

RESEARCH ARTICLE

Amyloid, p-tau, neurofilament light, and α -synuclein cerebrospinal fluid biomarkers across Alzheimer's disease, dementia with Lewy bodies, and Parkinson's disease

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Abstract

INTRODUCTION: Mounting evidence suggests overlapping pathology across Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and Parkinson's disease (PD), yet its extent and clinical implications remain unclear.

METHODS: Cerebrospinal fluid (CSF) amyloid beta (A β)42/40, phosphorylated tau 181 (p-tau181), neurofilament light chain (NfL), and total α -synuclein were centrally measured using fully-automated Elecsys immunoassays in 347 participants (European Platform for Neurodegenerative Diseases [EPND] cohort) and compared between groups. Associations of amyloid and tau positivity with cognitive and motor function were evaluated.

RESULTS: Compared to controls, amyloid and tau levels were abnormal in DLB, but not in PD. Amyloid and tau positivity in DLB were associated with worse global cognitive outcomes, but not with motor performance. NfL levels were elevated across diseases, and total α -synuclein levels were associated with tau positivity.

DISCUSSION: AD pathology is observed in DLB, and related to worse cognition, but it is less observed in PD. CSF NfL captures non-disease-specific processes, whereas

CSF total α -synuclein likely reflects CSF tau positivity. Results can help patient management in clinical practice and trials.

KEYWORDS

Alzheimer's disease, amyloid, cerebrospinal fluid, cognition, dementia with Lewy bodies, Elecsys, longitudinal, motor function, neurodegenerative diseases, neurofilament light, Parkinson's disease, risk factors, tau, α -synuclein

Highlights

- We centrally measured key cerebrospinal fluid (CSF) markers in Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and Parkinson's disease (PD) via fully-automated assays.
- AD pathology was observed in DLB, and related to worse cognition, but less in PD.
- CSF neurofilament light chain (NfL) captured nondisease-specific neurodegenerative processes.
- CSF total α -synuclein reflected CSF tau positivity in all groups.
- Results can aid patient diagnosis and management in clinical care and trials.

1 | BACKGROUND

Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and Parkinson's disease (PD) are among the most common neurodegenerative diseases and lead to loss of functional independence via their impact on cognition, motor function, or both. Although they are classified as distinct diseases due to differences in pathological substrates and clinical features, increasing evidence suggests that these diseases share considerably overlapping pathology.¹

Hallmarks of AD, namely amyloid plaques and tau tangles, are found at autopsy in $\approx 50\%$ – 80% of DLB and 25% – 50% of PD patients.^{2–5} Likewise, α -synuclein pathology, the hallmark of PD and DLB, is reported in $\approx 30\%$ – 50% of AD brains.^{2,6} In vivo assessment of co-pathology between AD, DLB, and PD via cerebrospinal fluid (CSF) biomarkers offers unique opportunities to improve clinical patient care and the design of clinical trials. However, it remains unclear how key pathological markers, namely amyloid, tau, and α -synuclein, as well as neurodegeneration biomarkers, such as neurofilament light (NfL), compare head-to-head across AD, DLB, and PD in CSF. Previous studies have most often evaluated the biomarkers in single disease groups and/or focused on one or a few biomarkers at a time. In addition, most studies have measured the biomarkers using enzyme-linked immunosorbent assays (ELISAs), which are characterized by poor intra- and inter-laboratory reproducibility.⁷ Together, these limitations have introduced variability unrelated to disease processes and have limited the comparability of findings across diseases. Elecsys immunoassays are novel tools that offer robust biomarker quantification across lots and laboratories by running on fully-automated platforms.⁸ Leveraging such assays to comprehensively investigate biomarkers across all disease groups simultaneously can therefore help reduce disease-unrelated variability and clarify overlapping pathologies and their implications for risk factors and clinical function.

Therefore, the primary aim of this multi-center study was to compare amyloid, p-tau, NfL, and total α -synuclein CSF biomarkers, centrally measured using fully-automated Elecsys immunoassays, between individuals with AD, DLB, PD, and controls in a unique multi-disease dataset. Based on findings from the first aim, we secondly aimed to evaluate the associations of relevant disease pathology biomarkers with neurodegeneration risk factors (age, sex, and apolipoprotein E [APOE] $\epsilon 4$ carriership) and clinical performance and decline across diseases. Findings are relevant to improve the research and clinical management of patients with AD, DLB, or PD disease manifestations, and to optimize participant selection and follow-up in AD, DLB, or PD clinical trials.

2 | METHODS

2.1 | Design and participants

This multi-center cohort study used data from the European Platform for Neurodegenerative Diseases (EPND) project.⁹ Between 2022 and 2024, EPND selected from seven European centers 350 participants with: (1) diagnosis of AD (biomarker-based), DLB, PD, or healthy controls (i.e., cognitively unimpaired, amyloid negative), and (2) available paired CSF and plasma samples. For the current study, we included from the EPND cohort participants with available baseline CSF amyloid, p-tau, NfL, and total α -synuclein measured via EPND, and without a diagnosis of other neurodegenerative disease than AD, DLB, and PD. Of the 350 participants, 3 were excluded due to unavailability of CSF marker measurements for insufficient sample volume (1 with AD, 1 with PD, and 1 with DLB, all from different cohorts), yielding a final sample of 347 participants.

