SUVR of approximately 1.8, and then decelerated at higher baseline PiB SUVR, forming an inverted U-shaped curve as a function of baseline PiB SUVR. Subsequently, the associations of change in PiB SUVR as a function of baseline PiB SUVR were integrated into PiB SUVR as a function of time associations in probable DLB and CU groups (ie, the cumulative density function) (Figure 1B). The integral association of PiB SUVR by time rendered sigmoid-shaped trajectories for both probable DLB and CU groups (Figure 1B).

Association of Baseline and Change in PiB SUVR With Clinical and Cognitive Decline in Patients With Probable DLB

In patients with probable DLB, the associations of baseline PiB SUVR and change in PiB SUVR with measures of clinical progression are summarized in Table 2 and Figure 2. Higher baseline PiB SUVR was associated with a greater longitudinal decline, as measured by the DRS (regression coefficient [SE], −22.40 [6.53]; $P = .002$; $R^2 = 0.312$), the CDR-SOB (regression coefficient [SE], 1.90 [0.63]; $P = .005$; $R^2 = 0.215$), the AVLT, delayed recall (regression coefficient [SE], −2.09 [0.95]; $P = .04$; $R^2 = 0.182$), the BNT (regression coefficient [SE], −2.39 [0.84]; $P = .009$; $R^2 = 0.245$), and the TMT-A (regression coefficient [SE], 43.43 [12.96]; $P = .002$; $R^2 = 0.286$). Similarly, greater change in PiB SUVR was associated with greater decline as measured by the CDR-SOB (regression coefficient [SE], 16.17 [7.47]; $P = .04$; $R^2 = 0.124$) and the AVLT, delayed recall (regression coefficient [SE], −25.05 [10.04]; $P = .02$; $R^2 = 0.221$). Baseline PiB SUVR and change in PiB SUVR were not associated with changes in MMSE score, UPDRS-III score, or visual-perceptual processing (Table 2).

The nature of the selection of the CU participants resulted in a restricted range of change in cognition and clinical scales. For example, only 8 CU participants (5.7%) had nonzero values for change in CDR-SOB score. Thus, the findings from only 8 influential participants would have to be interpreted with extreme caution. In addition, since we selected CU participants to match patients with probable DLB on age, sex, and APOE e4 status, we could only make inferences about this CU sample, which does not fully represent the CU population.

Figure 1. Trajectories of Change in Carbon-11 Labeled Pittsburgh Compound B Standardized Uptake Value Ratio (PiB SUVR) and Baseline PiB SUVR

A, Regardless of clinical group, change in PiB SUVR increases, peaks at a baseline PiB SUVR of approximately 1.8, and then decreases, forming an inverted U-shaped curve. Change in PiB SUVR did not differ between the probable dementia with Lewy bodies (DLB) and cognitively unimpaired (CU) groups in the shape or vertical shift between the trajectories; confidence bands, indicated by shaded areas, largely overlap. The widening of the confidence bands on the right side of the panel reflects the lower number of participants ($n = 11$) with higher baseline PiB SUVR values (ie, ≥1.7). B, The inverted U-shaped curves were integrated into the sigmoid-shaped trajectory of cumulative PiB SUVR as a function of time in years.
Sample Size Estimates for Hypothetical Clinical Trial in DLB

The sample size estimates for a hypothetical clinical trial in patients with DLB showed that using the change in PIB SUVR to measure therapeutic effect would require the smallest sample size. Change in PIB SUVR was followed by change in CDR-SOB score, whereas using the measurements of changes in DRS and MMSE scores would require larger samples (Table 3).

Discussion

In this longitudinal cohort PiB PET study, we determined the trajectories of change in PiB SUVR in patients with mild probable DLB compared with CU participants, matched on demographic variables and APOE e4 status. The trajectories of change in PiB SUVR did not differ between probable DLB and CU groups. In both groups, the trajectories were nonlinear, with an initial acceleration at lower baseline PiB SUVR followed by a deceleration at higher baseline PiB SUVR. The integral association between cumulative PiB SUVR and time showed a sigmoid-shaped functional form in both probable DLB and CU groups, very similar to the trajectories reported in AD continuum cohorts, which included CU participants with a range of baseline PiB SUVRs. Furthermore, the rate of clinical progression in probable DLB was associated with both baseline PiB SUVR and change in PiB SUVR. We showed that measuring change in PiB SUVR and change in CDR-SOB score would require a smaller sample size in a hypothetical clinical trial among patients with probable DLB. Altogether, our findings suggest that measuring change in PiB SUVR is a valid biomarker of longitudinal β-amyloid accumulation in individuals with probable DLB and that progression of β-amyloid pathology in probable DLB is associated with functional and cognitive decline.

