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Plasma neurofilament light chain as prognostic marker of cognitive decline in neurodegenerative diseases, a clinical setting study

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Abstract

Background Analysis of selected research cohorts has highlighted an association between plasma neurofilament light (NfL) protein and cross-sectional cognitive impairment as well as longitudinal cognitive decline. However, the findings have yielded inconsistent results regarding its possible application in clinical practice. Despite its potential prognostic significance, the role of plasma NfL in daily clinical practice with unselected patients suffering from cognitive impairment remains largely unexplored.

Methods This retrospective, cross-sectional and longitudinal monocentric study enrolled 320 patients with Alzheimer's disease ([AD], $n=158$), dementia with Lewy body ([DLB], $n=30$), frontotemporal dementia ([FTD], $n=32$), non-neurodegenerative diseases ([NND], $n=59$) or subjective cognitive decline ([SCD], $n=41$). Plasma NfL levels were measured at baseline on the Simoa platform. AD, DLB, and FTD patients were also analyzed altogether as a 'degenerative conditions' subgroup, whereas SCD and NND were grouped as a 'non-degenerative conditions' subgroup. We assessed the relationship between plasma NfL levels and cross-sectional cognitive performance, including global cognition and six specific cognitive domains. A subset of 239 patients had follow-up mini-mental state examinations (MMSE) up to 60 months. Models were adjusted on age, education level, glomerular filtration rate and body mass index.

Results In 320 patients, baseline plasma NfL levels were negatively associated with global cognition (β=-1.28 (-1.81 ; -0.75) $P<0.001$), memory (β=-1.48 (-2.38 ; -0.59), $P=0.001$), language (β=-1.72(-2.49 ; -0.95) $P<0.001$), praxis (β=-2.02 (-2.91 ; -1.13) $P<0.001$) and executive functions (β=-0.81, $P<0.001$). Across diagnosis, plasma NfL levels were negatively associated with cross-sectional global cognition in all but the SCD subgroup, specifically with executive

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functions and memory in AD (respectively β=-0.71(-1.21 ; -0.211), *P* = 0.005 and β=-1.29 (-2.17 ; -0.42), *P* = 0.004), and with attention in LBD (β=-0.81(-1.16 ; -0.002), *P* = 0.03). Linear mixed-effects models showed that plasma NfL predicted MMSE decline in the global population ($\beta_{PlasmaNfLxTime}$=-0.15 (-0.26 ; -0.04), *P* = 0.006), as in the neurodegenerative condition subgroup ($\beta_{PlasmaNfLxTime}$=-0.21 (-0.37 ; − 0.06), *P* = 0.007), but not in non-neurodegenerative condition subgroup.

Conclusion In our clinical cohort, plasma NfL was associated with faster cognitive decline in neurodegenerative dementia, which corroborates data obtained in research cohorts. Yet, plasma NfL was not predictive of accelerated cognitive decline in individuals without neurodegeneration, suggesting its use as a neurodegeneration-specific predictive biomarker.

Keywords Alzheimer's disease, Neurofilament proteins, Cognitive domains performance, Neuroimaging, Neurodegenerative diseases, Cognitive decline

Background

Neurofilament light chain (NfL) protein is an axonal cytoskeleton component, predominantly present in large calibre myelinated axons. NfL is released in CSF and plasma upon axonal and neuronal injury. With the development of novel assay techniques such as Single molecule array (Simoa) [1], plasma NfL has emerged as a biomarker of neurodegeneration and neuroaxonal injury across a broad set of neurological conditions, including neurocognitive disorders. In previous studies, plasma NfL has been found to discriminate accurately between Alzheimer's disease (AD) patients and frontotemporal dementia (FTD) from controls, and to gradually increase with disease severity in both research cohorts [2–5] and real-world studies [6–8]. However, plasma NfL was mostly related to global neurodegeneration, and the extent of its capacity to serve as a differential diagnostic biomarker among neurodegenerative diseases appears limited. As such, plasma NfL was not significantly different between AD and FTD in research cohorts [9, 10] and real-world studies [7, 11]. Similarly, plasma NfL levels in dementia with Lewy bodies (DLB) overlapped with those in AD [7, 9, 12]. More consistently, plasma NfL was suggested as an accurate biomarker to discriminate neurodegenerative from non-neurodegenerative conditions, as well as to differentiate rapidly from slowly progressing diseases [9, 13]. Yet, in our previous work, using data from daily life practice, we showed that plasma NfL had limited accuracy in discriminating neurodegenerative from non-neurodegenerative conditions. Our findings overall suggested that plasma NfL should be regarded as a screening tool rather than a diagnostic biomarker [7].

The prognostic value of plasma NfL has already been examined, but most studies compared clinical progression in AD patients with cognitively unimpaired individuals in cohort studies, including highly selected participants. Those studies reported a specific association between plasma NfL and both baseline domain-specific and general cognitive function, with higher plasma concentrations associating with worse performance [3, 14–17].

While group-level data from research cohorts consistently demonstrated that plasma NfL can serve as a reliable predictor of cognitive decline, a notable scarcity of real-world evidence persists. With most research cohorts studies assessing the link between plasma NfL and cognitive decline [3, 15, 18], some studies did not find any specific association between baseline plasma NfL and further cognitive decline in cognitively unimpaired participants [19]. As the prognostic value and potential uses of plasma NfL have been established, and its use is recommended as a neurodegeneration biomarker [20], further investigations are warranted to bridge this gap and enhance our understanding of the practical potential of plasma NfL in predicting cognitive outcomes and its application in clinical settings. In this study, our objective was : i/ to determine the association of plasma NfL with neuropsychological profile of diverse causes of cognitive impairment and ii/ to assess the prognostic value of plasma NfL across neurodegenerative and non-neurodegenerative conditions, in a real clinical setting cohort, with symptomatic patients, presenting for diagnosis.

Methods

Study design and participants

This observational monocentric retrospective study included 320 patients in the Cognitive Neurology Center, APHP Nord, Université Paris Cité, Paris, France. We consecutively included patients between 01/2010 and 06/2021, with diagnosis of AD, DLB and FTD hereafter referred to as the neurodegenerative condition group, and patients with subjective cognitive decline(SCD), or cognitive impairment without neurodegenerative disease (NND) for the non-neurodegenerative condition group who had undergone a lumbar puncture for AD biomarkers measurement with available plasma sample. All subjects underwent neuropsychological examination, conducted within a 6-month window from the lumbar

puncture. CSF biomarker results were classified according to the AT(N) classification system [21].

Diagnostic assessments

Diagnoses were made by a multidisciplinary team composed of clinicians, biochemists, neuroradiologists and neuropsychologists. Complex cases were systematically discussed in a multidisciplinary committee. Patients were classified as: i/ cognitively impaired or unimpaired, ii/ presenting an underlying neurodegenerative disease, or iii/ according to their etiological diagnosis. We considered the most recent diagnostic criteria: AD was diagnosed according to NIAAA classification 2011 updated in 2018 [21, 22], DLB was diagnosed according to Mc Keith et al. criteria 2017 [23], bvFTD was diagnosed according to Rascovski et al. 2011 [24], and PPA variants of fronto-temporal lobar degeneration (FTLD) were diagnosed according to Gorno-tempini et al. 2011 [25].

Patients with SCD reported a cognitive complaint without evidence of cognitive impairment. We classified patients as SCD when neurodegenerative etiologies were excluded by the referent physician and when the following criteria were fulfilled: i/ CSF amyloid and tau biomarkers were all negative (A-T-N-), according to the AT(N) classification), ii/ neuropsychological examination reported normative or subnormative scores for age, sex and education level, and follow up did not show significant decline iii/ MRI did not show significant atrophy on visual evaluation.

Patients were classified as having NND if they presented with cognitive impairment but did not fulfil any criteria of neurodegenerative disease, after multidisciplinary team assessment with examination of CSF biomarkers, MRI, PET imaging and cognitive evolution.

