Published Ahead of Print on April 4, 2022 as 10.1212/WNL.0000000000200259

Neurology®

The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000200259

Clinical Trajectories at the End of Life in Dementia Patients With Alzheimer Disease and Lewy Body Neuropathologic Changes

Author(s):
Yian Gu, PhD[1,2,3,4]; Anton Kociolek, MS[3]; Kayri K Fernandez, MS[3]; Stephanie A. Cosentino, PhD[1,2,3]; Carolyn Wei Zhu, PhD[5,6]; Zhezhen Jin, PhD[7]; James B. Leverenz, MD[8]; Yaakov B. Stern, PhD[1,2,3]

Corresponding Author:
Yian Gu, yg2121@cumc.columbia.edu

Affiliation Information for All Authors: 1. Department of Neurology, Columbia University Irving Medical Center, New York, NY, USA; 2. Gertrude H. Sergievsky Center, Columbia University Irving Medical Center, New York, NY, USA; 3. Taub Institute for Research in Alzheimer's Disease and the Aging, Columbia University Irving Medical Center, New York, NY, USA; 4. Department of Epidemiology, Columbia University Mailman School of Public Health, New York, NY, USA; 5. Department of Geriatrics and Palliative Care, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 6. Geriatrics Research, Education, and Clinical Center (GRECC), James J Peters VA Medical Center, Bronx, NY, USA; 7. Department of Biostatistics, Columbia University Mailman School of Public Health, New York, NY, USA; 8. Cleveland Lou Ruvo Center for Brain Health, Cleveland Clinic, Cleveland, OH, USA

Equal Author Contribution:

Contributions:
Yian Gu: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or intepretation of data
Anton Kociolek: Drafting/revision of the manuscript for content, including medical writing for content
Kayri K Fernandez: Drafting/revision of the manuscript for content, including medical writing for content
Stephanie A. Cosentino: Drafting/revision of the manuscript for content, including medical writing for content
Carolyn Wei Zhu: Drafting/revision of the manuscript for content, including medical writing for content
Zhezhen Jin: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or intepretation of data
James B. Leverenz: Drafting/revision of the manuscript for content, including medical writing for content
Yaakov B. Stern: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design

Figure Count:
1

Table Count:
2

Search Terms:
[26] Alzheimer's disease, [28] Dementia with Lewy bodies, [54] Cohort studies, [58] Natural history studies (prognosis), pathology

Acknowledgment:
This research was funded by the National Institute on Aging (AG07370). All authors report no conflict of interest.

Study Funding:
This study was funded by the National Institute on Aging (AG007370).

Disclosures:
The authors report no disclosures relevant to the manuscript.

Handling Editor Statement:
Solicited and not externally peer reviewed. The handling editor was Linda Hershey, MD, PhD, FAAN.

Abstract

Background and Objectives: Evaluating and understanding the heterogeneity in dementia course has important implications for clinical practice, healthcare decision-making, and research. However, inconsistent findings have been reported with regard to the disease courses of the two most common dementias, Alzheimer's disease (AD) and Dementia with Lewy bodies (DLB). Using autopsy-confirmed diagnoses, we aimed to examine the disease trajectories in the years before death among dementia patients with pure AD, pure DLB, or mixed (AD and DLB) pathologies.

Methods: The current retrospective longitudinal study included 62 participants with autopsy-confirmed diagnoses of pure AD (n=34), mixed AD and DLB (AD+DLB, n = 17), or pure DLB (n=11) from the Predictors 2 Cohort Study, a prospective, clinic-based, cohort of dementia patients. Generalized estimating equation models, with time zero at death, were used to examine the trajectory of cognition (Folstein Mini-Mental State Examination, MMSE), function (Activities of Daily Living, ADL), and dependence scale among patients with different autopsy-confirmed diagnosis (pure AD, AD+DLB, and pure DLB). The models were adjusted for age, sex, education, and baseline features including extrapyramidal signs, MMSE, ADL, and dependence scale.

Results: The participants on average received 9.4±4.6 assessments at 6-month intervals during a mean 5.4±2.9 years of follow-up time. The three groups were similar in both cognition and function status at baseline. Cognition and function were highly correlated among AD+DLB patients but not in pure AD or pure DLB patients at baseline. Patients of the three groups all declined in both cognition and function but had different trajectories of decline. More specifically, the pure DLB patients experienced approximately double the rate of both cognitive

decline and functional decline than the pure AD patients, and the mixed pathology group showed double the rate of functional decline as compared to pure AD patients.

Discussion: In this longitudinal study, we found that among patients with dementia, those with Lewy body pathology experienced faster cognitive and functional decline than those with pure AD pathology.

Key words: Lewy Body dementia, Alzheimer's disease, autopsy, prognosis.

Introduction

Alzheimer's disease (AD), the leading cause of dementia, is clinically characterized by progressive memory and functional decline, and pathologically characterized by neurofibrillary tau tangles beginning in the medial temporal lobes and amyloid plaques starting in the neocortex[1]. Dementia with Lewy bodies (DLB), the second most common type of dementia, has core clinical features including cognitive fluctuations, extrapyramidal motor features, rapid eye movement sleep behavior disorder, and visual hallucinations and is pathologically characterized by the accumulation of aggregated α-synuclein into Lewy bodies and Lewy neurites in neurons and neuronal processes[2]. Understanding differences in how these diseases progress has important implications for clinical management, healthcare utilization and decision making.

The current literature regarding the trajectory of clinical symptoms in AD compared with DLB show inconsistent results. Some studies suggest that DLB has a faster decline relative to AD[3-8], but not others[9-11]. Part of this inconsistency may be due to changes over time in clinical diagnosis guidelines[12]. Moreover, past studies have relied mainly on clinical diagnoses which likely represent a mixture of underlying pathologies[13-17]. For example, approximately half of AD patients also have α-synuclein pathology of the Lewy body type[2, 13, 18, 19], and similarly, up to half of the LBD patients have pathology characteristic of AD[16, 20].