### Table 2. Associations of Baseline PiB SUVR and Change in PiB SUVR With Clinical and Cognitive Decline in Probable Dementia with Lewy Bodies

| Change in Measure | Regression Coefficient (SE) | P Value | R² |
|-------------------|-----------------------------|---------|----|
| **Baseline PiB SUVR** |                            |         |    |
| DRS               | -22.40 (6.53)               | .002    | 0.312 |
| CDR-SOB           | 1.90 (0.63)                 | .005    | 0.215 |
| MMSE              | -2.25 (1.78)                | .22     | 0.046 |
| UPDRS-III         | -0.93 (1.74)                | .60     | 0.009 |
| AVLT              | -2.09 (0.95)                | .04     | 0.182 |
| BNT               | -2.39 (0.84)                | .009    | 0.245 |
| TMT-A             | 43.43 (12.96)               | .002    | 0.286 |
| ROCFT             | -4.26 (3.76)                | .27     | 0.047 |
| **Change in PiB SUVR** |                       |         |    |
| DRS               | -62.09 (86.67)              | .48     | 0.019 |
| CDR-SOB           | 16.17 (7.47)                | .04     | 0.124 |
| MMSE              | -28.40 (19.78)              | .16     | 0.059 |
| UPDRS-III         | 6.66 (19.39)                | .73     | 0.004 |
| AVLT              | -25.05 (10.04)              | .02     | 0.221 |
| BNT               | -13.81 (9.80)               | .17     | 0.074 |
| TMT-A             | 153.42 (167.73)             | .37     | 0.029 |
| ROCFT             | 30.08 (39.88)               | .46     | 0.021 |

Abbreviations: AVLT, Auditory Verbal Learning Test, delayed recall; BNT, Boston Naming Test; CDR-SOB, Clinical Dementia Rating, sum of boxes; DRS, Dementia Rating Scale; MMSE, Mini-Mental State Examination; PiB SUVR, carbon-11 labeled Pittsburgh compound B, standardized uptake value ratio; TMT-A, Trail Making Test, part A; UPDRS-III, Unified Parkinson Disease Rating Scale, part III, motor score.

* Regression coefficients for these associations are from simple linear regression models.
We compared change in PiB SUVR between participants with probable DLB and CU participants who were matched by age, sex, and APOE e4 status. We hypothesized that such matching could allow for an indirect evaluation of the effect of α-synuclein on the change in PiB SUVR in participants with probable DLB. Interestingly, we found that change in PiB SUVR in the probable DLB group did not diverge from the CU group. However, the trajectories of change in PiB SUVR seen in our study closely resembled the trajectories of change in PiB SUVR in previous longitudinal studies on change in PiB SUVR among CU patients, patients with MCI, and patients with AD.13-15 These similarities across large cohorts and studies would suggest a relatively uniform progression of β-amyloid pathology with respect to baseline β-amyloid load in various neurodegenerative syndromes (ie, AD and DLB) and individuals with no cognitive impairment.

Figure 2. Rate of Change in Clinical and Cognitive Measures by Baseline Carbon-11 Labeled Pittsburgh Compound B Standardized Uptake Value Ratios (PiB SUVR) and Change in PiB SUVR Among Patients with Probable Dementia with Lewy Bodies

A, Scatterplots show significant associations of the baseline cross-sectional PiB SUVR with the annualized rates of change in measures of clinical and cognitive decline in patients with probable DLB. B, Scatterplots show associations of annualized change in PiB SUVR with changes in measures of clinical and cognitive decline; associations with change in Clinical Dementia Rating, sum of boxes (CDR-SOB) score and Auditory Verbal Learning Test (AVLT), delayed recall are significant. The estimates for these associations are from simple linear regression models (Table 2). BNT indicates Boston Naming Test; DRS, Dementia Rating Scale; and TMT-A, Trail Making Test, part A.