We also grouped AD, DLB and FTD patients in the neurodegenerative condition group and NND and SCD patients in the non-neurodegenerative condition group.

Patients with no consensual diagnosis were not included. Patients without longitudinal MMSE follow up were non included in the longitudinal examination. Considering several studies showing lasting elevation of plasma NfL past the first months post stroke [26] or after epilepsy [27], we also excluded patients with plasma NfL measurement performed within three months following an acute neurological event (e.g., stroke, traumatic brain injury, seizure).

Neuropsychological examinations and neuroimaging markers

Neuropsychological examination

Neuropsychological examinations were performed by trained neuropsychologists. Neuropsychological tests included: delayed matching to sample – 48 item test (DMS48) [28] for visual memory, Free and Cued Selective Reminding test (FCSRT), with free and total recall [29] for verbal memory, Verbal categorial fluency [30], and BECS-GRECO naming task (40 or 80 items) [31, 32] for language abilities, Frontal assessment battery (FAB) [33], Verbal literal fluency, Trail making test B (TMTB) [30] for executive functions, Rey's figure (copy) [34] for visuospatial functions, Digit span forward [35], Trail making test A [30] for attention, and Mahieux screening scale for praxis [36]. The results of the neuropsychological examinations (using the raw scores) were converted into z-scores for each test, using the SCD subgroup as the reference group for Z-score calculation. Subsequently, an average Z-score was computed for each cognitive function: episodic memory, language, executive functions, praxis, and attention incorporating all Z-scores from the neuropsychological tests. A global cognition Z-score was calculated with the average of each cognitive function Z-score.

Mini-mental state examination scores over follow-up

All MMSE scores [37] were collected from baseline (i.e. CSF biomarker assessment) up to a follow-up period of 60 months.

Neuroimaging markers

Based on the daily clinical practice, brain MRIs were collected when available and were evaluated as in clinical practice by visual inspection. White matter hyperintensities were rated using the Fazekas scale [38], and medial temporal lobe atrophy using the Scheltens scale [39], initially by the radiologist of the respective radiological centre and reevaluated by a trained physician at the Cognitive Neurology Center to achieve consensus.

Plasma NfL, CSF biomarker measurements and apolipoprotein E genotype

CSF total Tau (T-Tau), phosphorylated-tau (pTau), along with the Aβ ratio (Aβ42/Aβ40) were measured in the Biochemistry department of Lariboisière Hospital (Paris). The measurements were carried out using Innotest® ELISA (Fujirebio, Gent, Belgium) from 2010 to 2018 and Elecsys® immunoassays on the *cobas e*601 analyzer (Roche-Diagnostics) after 2018 for Aβ42, pTau and T-Tau. CSF Aβ40 was measured using Innotest® ELISA (Fujirebio, Gent, Belgium).

Plasma samples were collected on a delay of 4 to 6 h from the CSF collection, on fasting patients. Plasma NfL levels were measured in singlicates, in Lariboisière Hospital (Paris, France) and Neurochemistry Laboratory of Mölndal (Sweden), across 11 analytic runs using the SIMOA HD-X platform (Quanterix®, Billerica, MA). We included high and low plasma NfL levels control samples, which were analyzed in duplicate. Inter-assay and intra-assay coefficients of variation (CVs), were 10.6%

and 3.41%, respectively. CVs between the two platforms in France and Sweden were determined using a subset of 10 samples in both platforms and were found to be 7.5%. Based on previously published studies on storage time effect on blood biomarkers of Alzheimer's disease, we did not exclude any sample for storage time duration [40].

Apolipoprotein E (*APOE*) genotype was determined using polymerase chain reaction followed by denaturing high-performance liquid chromatography (WAVE® DNA fragment analysis system, Transgenomic, Omaha, NE, USA) with appropriate controls according to the method previously described [41].

Statistical analyses

Plasma NfL, age, education level, body mass index and glomerular filtration rate were log-transformed to achieve normality in all analyses. Comparisons between continuous variables and categorical variables were performed using ANOVA. Categorical variables were compared using χ^2 test. $P<0.05$ was considered overall significant. Missing data for glomerular filtration rate (GFR) and body mass index (BMI) were assessed by mean imputation.

Sample size calculation

Based on previous studies exploring the association of plasma NfL with cognition, we calculated that a minimum of 304 participants would be necessary to detect a statistically significant effect of 0.04 with a power of 0.80 with a significance level (α) of 0.05 [14].

Cross-sectional analysis

Multiple linear regression models were performed to analyze the relationship between plasma NfL levels and cognitive domain performance (using z-scores), as well as Fazekas and Scheltens scores, in regard to plasma NfL levels. The models were adjusted for age, education level, body mass index (BMI) and glomerular filtration rate (GFR) for the first model, as suggested by the latest findings [42–44]. A second model with specific interaction between plasma NfL levels and diagnostic groups was performed, with all previously described covariates.

Longitudinal analysis

Linear mixed models with repeated measures were computed to analyze the change in MMSE scores over follow-up time regarding plasma NfL, age, education level, BMI, GFR and baseline MMSE in the global population. Random effects for intercepts and slopes were included. The same analysis was performed in the diagnosis subgroups, as well as dichotomizing the cohort in a neurodegenerative conditions group (AD, FTD, LBD) and a non-neurodegenerative conditions group (SCD, NND).

Finally, linear mixed models were used to predict MMSE scores in individuals from the neurodegenerative and non-neurodegenerative condition groups in simulated patients with mean age, education level and these groups, and plasma NfL values corresponding to the 10th, 50th, and 90th percentiles of the whole cohort. Statistical analyses were performed using R programming language, version 4.3.1 (R foundation), with lme4 package version 1.1–34.

Ethical considerations

All participants participated in the BioCogBank© protocol [7, 8, 45, 46] including a written consent for CSF and plasma samples preservation for further analyses. They also provided consent for the utilization of their clinical, MRI, CSF and plasma analysis data, in accordance with the Declaration of Helsinki. This protocol has been approved by the "Commission Nationale Informatique et Libertés" (CNIL) and the local and national Ethics Committees ("Comité d'évaluation et d'Ethique pour la recherche Paris Nord" on 30 May 2016).

Results

Population characteristics

Demographics and characteristics are illustrated in Table 1. A total of 320 participants were enrolled in the study including 158 patients with AD, 32 with FTD, 30 with DLB, 59 patients with NND and 41 individuals with SCD. Overall, 220 patients (68.7%) were diagnosed with a cognitive decline due to a neurodegenerative disease at various severity (AD, FTD, or DLB). With regards to clinical syndromes, 41 subjects (12.8%) were classified as having SCD, 131 individuals (40.9%) had mild cognitive impairment (MCI), and 148 (46.3%) had major cognitive impairment (dementia). Compared with other groups, SCD subjects were younger and had higher education level. The sex ratio differed between the groups and patients with AD had more frequently major cognitive impairment than MCI. Body mass index differed in between diagnoses, with AD having a lower BMI than other groups.