In contrast to clinical diagnoses, studies based on pathologically confirmed diagnoses provide an objective gold standard of disease and thus are needed to fully understand disease trajectories across these illnesses. Whereas cross-sectional neuropathological studies provide a "snapshot" of clinical symptoms at specific disease stages, and inform the pathologic substrates of specific clinical symptoms,[19, 21-24] longitudinal studies with pathological dementia diagnosis are necessary to understand the overall trajectory of disease course. Such studies are scarce and

often have few repeated ante-mortem clinical measurements, short follow-up periods, begin at later disease stages, or do not follow patients to the end of life[5, 11, 14, 15, 24-31].

In addition to cognitive impairment, loss of function, especially the ability to perform self-care tasks[32], is a defining feature of these degenerative diseases[33] and is inevitably linked to the dependence of the patient on family members or formal caregivers. However, few studies have examined the trajectories of non-cognitive features, such as functioning and dependence. In the current study, we aimed to compare the trajectories of key clinical features, including cognition, function, and dependence, in three autopsy-confirmed groups: AD, AD+DLB, and DLB, based on the Predictors 2 study[34], a longitudinal, multi-center, clinic-based study with detailed bi-annual clinical assessments designed to predict major disease outcomes in AD and DLB patients.

Methods

Participants

The participants of the current study were from the Predictors 2 study, a cohort of dementia patients clinically diagnosed with predominantly AD but also DLB[34]. Recruitment of this cohort was initiated in 1997 following the same methods as the Predictors 1 cohort[34]. Patients who were diagnosed with mild to moderate probable dementia in the clinic were referred by their physicians to be recruited into this study. Participants were then followed up every 6 months with repeated clinical measurements including medical, neuropsychological, functional and dependence measures. AD was clinically diagnosed according to NINCDS-ADRDA criteria[33] and DLB was diagnosed according to the 1996 Consensus Guidelines[36] for probable DLB. A total of 211 subjects with probable AD and 28 with DLB were recruited into the cohort

at three sites: Columbia University, Johns Hopkins University, and Massachusetts General Hospital. We limited our analyses to participants who had pathological data available and had longitudinal measure of clinical symptoms. Among 78 participants who donated brains, we excluded eight participants who did not have α-synuclein immunohistochemistry staining to confirm the presence of Lewy body disease/synucleinopathy, seven participants who did not have pathological features required for AD or DLB diagnosis, and one participant who had no follow-up visits to assess clinical trajectory. Thus, the current study included 62 participants who had autopsy-confirmed diagnosis of AD (n = 34), mixed AD and DLB (n = 17), or DLB (n=11), and had longitudinal measure of clinical symptoms. The 16 excluded participants were not significantly different from the included participants in age, sex, education, and baseline clinical symptoms.

Standard Protocol Approvals, Registrations, and Patient Consents The project was approved by the institutional review board at each of the three study sites. All patients and their proxy decision makers provided written informed consent.

Cognitive Measures

Participants underwent detailed cognitive and clinical assessment at baseline and follow-up visits. Global cognitive status was assessed with Folstein Mini-Mental State Examination (MMSE) (0-30, a higher score indicating better cognitive performance).

Functional Assessment

Functional capacity of the patients was reported by the patient's reliable informant using the Blessed Dementia Rating Scale (BDRS) Activities of Daily Living (ADL) sub-score[32], including seven instrumental ADL items: difficulty performing chores around the house (e.g., cleaning), handling money, remembering short lists (e.g., shopping), walking across a room, walking several blocks, recognizing one's whereabouts, and remembering things that happened recently, and three basic ADL items: eating, dressing, and bladder and bowel control. The response options for instrumental ADL items were none (0), some (0.5), and a lot of difficulty (1), and for basic ADL items, ranged from 0 to 3, with higher score indicating more difficulty. The total ADL score was the sum of scores on all 10 items (range: 0-16), with higher scores indicating worse functional capacity. The ADL scale has good reliability and validity, with reliability coefficients reported to be between 0.60 and 0.80[32].

Dependence Scale

The Dependence Scale (DS) was developed to measure the amount of assistance AD patients require to fulfill daily functions[35]. The DS was administered to the patient's reliable informant who lived with the patient or one who was well informed about the patient's daily activities and needs. The DS consists of 13 items representing different levels of care required by a patient, from mild (e.g., "Does the patient need frequent help finding misplaced objects?") to severe items (e.g., "Does the patient need to be tube fed?"). Two items ("needs reminders to manage chores", "needs help to remember important things such as appointments") are coded as 0 (no), 1 (occasionally, at least once a month), and 2 (frequently, at least once a week), while responses to the rest of the items are coded dichotomously, indicating whether the patient

requires assistance in a particular item (0=no, 1=yes). The total DS score ranges 0-15, with higher score indicating greater dependence on others. The DS scale has strong psychometric properties and is reliable and valid, with reliability coefficients ranging between 0.66 and 0.93[35, 36]. It is related to, but distinct from, existing cognitive, functional, and behavioral measures of disease severity, and predicts disease progression independent of other measures of functional and cognitive status[35, 36].

Other Demographic and Clinical Measurements

Patients' age at baseline, sex, and highest level of education were recorded. Sex was used as a dichotomous variable with male as the reference group. Age and years of education were used as continuous variables. Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD) was used to measure patients' psychotic, behavioral, and depressive symptoms[37]. The Unified Parkinson's Disease Rating Scale (UPDRS)[38] was used to measure extrapyramidal signs (EPSs) and treated as a binary variable with 1 indicating severity rating of mild-to-moderate or greater on any item.

Pathological Diagnoses

The pathological categorization for each case into AD, DLB or AD-DLB was based on review of neuropathologic reports, and slides if necessary, by a co-author (JBL), and staging of AD and Lewy body pathology outlined in the National Institute on Aging-Alzheimer's Association (NIA-AA) pathologic assessment of AD and Lewy body disease[39]. For this study, an AD pathologic diagnosis required both a staging of moderate or frequent neuritic plaques (CERAD criteria)[40] and Braak Stage IV, V or VI neurofibrillary tangle stage[41]. Braak Stages IV,

V and VI have been consistently associated with clinical dementia[42, 43]. For a pathologic DLB classification, Lewy body pathology required a staging of either limbic or neocortical Lewy body disease[44]. Participants were diagnosed as *pure AD* (pure-AD) if they had above-mentioned AD neuropathologic changes but no LB neuropathologic changes or with insufficient LB pathology density or spread to meet criteria for DLB, *pure DLB* (pure-DLB) if had limbic or neocortical LB neuropathologic changes but insufficient neuropathologic changes for AD, *AD+DLB* if met the above-defined neuropathological changes for both DLB and AD, or *negative* pathology if did not meet the pathologic criteria for either AD or DLB as defined above.

