RESEARCH ARTICLE

Plasma and CSF NfL are differentially associated with biomarker evidence of neurodegeneration in a community-based sample of 70-year-olds

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Abstract
Neurofilament light protein (NfL) in cerebrospinal fluid (CSF) and plasma (P) are suggested to be interchangeable markers of neurodegeneration. However, evidence is scarce from community-based samples. NfL was examined in a small-scale sample of 287 individuals from the Gothenburg H70 Birth cohort 1944 study, using linear models in relation to CSF and magnetic resonance imaging (MRI) biomarker evidence of neurodegeneration. CSF-NfL and P-NfL present distinct associations with biomarker evidence of Alzheimer’s disease (AD) pathology and neurodegeneration. P-NfL was associated with several markers that are characteristic of AD, including smaller hippocampal volumes, amyloid beta (Aβ42), Aβ42/40, and Aβ42/t-tau (total tau). CSF-NfL demonstrated associations with measures of synaptic and neurodegeneration, including t-tau, phosphorylated tau (p-tau), and neurogranin. Our findings suggest that P-NfL and...
CSF-NfL may exert different effects on markers of neurodegeneration in a small-scale community-based sample of 70-year-olds.

KEYWORDS
cerebrospinal fluid, human, magnetic resonance imaging, neurodegeneration, neurofilament light protein

1 | BACKGROUND

Neurofilament light protein (NfL) is a sensitive marker of neural degeneration, traditionally measured in cerebrospinal fluid (CSF), and now measurable in plasma (P). NfL in circulation is closely correlated with CSF in clinical samples, providing a more accessible determination of neurodegeneration. However, reports in healthy controls regarding this correlation are inconsistent.

In different neurodegenerative conditions, specific changes can be found in CSF biomarkers as well as on magnetic resonance imaging (MRI) scans. As an example, amyloid beta (Aβ) and tau are established CSF biomarkers in Alzheimer’s disease (AD), whereas white matter lesions (WMLs) and cerebral microbleeds on MRI are associated with vascular dementia. Clinically, P-NfL and CSF-NfL concentrations have been reported to be increased in several neurological conditions including AD, other forms of dementia, as well as traumatic brain injury. P-NfL segregates Parkinson disease from atypical Parkinson disease and predicts mortality risk in patients with cerebral stroke, as well as after cardiac arrest. Therapeutically, NfL normalizes during treatment in multiple sclerosis. Although demonstrating similar outcomes of NfL in plasma and CSF, studies comparing the associations in community-based samples are scarce. Furthermore, it is not specifically known if these markers indeed measure the same pathological changes in individuals from the general public, where neurodegeneration is less pronounced.

We therefore sought to cross-sectionally examine P-NfL and CSF-NfL in relation to MRI measurements and CSF markers in a well-characterized small-scale community-based sample of 70-year-olds.

2 | METHODS

2.1 | Study design and population using data from The Gothenburg H70 Birth Cohort 1944 Study

The sample was derived from the Gothenburg H70 Birth Cohort 1944 Study, conducted in 2014 to 2016, including participants based on birth dates. The response rate was 72.2%, and a total of 1203 people (559 men, 644 women, 96.5% born in Europe) agreed to participate. All participants without contraindications were invited to undergo MRI.
RESEARCH IN CONTEXT

1. **Systematic Review**: Literature available on PubMed was reviewed. Neurofilament light protein (NfL) is one of the most sensitive markers of neural degeneration, and studies suggest a potential for NfL in plasma (P) similar to that in cerebrospinal fluid (CSF). Because P-NfL will be used in the general population, understanding if P-NfL and CSF-NfL are equally related to neurodegeneration in individuals from this demographic is important.

2. **Interpretation**: Our findings demonstrate that CSF-NfL and P-NfL present distinct associations with biomarker evidence of Alzheimer’s disease (AD) pathology and neurodegeneration in a small-scale, community-based sample of 70-year-olds. P-NfL was associated with several markers that are characteristic for AD, whereas CSF-NfL demonstrated associations with measures of synaptic and neurodegeneration.

3. **Future Directions**: The different association patterns between P-NfL and CSF-NfL should be explored in future studies as they may be related to different pathophysiological changes during preclinical AD, with possible implications for preclinical AD research.

Blood and CSF sampling, cognitive testing, a general health interview, and a physical examination with anthropometrics, previously described in detail, were performed at the Neuropsychiatric Clinic at Sahlgrenska University Hospital in Gothenburg, Sweden, by the H70 study team.