Plasma NfL levels results were positively correlated with age ($r=0.46$, $P<0.001$), glomerular filtration rate ($r = -0.34$, $P<0.001$), BMI ($r = -0.24$, $P<0.001$), but no associations were observed with sex ($P=0.32$) or *APOE* ε4 carriership ($P=0.24$). In subgroup analysis plasma NfL was associated with sex only in SCD ($P=0.025$), but not in any other subgroup. ApoE carriership was associated with plasma NfL only in LBD subgroup, with more elevated levels beeing associated with non-carriers $P=0.04$. Regarding BMI, significant and negative correlations were found in AD and FTD subgroups (respectively $r = -0.2$, $P=0.01$; $r=-0.38$, $P=0.03$). Glomerular filtration rate was significantly and negatively correlated with plasma

Table 1 Demographics, clinical characteristics and biomarker results [a]ANOVA test [b]χ^2squared test [c]Kruskall-Wallis test

N (%)	Overall *N* = 320 (100)	SCD *N* = 41 (12.8)	NND *N* = 59 (18.4)	AD *N* = 158 (49.3)	FTD *N* = 32 (10.0)	LBD *N* = 30 (9.4)	*p*
Demographics							
Age, years, mean (SD)	68.3 ± 9.11	61.0 ± 8.3	66.9 ± 10.3	70.9 ± 8.5	67.2 ± 7.8	69.0 ± 5.8	< .001[a]
Female, n (%)	176 (55.0)	28 (68.3)	34 (57.6)	96 (60.8)	6 (18.8)	12 (40.0)	< .001[b]
Education levels, yo	11.5 ± 3.5	12.8 ± 3.0	10.7 ± 3.7	11.3 ± 3.6	11.8 ± 3.2	12.0 ± 3.4	< 0.001 [a]
Body mass index (kg/m^2), mean (SD)	25.1 ± 4.2	26.2 ± 3.9	25.8 ± 5.0	24.3 ± 3.9	25.9 ± 4.5	25.5 ± 3.5	0.02 [a]
ApoE4 carriership, n (%)	144 (46.9)	13 (33.3)	9 (15.8)	100 (66.2)	9 (29.0)	13 (44.8)	< 0.001 [b]
Baseline MMSE (/30), median (IQR)	24 (20 ; 27)	27 (25 ; 28.5)	25 (22.75 ; 26.25)	21 (18 ; 26)	26 (24 ; 27.5)	25 (22 ; 27)	< .001[c]
Cognitive status							< 0.001 [b]
Cognitively unimpaired, n (%)	41 (12.8)	41 (12.8)	0 (0)	0 (0)	0 (0)	0 (0)	
Mild cognitive impairment, n (%)	131 (40.9)	0 (0)	47 (79.7)	56 (35.4)	14 (43.8)	14 (43.8)	
Dementia, n (%)	148 (46.3)	0 (0)	12 (20.3)	102 (64.6)	18 (56.3)	16 (53.3)	
Core CSF Biomarkers							< 0.001 [b]
A-T-, n (%)	119 (37.2)	41 (100)	41 (69.5)	0 (0)	19 (59.4)	18 (60.0)	
A-T+, n (%)	32 (10)	0 (0)	15 (25.4)	0 (0)	11 (34.4)	6 (20.0)	
A + T-, n (%)	27 (8.4)	0 (0)	3 (5.1)	17 (10.8)	2 (6.2)	5 (16.6)	
A + T+, n (%)	142 (44.4)	0 (0)	0 (0)	141 (89.2)	0 (0)	1 (3.3)	
Baseline cognitive z scores							
Global (z score), mean (SD)	-0.92 ± 1.14	-0.03 ± 0.60	-0.79 ± 0.98	-1.23 ± 1.09	-0.89 ± 1.48	-0.74 ± 1.21	< 0.001 [a]
Memory (z score), mean (SD)	-1.35 ± 1.68	0.04 ± 0.75	-1.12 ± 1.39	-2.08 ± 1.79	-1.02 ± 1.25	-0.58 ± 1.17	< 0.001 [a]
Language (z score), mean (SD)	-0.66 ± 1.50	0.01 ± 0.9	-0.54 ± 1.5	-0.92 ± 1.47	-0.88 ± 2.28	-0.34 ± 0.99	0.004 [a]
Praxies (z score), mean (SD)	-0.90 ± 1.71	-0.02 ± 0.78	-0.9 ± 1.60	-1.14 ± 1.77	-1.15 ± 2.14	-0.55 ± 1.76	0.006 [a]
Visuospatial (z score), mean (SD)	-1.08 ± 2.32	-0.00 ± 1.00	-0.66 ± 1.52	-1.55 ± 2.49	-0.97 ± 3.12	-1.39 ± 2.58	0.007 [a]
Attention (z score), mean (SD)	-0.51 ± 1.17	0.001 ± 0.80	-0.48 ± 1.06	-0.68 ± 1.12	-0.19 ± 0.96	-0.79 ± 1.84	0.005 [a]
Executive (z score), mean (SD)	-0.89 ± 1.32	-0.06 ± 0.85	-0.68 ± 0.91	-1.00 ± 0.99	-0.62 ± 1.23	-0.66 ± 1.06	< 0.001 [a]
Neuroimaging outcomes							
WMH (Fazekas scale ≥ 2), n (%)	50 (25)	3 (10.7)	13 (36.1)	30 (30.6)	1 (5.9)	3 (14.3)	0.025 [b]
Mean Scheltens Score, mean (SD)	1.75 ± 0.96	1.09 ± 0.64	1.48 ± 1.12	1.96 ± 0.87	2.22 ± 1.02	1.62 ± 0.85	< 0.001 [a]
Plasma NfL							
NfL (pg/mL, mean (SD)	22.23 ± 14.11	12.71 ± 8.15	21.41 ± 19.45	24.79 ± 12.47	27.05 ± 14.50	18.28 ± 8.30	< 0.001 [a]

NfL across all diagnosis subgroups ($P<0.04$ in all subgroups), except for FTD.

Association of neuropsychological and imaging data with plasma NfL levels across the whole population

All cognitive z-scores, except for attention and visuospatial abilities, were associated with plasma NfL levels across the overall population, even after adjusting for age and education level. Specifically, language (β = -1.72 (-2.49 ; -0.95), $P<0.001$), praxis (β = -2.02 (-2.91 ; -1.13), $P<0.001$), and memory (β = -1.48 (-2.38 ; -0.59), $P<0.001$) displayed the strongest associations with plasma NfL levels when compared with executive functions (β = -0.81 (-1.30 ; -0.37), $P=0.001$).

Except for praxis (β=5.18 (1.50 ; 8.85), $P=0.006$), age was not associated with any cognitive z-score, whereas education level was strongly associated with all cognitive domains ($P<0.001$ for each cognitive function). BMI and GFR were not associated with any cognitive function, except with visuospatial functions (β = -1.9 (-3.76 ; -0.08), $P=0.04$) and (β = -1.52 (-2.97 ; -0.05), $P=0.04$).

Considering neuroimaging scores, plasma NfL levels were associated with medial temporal lobe atrophy (β=1.31 (0.73 ; 1.90), $P<0.001$) and white matter hyperintensities (β=0.63 (0.11 ; 1.15), $P=0.02$) in the global population. Age was also associated with medial temporal lobe atrophy (β=2.75 (0.36 ; 5.14), $P=0.02$) and white matter hyperintensities (β=4.46 (2.35 ; 6.60), $P<0.001$). Detailed results are reported in Table 2A.

Association of neuropsychological tests' results and imaging scores with plasma NfL levels across diagnostic groups

Global cognition was associated with plasma NfL levels in all but SCD diagnosis groups (AD, β = -1.13 (-1.67 ; -0.59), $P<0.001$; LBD β = -0.89 (-1.52 ; -0.25), $P<0.001$; FTD β = -0.87 (-1.43 ; -0.33), $P=0.002$; NND β = -0.80 (-1.38 ; -0.22), $P=0.007$), with a stronger association found in the AD group.

Concerning memory, an association was only found with plasma NfL levels in the AD group (β = -1.29 (-2.17 ; -0.42), $P=0.004$), but not in other diagnosis groups.