Statistical analysis

The demographic and clinical characteristics were summarized by mean and standard deviation (SD) for continuous measures and by frequency and proportions for categorical measures. The measures were compared among the three autopsy-confirmed groups using Chi-square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Pearson correlation coefficient was used to examine the relationship among baseline MMSE, ADL, and DS.

We used generalized estimating equation (GEE) models, with linear identity link function and independent working correlation matrix structure, to examine the trajectory of the outcomes. The time variable was the main predictor in the model, which was calculated as years before death, with time zeroed on confirmed death date and a visit occurring one year before death coded as -1, 2 years before death coded as -2, etc.[3] The model was adjusted for age, sex, education, the autopsy-confirmed diagnosis group (pure-AD, AD+DLB, pure-DLB), and baseline features including extrapyramidal signs, MMSE, ADL, and DS.

To compare the trajectories among the diagnosis groups (as the predictor, treated as a categorical variable with pure-AD being the reference group), separately for the three outcomes (i.e., MMSE, ADL, DS), the interaction term between "diagnosis group X time" was added to the GEE model, with a significant interaction indicating different trajectory rate between AD+DLB and pure-AD, and between pure-DLB and pure-AD. The models were adjusted for age, sex, education, and extrapyramidal signs at baseline (Model 1), and additionally adjusted for the outcome status at baseline, individually (Model 2) and simultaneously (Model 3). Non-linear trajectories of decline including quadratic and piecewise regression were assessed for suitability but did not improve model fit over the linear alternative, consistent with the literature[15].

Due to the unbalanced duration from the baseline to death among diagnostic groups, we performed sensitivity analyses by limiting the analysis to the last five years of life and repeated the analyses. As APOE was missing in a quarter of the participants (n=15) and cholinesterase inhibitor use was missing in 11 participants, we did not include these two variables in the main analyses but performed sensitivity analyses adjusting for APOE and cholinesterase inhibitor use in addition to Model 3 covariates.

All analyses were conducted using SPSS 26. Due to the exploratory nature of this analysis, the significance level was defined as $p < 0.05$ without corrections for multiple comparisons.

Data Availability

De-identified participant data will be made available to qualified investigators with appropriate data transfer agreements and institutional board approval.

Results

Characteristics of the dementia patients with postmortem diagnoses of pure-AD, AD+DLB, and pure-DLB.

At time of recruitment, the participants of the study were 73.5±7.9 (Mean±SD) years old, had 15±2.9 years of education, scored 20.8±4.3 on MMSE, 4.68±3.0 on ADL, and 4.48±2.6 on DS (Table 1). The majority (87%) of the participants had mild dementia with the other13% having moderate (Clinical Dementia Rating, CDR≥2) dementia. Half of the participants were female; 36% had extrapyramidal signs, and 42% had psychotic symptoms (Table 1). At baseline, MMSE was negatively correlated with ADL ($r= -0.51$, $p<0.0001$) and DS ($r= -0.43$, $p<0.0001$), while the latter two were positively correlated ($r=0.79$, $p<0.0001$). The participants on average received 9.4±4.6 assessments on 6-month intervals during a mean 5.4±2.9 years of follow-up time, and survived 6.0±3.5 years with 54.8% surviving at least 5 years (Table 1).

About two-thirds of the study participants entered the study with a clinical diagnosis of AD (c-AD), 91% (42 of 46) of whom were confirmed to have AD pathology; among patients with a clinical diagnosis of DLB (c-DLB), 88% (14 of 16) were found to have LB neuropathologic changes in the autopsy. However, 30% (14/46) of the c-AD patients also had LB neuropathological changes and 56% (9/16) of the c-DLB patients had AD pathology.

Patients with pure-DLB were more likely to be men compared with the pure-AD ($p=0.044$) or AD+DLB ($p=0.016$) groups, while the latter two groups did not differ ($p=0.424$). Patients with pure-AD were less likely to have extrapyramidal signs compared with AD+DLB ($p=0.004$) or pure-DLB ($p<0.0001$) group, while the latter two did not differ ($p=0.295$). The pure-AD patients on average survived longer than pure-DLB patients from baseline (7.0±3.7 vs. 4.4±2.7 years, $p=0.031$). Five-year survival rate was higher ($p=0.018$) among the pure-AD

patients (68%) than the pure-DLB patients (27%).

At the last visit, patients with AD+DLB had worse ADL (p=0.015) and DS (p=0.038) scores than the pure-DLB patients. The AD+DLB patients were followed up to a later stage of life compared to pure-AD patients (p=0.01).

The pairwise correlations among MMSE, ADL, and DS were all statistically significant in AD+DLB patients (r=-0.85 for MMSE-ADL, r=-0.83 for MMSE-DS, and r=0.93 ADL-DS correlations, p<0.0001 for all). The ADL was highly correlated with DS in both pure-AD (r = 0.76, p<0.0001) and pure-DLB (r = 0.71, p=0.014) patients. However, MMSE was neither correlated with ADL in pure-AD (r=-0.25, p=0.152) or pure-DLB (r=-0.39, p=0.237) patients, nor with DS in pure-AD (r = -0.20, p=0.277) or pure-DLB (r = -0.55, p=0.077) patients.

Change of cognition and function in dementia patients at the end of life.

Among all subjects, there was a significant change over time for all outcomes. Specifically, MMSE declined 0.74 (SE=0.17, p<0.0001), ADL increased 0.66 (SE=0.14, p<0.0001), and DS increased 0.47 (SE=0.09, p<0.0001) points per year.

Differential trajectory of cognition and function among dementia patients with postmortem diagnoses of pure-AD, AD+DLB, and pure-DLB.