RESEARCH IN CONTEXT

- 1. Systematic review:** PubMed and Google Scholar were searched for studies evaluating amyloid, tau, neurodegeneration, and/or α -synuclein cerebrospinal fluid (CSF) biomarkers in Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and/or Parkinson's disease (PD). Previously, neurodegenerative diseases and/or biomarkers were evaluated separately, and biomarkers measured through poorly reproducible assays, limiting finding validity. We addressed this by centrally measuring biomarkers across diseases using fully-automated immunoassays.
- 2. Interpretation:** AD pathology was frequent in DLB, but less in PD. In DLB, AD pathology was related to worse cognitive outcomes, but not worse motor performance. Neurofilament light chain (NfL) represented non-disease-specific neurodegenerative processes, and total α -synuclein mirrored CSF tau positivity.
- 3. Future directions:** Confirmation in independent cohorts is needed, also including PD patients with advanced cognitive impairment. α -Synuclein pathology, rather than total levels, should be assessed using seed amplification assays. Long-term clinical studies are required to validate the prognostic utility of amyloid biomarkers in DLB.

Participants were selected from the following cohorts: Amsterdam Dementia Cohort (ADC)¹⁰; DZNE Clinical Register Study of Neurodegenerative Disorders (DESCRIBE, www.dzne.de/en/research/studies/clinical-studies/describe/); Gut microbiota for Alzheimer's disease/ Brain connectivity and metacognition in persons with subjective cognitive decline (COSCODE/gMAD)¹¹; Luxembourg Parkinson's study (LPS)¹²; Marker in GBA-assoziertem Parkinson - Früherkennung, Progression, Mechanismen, Protektion (MiGAP, www.dzne.de/en/research/studies/clinical-studies/migap/); Czech Brain Aging Study (CBAS)¹³; Norwegian part of the European DLB consortium (NOR-DLB)¹⁴; Dementia Disease Initiation (DDI)¹⁵; DZNE - Longitudinal Cognitive Impairment and Dementia Study (DELCODE)¹⁶; DZNE - Degeneration Controls and Relatives (DANCER, www.dzne.de/en/research/studies/clinical-studies/dancer/). Participants were recruited by the cohorts via research or clinical settings (eText 1). Cohorts contributing to each diagnostic group are shown at eTable 1. All centers obtained approval of protocol and relevant documentation by local ethics committees or institutional review boards. Cohort studies were performed in accordance with the Declaration of Helsinki. Participants provided written informed consent before enrollment into their cohorts, and material/data transfer agreements were signed as relevant.

2.2 | CSF measurements

CSF samples were collected at each center following established local procedures and shipped on dry ice to VUmc (Amsterdam) for aliquoting and randomization. Next, samples were transferred to University of Gothenburg for measurement of amyloid beta ($A\beta$)₄₂, $A\beta$ ₄₀, phosphorylated tau181 (p-tau181), NfL, and total α -synuclein via the NeuroToolKit (NTK), a panel of exploratory robust prototype assays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland).¹⁷ Elexsys immunoassays were used for marker quantification ($A\beta$ ₄₂, $A\beta$ ₄₀, and p-tau181 on the cobas e601; NfL and total α -synuclein on the cobas e411). Measurements were performed after calibration and quality control by board-certified laboratory technicians blinded to clinical information. To control for potential blood contamination, samples were visually checked for hemolysis, and none was detected. Values outside immunoassay detection ranges (seven values for $A\beta$ ₄₂, five for p-tau181) were set to detection limits. The previously established cutoffs of <0.06 for CSF $A\beta$ ₄₂/40^{18,19} and >24 pg/mL for CSF p-tau181²⁰ were used to establish amyloid and tau positivity, respectively, since NTK measures have been proven consistent across cohorts, and since positivity estimates aligned with those from Gaussian mixture modeling and from local assays.

2.3 | Baseline diagnosis

AD was defined by CSF $A\beta$ ₄₂/40 positivity (across the clinical spectrum) and absence of DLB or PD diagnosis. Based on cognitive status as assessed by the centers, participants with AD were further classified as preclinical AD (cognitively unimpaired, including subjective cognitive decline [SCD]), prodromal AD (mild cognitive impairment), or AD dementia. DLB and PD were defined using the diagnosis assigned by the centers, based on established criteria^{21–25} (more information at eTable 2). Controls were cognitively unimpaired (including SCD) individuals as assessed by the centers without a diagnosis of AD, DLB, or PD, and with negative CSF $A\beta$ ₄₂/40 status.

2.4 | Clinical measurements

Clinical assessment was performed at each center following established local procedures. Global cognition was evaluated using Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) score; when MMSE was unavailable, we converted MoCA to MMSE as described previously (harmonized MMSE measure).²⁶ To assess cognitive function across domains, we selected measures of executive functioning, attention, memory, language, and visuo-construction (summarized in eTable 3), standardizing scores when different tests were used for the same domain (with lower z-scores representing worse function). Motor function was assessed using Part III

of the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

2.5 | Statistical analyses

Baseline characteristics were compared across diagnoses using analysis of variance (ANOVA) for continuous variables and chi-square for categorical variables. Linear regression models were used to compare CSF levels of A β 42/40, p-tau181, NfL, and total α -synuclein between AD, DLB, PD, and controls. To assess the influence of cognitive level, we stratified groups with substantial variability in baseline cognition (i.e., with a standard deviation [SD] >3 in the harmonized MMSE), namely AD and DLB, into low (harmonized MMSE $\leq$ 23), intermediate (harmonized MMSE 24–27), and high (harmonized MMSE $\geq$ 28) cognitive level. We then compared the CSF marker levels in the AD and DLB stratified groups with those in the PD and control groups. Subsequently, we compared within each diagnostic group CSF p-tau181, NfL, and total α -synuclein levels by amyloid status, and CSF NfL and total α -synuclein levels by tau status; here, we did not compare amyloid levels to avoid redundancy, as they typically decrease before tau abnormality.