Table 3. Sample Size Estimates for Hypothetical Clinical Trial in Dementia with Lewy Bodies*

| Measure            | Participants, No. (95% CI) |
|--------------------|----------------------------|
| Follow-up, mo      | 12                         | 12                         | 18                         | 18                         | 24                         | 24                         | 24                         | 36                         |
| Reduction in slope | 25                         | 25                         | 25                         | 25                         | 25                         | 25                         | 25                         | 50                         |
| PiB SUVR           | 602 (521-682)              | 151 (131-170)              | 258 (224-292)              | 65 (57-73)                 | 151 (131-171)              | 38 (33-43)                 | 61 (53-69)                 | 16 (14-17)                 |
| CDR-SOB            | 768 (655-882)              | 193 (164-221)              | 328 (280-377)              | 83 (71-95)                 | 193 (164-222)              | 49 (42-56)                 | 77 (66-89)                 | 20 (17-22)                 |
| DRS                | 867 (735-1000)             | 215 (181-251)              | 370 (309-431)              | 94 (79-108)                | 218 (185-250)              | 55 (46-63)                 | 87 (75-100)                | 22 (19-26)                 |
| MMSE               | 1583 (1262-1904)           | 397 (321-472)              | 681 (543-820)              | 170 (138-203)              | 395 (313-477)              | 99 (79-118)                | 159 (127-190)              | 40 (32-48)                 |

Abbreviations: CDR-SOB, Clinical Dementia Rating, sum of boxes; DRS, Dementia Rating Scale; MMSE, Mini-Mental State Examination; PiB SUVR, carbon-11 labeled Pittsburgh compound B, standardized uptake value ratio.

* Slope estimates and variances are from mixed models. Sample sizes are estimated using jackknife resampling as mean values along with asymptotic confidence intervals.
We note that the primary underlying pathology contributing to cognitive impairment in probable DLB patients is α-synuclein, with additional β-amyloid, NFT-tau, and possibly other pathologies, such as vascular disease or TAR DNA-binding protein-43. There is growing evidence of complex interactions between α-synuclein, β-amyloid, and NFT-tau, such that individuals with higher α-synuclein levels also tend to have higher β-amyloid and NFT-tau burdens. However, our findings suggest that the likely presence of α-synuclein in patients with mild probable DLB does not significantly alter the trajectory of β-amyloid accumulation as measured by PET.

The associations of baseline PiB SUVR with clinical and cognitive impairment have been ambiguous in probable DLB, which may be because of discrepancies in study design, small sample sizes of generally cross-sectional cohorts, and discrepancies in the interpretation of findings because observing an association is not equal to finding a causal association. Many studies combined patients with probable DLB, Parkinson disease dementia, or even MCI with Parkinson disease in 1 group. Some reported an association of higher PiB SUVR with lower MMSE scores, worse semantic memory, or lower CDR scores, whereas others did not find an association with MMSE or CDR scores. A study performed by our group observed an association of higher baseline PiB SUVR with worsening in CDR-SOB score over time. In the current study, we showed associations of baseline PiB SUVR with measures of longitudinal clinical and cognitive decline in patients with DLB. We found that a higher baseline PiB SUVR was associated with a more rapid decline as measured by DRS, CDR-SOB, AVLT, BNT, and TMT-A. Moreover, longitudinally, a greater change in PiB SUVR was associated with greater changes in CDR-SOB and AVLT scores. Thus, these 2 measures may be more sensitive and optimal for monitoring the cooccurrence of β-amyloid progression and clinical progression in probable DLB.