2.2 | Standard protocol approvals, registrations, and patient consents

This study was conducted according to the Declaration of Helsinki approved by the regional ethical review board. All the participants and/or their close relatives gave written consent before any study-related procedures were done.

2.3 | Medical history

Stroke was diagnosed if (1) reported by the participant or a close relative, (2) diagnosed in the Swedish National In-patient register, or (3) there were findings specific for stroke on MRI scan also without symptoms. Transitory ischemic attacks were not classified as a stroke. Dementia was diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R). Hypertension was defined as systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or history of hypertension with ongoing medication reported by the participant. Diabetes was defined as a previous diagnosis of diabetes reported by the participant, or a fasting blood glucose > 7.0 mmol/L at the day of blood sampling for the study. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate below 60 mL/min/1.73 m².19

2.4 | Cognitive assessments

Mini Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) assessments were conducted by research nurses with specific training. CDR scores and dementia diagnoses were verified by study physicians in consensus conferences.

Participants were defined as cognitively unimpaired (CU) with CDR = 0, and as mild cognitive impairment (MCI) with CDR = 0.5.

2.5 | Blood measurements

Blood sampling was performed at the initial study visit for all participants. The P-NfL measurements were performed in the Neurochemistry Laboratory at Sahlgrenska University Hospital, Mölndal, using the NF-Light kit on a Simoa HD-X Analyser (Quanterix, Billerica, MA, USA) according to the manufacturer’s instructions. Calibrators were run in
duplicates and samples were diluted 4-fold and run in singlicate without information on any clinical data. The dynamic range of the assay was 0.174 to 1800 pg/mL. Two quality control (QC) plasma samples were run in duplicate in the beginning and the end of each run. For a QC sample with a concentration of 6.6 pg/mL, repeatability was 7.6% and intermediate precision was 8%. For a QC sample with a concentration of 50.5 pg/mL, repeatability was 7.2% and intermediate precision was 7.8%.

### 2.6 APOE ε4 genotyping

Genotyping was performed on collected blood, with the KASPar PCR SNP genotyping system (LGCGenomics, Hoddesdon, Herts, UK). Single nucleotide polymorphisms rs7412 and rs429358 in apolipoprotein E gene (APOE) (gene map locus 19q13.2) were used to define the ε2, ε3, and ε4 alleles.

### 2.7 CSF sampling

MRI scans to detect contraindications were conducted within 2 months of the lumbar puncture (LP). A neurologist or psychiatrist conducted the LP in the morning. CSF was collected and immediately centrifuged for 10 minutes. The supernatant was gently mixed to avoid gradient effects, and stored in polypropylene tubes at −80°C. CSF total tau (t-tau) and tau phosphorylated at threonine 181 (p-tau) concentrations were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) (INNOTEST htau Ag and PHOSPHO_TAU [181P], Fujirebio [formerly Innogenetics], Ghent, Belgium). \( \text{A}_\beta_{42} \) concentration was measured using an ELISA (INNOTEST A\(_\beta\)1-42), specifically constructed to measure \( \text{A}_\beta \), amino acid 1-42. For the \( \text{A}_\beta_{42}/40 \) ratio, the V-PLEX \( \text{A}_\beta \) Peptide Panel 1 (6E10) Kit (MesoScale Discovery, Rockville, MD, USA) was used.

The biomarkers were quantified using validated in-house ELISAs developed at the Mölndal Clinical Neurochemistry Laboratory. The CSF-NfL assay has a correlation coefficient \( r > 0.99 \) for other commercial assays, an interplate coefficient of variation less than 13%, and presents no cross-reactivity for other neurofilaments. The cut point for the presence of AD-related biomarker pathology in CSF was defined as a \( \text{A}_\beta_{42} \) concentration \( \leq 530 \) pg/mL. Stratification by \( \text{A}_\beta \) pathology was performed, as this is the earliest manifestation in AD, and resulted in a balanced separation of the population into similar-sized groups. The cut point was based on a previous longitudinal study.