For pure-AD patients, MMSE declined 0.61(SE=0.19, p=0.002), ADL increased 0.55 (SE=0.15, p<0.0001), and DS increased 0.40 (SE=0.09, p<0.0001) points per year (Table 2, Model 3; Figure 1). Compared with the pure-AD group, the pure-DLB group experienced a faster decline in MMSE [b= -1.02 (SE=0.39), p=0.010] and faster deterioration in DS [b=0.41 (SE=0.17), p=0.015] in the fully adjusted model (Table 2, Model 3; Figure 1). That is, compared

with a pure-AD patient who experienced 0.61 points decline in MMSE in one year, a pure-DLB patient of similar characteristics would decline additional 1.02 points, or a total of 1.63 points per year (approximately 2.7 times of the rate in pure-AD patients). In other words, the changes a pure-DLB patient experienced in one year was similar to the changes typically seen in a pure-AD patient of similar characteristics in approximately 2.7, 1.8, and 2.0 years for MMSE, ADL, and DS, respectively.

Compared with the pure-AD group, the AD+DLB group experienced a faster deterioration in ADL [b=0.48 (SE=0.21), p=0.026] (Table 2, Model 3; Figure 1). The annual change of ADL in an AD+DLB patient experienced was similar to the change typically seen in a pure-AD patient of similar characteristics in approximately 1.9 years.

There was no difference in the trajectory of MMSE, ADL, or DS between AD+DLB and pure-DLB groups (data not shown).

Supplementary analyses

Limiting the analyses to the assessments within 5 years preceding death, the results in the fully adjusted model were similar to, even with larger effect sizes, the main results, although the results were no longer significant. Specifically, compared with the AD group, the DLB group experienced a non-significant faster deterioration in MMSE [b= -1.50 (SE=0.96), p=0.120], DS [b=0.53 (SE=0.32), p=0.096], and ADL [b=0.81 (SE=0.50), p=0.106]. There was no difference between pure-AD and AD+DLB groups. Compared with the AD+DLB group, the pure-DLB group experienced a significantly faster deterioration in DS [b= 0.77 (SE=0.31), p=0.01] and in ADL [b= 0.94 (SE=0.48), p=0.053], but not in MMSE [b= -1.10 (SE=0.93), p=0.24],.

When we included APOE status (ε4 carriers, non-carriers, and unknown) into the Model 3, we found the results were attenuated but remained similar to the main findings. The results remained similar to main results when cholinesterase inhibitor use was further adjusted in the models (data not shown).

Discussion

In this clinic-based, longitudinal study of an autopsy-confirmed dementia patient cohort, we described and compared the trajectories among pure-AD, pure-DLB, and AD+DLB patients. We found the three groups were similar in both cognitive and functional status at baseline but had different trajectories of decline. In comparison to the pure-AD group, the pure-DLB patients experienced approximately doubled rates of cognitive and functional decline, and the AD+DLB experiencing approximately doubled rates of functional decline only.

The clinical diagnoses of the study participants were confirmed in most patients by presence of the corresponding pathological features in autopsy. However, consistent with the literature, a large proportion of the patients also had other neuropathological changes[2, 13, 16, 18, 20]. The current study showed that pure-AD patients were less likely to have extrapyramidal signs[19, 22] at study enrollment than those with LB neuropathology.

We found baseline cognition and function were highly correlated in AD+DLB patients but not in pure-AD or pure-DLB patients, probably due to the mixed pathologies affecting a wider range of brain areas responsible for the phenotypes. The correlation between cognition and function has rarely been evaluated in the literature, and the only autopsy-based study evaluated both cognition and function and found cognition predicted ADL in both autopsy-confirmed AD and DLB patients[45]. In clinically diagnosed AD and DLB patients, the additional functional impairments in DLB patients compared to AD patients were found to be mainly attributable to

extrapyramidal motor symptoms[46]. Thus, the stronger cognition-function correlation among AD+DLB patients than in pure-AD patients in the current study might at least partially be due to the higher prevalence of extrapyramidal symptoms in AD+DLB patients. Meanwhile, cognition fluctuation is one of the core clinical features in DLB patients[2], while the AD+DLB patients might have progressive cognitive deterioration and more consistent cognitive impairment due to the underlying AD pathology, thus overriding the cognitive fluctuation feature and leading to a stronger cognition-function correlation compared with pure-DLB patients[2, 11]. More studies are needed to confirm our findings and explore the reasons for difference in cognition-function correlation in AD+DLB patients than pure-AD or pure-DLB patients. Such studies may also help to confirm whether the extrapyramidal signs and a parallel impairment in cognition and function seen in a clinically diagnosed AD patient indicate the underlying mixed AD and DLB pathologies.

Nevertheless, we found the individual key cognitive and functional features were similar across the three groups at enrollment and at the last visit, except that the AD+DLB patients were functionally worse compared to the pure-DLB group at the last visit, which does not seem to be explained by the starting level, assessments proximity to the death time, or duration of follow-up. Meanwhile, while there was no significant difference in symptoms at the last assessment between pure-AD and pure-DLB groups, it is unclear whether pure-AD patients would have been worse than pure-DLB at the last visit if the pure-AD patients continued to be assessed until a later date. Cross-sectional neuropathological studies have suggested that concomitant LB pathology makes little difference on the clinical phenotype of AD[19, 21-24]. With the potential limitations of such 'snapshot' analyses mentioned above, however, it may be important to examine the longitudinal trajectory to capture the full disease course.

Many longitudinal studies have focused on comparing the duration of disease or survival. Consistent with the reported 1.6 years shorter survival in c-DLB than in c-AD in 11 previous studies[3, 4], we found that pure-AD patients had longer disease duration than pure-DLB patients, suggesting pure-AD patients have better survival than pure-DLB patients. In one study[9] using CSF biomarkers to assess pathology, it was found that AD+DLB patients had a higher risk of nursing home admittance and death while no differences in the rate of cognitive decline was found between groups. To be noted, the study had a mean 1.65 years of follow up and neuropsychological scores were derived from multiple imputation due to missing data. Another study found different survival rates but similar cognitive trajectories between autopsy-diagnosed AD and DLB patients, but the study was limited by having few repeated cognitive measures[26].In contrast, some studies do not find significant difference in disease duration or survival between patients with different pathologies[21]. In another study, disease duration was not different across the three groups, but the AD+DLB and DLB groups had a faster cognitive decline than the AD group [25]. One potential limitation of studies examining survival, though, is that the disease duration or survival can be influenced by many factors, such as comorbidities especially cardiovascular diseases and pneumonia, hospice use, and end-of-life treatment intensity. Thus, disease course is best described not by the survival time itself, but rather by direct, repeated measurements of the key clinical features of the disease, ideally through a reasonably long follow up time with multiple measures.