Next, we evaluated associations of amyloid and tau positivity with risk factors (age, sex, APOE ϵ 4 carriership), clinical performance, and clinical decline in all groups, using controls as reference. To avoid confounding, five tau-positive participants were excluded as controls in tau analyses. When APOE ϵ 4 carriership or clinical function were associated with amyloid positivity in DLB or PD, these variables were compared between the amyloid-positive DLB or PD subgroups and the AD group. Associations between tau positivity and clinical function in AD were evaluated only when sufficient data were available in DLB or PD for comparison. Overall, to support statistical power, associations were evaluated only when the size of each biomarker-stratified subgroup was $\geq$ 10.

Cross-sectional associations were tested using linear regression (continuous outcomes) or logistic regression (binary outcomes). Longitudinal associations were tested using random-intercept and random-slopes linear mixed models (R package *nlme*). All models were adjusted for age and biological sex, unless either was used as outcome. Models with cognitive outcomes were additionally adjusted for education years. To align with statistical model assumptions, four extreme outliers in NfL and total α -synuclein were capped at the 99th percentile (winsorization), and all CSF marker concentrations were log-transformed. Similarly, neuropsychological tests z-scores were capped at $\pm$ 5 values. Statistical significance was defined as two-sided $p < 0.05$. Data were analyzed via R v2024.9.0.375 between 2024 and 2025.

3 | RESULTS

3.1 | Sample characteristics

Sample characteristics are shown in Table 1. A total of 150 individuals were classified as AD (45 preclinical AD, 52 prodromal AD, 53

AD dementia), 66 as DLB (8 prodromal DLB, 1 possible DLB, 9 probable DLB, 48 DLB unspecified), 74 as PD (2 PD with mild cognitive impairment [MCI], 3 PD with dementia, 42 idiopathic Parkinson's syndrome, 27 PD unspecified), and 57 as control. On average, AD and DLB participants were older than PD and controls. Compared to DLB, AD participants were more often female. Education years were higher in controls compared to all groups. AD participants were most often APOE ϵ 4 carriers, followed by DLB, PD, and finally, controls. Global cognition level was lowest in DLB, and lower in AD compared to controls, but it was similar between PD and controls, highlighting that our PD group was mainly cognitively unimpaired. Motor function was most affected in PD, and more affected in DLB than in controls.

3.2 | CSF markers across AD, DLB, and PD

A β 42/40 levels were lower in AD compared to all groups (AD vs control mean difference (MD) = -0.74 , 95% confidence interval (CI); hereafter between square brackets) -0.83 to -0.65 ; AD vs DLB MD = -0.37 [-0.45 to -0.29]; AD vs PD MD = -0.66 [-0.74 to -0.58]; all $p < 0.001$), and were lower in DLB compared to PD (MD = -0.28 [-0.38 to -0.19], $p < 0.001$) and to controls (MD = -0.37 [-0.47 to -0.27], $p < 0.001$). Conversely, A β 42/40 levels were similar in PD and controls (MD = -0.08 [-0.18 to 0.01], $p = 0.097$; Figure 1A). Similarly, p-tau181 levels were higher in AD compared to all groups (AD vs control MD = 0.46 [0.35 to 0.58]; AD vs DLB MD = 0.30 [0.19 to 0.40]; AD vs PD MD = 0.50 [0.40 to 0.61]; all p 's < 0.001), and were higher in DLB compared to PD (MD = 0.21 [0.08 to 0.33], $p = 0.002$) and to controls (MD = 0.16 [0.03 to 0.30], $p = 0.018$), but were similar in PD and controls (MD = -0.04 [-0.17 to 0.09], $p = 0.538$, Figure 1B). NfL levels were elevated in all disease groups compared to controls (vs AD MD = 0.37 [0.22 to 0.52]; vs DLB MD = 0.33 [0.15 to 0.50]; both p 's < 0.001 ; vs PD MD = 0.17 [0.01 to 0.34], $p = 0.037$), and were higher in AD than in PD (MD = 0.20 [0.06 to 0.33], $p = 0.005$), but were similar in AD and DLB (MD = 0.04 [-0.09 to 0.18], $p = 0.525$; Figure 1C). Total α -synuclein levels did not differ between groups (AD vs controls MD = 0.11 [-0.08 to 0.30], $p = 0.255$; DLB vs controls MD = 0.03 [-0.19 to 0.25], $p = 0.798$; PD vs controls MD = 0.04 [-0.17 to 0.25], $p = 0.701$; eTable 4; Figure 1D).

As a sensitivity analysis in AD and DLB, we assessed the influence of cognitive level on the biomarker level group differences. Cognitive level was classified as high, intermediate, and low in 45, 59, and 41 AD participants, and in 16, 18, and 30 DLB participants, respectively. Compared to the overall analysis, in DLB, p-tau181 and NfL levels were higher than controls only among individuals with intermediate or low cognitive scores (eTable 5). Similarly, in AD, NfL levels were higher than controls only among individuals with intermediate or low cognitive scores (eTable 5). A β 42/40 and total α -synuclein associations were not influenced by cognitive level in AD and DLB (eTable 5).

Overall, 61% [95% CI 48 to 72] of individuals with DLB and 20% [12 to 32] of individuals with PD had positive amyloid CSF levels. In DLB, amyloid positivity was associated with higher p-tau181 lev-

TABLE 1 Baseline sample characteristics.