The association of memory decline with PiB SUVR in probable DLB is interesting because, early in the AD continuum, many studies did not confirm associations of baseline PiB SUVR or change in PiB SUVR with memory decline. This could be owing to floor effect in AD and MCI studies, in which baseline memory performance is already moderately to severely impaired, but in DLB, baseline memory scores are less impaired. Aside from methodological issues, a potential biological explanation has been that β-amyloid alone is insufficient to influence cognitive impairment directly and rather constitutes an early event causing a chain of downstream pathologic changes leading to cognitive decline. We have shown that a higher PiB SUVR in patients with probable DLB was associated with higher fluoride-18 flortaucipir (AV-1451) uptake. It remains to be seen whether the associations of baseline PiB SUVR and change in PiB SUVR with clinical and cognitive decline in probable DLB are direct effects of the progression of β-amyloid accumulation or whether it is the progression of α-synuclein or NFT-tau that influences cognitive decline, thus making the association of β-amyloid progression with clinical and cognitive decline indirect.

There was no association of PiB SUVR or change in PiB SUVR with changes in MMSE score, UPDRS-III score, or RCF-measured visual-perceptual performance. A potential explanation is lower statistical power or relatively narrow range of values in a probable DLB group of this size. Additionally, cognitive fluctuations may contribute to both short-term and long-term variability in clinical and cognitive evaluations. Moreover, the MMSE might not be an optimal measure of global cognitive decline in probable DLB, although some studies have suggested otherwise. Most importantly, these clinical and cognitive measures may be influenced by other pathologies, such as NFT-tau or α-synuclein, or by other neurologic and functional factors, such as mood or daytime sleepiness.

Sample size calculations for a hypothetical clinical trial in patients with probable DLB showed that measuring change in PiB SUVR followed by change in CDR-SOB score required the smallest sample size compared with the most often–used global cognitive and functional measures. Favorable sample size estimates using change in CDR-SOB score may again suggest that global functional measures may be more optimal for tracking overall impairment in probable DLB and may track better with complex symptoms, such as cognitive, motor, sleep-related, affective, and psychiatric symptoms. Conversely, a large sample size by change in MMSE score indicated that the MMSE may not be an optimal measure for global cognitive decline in probable DLB in a clinical trial setting.
Limitations
Our study has some limitations. Although this longitudinal study sample was larger than most cross-sectional β-amyloid PET studies among individuals with probable DLB, it may still not have the sufficient power to detect subtle associations or conduct subgroup analyses, such as change in PiB SUVr by APOE e4 status or by sex. The differences in change in PiB SUVr between CU APOE e4 carriers vs noncarriers were previously investigated but need to be investigated among individuals with probable DLB. A recent meta-analysis did not show greater prevalence of β-amyloid pathology by PET in women vs men within the AD continuum, but the sex effects need to be investigated further in probable DBL. Furthermore, CU participants may have various subthreshold pathologies owing to their population-based origin. Approximately 30% of CU participants have elevated baseline PiB SUVr. Some of them develop cognitive impairment and dementia, whereas others remain without cognitive impairment. It is likely that some of the CU participants in this study will later develop cognitive impairment. To mitigate this, CU participants had to remain clinically unimpaired during the follow-up period.

Conclusions
In this cohort study, the sigmoid trajectory of cumulative PiB SUVr by time observed in patients with probable DBL was consistent with the trajectories in the AD continuum, including the CU participants with lower baseline PiB SUVr. This finding suggests that, at sufficiently high baseline PiB SUVr, PiB uptake would reach equilibrium. This has potential implications for the timing of potential anti-β-amyloid strategies in probable DBL. Whereas the consequences of anti-β-amyloid approaches among patients with probable DBL are unknown at this time, associations of PiB SUVr and change in PiB SUVr with clinical and cognitive decline suggest that anti-β-amyloid strategies may have a place in clinical trials involving patients with probable DBL. However, how an anti-β-amyloid treatment would affect the progression of α-synuclein and NFT-tau in probable DBL remains to be seen. Because of the interactions among β-amyloid, α-synuclein, and NFT-tau, it is possible that targeting β-amyloid alone might contribute to overall pathologic progression and functional improvement in probable DBL patients. However, owing to the heterogeneity and complexity of underlying proteinopathies and clinical symptoms in probable DBL, individualized combination therapies with acetyl-cholinesterase inhibitors, lifestyle interventions, treatment of age-related comorbidities, and anti-tau treatments will need to be considered.
Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Nedelska, Schwartz, Lesnick, Przybelski, Kremers.

Obtained funding: Lowe, Kantarcı.