Table 2 a. Cross-sectional association of plasma NfL, age, education levels, GFR and BMI with neurocognitive functions and neuroimaging markers in the global population

Model 1, multiple linear regressions of cognitive z scores and neuroimaging scores with adjustment on age, plasma NfL levels and education level. Plasma NfL, age, glomerular filtration rate (GFR), body mass index (BMI) and education levels were log-transformed for the analysis

	Plasma NfL		Age		Education level		GFR		BMI	
	β (95CI)	*P*	*β (95CI)*	*P*	*β (95CI)*	*P*	*β (95CI)*	*P*	*β (95CI)*	*P*
Cognitive z scores										
Global cognition	-1.28 (-1.81 ; -0.75)	**<0.001**	0.26 (-1.88 ; 2.40)	0.813	3.42 (2.71 ; 4.12)	**<0.001**	-0.44 (-1.03 ; 0.15)	0.140	-0.27 (-0.97 ; 0.44)	0.455
Memory	-1.48 (-2.38 ; -0.59)	**0.001**	-3.47 (-7.13 ; 0.19)	0.063	2.58 (1.35 ; 3.83)	**<0.001**	-0.37 (-1.35 ; 0.62)	0.465	0.22 (-0.94 ; 1.39)	0.708
Langage	-1.72 (-2.49 ; -0.95)	**<0.001**	1.71 (-1.43 ; 4.85)	0.285	2.93 (1.89 ; 3.96)	**<0.001**	-0.30 (-1.15 ; 0.54)	0.478	-0.18 (-1.20 ; 0.84)	0.729
Visuospatial	-1.14 (-2.54 ; 0.25)	0.108	-0.82 (-6.41 ; 4.77)	0.772	4.66 (2.71 ; 6.61)	**<0.001**	-1.52 (-2.97 ; -0.05)	**0.042**	-1.92 (-3.76 ; -0.08)	**0.041**
Praxis	-2.02 (-2.91 ; -1.13)	**<0.001**	5.18 (1.50 ; 8.85)	**0.006**	3.26 (2.06 ; 4.47)	**<0.001**	0.19 (-0.82 ; 1.19)	0.716	0.21 (-0.99 ; 1.41)	0.734
Executive functions	-0.81 (-1.30 ; -0.37)	**0.001**	-0.29 (-2.23 ; 1.65)	0.770	3.49 (2.85 ; 4.13)	**<0.001**	-0.30 (-0.83 ; 0.23)	0.270	0.16 (-0.47 ; 0.80)	0.613
Attention	-0.55 (-1.16 ; 0.06)	0.079	-0.93 (-3.33 ; 1.46)	0.443	3.29 (2.5 ; 4.08)	**<0.001**	-0.50 (-1.15 ; 0.15)	0.134	-0.57 (-1.36 ; 0.22)	0.154
Neuroimaging markers										
White matters hyperintensities (Fazekas scale)	0.63 (0.11 ; 1.15)	**0.02**	4.46 (2.35 ; 6.60)	**<0.001**	0.68 (-0.01 ; 1.38)	0.053	-0.32 (-0.89 ; 0.25)	0.26	0.54 (-0.17 ; 1.24)	0.14
Hippocampal atrophy (Scheltens scale, mean)	1.31 (0.73 ; 1.90)	**<0.001**	2.75 (0.36 ; 5.14)	**0.02**	-0.41 (-1.20 ; 0.39)	0.31	0.11 (-0.59 ; 0.81)	0.76	-0.23 (-1.03 ; 0.58)	0.57

Plasma NfL levels were associated with language in all diagnosis groups (AD, β = -1.56 (-2.37 ; -0.74), $P<0.001$; LBD β = -1.28 (-2.22; -0.33), $P<0.001$: FTD β = -1.52 (-2.35 ; -0.69), $P<0.001$; NND β = -1.30 (-2.17 ; -0.43), $P=0.003$; SCD β = -1.06 (-2.08 ; -0.004), $P=0.0042$). The strongest associations were found in the AD and FTD groups.

Praxis was also associated with plasma NfL levels in all but the SCD group (AD, β = -1.81 (-2.74 ; -0.87), $P<0.001$; LBD, β = -1.60 (-2.70 ; -0.50), $P=0.004$; FTD, β = -1.79 (-2.73 ; -0.84), $P<0.001$; NND, β = -1.63 (-2.64 ; -0.63), $P=0.001$; SCD, β = -1.12 (-2.29 ; 0.63), $P=0.06$). The strongest associations were found in the AD and FTD groups.

Executive functions were associated with plasma NfL levels in AD (β = -0.71 (-1.21 ; -0.211), $P=0.005$), LBD (β = -0.58 (-1.16 ; -0.002), $P=0.05$), and tend to be associated with plasma NfL levels in FTD (β = -0.49 (-1.01 ; 0.02), $P=0.06$).

DLB was the only group where plasma NfL and attention were associated (β = -0.81 (-1.55 ; -0.08), $P=0.03$). No association was found between visuospatial functions and plasma NfL levels in diagnosis groups.

BMI, but not GFR, is also associated with visuospatial functions in this model (β = -2.01, $P=0.03$). Education level displayed an association with all cognitive functions ($P<0.001$).

Concerning neuroimaging scores, medial temporal lobe atrophy, measured with Scheltens' visual scale, showed an association with plasma NfL levels across all diagnostic groups (AD, β=1.16 (0.55 ; 1.77), $P<0.001$; FTD, β=1.35 (0.73 ; 1.96), $P<0.001$; LBD, β=1.04 (0.32 ; 1.75) $P=0.005$; NND, β=0.91(0.29 ; 1.54), $P=0.004$; SCD, β=0.8 (0.04 ; 1.57), $P=0.039$). Detailed results are described in Table 2B and Fig. 1. Associations between plasma NfL levels and white matter hyperintensities were found in the AD group (β=0.62 (0.08 ; 1.17), $P=0.026$) and the NND group (β=0.78 (0.22 ; 1.35), $P=0.007$).

Association of plasma NfL levels with cognitive decline across the global population

239 patients had available follow-up MMSE data and were included in a longitudinal analysis. Patients with no follow up examinations ($n=81$) were not included in the longitudinal analysis. Their characteristics did not differ significantly with the included patients. See supplementary Table 2. The mean follow-up duration was 29.7±15.2 months, with a mean of 3.7±1.4 MMSE time points by patient. 127 had AD (53.1%), 21 had DLB (8.8%), 21 had FTD (8.8%), 40 had NND (16.7%), and 30 had SCD (12.6%). Considering neurodegeneration, 169 patients

Table 2 b. Cross-sectional association of plasma NfL, age, education levels, GFR and BMI with neurocognitive functions and neuroimaging markers across diagnosis
Model 2, Multiple linear regressions of cognitive z scores and neuroimaging scores with adjustment on age, education level, glomerular filtration rate, body mass index and plasma NfL with interaction on diagnosis. Plasma NfL, age, education level, body mass index and glomerular filtration rate were log-transformed for the analysis.

	Plasma NfL x AD		Plasma NfL x LBD		Plasma NfL x FTD		Plasma NfL x NND		Plasma NfL x SCD	
	β (SE)	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*
Cognitive z scores										
Global cognition	-1.13 (-1.67 ; -0.59)	**< 0.001**	-0.89 (-1.52 ; -0.25)	**0.006**	-0.88 (-1.43 ; -0.33)	**0.002**	-0.80 (-1.38 ; -0.22)	**0.007**	-0.37 (-1.05 ; 0.32)	0.292
Memory	-1.29 (-2.17 ; -0.42)	**0.004**	-0.26 (-1.28 ; 0.75)	0.608	-0.53 (-1.42 ; 0. 36)	0.239	-0.65 (-1.59 ; 0.28)	0.167	0.19 (-0.91 ; 1.29)	0.728
Langage	-1.56 (-2.37 ; -0.74)	**< 0.001**	-1.28 (-2.22 ; -0.33)	**0.008**	-1.52 (-2.35 ; -0.69)	**< 0.001**	-1.30 (-2.17 ; -0.43)	**0.003**	-1.06 (-2.08 ; -0.04)	**0.042**
Visuospatial	-1.09 (-2.54 ; 0.35)	0.137	-0.95 (-2.59 ; 0.68)	0.253	-0.58 (-2.01 ; 0.86)	0.432	-0.36 (-1.92 ; 1.20)	0.649	0.05 (-1.70 ; 1.81)	0.95
Praxis	-1.81 (-2.74 ; -0.87)	**< 0.001**	-1.60 (-2.70 ; -0.50)	**0.004**	-1.79 (-2.73 ; -0.84)	**< 0.001**	-1.63 (-2.64 ; -0.63)	**0.001**	-1.12 (-2.29 ; 0.63)	0.063
Executive functions	-0.71 (-1.21 ; -0.211)	**0.005**	-0.58 (-1.16 ; -0.002)	**0.049**	-0.49 (-1.01 ; 0.02)	0.058	-0.49 (-1.03 ; 0.05)	0.074	-0.15 (-0.78 ; 0.48)	0.635
Attention	-0.6 (-1.24 ; 0.05)	0.069	-0.81 (-1.55 ; -0.08)	**0.030**	-0.32 (-0.96 ; 0.32)	0.328	-0.42 (-1.12 ; 0.28)	0.241	-0.27 (-1.07 ; 0.52)	0.500
Neuroimaging outcomes										
White matters hyperintensities (Fazekas scale)	0.62 (0.08 ; 1.17)	**0.026**	0.53 (-0.11 ; 1.17)	0.101	0.44 (-0.12 ; 1.01)	0.120	0.78 (0.22 ; 1.35)	**0.007**	0.56 (-0.12 ; 1.24)	0.108
Hippocampal atrophy (Scheltens scale, mean)	1.16 (0.55 ; 1.77)	**< 0.001**	1.04 (0.32 ; 1.75)	**0.005**	1.35 (0.73 ; 1.96)	**< 0.001**	0.91 (0.29 ; 1.54)	**0.004**	0.81 (0.04 ; 1.57)	**0.039**