	Control (N = 57)	AD (N = 150)	DLB (N = 66)	PD (N = 74)	p-value
Age	62.8 (9.2) ^{b,c}	69.4 (8.3) ^{a,d}	70.3 (6.7) ^{a,d}	62.7 (10.2) ^{b,c}	<0.001
Female sex	23 (40%)	67 (45%) ^c	16 (24%) ^b	24 (32%)	0.026
Education, years	14.6 (3.3) ^{b,c,d}	12.8 (3.4) ^a	12.4 (3.2) ^a	13.2 (3.5) ^a	0.002
APOE $\epsilon 4$ carriers	5 (9.1%) ^{b,c,d}	97 (65%) ^{a,c,d}	28 (47%) ^{a,b,d}	16 (25%) ^{a,b,c}	<0.001
MMSE	29.0 (1.1) ^{b,c}	25.2 (4.0) ^{a,c,d}	23.8 (3.9) ^{a,b,d}	28.7 (1.6) ^{b,c}	<0.001
MDS-UPDRS-III	3.3 (2.5) ^{c,d}	6.0 (7.9) ^{c,d}	20.9 (14.5) ^{a,b,d}	31.3 (15.0) ^{a,b,c}	<0.001
CSF A β 42/40	0.072 (0.008) ^{b,c}	0.034 (0.009) ^{a,c,d}	0.052 (0.020) ^{a,b,d}	0.068 (0.013) ^{b,c}	<0.001
CSF p-tau181	16.1 (5.3) ^{b,c}	28.5 (13.4) ^{a,c,d}	20.6 (8.5) ^{a,b,d}	15.5 (5.7) ^{b,c}	<0.001
CSF NfL	107.8 (76.8) ^{b,c}	191.7 (136.1) ^{a,d}	202.4 (170.6) ^{a,d}	139.5 (123.6) ^{b,c}	<0.001
CSF total α -syn	108.3 (75.4)	126.9 (67.2)	128.4 (102.4)	112.3 (67.9)	0.200

Abbreviation: AD, Alzheimer's disease; ANOVA, analysis of variance; APOE, apolipoprotein E; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; MDS-UPDRS-III, Movement Disorders Society Unified Parkinson Disease Rating Scale Part III; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain; PD, Parkinson's disease.

The table shows key baseline characteristics by diagnostic group. Values represent mean (SD) for continuous variables or participant number (%) for dichotomous variables. CSF marker levels are expressed in pg/mL. Due to extreme outliers, NfL and α -synuclein levels were winsorized at the 99th percentile. As described in Section 2.4, MMSE consisted of MMSE score or, when this was unavailable, MoCA score converted to MMSE (harmonized MMSE). Education years were available for 340 participants (56 control, 150 AD, 66 DLB, 68 PD), APOE $\epsilon 4$ carriership for 328 (55 control, 150 AD, 59 DLB, 64 PD), harmonized MMSE for 331 (55 control, 143 AD, 62 DLB, 71 PD), and MDS-UPDRS-III for 110 (7 control, 6 AD, 26 DLB, 71 PD). Variables were compared across groups using one-way ANOVA with post hoc pairwise t-tests for continuous variables, and chi-square with post hoc pairwise proportion tests for categorical variables. Unadjusted group comparisons $p < 0.05$ compared to:

^acontrols.

^bAD.

^cDLB.

^dPD.

els (MD = 0.23 [0.07 to 0.39], $p = 0.004$), whereas it was not in PD (MD = -0.01 [-0.19 to 0.17], $p = 0.907$). Amyloid status was not associated with NfL and total α -synuclein levels in either DLB or PD (eTable 6). Positive tau CSF levels were observed in 57% [48 to 65] of AD, 26% [16 to 38] of DLB, and 9% of PD [4 to 19] and of controls [3 to 20]. In AD, tau positivity was associated with higher NfL levels (MD = 0.42 [0.28 to 0.57], $p < 0.001$); this was also observed in DLB (MD = 0.34 [0.09 to 0.58], $p = 0.008$). Conversely, in PD or in controls, tau status was not associated with NfL levels (eTable 7). In all groups, tau positivity was associated with higher total α -synuclein levels (T+ vs T-: MD = 0.57 [0.40 to 0.75] in AD; MD = 0.55 [0.24 to 0.85] in DLB; MD = 0.81 [0.39 to 1.24] in PD; all p 's < 0.001; MD = 0.55 [0.04 to 1.05], $p = 0.033$ in controls; Figure 2).

3.3 | Amyloid and tau associations with risk factors and clinical function

Because total α -synuclein levels did not differ between groups and were related to tau positivity, we only analyzed associations of risk factors and clinical function with amyloid and tau as biomarkers of pathology. Tested associations, based on subgroup size ≥ 10 , are presented at eTable 8. Due to small subgroup sizes, in PD tau and longitudinal amyloid analyses could not be performed. Longitudinal analyses were therefore only performed for DLB, AD, and controls.

Average clinical follow-up years were 1.8 (SD 1.0, range 1–6) for AD, 2.6 (SD 2.1, range 1–10) for DLB, and 3.0 (SD 2.2, range 1–11) for controls, with an average of three visits for all groups (more information on follow-up by disease and outcome at eTable 9).

3.3.1 | Associations with risk factors: age, sex, APOE $\epsilon 4$

In both DLB and PD, amyloid positivity was associated with older age (A+ vs A-: MD = 4.82 [0.54 to 9.11], $p = 0.028$ in DLB; MD = 7.27 [2.34 to 12.20], $p = 0.004$ in PD), but not with sex (A+ vs A-: MD = -0.43 [-1.64 to 0.78], $p = 0.485$ in DLB; MD = -0.72 [-1.91 to 0.47], $p = 0.236$ in PD). In DLB, amyloid positivity was also associated with more frequent APOE $\epsilon 4$ carriership (logOR = 2.10 [0.83 to 3.37], $p = 0.001$), whereas in PD this was not clearly the case (logOR = 1.41 [-0.02 to 2.84], $p = 0.053$). Interestingly, post hoc analysis revealed that the frequency of APOE $\epsilon 4$ carriership in amyloid-positive DLB individuals was similar to that observed in the AD group (logOR = 0.10 [-0.66 to 0.87], $p = 0.788$, Figure 3).