Administrative, technical, or material support: Boeve, Lowe, Serjent, Graff-Radford, Jack, Jr, Kantarcı.

Supervision: Nedelska, Lowe, Kantarcı.

Conflict of Interest Disclosures: Dr Schwarz reporting receiving grants from the National Institutes of Health outside the submitted work. Dr Boeve reported receiving grants from the National Institutes of Health, the Little Family Foundation, and the Turner Foundation during the conduct of the study; and receiving grants from Alector and Biogen; serving as an investigator for clinical trials sponsored by Axovant Gene Therapies and Biogen; receiving personal fees from the Tau Consortium for serving on its advisory board; and receiving royalties from Cambridge Medicine for *Behavioral Neurology of Dementia* outside the submitted work. Dr Lowe reported receiving grants from GE Healthcare, Siemens Healthcare, Avid Radiopharmaceuticals, the Minnesota Partnership for Biotechnology and Medical Genomics, and the Leukemia and Lymphoma Society; receiving research support from the National Institutes of Health, and serving as a consultant for Bayer Pharmaceuticals and Piramal Inc outside the submitted work. Dr Kremers reported receiving grants from the National Institutes of Health during the conduct of the study and grants from AstraZeneca, Biogen, and Roche outside the submitted work. Mr Serjent reported receiving grants from the National Institutes of Health during the conduct of the study; having stock options in Align Technology, CRISPR Therapeutics, Gilead Sciences, Globus Medical Inc, Inovio Pharmaceuticals, Ionis Pharmaceuticals, Johnson and Johnson, LHC Group Inc, Medtronic, Mesa Labs, Natus Medical Incorporated, Parexel International, and Varax Imaging outside the submitted work. Dr Graff-Radford reported receiving research support from the National Institutes of Health outside of the submitted work. Dr Fields reported receiving grants from the National Institutes of Health during the conduct of the study. Dr Knopman reported serving as a deputy editor of *Neurology*; serving on the data and safety monitoring boards for Eli Lilly and Co, Lundbeck Pharmaceuticals, and the Dominantly Inherited Alzheimer Disease Network Trials Unit; being an investigator in clinical trials supported by Baxter, Eli Lilly Pharmaceuticals, and the Tau Consortium; and receiving grants from the National Institutes of Health outside the submitted work. Dr Petersen reported receiving grants from the National Institutes of Health during the conduct of the study; and serving as a consultant for Roche Holding, Merck, Biogen, Eli Lilly and Company, Pfizer, Eli Lilly Pharmaceuticals, Wyeth Pharmaceuticals, GE Healthcare, and Eisai; receiving royalties from Oxford University Press for *Mild Cognitive Impairment*; serving on the data and safety monitoring board for Genentech; and presenting at GE Healthcare outside the submitted work. Dr Jack reported serving as a consultant for Eli Lilly and Co, serving on an independent data monitoring board for Roche Holding, and speaking for Eisai, but he received no personal compensation from any commercial entity; and receiving research support from the National Institutes of Health and the Alexander Family Alzheimer Disease Research Professorship of the Mayo Clinic outside the submitted work. Dr Kantarcı reported serving on the data and safety monitoring board for Takeda Pharmaceutical Company; receiving research support from Avid Radiopharmaceuticals and Eli Lilly and Co; and receiving funding from the National Institutes of Health, the Bluefield Project to Cure Frontotemporal Dementia, the National Center for Advancing Translational Sciences, and the Alzheimer’s Drug Discovery Foundation outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by grants U01-NS100620, P50-AG016574, U01-AG006786, RO1-AG01378, RO1-AG01851, RO1-AG040042, C06-RR018898, and RO1-NS080820 from the National Institutes of Health, by the Fondation Dr Corinne Schuler, the Mangurian Foundation for Lewy Body Research, the Elsa and Marvin Dekelboum Family Foundation, and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer Disease Research Program. Dr Nedelska was supported by Clinical and Translational Science Awards grant UL1 TRO2377 from the National Center for Advancing Translational Sciences.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The National Center for Advancing Translational Sciences is a component of the National Institutes of Health; the article’s contents are solely the responsibility of the authors and do not necessarily represent the official view of the National Institutes of Health.

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