had a neurodegenerative disorder (70.7%), while 70 had any neurodegenerative disease (both SCD and NND groups, 29.3%).

In the global population, mixed model cross-sectional analysis revealed an association of plasma NfL levels (β = -5.27 (-7.60 ; -2.94), $P<0.001$) and education level (β=11.27 (8.19 ; 14.36), $P<0.001$) with MMSE score (Table 3; Fig. 2A). Age, GFR and BMI were not associated with MMSE. In longitudinal analysis, the change in MMSE scores over time was inversely associated with plasma NfL levels at baseline (β =-0.15 (-0.26 ; -0.04), $P=0.006$), but not with age, education level, BMI, GFR or baseline MMSE.(Table 3; Fig. 2B).

Association of plasma NfL levels with cognitive decline in subgroups analysis

In the non-neurodegenerative condition group, no association was found between plasma NfL levels, age, BMI or GFR and MMSE score cross-sectionally. Similarly, no association was found in longitudinal analyses. (Table 4; Fig. 2E and F)

In the neurodegenerative condition group, cross-sectional analysis revealed an association of plasma NfL levels (β =-5.66 (-8.87 ; -2.46), $P=0.001$), age (β=13.86 (1.93 ; 25.79), $P=0.001$) and education level (β=12.45 (8.74 ; 16.15), $P<0.001$) with MMSE score. GFR and BMI were not associated with MMSE.

In the longitudinal analysis, plasma NfL levels at baseline were associated with MMSE change over time (β =-0.21 (-0.37 ; -0.06), $P=0.07$), as well as baseline MMSE (β =-0.17 (-0.31 ; -0.03), $P=0.17$). Results are reported Tables 4**and** Fig. 2C and D. Figure 3 illustrates the predicted MMSE change over time according to linear mixed model coefficients. For each group, we computed the MMSE evolution according to linear mixed model coefficients, with neurodegenerative and non-neurodegenerative conditions groups mean age, education level, as well as plasma NfL 10th, 50th and 90th quantiles values of the whole population.

Discussion

This original study aimed to bring real-world evidence regarding plasma NfL levels as a prognostic biomarker of cognitive decline in a memory clinic setting. Plasma NfL appeared as a prognostic marker of cognitive decline in patients with neurodegenerative conditions. More specifically, we observed an association between plasma NfL levels and baseline cognitive domain performance regarding global cognition, memory, language, executive functions, and praxis. We also report disease-specific associations between plasma NfL levels and cognitive

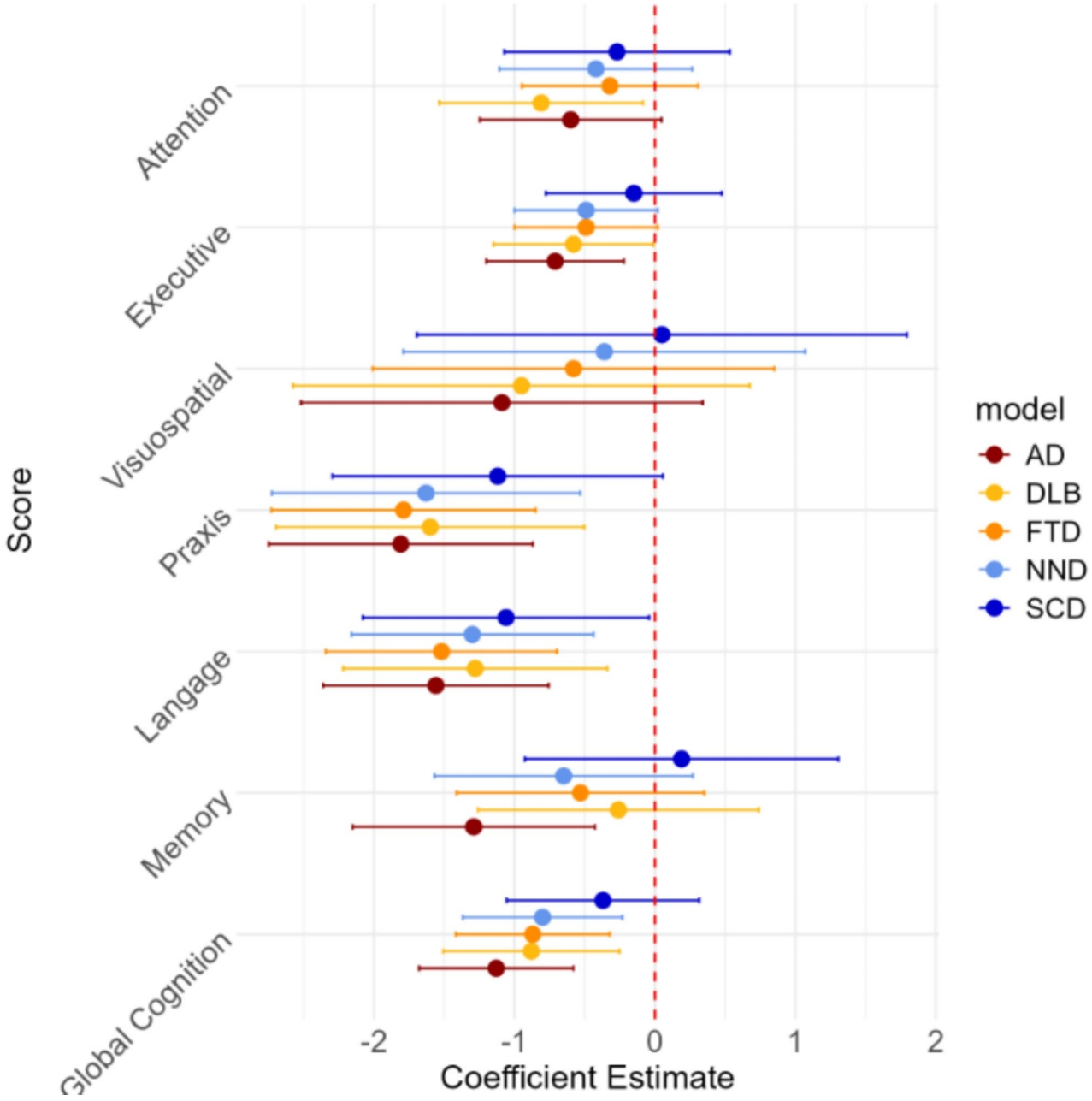

Fig. 1 Association of plasma NfL with cognitive function across diagnosis subgroups
Plasma NfL association with global cognition and specific cognitive domains by diagnosis subgroups, including AD, FTD, LBD, NND and SCD. Standardized estimates with the corresponding 95% CI were plotted for the association of baseline plasma NfL levels with baseline cognitive domain scores for each diagnosis group. Linear regressions were adjusted on age, sex and education level.

functions, such as memory and executive functions in patients with AD, or attention and executive functions in patients with LBD. Plasma NfL levels were also associated with medial temporal lobe atrophy in all groups and with white matter hyperintensities in patients with AD and FTD.