In DLB, tau positivity was associated with older age (MD = 5.69 [1.25 to 10.13], $p = 0.012$), whereas this was not observed in AD (MD = 0.13 [-2.47 to 2.72], $p = 0.925$). Tau positivity was not associated with sex or APOE $\epsilon 4$ carriership in either AD or DLB (eTable 10).

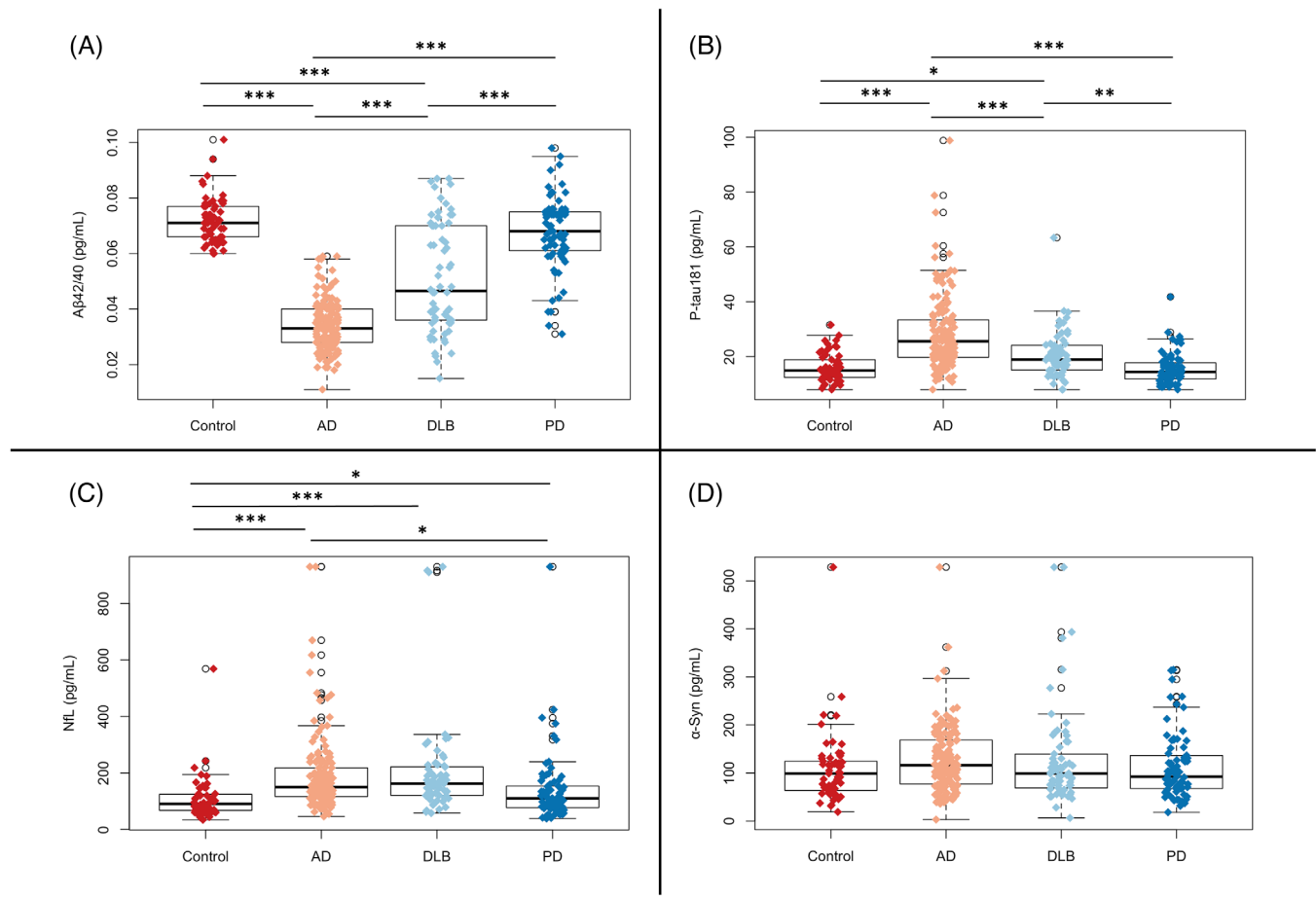


FIGURE 1 Cerebrospinal fluid (CSF) amyloid beta ($A\beta$)42/40, phosphorylated tau 181 (p-tau181), neurofilament light chain (NfL), and total α -synuclein levels across Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and Parkinson's disease (PD) and controls. The boxplots show levels of CSF (A) $A\beta$ 42/40, (B) p-tau181, (C) NfL, and (D) total α -synuclein across AD, DLB, PD, and controls. Due to extreme outliers, NfL and α -synuclein levels were winsorized at the 99th percentile. The line through the boxes represents the median, box boundaries represent the interquartile range (IQR), and whiskers extend to 1.5 x IQR. Log-transformed marker levels were compared between groups via linear regression models adjusted for age and sex. Group comparisons *** $p < 0.001$, ** $p < 0.005$, * $p < 0.05$.