### 2.9 Statistical methods

Data in tables are presented as median [interquartile range (IQR)]. All linear regressions were performed with and without adjusting for age and sex. Variables that were not normally distributed were log transformed using the natural logarithm for a near-normal distribution and to minimize the potential influence of outliers. NfL variables as well as MMSE were also standardized with z-scores to enable comparison of effect sizes between P-NfL and CSF-NfL. \( p \)-values < 0.05 were considered to be statistically significant, two-sided. Kruskal-Wallis tests were used to assess differences between non-transformed data presented as quartiles. Correlations were tested with Spearman’s rank-order correlation. Data were analyzed for the full group of \( n = 287 \), as well as stratified by the presence of \( \text{A}_\beta \) pathology. No outliers were excluded in any analysis. In a separate sensitivity analysis, five participants with dementia were excluded and all analyses were performed on the remaining sample of 282 individuals. SPSS (version 26, IBM) was used for statistical analysis. GraphPad Prism (version 9.0.0, GraphPad Software) was used to draw box plots.

### 3 RESULTS

### 3.1 Characteristics

Characteristics of participants (\( n = 287 \)) are provided in Table 1. Participants had a median age of 70 years (male, 52%, mean educational length 12.8 (SD ± 3.9) years). MCI prevalence was 17.8% (29 male, 22 female). There were no major differences between the 287 participants...
### Table 1: Characteristics of participants

| Characteristic                        | Median [IQR]/n (%) |
|--------------------------------------|--------------------|
| Male                                 | 148 (52)           |
| Age (years)                          | 71 [70; 71]        |
| Education (years)                    | 12 [10; 15]        |
| Stroke                               | 7 (2)              |
| Dementia                             | 5 (2)              |
| APOE ε4                               | 107 (37)           |
| Hypertension                         | 209 (73)           |
| Diabetes                             | 34 (12)            |
| Chronic kidney disease               | 21 (7)             |
| Body mass index (kg/m²)              | 24.9 [22.8; 27.9]  |

**Cognitive assessments**

| CDR = 0b                               | 230 (80)           |
| CDR = 0.5b                             | 51 (18)            |
| MMSE (total points)                    | 29 [28; 30]        |

**MRI measurements**

| Characteristic                        | Median [IQR]      |
|--------------------------------------|-------------------|
| Mean cortical thickness (mm)         | 2.34 [2.27; 2.39] |
| Hippocampal volume (mm³)             | 3979 [3535; 4248] |
| Mean lateral ventricle volume (mm³)  | 14562 [10898; 19330] |
| White matter lesion, volume (mL)     | 3.94 [2.11; 7.93]  |
| White matter lesions (number)        | 18 [12; 24]       |
| Visible microbleeds                   | 25 (9)            |

**CSF markers**

| Characteristic                        | Median [IQR]      |
|--------------------------------------|-------------------|
| Aβ42 (pg/mL)                         | 543 [407; 665]    |
| t-tau (pg/mL)                        | 299 [249; 387]    |
| p-tau (pg/mL)                        | 48 [38; 56]       |
| Neurofilament light protein (pg/mL)  | 726 [556; 927]    |
| Neurogranin (pg/mL)                  | 195.92 [157.63; 231.82] |
| Aβ42/40                              | 0.95 [0.72; 1.00] |
| Aβ42/t-tau                           | 1.89 [1.39; 2.2]  |
| Qab                                   | 6.1 [4.9; 7.9]    |

**Plasma marker**

| Characteristic                        | Median [IQR]      |
|--------------------------------------|-------------------|
| Neurofilament light (pg/mL)          | 14.2 [10.5; 17.8] |

Abbreviations: CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; IQR, interquartile range; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; Qab, CSF/serum albumin-ratio.

n = 287.

(*Participants carrying one or two ε4 alleles were considered positive.
 **Participants with a dementia diagnosis are not included.
 **Normalized volume.

3.2 | Associations between P- and CSF-NfL and clinical variables

Associations between each demographic, medical, or cognitive variable and P-NfL and CSF-NfL are provided in Table 2. Higher P-NfL was associated with dementia, CKD, and with lower BMI (Table 2). P-NfL did not differ by sex, age, education, stroke, APOE ε4 carriership, hypertension, diabetes, or MMSE score.

CSF-NfL was associated with lower BMI but was not associated with any other clinical variables (Table 2).

3.3 | The association between NfL and MRI measures of neurodegeneration

Higher P-NfL was associated with a smaller hippocampal volume and larger volumes of WMLs (Table 2). There was no association between P-NfL and cortical thickness, mean lateral ventricular volume, number of WMLs, or visible microbleeds (Table 2). Analyzing quartiles (Q) of P-NfL showed that participants with the highest P-NfL levels (Q4) had smaller hippocampal volumes than participants with P-NfL levels in Q2 and Q3, and larger WML volumes in Q4 versus Q1 and Q3 (Figure 2B and 2D). There was no difference in quartiles regarding cortical thickness or lateral ventricular volume (Figure 2A and 2C).