With an average of nine repeated measurements over five years, we found the three groups had different rates of decline, with the pure-DLB or AD+DLB patients experiencing approximately doubled rates of decline as compared to the pure-AD patients. Only a few longitudinal autopsy studies have examined cognitive trajectories or overall disease stage

trajectories. Some studies have suggested that AD+DLB patients exhibit faster cognitive decline or disease progression compared with pure-AD[11, 15, 25]. However, other studies report no difference in rate of cognitive decline [14, 24, 26, 27]. In a large national autopsy sample from National Alzheimer's Coordinating Center, AD+DLB patients were found to have faster decline in CDR-SB than pure-AD patients[15]. In the Arizona Study of Aging and Neurodegenerative Disorders study, the Alzheimer's disease with Lewy bodies group (those with LBD pathology restricted to a limbic-predominant stage but not yet in the neocortical regions), but not the pure-DLB group, had a significantly greater MMSE decline compared to the pure-AD group [5]. There are few autopsy-based studies comparing disease progression of pure-DLB with pure-AD, or pure-DLB with AD+DLB [28]. We found faster cognitive decline in pure-DLB than in pure-AD in our study, consistent with previous findings that showed a faster MMSE decline [25, 31] or shorter survival[26, 31] in pure-DLB than in pure-AD. However, in several pathological studies, pure-DLB patients did not seem to decline significantly faster than pure-AD patients[5, 15, 24, 26, 29, 30]. Several previous studies have found that there was no difference in survival between participants with pure-DLB and AD+DLB group[14, 26], consistent with our findings.

Therefore, existing evidence has been inconsistent, but rarely have studies found pure-AD patients to decline faster than pure-DLB or AD+DLB. Given the emerging evidence suggesting both AD+DLB and pure-DLB patients may have faster decline than pure-AD, it is possible that the LB pathology might play a key role in aggressive disease progression. The faster decline of AD+DLB than pure-AD patients can be due to increased neurodegeneration as a result of the multiple pathologies[47]. More research is needed to fully understand the potential synergistic interactions of AD and DLB pathology at molecular levels. In addition, as the neocortical-type (diffuse) LB pathology and limbic-type (transitional) LB may have different

patterns of cognitive decline for special cognitive domains[14] and survival rates[48, 49], future studies may want to further investigate the different types of LB pathology and use more specific cognitive measures.

Functional trajectory has rarely been compared among autopsy-confirmed dementia patients. We previously reported that compared to AD patients, patients with DLB were significantly more impaired in ADLs and showed greater dependence on caregivers at first evaluation, but there were no significant differences in the rate of decline between the two groups[29]. In a separate cross-sectional study, no difference in functional impairment was observed between AD and DLB [24]. Findings from the current study that both AD+DLB and pure-DLB groups had faster functional decline than pure-AD groups may point to a role of the LB pathology in functional changes of dementia patients.

This study has some limitations. Participants in our study were not incident dementia cases, so we may have missed the observation of the earliest period of the disease. However, most of the participants were at the mild stage of dementia when enrolled into the study, and the age at baseline was similar to the age at onset of dementia symptoms reported by other studies[3]. Similar to other neuropathological studies that have an over-representation of APOE ε4 carriers[9, 22], the current study also found a high percentage of participants carrying APOE ε4 allele, which might indicate a potential selection bias. The MMSE is an overall measure of cognition, and more specific neuropsychological tests tapping into individual cognitive domains might have larger or smaller difference among the three pathological groups[19]. We only examined a few cognitive and functional measures, however, other clinical symptoms, such as urinary incontinence, that shows higher prevalence in DLB than in AD[50] are worth of exploration in future studies. Although the clinical symptoms are assumed to be driven by the underlying

neuropathological changes, the post-mortem neuropathological assessments may not reflect neuropathological burden when clinical progression was measured as neuropathologic changes might continue to accumulate over time. However, limiting the analyses to the last 5 years before death found similar results to the main findings. We did not adjust for APOE in our main analysis as a large number of subjects did not have APOE ε4 information. However, sensitivity analyses taking into consideration of APOE did not change main findings, same as previously reported[17]. Previous studies showed that individuals meeting neuropathological criteria for AD and having insufficient Lewy body pathology to meet distribution and density thresholds for DLB may have a faster clinical course than pure-AD[5]. We did not examine this group separately due to small number of participants (n=6). However, including these participants in the pure-AD group may have biased our results toward null and would not change our main findings that the pure-DLB and AD-DLB groups had faster decline than pure-AD participants. The relatively small sample size also limited our ability to perform additional subgroup analyses according to severity of AD neuropathology, types of LB pathology[15, 48, 49], or sex[26]. Finally, the study participants were predominantly white and well□educated, limiting the generalizability of the findings.

Our study has many advantages. The current study added innovative information to the literature by providing an almost complete disease history for pure-AD, AD+DLB, and pure-DLB patients. The clinical symptoms were directly and frequently measured (bi-annually, on average nine antemortem visits) throughout the disease course until close to death, ensuring more accurate and reliable information compared to less frequent measures. We performed comprehensive clinical assessments in a standardized and consistent manner. To our knowledge, the current study is the first to examine the functional and dependence trajectory, among

dementia patients. The pathological data were carefully reviewed and diagnosed by an experienced neuropathologist according to the most recent guidelines. We included three diagnosis groups to provide a more comprehensive comparison of these conditions involving AD and DLB pathologies.

In conclusion, in this longitudinal study, we found dementia patients with Lewy body pathology experienced faster cognitive and functional decline than pure-AD patients. The findings of this autopsy-based study have great implications for clinical management, future clinical study design, and research on pathology-specific biomarkers.

References

1. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Neurobiology of aging 1997;18:S1-2.

2.McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017;89:88-100.

3.Mueller C, Soysal P, Rongve A, et al. Survival time and differences between dementia with Lewy bodies and Alzheimer's disease following diagnosis: A meta-analysis of longitudinal studies. Ageing Res Rev 2019;50:72-80.