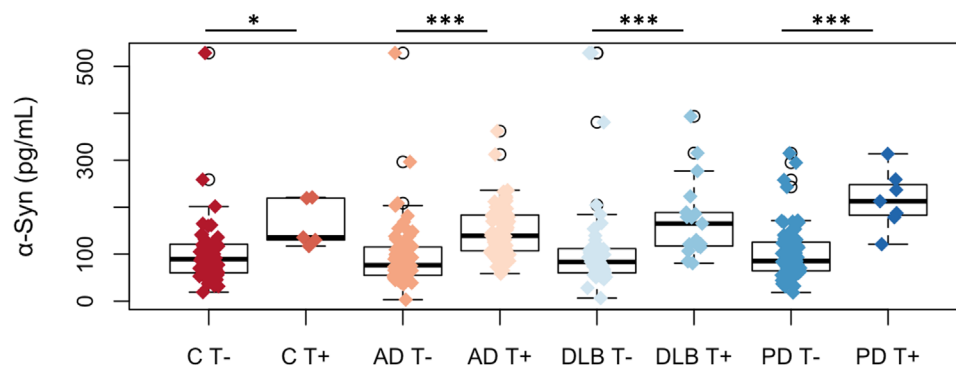


FIGURE 2 Cerebrospinal fluid (CSF) total α -synuclein levels in tau-positive and tau-negative individuals across Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease (PD), and controls. The boxplot shows CSF total α -synuclein levels in CSF tau-positive (T+) and negative (T-) controls and individuals with AD, DLB, and PD. Due to extreme outliers, α -synuclein levels were winsorized at the 99th percentile. The line through the boxes represents the median, box boundaries represent the interquartile range (IQR), and whiskers extend to 1.5 x IQR. Log-transformed total α -synuclein levels were compared between groups via linear regression models adjusted for age and sex. The figure only highlights within-group comparisons: *** $p < 0.001$, * $p < 0.05$.

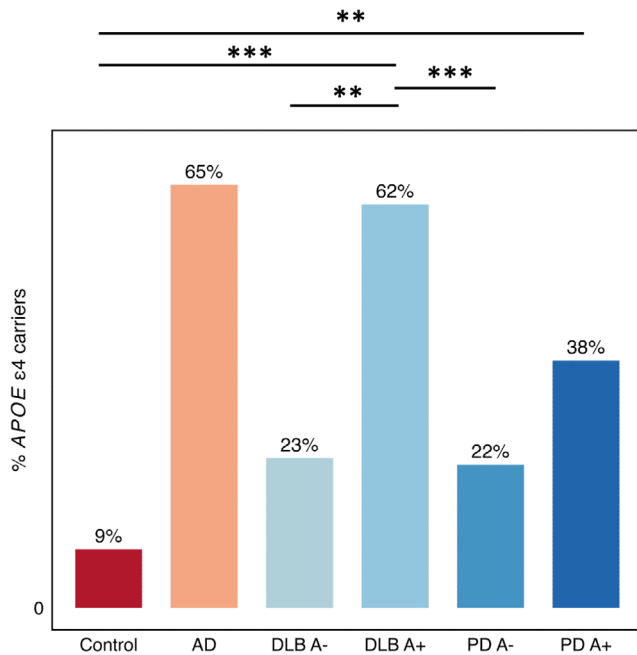


FIGURE 3 Apolipoprotein E (APOE) ε4 carriership in amyloid-positive and amyloid-negative dementia with Lewy bodies (DLB) and Parkinson's disease (PD), in Alzheimer's disease (AD), and in controls. The histogram shows percentage of APOE ε4 carriers in cerebrospinal fluid (CSF) amyloid-positive (A+) and amyloid-negative (A-) participants with DLB and PD, as well as in AD (all A+) and controls (all A-). Number of APOE ε4 carriers/total: control 5 of 55, AD 97 of 150, DLB A+ 23 of 37, DLB A- 5 of 22, PD A+ 5 of 13, PD A- 11 of 51. APOE ε4 carriership was compared between groups via logistic regression, adjusting for age and sex. Group comparisons: *** $p < 0.001$, ** $p < 0.005$.

3.3.2 | Associations with clinical performance and decline

At baseline, amyloid positivity was associated with worse attention in DLB (MD = -1.04 [-1.78 to -0.030], $p = 0.007$), and also after adjusting for tau status (MD = -0.97 [-1.73 to -0.21], $p = 0.013$), whereas this was not observed in PD (eTable 11). Post hoc analysis indicated that attention performance was worse in amyloid-positive individuals with DLB compared to individuals with AD (MD = -1.85 [-2.42 to -1.27], $p < 0.001$). No other association of amyloid positivity with baseline cognitive or motor performance was found in DLB or PD (eTable 11). Longitudinally, in DLB, amyloid positivity was associated with a decline in global cognition (harmonized MMSE measure), with only amyloid-positive DLB exhibiting decline (DLB A+ $\beta = -1.67$ [-2.06 to -1.28], $p < 0.001$; DLB A- $\beta = -0.34$ [-0.91 to 0.23], $p = 0.241$; β difference = -1.33 [-2.02 to -0.63], $p < 0.001$), also after adjusting for tau status (eTable 12). Post hoc analysis showed that the global cognitive decline observed in amyloid-positive DLB individuals was slightly more pronounced than that observed in the overall AD group (AD vs DLB A+ β difference = 0.71 [0.05 to 1.37], $p = 0.034$), yet similar to that observed in cognitively impaired (CI) AD, that is, with MCI or dementia (CI AD vs DLB A+ β difference = -0.05 [-0.76 to 0.66], $p = 0.889$;