CSF-NfL was not associated with MRI measurements (Table 2). When participants were separated by quartiles, participants in Q4 had significantly smaller hippocampal volume than participants in Q1 and Q3 (Figure 2F). There were no differences between CSF-NfL quartiles for any other MRI measurement (Figure 2E and 2G-H).

3.4 | The association between NfL and CSF markers

Higher P-NfL levels were associated with lower levels of Aβ42, higher levels of CSF-NfL, lower Aβ42/40, lower Aβ42/t-tau and higher CSF/serum albumin ratio (Qab) after adjustment for age and sex (Table 2). P-NfL was not associated with t-tau, p-tau, or neurogranin (Table 2). Similar to the linear models, Aβ42/t-tau was lower in Q4 versus Q1 of P-NfL (Figure 3D). No other CSF marker presented any difference between quartiles of P-NfL (Figure 3A-C).

Higher CSF NfL was associated with higher t-tau, p-tau, neurogranin, Qab, and P-NfL (Table 2). CSF-NfL was not associated with Aβ42, Aβ42/40, or Aβ42/t-tau (Table 2).
FIGURE 2 Association between NfL and MRI measurements. Different radiological markers of neural degeneration presented for study participants separated by quartiles of P-NfL concentration (A-D), or CSF-NFL concentration (E-H). MRI measurements presented for cortical thickness (A, E), hippocampal volume (B, F), ventricular volume (C, G), and white matter lesion volume (D, H). Statistical comparisons were performed with Kruskal-Wallis test. CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; NfL, neurofilament light protein; P, plasma; Q, quartile.

FIGURE 3 Association between NfL and CSF markers. Different clinical markers of neural degeneration presented for study participants separated by quartiles of P-NfL concentration (A-D), or CSF-NFL concentration (E-H). CSF levels presented for CSF amyloid beta (Aβ42 (A, E), CSF t-tau (B, F), CSF p-tau (C, G), and CSF Aβ42/t-tau (D, H). Statistical comparisons were performed with Kruskal-Wallis test. CSF, cerebrospinal fluid; NfL, neurofilament light protein; P, plasma; p-tau, phosphorylated tau; Q, quartile; t-tau, total tau.
TABLE 2  Univariate associations between each characteristic and z log-transformed neurofilament light in plasma and cerebrospinal fluid, as well as values adjusting for age and sex