We brought further evidence on the independent association of plasma NfL levels with cognitive decline, regardless of the diagnostic group, age and education level. Last, we described an association of plasma NfL levels with faster cognitive decline that was only observed in the neurodegenerative condition group, suggesting that NfL should be considered as a neurodegeneration-specific predictive biomarker. We illustrated that high plasma NfL levels in patients diagnosed with neurodegenerative conditions is predictable for faster cognitive decline, which is not the case in non-neurodegenerative patients. This highlights the potential use of plasma NfL

Table 3 Association of plasma NfL and covariates with longitudinal MMSE in the global population. Linear mixed-effects model with longitudinal MMSE as the outcome, including plasma NfL levels (log) added to relevant covariates: age (log), GFR (glomerular filtration rate, CKD-EPI, log), education levels (years, log), body mass index (kg/m^2, log) and baseline MMSE (log). Random intercepts and slopes were included

Predictors	Estimates	CI	*P* value
Plasma NfL (log)	**-5.27**	**(-7.60 ; -2.94)**	**< 0.001**
Age (log)	2.78	(-6.76 ; 12.33)	0.568
Education levels (log, years)	**11.27**	**(8.19 ; 14.36)**	**< 0.001**
GFR (CKD-EPI, log)	-2.25	(-4.74 ; 0.24)	0.076
Body mass index (kg /m^2, log)	0.63	(-2.43 ; 3.68)	0.687
Plasma NfL (log) x Time	**-0.15**	**(-0.26 ; -0.04)**	**0.006**
Age (log) x Time	-0.30	(-0.72 ; 0.13)	0.171
Education levels (log, years) x Time	0.03	(-0.11 ; 0.17)	0.643
GFR (CKD-EPI, log) x Time	-0.10	(-0.21 ; 0.01)	0.089
Body mass index (kg /m^2, log) x Time	0.08	(-0.06 ; 0.21)	0.269
Baseline MMSE (log) x Time	-0.08	(-0.20 ; 0.03)	0.155
Random Effets			
σ^2	3.96		
τ00 ID	11.03		
τ11 IDxTime	0.02		
ρ01 ID	0.62		
ICC	0.87		
Observations	865		
Marginal R^2 / Conditional R^2	0.210 / 0.896		

in clinical practice as a multifunction tool, predictive for cognitive decline and associated with cognitive functions among neurodegenerative diseases.

Language and praxis at baseline displayed significant association with plasma NfL levels, regardless of the diagnostic groups. This specific association between language impairment had already been reported by Sugarman et al. [14], where categorical fluency was strongly associated with plasma NfL levels in AD patients. Similar results were assessed in a longitudinal study, in which plasma NfL levels were associated with both memory and language in cognitively unimpaired patients [18]. Our results confirm these findings from a research cohort including selected patients with AD. However, including a wide range of diseases from daily clinical practice, we were able to demonstrate that this association was also present in individuals with non-AD diagnoses.

Cross-sectional studies on the association of plasma NfL levels and cognitive impairment have yielded inconsistent results. Two previous studies, based on research cohorts (Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort and Mayo Clinic Study of Aging (MCSA) cohort) reported no associations between baseline plasma NfL and baseline cognitive assessment, on a population of cognitively unimpaired or MCI patients [15, 16]. Similar results were also found more recently by Dark et al. [19], on a research cohort study (Baltimore Longitudinal Study of Aging), where plasma NfL was not associated with cognitive decline in attention, executive or memory functions in patients without cognitive impairment. On the contrary, including cognitively unimpaired and MCI patients from the MCSA and ADNI cohorts, Marks et al. [47] demonstrated an association of plasma NfL levels at baseline with global cognition, memory, language and attention, whereas no association was found with visuospatial skills. In our work, we demonstrated that our real-world practice findings were consistent with previous evidence from the ADNI and MCSA cohorts. We also reported a cross-sectional association of plasma NfL levels with global cognition, memory, language, praxis and executive functions, and were not specific to the AD population. In patients without cognitive impairment (SCD group), plasma NfL levels were found to be associated with language dysfunction.

In the ADNI cohort including control subjects, MCI due to AD and AD dementia patients, Mattsson et al. [3]. found an association between baseline plasma NfL levels and baseline executive and global cognitive performance (MMSE and ADAS-Cog tests). In a similar population, based on the Boston University Alzheimer's Disease Research Center (ADRC) patients registry, Sugarman et al. [14]. found a correlation of plasma NfL with language, global cognition, attention and memory. These results came from selected cohorts with stringent exclusion criteria (i.e. exclusion of non-neurodegenerative neurological diseases in the Boston University ADRC patient registry) which may limit their external validity. Our results extend these results to real-world practice, as plasma NfL levels were associated with global cognition, praxis, and language in all groups (excepting global

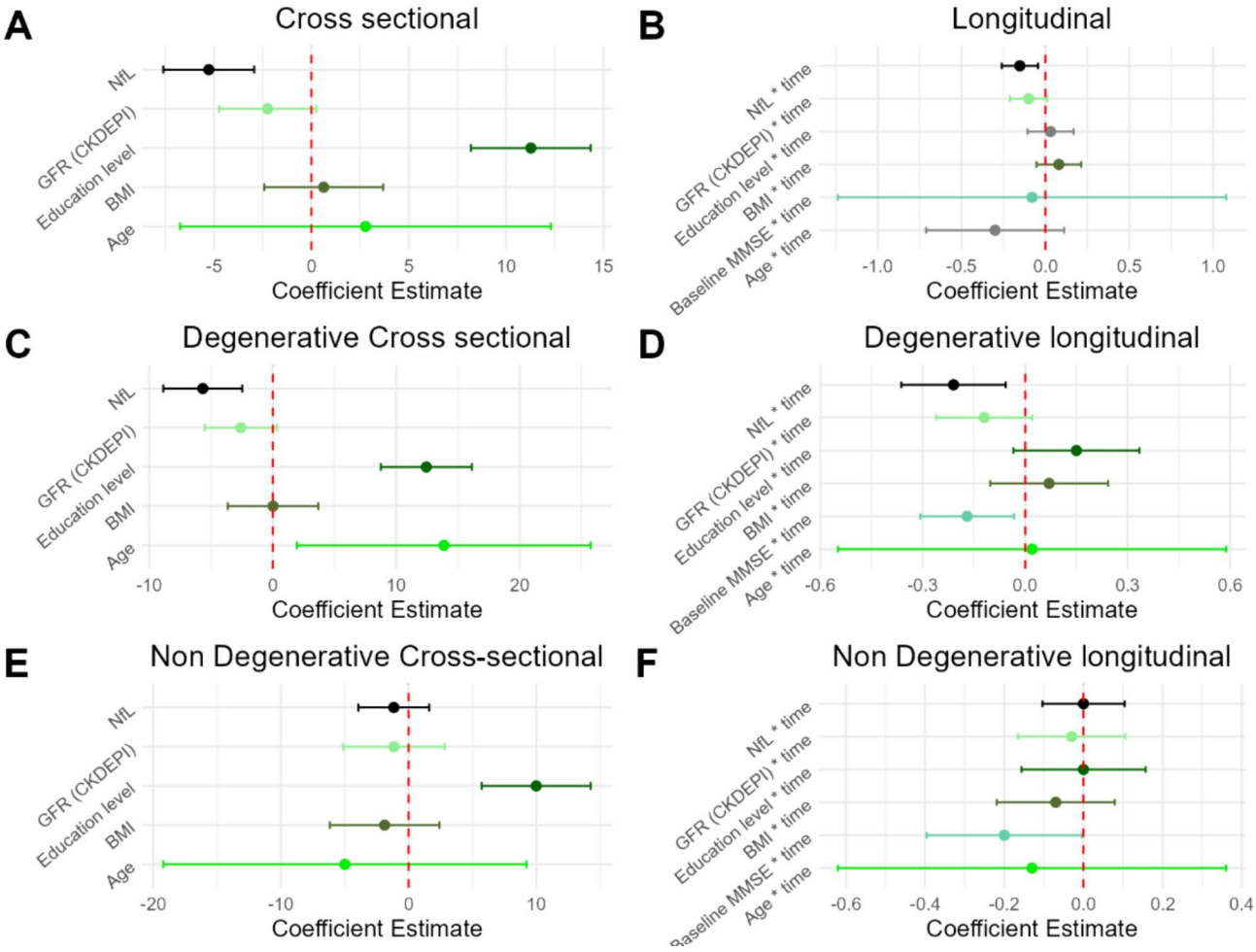

Fig. 2 Association of plasma NfL and confounding variables with MMSE over time in the whole cohort, neurodegenerative conditions group and non-neurodegenerative conditions group