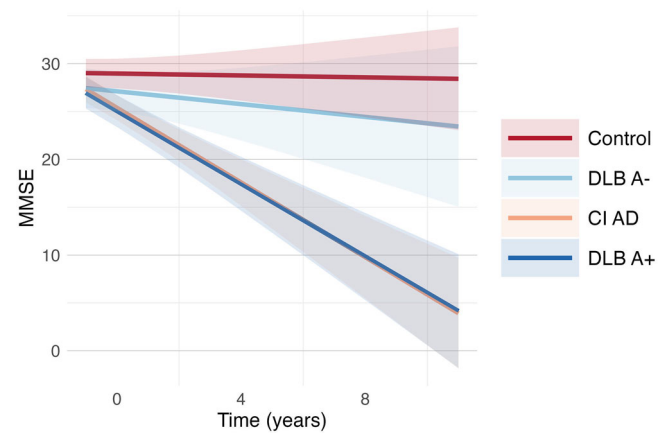


FIGURE 4 Longitudinal change in global cognition. The graph shows change in global cognition over time for controls ($N = 26$), amyloid-positive ($N = 28$) and amyloid-negative ($N = 15$) individuals with dementia with Lewy bodies (DLB), and cognitively impaired (CI) individuals with Alzheimer's disease ($N = 43$). As described in Section 2.4, global cognition was measured via Mini-Mental State Examination (MMSE) score or, when this was unavailable, via Montreal Cognitive Assessment (MoCA) score converted to MMSE. Associations were tested using random-intercept and random-slopes linear mixed models adjusted for baseline age, sex, and education years. Lines are linear mixed-model slopes, and shades depict the 95% confidence intervals.

Figure 4; full results in eTable 13). No other longitudinal association of amyloid positivity with cognitive decline was found in DLB (eTable 12).

Finally, we examined clinical associations of tau positivity. At baseline, tau positivity in DLB was associated with worse global cognition (MD = -2.84 [-4.82 to -0.87], $p = 0.005$) and worse visuoconstruction (MD = -1.22 [-2.23 to -0.21], $p = 0.018$), both also after adjusting for amyloid status (eTable 14). Neither associations were observed in AD (harmonized MMSE MD = -0.91 [-2.03 to 0.20], $p = 0.107$; visuoconstruction MD = 0.084 [-0.40 to 0.57], $p = 0.736$), for which baseline tau positivity was instead associated with worse delayed memory performance (MD = -0.80 [-1.48 to -0.13], $p = 0.020$). Tau positivity in DLB was not further associated with cognitive or motor performance (eTable 14). Longitudinally, tau positivity in DLB was not associated with decline in global cognition (T+ vs T- β difference = -0.46 [-1.54 to 0.61], $p = 0.394$), whereas it was in AD (T+ vs T- β difference = -1.37 [-2.23 to -0.50], $p = 0.002$). Longitudinal associations with neuropsychological or motor function could not be tested in DLB ($N < 10$).

4 | DISCUSSION

In this multi-center study, we compared CSF markers of amyloid, tau, NfL, and total α -synuclein, centrally measured using robust fully-automated Elecsys immunoassays, head-to-head between AD, DLB, PD, and controls in a unique multi-disease dataset. In addition, we evaluated associations of amyloid and tau positivity with risk factors and clinical function across diseases. Our main findings are that compared

to controls, amyloid and tau levels were abnormal in DLB, but not in PD. In DLB, amyloid and tau positivity were associated with older age and worse global cognitive outcomes, but not with motor performance, and amyloid positivity was associated with APOE ϵ 4 carriership. NFL levels were non-specifically elevated across diseases, and total α -synuclein levels reflected tau positivity in all groups.

AD CSF biomarker (i.e., amyloid and tau) levels were more abnormal in DLB compared to controls, and tau levels were highest in AD, as expected. Among DLB patients, $\approx$ 60% had positive amyloid levels and $\approx$ 25% positive tau levels, with tau levels being elevated mostly in cases of intermediate-to-high cognitive impairment. Conversely, amyloid and tau levels were not altered in PD compared to controls. These findings align with previous studies in suggesting that AD co-pathology is frequent in DLB, but less frequent in PD, and especially in non-demented PD,^{27–29} which represented the majority of our PD sample. In addition, we found that in DLB, amyloid positivity was associated with older age, APOE ϵ 4 carriership, and higher p-tau, and tau positivity was associated with higher NFL, suggesting a similar pattern as in AD. These associations, except that with older age, were not observed in PD. These findings are consistent with the hypothesis that DLB stands on a disease continuum between AD and PD and biologically overlaps with both diseases, as suggested by a recent genome sequencing analysis showing independent contribution of genetic variants associated with both AD and PD to DLB risk.³⁰ Future studies should investigate the associations of an AD-like biomarker profile in DLB with PD-risk genes (e.g., *GBA*, *SNCA*). An important clinical implication of our findings is that clinicians can expect positive AD CSF biomarkers in patients with a DLB clinical diagnosis or primarily DLB clinical presentations. The lack in PD of the amyloid and tau positivity associations that were observed in DLB suggests a dissociation between the DLB and PD biological profiles; yet, these results might also be affected by differences in disease stage or statistical power.

NfL levels were elevated in all diseases, and especially in AD and DLB, compared to controls, consistent with previous findings.^{31,32} This confirms the use of NfL as a non-disease-specific marker of neuroaxonal injury or degeneration. In AD and DLB, elevated NfL levels reflected the presence of cognitive impairment, in line with previous studies.^{33,34}

It must be noted that our PD group was on average younger, mostly cognitively unimpaired, and with mild motor deficits.³⁵ It may be speculated that PD patients with more advanced cognitive impairment and later disease stages would show more AD-like profiles, both in pathology and risk factors, higher NfL levels, and clinical phenotypes more similar to DLB.^{2,36} Similarly, individuals at earlier DLB clinical stages might show less AD pathology compared to what was observed in our DLB sample, which was characterized by a greater cognitive impairment on average.