| Characteristic                     | Plasma marker (P-NFL) | CSF marker (CSF-NFL) |
|------------------------------------|-----------------------|----------------------|
|                                    | B (SE)                | P-value              | Adjusted B (SE) | P-value | B (SE)    | P-value | Adjusted B (SE) | P-value |
| Sex                                | 0.193 (0.118)         | .102                 | 0.211 (0.118)   | .073    | −0.160 (0.118) | .177    | −0.144 (0.118) | .222    |
| Age (years)                        | 29.301 (16.142)       | .071                 | 31.584 (16.129) | .051    | 28.215 (16.149) | .082    | 26.656 (16.185) | .101    |
| Education (years)                  | 0.364 (0.195)         | .062                 | 0.378 (0.193)   | .051    | 0.223 (0.195)   | .254    | 0.229 (0.195)   | .240    |
| Stroke                             | −0.352 (0.383)        | .358                 | −0.306 (0.382)  | .423    | −0.091 (0.383)  | .813    | −0.164 (0.384)  | .670    |
| Dementia                           | 1.020 (0.448)         | .024                 | 0.951 (0.446)   | .034    | 0.421 (0.451)   | .352    | 0.464 (0.451)   | .304    |
| APOE ε4                            | 0.028 (0.122)         | .820                 | 0.029 (0.122)   | .812    | 0.048 (0.122)   | .693    | 0.026 (0.122)   | .831    |
| Hypertension                       | 0.007 (0.133)         | .960                 | 0.034 (0.132)   | .795    | −0.059 (0.133)  | .657    | −0.060 (0.133)  | .650    |
| Diabetes                           | −0.017 (0.183)        | .924                 | −0.002 (0.184)  | .992    | 0.301 (0.182)   | .099    | 0.251 (0.184)   | .174    |
| Chronic kidney disease             | 0.271 (0.104)         | .010                 | 0.259 (0.104)   | .013    | −0.071 (0.113)  | .533    | −0.060 (0.113)  | .595    |
| Body mass index (kg/m²)            | −1.544 (0.363)        | <.001                | −1.477 (0.365)  | <.001   | −0.737 (0.370)  | .048    | −0.794 (0.371)  | .033    |
| MMSE (total points, z score)       | −0.021 (0.058)        | .716                 | −0.049 (0.059)  | .407    | 0.040 (0.060)   | .498    | 0.025 (0.061)   | .681    |
| MRI measurements                   |                       |                      |                   |         |                       |         |                   |         |
| Mean cortical thickness (mm)       | −0.641 (0.637)        | .315                 | −0.676 (0.635)  | .288    | 0.984 (0.636)    | .123    | 1.111 (0.635)   | .081    |
| Hippocampal volume (mm³)           | −1.136 (0.455)        | .013                 | −1.532 (0.475)  | .001    | −0.532 (0.459)   | .247    | −0.343 (0.485)  | .480    |
| Mean lateral ventricle volume (mm³)| 0.232 (0.141)         | .101                 | 0.260 (0.142)   | .068    | 0.160 (0.141)   | .258    | 0.121 (0.143)   | .400    |
| White matter lesion, volume (mL)   | 0.159 (0.055)         | .004                 | 0.159 (0.055)   | .004    | 0.009 (0.056)   | .867    | −0.006 (0.056)  | .916    |
| White matter lesion (number)       | 0.182 (0.115)         | .113                 | 0.228 (0.117)   | .052    | −0.019 (0.115)  | .872    | −0.074 (0.118)  | .534    |
| Visible microbleeds                | 0.318 (0.209)         | .130                 | 0.290 (0.208)   | .164    | −0.125 (0.210)  | .553    | −0.137 (0.209)  | .512    |
| CSF markers                         |                       |                      |                   |         |                       |         |                   |         |
| Aβ42 (pg/mL)                       | −0.001 (0.000)        | .046                 | −0.001 (0.000)  | .043    | 0.000 (0.000)    | .315    | 0.000 (0.000)   | .240    |
| t-tau (pg/mL)                      | 0.181 (0.162)         | .264                 | 0.184 (0.161)   | .253    | 0.533 (0.159)    | .001    | 0.524 (0.159)   | .001    |
| p-tau (pg/mL)                      | 0.139 (0.181)         | .443                 | 0.173 (0.180)   | .338    | 0.785 (0.175)    | <.001   | 0.815 (0.175)   | <.001   |
| Neurofilament light protein (pg/mL)| 0.593 (0.114)         | <.001                | 0.595 (0.114)   | <.001   | −         | −       | −         | −       |
| Neurogranin (pg/mL)                | −0.163 (0.182)        | .372                 | −0.219 (0.182)  | .228    | 0.448 (0.180)   | .014    | 0.447 (0.181)   | .014    |
| Aβ42/40                            | −0.379 (0.194)        | .051                 | −0.381 (0.192)  | .049    | −0.115 (0.195)  | .554    | −0.095 (0.194)  | .625    |
| Aβ42/t-tau                         | −0.324 (0.123)        | .009                 | −0.329 (0.122)  | .007    | −0.239 (0.123)  | .053    | −0.221 (0.123)  | .074    |
| Qab                                | 0.238 (0.168)         | .158                 | 0.358 (0.173)   | .040    | 0.580 (0.165)   | .001    | 0.574 (0.172)   | .001    |
| Plasma marker                      |                       |                      |                   |         |                       |         |                   |         |
| P-Neurofilament light protein (pg/mL)| −         | −                   | −                   | −       | 0.637 (0.122)   | <.001   | 0.644 (0.123)   | <.001   |

Note: Neurofilament light protein in plasma and CSF were log-transformed and z scored to compare the coefficients. Models including cognitive variables also adjusted for education.

CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; NFL, neurofilament light; Qab, CSF/serum albumin-ratio; SE, standard error.

*Participants carrying one or two ε4 alleles were considered positive.

#Normalized volume.

n = 287. P < .05 was considered statistically significant.

Similar to the linear models, t-tau was significantly higher in Q4 versus Q1 of CSF-NFL, and p-tau was higher in Q4 versus Q1 of CSF-NFL (Figure 3F and 2G). In addition, Aβ42/t-tau was also significantly lower in Q4 versus Q1 of CSF-NFL (Figure 3H). There was no difference in levels of Aβ42 between quartiles of CSF-NFL (Figure 3E).