(A) Factors associated with MMSE in cross-sectional analysis in the whole cohort. **(B)** Factors associated with MMSE change over time in the whole cohort **(C)** Factors associated with baseline MMSE in the neurodegenerative condition group. **(D)** Factors associated with MMSE decline in the neurodegenerative condition group. **(E)** Factors associated with baseline MMSE in the non-degenerative condition group. **(F)** Factors associated with MMSE decline in the non-degenerative group.

Standardized estimates with the corresponding 95% CI were plotted for the association of baseline plasma NfL levels and confounding variables with MMSE scores at baseline (cross-sectional) and during follow-up (longitudinal) in the different groups.

All models represented are linear mixed models with fixed effects on plasma NfL, age, education level, body mass index and glomerular filtration rate. Random intercepts and slopes were included. All variables were log-transformed prior to analysis.

cognition and praxis in the SCD group), with memory and executive functions in AD, and with executive functions and attention in patients with LBD.

More recently, one study reported a selective mediation of hippocampal volume on the association between plasma NfL levels and episodic memory performance and decline and executive function decline [17]. Baseline executive functions, although associated with plasma NfL, were not mediated by hippocampal volume but probably mediated by white matter injuries or focal atrophy.

With a methodology based on a visual scale, we reported an association of plasma NfL levels with both medial temporal lobe atrophy and white matter hyperintensities in AD, and with medial temporal lobe atrophy in all groups of disease. Together, all these results corroborate plasma NfL as a global neurodegeneration biomarker.

In three longitudinal research cohorts focused on AD, plasma NfL levels have already been described as a predictor of incident cognitive decline (regarding global cognition) in MCI due to AD or AD dementia [3], but also in cognitively unimpaired or MCI patients [16, 47]. Similarly, in the ADNI cohort, on a population with cognitively unimpaired patients with 59% AD biomarker positivity, Bangen et al. [15]. demonstrated an association of high plasma NfL levels with accelerated memory and composite cognitive scores decline, particularly in MCI

Table 4 Association of plasma NfL with longitudinal MMSE in the non-neurodegenerative and neurodegenerative groups
Linear mixed model of MMSE evolution across time in the non-neurodegenerative (SCD and NND groups) and degenerative group (AD, FTD, LBD groups). Fixed effects education levels (log), age (log), glomerular filtration rate (CKD-EPI, log), body mass index (kg/m^2, log), Baseline MMSE (log) and NfL (log). Random intercepts and slopes were included.

	Non neurodegenerative			**Neurodegenerative**		
Predictors	*Estimates*	*CI 95%*	*P*	*Estimates*	*CI 95%*	*P*
Plasma NfL (log)	-1.16	(-3.95 ; 1.63)	0.412	**-5.66**	**(-8.87 ; -2.46)**	**0.001**
Age (log)	-4.99	(-19.28 ; 9.3)	0.492	**13.86**	**(1.93 ; 25.79)**	**0.001**
Education levels (log, years)	**9.99**	**(5.70 ; 14.29)**	**< 0.001**	**12.45**	**(8.74 ; 16.15)**	**< 0.001**
Glomerular filtration rate (CKD-EPI, log)	-1.15	(-5.16 ; 2.85)	0.572	-2.60	(-5.53 ; 0.34)	0.083
Body mass index (kg/m^2, log)	-1.89	(-6.20 ; 2.43)	0.389	0.03	(-3.65 ; 3.71)	0.986
Plasma NfL (log) x Time	0.00	(-0.11 ; 0.10)	0.987	**-0.21**	**(-0.37 ; − 0.06)**	**0.007**
Age (log) x Time	-0.13	(-0.62 ; 0.36)	0.608	0.02	(-0.55 ; 0.60)	0.936
Education level (log, years) x Time	-0.00	(-0.16 ; 0.15)	0.959	0.15	(-0.04 ; 0.33)	0.115
Glomerular filtration rate (CKD-EPI, log) x Time	-0.03	(-0.17 ; 0.10)	0.646	-0.12	(-0.26 ; 0.02)	0.093
Body mass index (kg/m^2, log) x Time	-0.07	(-0.22 ; 0.08)	0.345	0.07	(-0.11 ; 0.24)	0.452
Baseline MMSE (log) x Time	-0.20	(-0.41 ; 0.01)	0.056	-0.17	**(-0.31 ; -0.03)**	**0.017**
Random Effects						
σ^2	1.99			4.48		
τ_{00}	6.20 $_{ID}$			10.87 $_{ID}$		
τ_{11}	0.00 $_{ID.Time}$			0.02 $_{ID.Time}$		
ρ_{01}	0.51 $_{ID}$			0.66 $_{ID}$		
ICC	0.85			0.86		
Observations	216			649		
Marginal R^2 / Conditional R^2	0.195 / 0.875			0.247 / 0.897		

patients. In this study, high plasma NfL levels at baseline were associated with memory decline in objective subtle cognitive decline patients, whereas memory did not decline in objective subtle cognitive decline patients with low baseline plasma NfL levels. Dark et al. [19] reported different results, based on a population without cognitive impairment at baseline on a longitudinal cohort study, plasma NfL levels at baseline were not found to be associated with cognitive decline in verbal memory, executive functions, visuospatial functions or attention. Plasma NfL levels were also found to be a 5-year predictor of progression from MCI to dementia in AD [48].

However, all these studies were conducted with highly selected patients who met stringent inclusion/exclusion criteria (such as age between 55 and 90 and no other neurological conditions than AD in the ADNI cohort), raising concerns about the generalizability of their findings to patients from memory clinics. In light of these studies, plasma NfL tends to predict cognitive decline in patients with cognitive impairment, but it does not accurately predict cognitive decline in patients without cognitive impairment. We demonstrated that those previous results were in line with clinical practice, albeit not specific to AD.

This study is in line with our previous study, where plasma NfL was described as a potential screening (but not diagnostic) tool to differentiate neurodegenerative and non- neurodegenerative conditions [7]. In the present study, we highlighted a strong association of baseline plasma NfL levels with 5-year cognitive decline in individuals affected by a neurodegenerative condition, but not in those with non-neurodegenerative conditions.

As other non-neurological comorbidities could influence plasma NfL levels, we adjusted our models on body mass index and glomerular filtration rates, which are two major confounding factors that could influence plasma NfL levels [42–44].

Moreover, patients with acute neurological events in the prior 3 months before inclusion were excluded, which minimize the effect of those neurological events, known to be highly related to plasma NfL.

The main strength of our work is the use of real-world evidence for the evaluation of plasma NfL levels, based on the most recent diagnosis criteria, including visual evaluation of the brain MRI in a large-sampled population, representative of real-life practice. Moreover, plasma NfL results were adjusted on comorbidities such as chronic kidney disease and BMI, consistent with most recent studies [42–44].