4.Price A, Farooq R, Yuan JM, Menon VB, Cardinal RN, O'Brien JT. Mortality in dementia with Lewy bodies compared with Alzheimer's dementia: a retrospective naturalistic cohort study. BMJ open 2017;7:e017504.

5.Malek-Ahmadi M, Beach TG, Zamrini E, et al. Faster cognitive decline in dementia due to Alzheimer disease with clinically undiagnosed Lewy body disease. PLoS One 2019;14:e0217566.

6.Kramberger MG, Auestad B, Garcia-Ptacek S, et al. Long-Term Cognitive Decline in Dementia with Lewy Bodies in a Large Multicenter, International Cohort. Journal of Alzheimer's disease : JAD 2017;57:787-795.

7.Wilson RS, Capuano AW, Bennett DA, Schneider JA, Boyle PA. Temporal course of neurodegenerative effects on cognition in old age. Neuropsychology 2016;30:591-599.

8.Galasko DR, Gould RL, Abramson IS, Salmon DP. Measuring cognitive change in a cohort of patients with Alzheimer's disease. Stat Med 2000;19:1421-1432.

9.Lemstra AW, de Beer MH, Teunissen CE, et al. Concomitant AD pathology affects clinical manifestation and survival in dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2017;88:113-118.

10.Breitve MH, Chwiszczuk LJ, Hynninen MJ, et al. A systematic review of cognitive decline in dementia with Lewy bodies versus Alzheimer's disease. Alzheimers Res Ther 2014;6:53.

11.Kraybill ML, Larson EB, Tsuang DW, et al. Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. Neurology 2005;64:2069-2073.

12.Yamada M, Komatsu J, Nakamura K, et al. Diagnostic Criteria for Dementia with Lewy Bodies: Updates and Future Directions. J Mov Disord 2020;13:1-10.

13.Hamilton RL. Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. Brain Pathol 2000;10:378-384.

14.Schneider JA, Arvanitakis Z, Yu L, Boyle PA, Leurgans SE, Bennett DA. Cognitive impairment, decline and fluctuations in older community-dwelling subjects with Lewy bodies. Brain 2012;135:3005-3014.

15.Brenowitz WD, Hubbard RA, Keene CD, et al. Mixed neuropathologies and estimated rates of clinical progression in a large autopsy sample. Alzheimers Dement 2017;13:654-662.

16.Irwin DJ, Hurtig HI. The Contribution of Tau, Amyloid-Beta and Alpha-Synuclein Pathology to Dementia in Lewy Body Disorders. J Alzheimers Dis Parkinsonism 2018;8.

17.Brenowitz WD, Keene CD, Hawes SE, et al. Alzheimer's disease neuropathologic change, Lewy body disease, and vascular brain injury in clinic- and community-based samples. Neurobiology of aging 2017;53:83-92.

18.Nelson PT, Abner EL, Schmitt FA, et al. Modeling the association between 43 different clinical and pathological variables and the severity of cognitive impairment in a large autopsy cohort of elderly persons. Brain Pathol 2010;20:66-79.

19.Yoshizawa H, Vonsattel JP, Honig LS. Early neuropsychological discriminants for Lewy body disease: an autopsy series. J Neurol Neurosurg Psychiatry 2013;84:1326-1330.

20.Barker WW, Luis CA, Kashuba A, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord 2002;16:203-212.

21.Roudil J, Deramecourt V, Dufournet B, et al. Influence of Lewy Pathology on Alzheimer's Disease Phenotype: A Retrospective Clinico-Pathological Study. Journal of Alzheimer's disease : JAD 2018;63:1317-1323.

22.Savica R, Beach TG, Hentz JG, et al. Lewy body pathology in Alzheimer's disease: A clinicopathological prospective study. Acta Neurol Scand 2019;139:76-81.

23.Stern Y, Jacobs D, Goldman J, et al. An investigation of clinical correlates of Lewy bodies in autopsy-proven Alzheimer disease. Arch Neurol 2001;58:460-465.

24.Lopez OL, Hamilton RL, Becker JT, Wisniewski S, Kaufer DI, DeKosky ST. Severity of cognitive impairment and the clinical diagnosis of AD with Lewy bodies. Neurology 2000;54:1780-1787.

25.Nelson PT, Kryscio RJ, Jicha GA, et al. Relative preservation of MMSE scores in autopsy-proven dementia with Lewy bodies. Neurology 2009;73:1127-1133.

26.Williams MM, Xiong C, Morris JC, Galvin JE. Survival and mortality differences between dementia with Lewy bodies vs Alzheimer disease. Neurology 2006;67:1935-1941.

27.Hamilton JM, Salmon DP, Galasko D, et al. Visuospatial deficits predict rate of cognitive decline in autopsy-verified dementia with Lewy bodies. Neuropsychology 2008;22:729-737.

28.Breitve MH, Chwiszczuk LJ, Brønnick K, et al. A Longitudinal Study of Neurocognition in Dementia with Lewy Bodies Compared to Alzheimer's Disease. Front Neurol 2018;9:124.

29.Stavitsky K, Brickman AM, Scarmeas N, et al. The progression of cognition, psychiatric symptoms, and functional abilities in dementia with Lewy bodies and Alzheimer disease. Arch Neurol 2006;63:1450-1456.

30.Ballard CG, O'Brien J, Lowery K, et al. A prospective study of dementia with Lewy bodies. Age Ageing 1998;27:631-636.

31.Olichney JM, Galasko D, Salmon DP, et al. Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. Neurology 1998;51:351-357.

32.Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968;114:797-811.

33.McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939-944.

34.Stern Y, Folstein M, Albert M, et al. Multicenter study of predictors of disease course in Alzheimer disease (the "predictors study"). I. Study design, cohort description, and intersite comparisons. Alzheimer Dis Assoc Disord 1993;7:3-21.

35.Stern Y, Albert SM, Sano M, et al. Assessing patient dependence in Alzheimer's disease. J Gerontol 1994;49:M216-222.

36.Lenderking WR, Wyrwich KW, Stolar M, et al. Reliability, validity, and interpretation of the dependence scale in mild to moderately severe Alzheimer's disease. Am J Alzheimers Dis Other Demen 2013;28:738-749.