Total α -synuclein CSF levels were not different across disease and control groups. Contrasting evidence exists on the diagnostic value of total α -synuclein levels in synucleinopathies, as several studies found reduced levels in PD and DLB compared to controls or AD, but others found null or conflicting findings.^{37–39} Reasons for this overlap may be that other forms of α -synuclein (e.g., phosphorylated/aggregated),

rather than total levels, may reflect α -synuclein pathology more directly, as well as the vulnerability of CSF total α -synuclein to sample processing challenges.⁴⁰ In our study, higher total α -synuclein levels were associated with positive p-tau levels in all groups. A crosstalk between α -synuclein and tau has been documented previously,^{41,42} and positive correlations reported in AD.⁴³ Total α -synuclein has also been associated previously with synaptic dysfunction,^{40,44} raising the possibility that the observed association between total α -synuclein and tau positivity in CSF may reflect tau-associated synaptic dysfunction. In addition, increased CSF total α -synuclein levels have been observed previously in other neurodegenerative disorders such as multiple sclerosis⁴⁵ and Creutzfeldt–Jakob disease.⁴⁶ Altogether, this suggests that total α -synuclein CSF levels may reflect heterogeneous processes, part of which are implicated in PD/DLB pathophysiology and part in non-disease-specific neurodegenerative processes. Newly developed CSF seed amplification assays (SAAs), which reliably detect misfolded α -synuclein aggregates, will play an important role in clarifying the differential α -synuclein involvement across neurodegenerative diseases.

In DLB, positive AD biomarkers were overall related to worse cognitive function, as reported previously,^{47,48} but not to motor performance. Specifically, at baseline, amyloid positivity was associated with worse attention and tau positivity with worse global cognition, potentially reflecting its association with worse visuoconstruction. This highlights that AD pathology impacts core DLB symptomatic cognitive domains.²¹ Longitudinally, amyloid, rather than tau, positivity in DLB predicted global cognitive decline over 2 years on average. Of note, such decline occurred only among amyloid-positive DLB participants (1.7 points/year in the harmonized MMSE measure) and was comparable to that of (amyloid-positive) cognitively impaired AD participants. This indicates that CSF amyloid may hold prognostic value in DLB patients, as proposed previously,^{49,50} although contrasting findings have been reported in another study.⁵¹ Our findings can be applied to clinical trial design and suggest that CSF AD biomarkers should be tested upon participant inclusion in DLB clinical trials, in line with recent suggestions.^{31,52} Based on our results, treatments combining AD disease-modifying targets with DLB-specific targets should be evaluated for DLB patients with AD co-pathology, and, when not possible for example due to safety concerns, patients should be stratified by AD pathology when evaluating therapy efficacy.⁵² Unlike in DLB, we found that in AD tau positivity predicted worse baseline delayed memory and longitudinal global cognitive decline. This revealed disease-specific clinical associations of tau, likely as combined with co-pathologies.

Overall, our findings offer important practical insights for the differential diagnosis of AD, DLB, and PD using CSF biomarkers in clinical practice and trial participant selection and follow-up. However, they warrant validation with a larger cohort including extended pathological and neuropsychological data.

Key strengths of our study include a cohort of common neurodegenerative diseases phenotyped with widely used CSF biomarkers. Biomarkers were measured centrally via a robust assay, minimizing assay-driven differences, which may have confounded previous studies. Moreover, biomarker measures were linked with clinical data with

up to 11-year follow-up. However, CSF α -synuclein SAA and CSF p-tau217, recently validated as best performing measures of α -synuclein and tau AD pathology, respectively, were unavailable. In addition, unlike the AD and DLB groups spanning the cognitive spectrum, the PD group was mostly cognitively unimpaired with mild motor deficits, potentially suggesting earlier disease stages. This may have limited our ability to investigate clinical associations of AD biomarkers in PD and attenuated PD biomarker differences. Future work should assess this by including PD groups with varying degrees of cognitive impairment. Moreover, although we aimed to reflect current clinical practice, the primarily biomarker-based definition of AD, unlike the primarily non-biomarker-based definitions of DLB and PD, may have introduced some variability. Diagnostic confirmation using α -synuclein SAA in DLB and PD will be valuable in follow-up studies. Furthermore, because some cohorts included a single diagnostic group, cohort-related variability (e.g., setting, procedures) could not be statistically disentangled from disease-related differences. Yet, this variability is expected to be random. Finally, although recruiting from different European countries increased the sample representativeness, participants were mostly white, thereby limiting result generalizability.

In summary, our study showed that AD pathology, as assessed in CSF, was observed in individuals with DLB, for whom it was related to a worse global cognition, but it was less observed in individuals with PD. In addition, we showed that CSF NfL was non-specifically altered across AD, DLB, and PD, and that CSF total α -synuclein reflected CSF tau positivity. These results have implications for the differential diagnosis and the management of AD, DLB, and PD in clinical care and trials.

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C.E. Teunissen has research contracts with Acumen, ADx Neurosciences, AC-Immune, Alamar, Aribio, Axon Neurosciences, Beckman-Coulter, BioConnect, Bioorchestra, Brainstorm Therapeutics, C2N diagnostics, Celgene, Cognition Therapeutics, EIP Pharma, Eisai, Eli Lilly, Fujirebio, Instant Nano Biosensors, Merck, Muna, Nitrase Therapeutics, Novo Nordisk, Olink, PeopleBio, Quanterix, Roche, Sysmex, Toyama, Vaccinex, and Vivoryon. She is an editor-in-chief of *Alzheimer's Research & Therapy*, and serves on editorial boards of *Molecular Neu-*

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DATA AVAILABILITY STATEMENT

The European Platform for Neurodegenerative Diseases (EPND) dataset is accessible upon request at <https://discover.epnd.org/catalogue/studies> in collaboration with the Alzheimer's Disease Workbench (ADWB).

CONSENT STATEMENT

The study was designed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

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

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