The primary limitations of this study are related to the monocentric and retrospective approaches, which introduced bias in the recruitment process by focusing solely on a tertiary memory centre. Patients without diagnosis or available plasma sample were not included, which constitute a recruitment bias. The use of z scores based on the SCD group as the normative population is another limitation of our study, as SCD patients cannot be fully considered as healthy controls. Consequently,

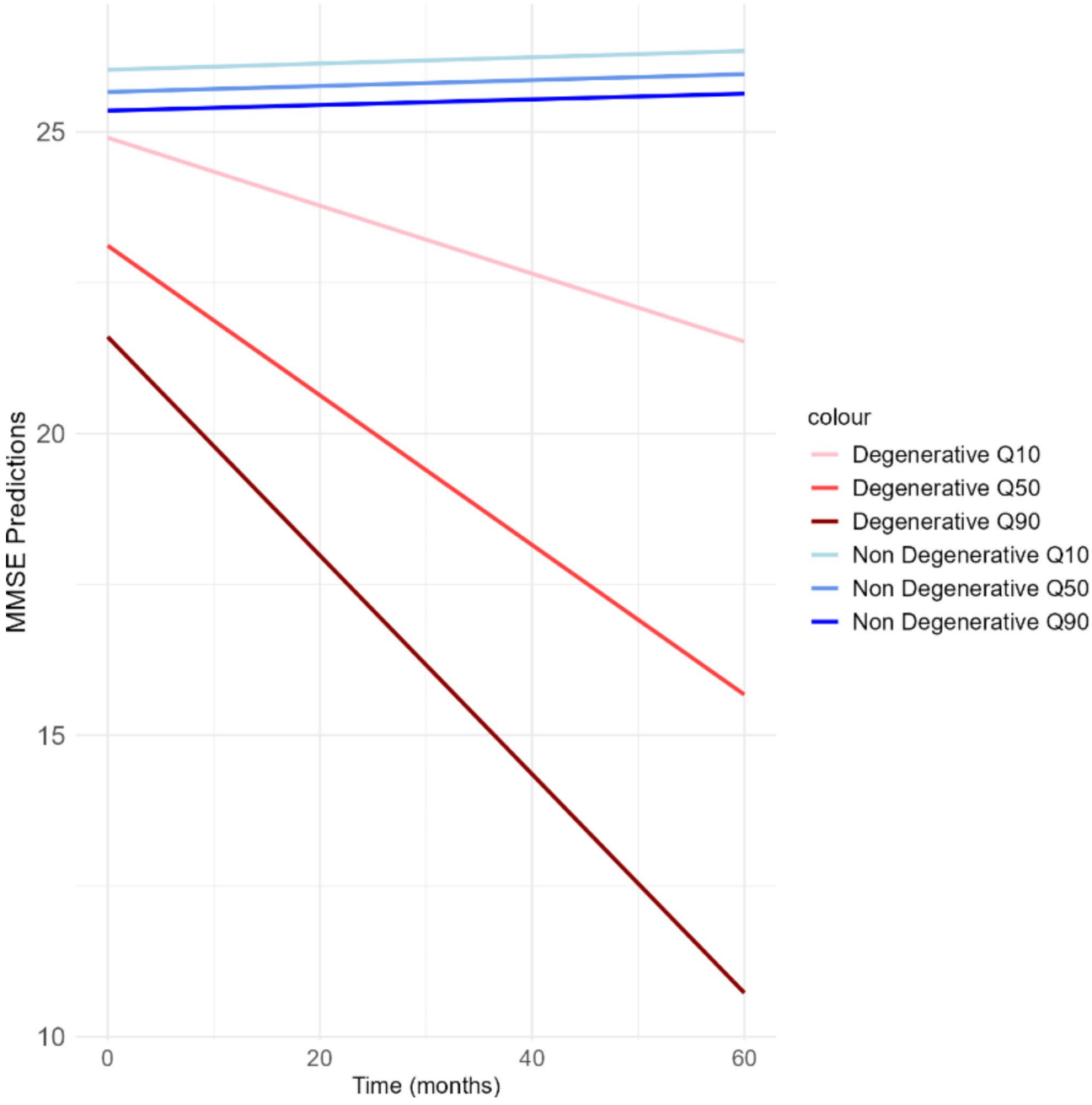

Fig. 3 Predicted MMSE trajectories at hypothesized 10th, 50th and 90th deciles plasma NfL levels in the non-neurodegenerative and degenerative subgroups

Predicted MMSE trajectories for hypothesized individuals with plasma NfL levels at the 10th, 50th and 90th centiles, respectively with a non-neurodegenerative (blue curves) and a degenerative (red curves) disorder, computed using mixed model coefficients. Age, sex, education level, glomerular filtration rate and body mass index used for analysis are, respectively, the mean of the neurodegenerative group and non-neurodegenerative groups.

The stratified lines represent the estimated slope across time for each baseline plasma NfL levels (Q10 = 9.27 pg/mL; Q50 = 19.18 pg/mL; Q90 = 35.48 pg/mL).

this restrains the external validity of our findings. The absence of longitudinal extensive characterization with neuropsychological assessment is another limit of our study.

Besides, conducting neuropsychological tests was unfeasible for patients experiencing severe cognitive impairment, limiting our evidence to mild and moderate dementia stages. The disease frequencies observed in our population reflected the epidemiological data. However, they may account for a lack of statistical power in the cross-sectional analysis, particularly in elucidating with

specific interaction between plasma NfL and non-AD diagnoses.

Conclusion

This original study supports the potential role of plasma NfL assessment as a prognostic biomarker of cognitive decline in patients with neurodegenerative diseases recruited in memory clinical settings. Plasma NfL levels were mostly associated with language and praxis dysfunction in cross-sectional analysis, as well as with memory dysfunction in individuals with AD. Further studies are needed to elucidate the precise use of plasma NfL as neurodegeneration-specific predictive biomarker, especially in light of the advent of anti-amyloid immunotherapies and other disease-modifying therapies in AD.

Abbreviations

AD	Alzheimer's disease
CSF	Cerebrospinal fluid
DLB	Dementia with lewy bodies
FTD	Fronto-temporal dementia
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
MMSE	Mini mental state examination
NfL	Neurofilament light chain
ND	Neurodegenerative disease
NND	Non-neurodegenerative disease
p-Tau	Phosphorylated tau protein
SCD	Subjective cognitive decline

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01593-7.

Supplementary Material 1

Author contributions

KG, ML, CP, SI and MSO designed the approach. KG, AV and collected data KG, AV, MM and EBA analysed biological samples. KG, AV, JD analysed the data and drafted the manuscript. ML, CP, KG developed the original idea. KG, AV, JD, MSO, SI, HS, ARS, EC, MM, KB, HZ, CH, EBA, CP, ML reviewed and revised the manuscript.

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Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethical authorizations and Consent Statement

All the participants were provided written information about the opportunity to collect additional blood and CSF samples for further research analyses, in the BioCogBank© protocol, in accordance with the Declaration of Helsinki. They also provided informed consent for the anonymous use of their clinical data and the results of their CSF and plasma analyses. The "Comité d'Evaluation de l'Ethique des projets de Recherche Biomédicale (CEERB) Paris Nord" (Institutional Review Board-IRB 00006477-of HUPNVS, Paris 7 University, AP-HP), has reviewed and approved the research project entitled «Clinico-biological database of cognitive disorders» (Pr Paquet, principal investigator) on May 30, 2016, and the "Commission Nationale Informatique et Libertés" (CNIL).

Competing interests

KB has served as a consultant and at advisory boards for Abbvie, AC Immune, ALZPath, AriBio, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Neurimmune, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers; has served at data monitoring committees for Julius Clinical and Novartis; has given lectures, produced educational materials and participated in educational programs for AC Immune, Biogen, Celdara Medical, Eisai and Roche Diagnostics; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper.HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, LabCorp, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). CP Serves at scientific international and national advisory boards and/or as a consultant for Abbvie, Eisai, Roche, Lilly, QWorld, France Alzheimer, Fondation Vaincre Alzheimer, a2MCL association, and Biodimed has given lectures in symposia sponsored by Lilly, Roche, Fujirebio.The other authors report no conflict of interest.

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