37.Devanand DP. Use of the Columbia University Scale to assess psychopathology in Alzheimer's disease. Int Psychogeriatr 1997;9 Suppl 1:137-142; discussion 143-150.

38.Louis ED, Lynch T, Marder K, Fahn S. Reliability of patient completion of the historical section of the Unified Parkinson's Disease Rating Scale. Movement disorders : official journal of the Movement Disorder Society 1996;11:185-192.

39.Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta neuropathologica 2012;123:1-11.

40.Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41:479-486.

41.Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta neuropathologica 1991;82:239-259.

42.Knopman DS, Parisi JE, Salviati A, et al. Neuropathology of cognitively normal elderly. Journal of neuropathology and experimental neurology 2003;62:1087-1095.

43.Gold G, Bouras C, Kövari E, et al. Clinical validity of Braak neuropathological staging in the oldest-old. Acta neuropathologica 2000;99:579-582; discussion 583-574.

44.McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863-1872.

45.Hamilton JM, Salmon DP, Raman R, et al. Accounting for functional loss in Alzheimer's disease and dementia with Lewy bodies: beyond cognition. Alzheimers Dement 2014;10:171-178.

46.McKeith IG, Rowan E, Askew K, et al. More severe functional impairment in dementia with lewy bodies than Alzheimer disease is related to extrapyramidal motor dysfunction. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 2006;14:582-588.

47.Nedelska Z, Ferman TJ, Boeve BF, et al. Pattern of brain atrophy rates in autopsy-confirmed dementia with Lewy bodies. Neurobiology of aging 2015;36:452-461.

48.Ferman TJ, Aoki N, Crook JE, et al. The limbic and neocortical contribution of α-synuclein, tau, and amyloid β to disease duration in dementia with Lewy bodies. Alzheimers Dement 2018;14:330-339.

49.Graff-Radford J, Aakre J, Savica R, et al. Duration and Pathologic Correlates of Lewy Body Disease. JAMA Neurol 2017;74:310-315.

50.Ransmayr GN, Holliger S, Schletterer K, et al. Lower urinary tract symptoms in dementia with Lewy bodies, Parkinson disease, and Alzheimer disease. Neurology 2008;70:299-303.

Table 1. Demographics and clinical characteristics of the study participants.

Characteristics	**All subjects**	**AD**	**AD+DLB**	**DLB**	**p**
Number of subjects	62	34	17	11	
Age, years, mean (SD)	73.47 (7.87)	74.18 (7.97)	72.65 (7.97)	72.55 (7.90)	0.743
Female, N (%)	31 (50)	**18 (52.9%)** [b]	**11 (64.7%)** [c]	**2 (18.2%)** [b,c]	**0.049**
Education, years, mean (SD)	15.05 (2.94)	14.62 (3.04)	15.53 (2.76)	15.64 (2.94)	0.451
Follow up duration, years, mean (SD; range); median (interquartile)	5.42 (2.94); 4.3 (2.5-7.1)	5.91 (2.71); 5.6 (2.8-7.7)	5.06 (3.24); 4.4 (1.6-7.8)	4.45 (3.12); 2.5 (2.2-4.0)	0.306
Duration from last visit to death, years, mean (SD)	1.28 (1.64)	**1.75 (1.87)** [b]	**0.51 (0.69)** [b]	1.03 (1.52)	**0.030**
Duration from first visit to death, years, mean (SD); median (interquartile)	6.04 (3.51); 5.2 (3.1-8.3)	**6.96 (3.7)** [b]; 7.0 (4.4-9.3)	5.27 (3.14); 4.8 (2.4-8.3)	**4.35 (2.69)** [b]; 3.2 (2.6-6.1)	0.055
Five-year survival from baseline, N (%)	34 (54.8)	**23 (67.6)** [b]	8 (47.1)	**3 (27.3)** [b]	**0.049**
Number of visits, mean (SD)	9.4 (4.6)	10.1 (4.3)	9.2 (5.4)	7.5 (3.5)	0.233
APOE ε4 carrier, N (%)[d]	29 (61.7)	19 (65.5)	6 (60)	4 (50)	0.72
Clinical diagnosis					<0.0001
AD, N (%)	46 (74.2)	32 (94.1)	10 (58.8)	4 (36.4)	
DLB, N (%)	16 (25.8)	2 (5.9)	7 (41.2)	7 (63.6)	
Cholinesterase inhibitor use, N (%)[d]	48 (94.1)	30 (100)	7 (87.5)	11 (84.6)	0.10
At baseline					
Moderate stage (CDR≥2), N (%)	8 (12.9)	4 (11.8)	4 (23.5)	0 (0)	0.212
Extrapyramidal symptoms, N (%)	22 (35.5)	**5 (14.7)** [a,b]	**9 (52.9)** [a]	**8 (72.7)** [b]	**<0.0001**
Any psychiatric symptom, N (%)	26 (41.9)	13 (39.4）	8 (47.1)	5 （55.6）	0.658
MMSE, years, mean (SD)	20.77 (4.33)	21.15 (3.58)	19.44 (5.09)	21.55 (5.20)	0.353
BDRS-ADL, mean (SD)	4.68 (3.03)	4.05 (2.59)	6.03 (3.71)	4.50 (2.69)	0.087
Dependence scale, mean (SD)	4.48 (2.59)	4.24 (2.46)	5.13 (2.96)	4.22 (2.44)	0.515

At the last visit	20.77 (4.33)	21.15 (3.58)	19.44 (5.09)	21.55 (5.20)	0.353
MMSE, years, mean (SD)	11.73 (7.33)	12.45 (7.76)	10.00 (5.47)	12.09 (9.03)	0.555
BDRS-ADL, mean (SD)	11.91 (4.27)	11.78 (4.04)	**13.65 (3.79)** [c]	**9.64 (4.82)** [c]	**0.048**
Dependence scale, mean (SD)	9.26 (2.92)	9.12 (2.98)	**10.35 (2.29)** [c]	**8.00 (3.26)** [c]	0.104
At death					
Age at death, years, mean (SD)	80.05 (8.49)	81.73 (8.44)	78.53 (8.37)	77.24 (8.40)	0.218
Vascular burden, N (%)	21 (34.4)	13 (39.4)	4 (23.5)	4 (36.4)	0.529

P values were from ANOVA test for continuous variables and chi-square test for categorical variables. Post-hoc LSD analyses were used to examine pair-wise differences among the three diagnosis groups, and results are noted as a: $p<0.05$ between AD and AD+DLB; b: $p<0.05$ between AD and DLB; c: $p<0.05$ between AD+DLB and DLB.

d:15 individuals did not have APOE information, and 11 individuals did not report cholinesterase inhibitor use.

Table 2. Rate of change on cognition and function in autopsy-confirmed dementia patients with different postmortem diagnoses.

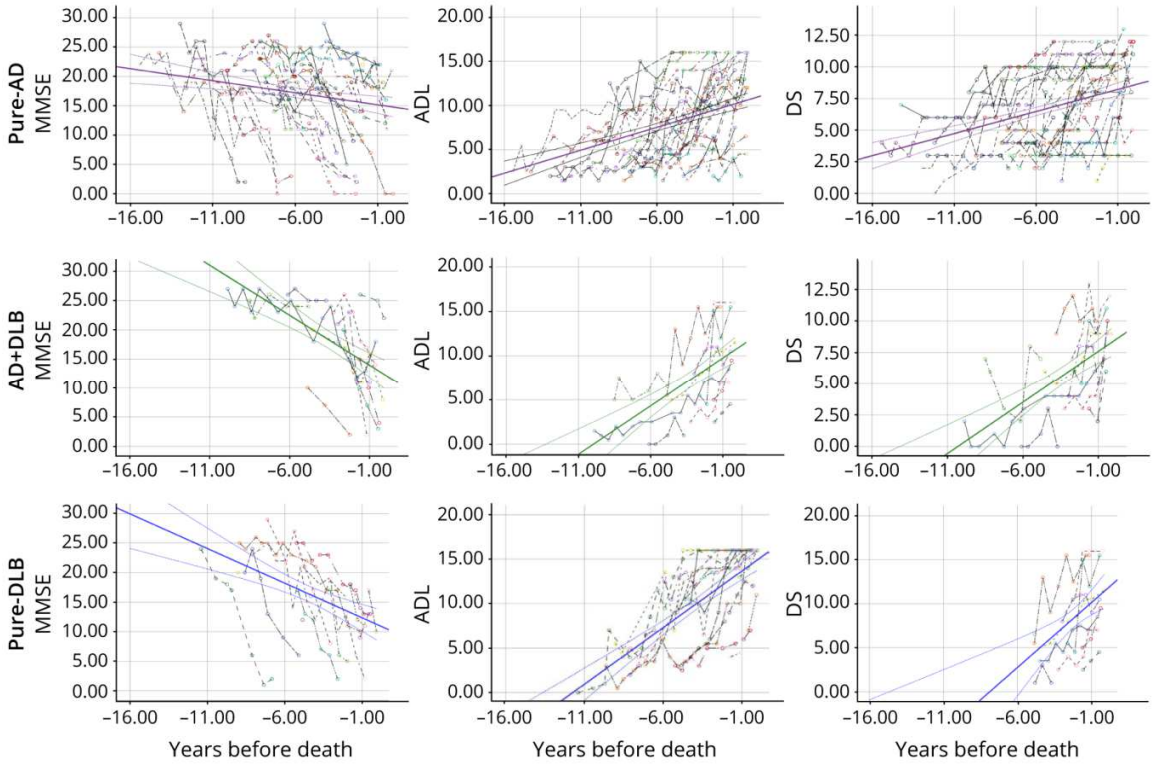
		Model 1			Model 2			Model 3		
		B	SE	p	B	SE	p	B	SE	p
MMSE	Time	**-0.635**	**0.210**	**0.003**	**-0.563**	**0.215**	**0.009**	**-0.608**	**0.193**	**0.002**
	DLB*time	**-1.097**	**0.413**	**0.008**	**-0.931**	**0.392**	**0.018**	**-1.020**	**0.394**	**0.010**
	Mixed*time	-0.550	0.363	0.130	-0.398	0.407	0.328	-0.339	0.420	0.420
ADL	Time	**0.565**	**0.153**	**<0.0001**	**0.531**	**0.163**	**0.001**	**0.552**	**0.153**	**<0.0001**
	DLB*time	0.568	0.325	0.080	0.402	0.268	0.133	0.446	0.254	0.079
	Mixed*time	**0.727**	**0.188**	**<0.0001**	**0.514**	**0.218**	**0.018**	**0.478**	**0.215**	**0.026**
DS	Time	**0.383**	**0.100**	**<0.0001**	**0.390**	**0.092**	**<0.0001**	**0.400**	**0.094**	**<0.0001**
	DLB*time	0.469	0.257	0.068	**0.386**	**0.166**	**0.020**	**0.408**	**0.167**	**0.015**
	Mixed*time	**0.470**	**0.145**	**0.001**	0.257	0.161	0.111	0.259	0.161	0.109

The AD group was treated as the reference group in all models, and DLB indicated the patients with DLB diagnosis and mixed indicated the patients with AD with concomitant LBD diagnosis. Time is the number of years before death time, coded as -1 for 1 year before death, -2 for 2 years before death, etc. Model 1 was adjusted for age, sex, education, and baseline extrapyramidal signs. Model 2 was additionally adjusted for the corresponding baseline outcome. Model 3 was adjusted for all Model 1 variables as well as all the three outcomes (MMSE, ADL, and DS) at baseline.

Figure 1. Cognition and functional change in the years preceding death in autopsy-confirmed dementia patients.

The figures show cognition (MMSE) and functional (ADL, DS) changes in the years preceding death in autopsy-confirmed dementia patients, for dementia patients with pure-AD (purple), AD+DLB (green), or pure-DLB (blue). Each colored dashed line shows the observed MMSE (first column), ADL (second column), and DS (third column) scores for each individual.

Abbreviations: MMSE, mini□mental state examination; ADL, activities of daily living; DS, dependence scale.



Clinical Trajectories at the End of Life in Dementia Patients With Alzheimer Disease and Lewy Body Neuropathologic Changes

Yian Gu, Anton Kociolek, Kayri K Fernandez, et al.

Neurology published online April 4, 2022
DOI 10.1212/WNL.0000000000200259