Results remained generally the same after excluding five participants with dementia (n = 282, Table S3). In addition, higher P-NFL was associated with years of education and with a diagnosis of stroke. The associations between P-NFL and Aβ42, and Aβ42/40 remained close to P < .05 but were no longer statistically significant.
TABLE 3  Associations between each characteristic and z log-transformed neurofilament light protein in plasma for participants with and without Aβ pathologya (±, n = 135/152), before and after adjustment for age and sex

| Characteristic                        | Aβ+                  | Aβ−                  |
|--------------------------------------|----------------------|----------------------|
|                                      | B (SE)               | P-value              | Adjusted B (SE) | P-value | B (SE)               | P-value              | Adjusted B (SE) | P-value |
|                                      | .320                 | .248                 | .153              |         | .175                 | .275                 | .235              |         |
| Sex                                  | .107 (0.173)         | .069                 | .072              |         | .067 (0.191)         | .062 (0.192)         | .749              |         |
| Education (years)                    | 0.208                | .247                 | .370              |         | 0.221 (0.190)        | .064 (0.185)         | .621              |         |
| Age (years)                          | 0.208                | .247                 | .370              |         | 0.221 (0.190)        | .064 (0.185)         | .621              |         |
| Dementia                             | 0.112 (0.447)        | .043                 | .001              | <.001   | 1.036 (0.541)        | .001                 | 1.815 (0.504)    | <.001   |
| Hypertension                         | 0.077 (0.191)        | .067                 | .062              |         | 0.067 (0.191)        | .062                 | .062              |         |
| Diabetes                             | 0.134 (0.267)        | .066                 | .074              |         | 0.122 (0.252)        | .068                 | .074              |         |
| Chronic kidney disease               | 0.205 (0.152)        | .021                 | .021              |         | 0.245 (0.143)        | .090                 | .119              |         |
| Body mass index (kg/m²)              | −0.333 (0.152)       | .107                 | .122              |         | −0.333 (0.152)       | .107                 | .119              |         |
| MMSE (total points, z score)         | 0.097 (0.085)        | .069                 | .062              |         | 0.097 (0.085)        | .069                 | .062              |         |
| Mean cortical thickness (mm)         | −0.132 (0.928)       | .000                 | .000              | .561    | 0.000 (0.001)        | .561                 | .000              | .561    |
| Hippocampal volume (mm³)             | −0.845 (0.625)       | .000                 | .000              | .547    | −0.845 (0.625)       | .000                 | .000              | .547    |
| Mean lateral ventricle volume (mm³)  | 0.072 (0.192)        | .000                 | .000              | .550    | 0.072 (0.192)        | .000                 | .000              | .550    |
| White matter lesion volume (mL)      | 0.151 (0.080)        | .047                 | .001              | .048    | 0.151 (0.080)        | .047                 | .001              | .048    |
| White matter lesion (number)         | 0.009 (0.180)        | .000                 | .000              | .98     | 0.009 (0.180)        | .000                 | .000              | .98     |
| Visible microbleeds                  | 0.285 (0.303)        | .046                 | .046              | .458    | 0.285 (0.303)        | .046                 | .046              | .458    |
| Neurogranin (pg/mL)                  | −0.002 (0.001)       | .561                 | .561              | .457    | −0.002 (0.001)       | .561                 | .561              | .457    |
| t-tau (pg/mL)                        | 0.006 (0.01)         | .130                 | .130              | .722    | 0.006 (0.01)         | .130                 | .130              | .722    |
| p-tau (pg/mL)                        | 0.055 (0.225)        | .078                 | .078              | .941    | 0.055 (0.225)        | .078                 | .078              | .941    |
| Neurofilament light protein (pg/mL)  | 0.709 (0.171)        | .032                 | .032              | .234    | 0.709 (0.171)        | .032                 | .032              | .234    |
| Qab                                   | 0.158 (0.253)        | .000                 | .000              | .98     | 0.158 (0.253)        | .000                 | .000              | .98     |

Note: Neurofilament light protein in plasma and CSF were log-transformed and z scored to compare the coefficients. Models including cognitive variables also adjusted for education. Abbreviations: CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; NFL, neurofilament light; Qab, CSF/serum albumin-ratio; SE, standard error.

aAβ pathology defined as Aβ42 ≤530 pg/mL.
bNo prevalent dementia in participants without Aβ pathology.
cParticipants carrying one or two ε4 alleles were considered positive.
dNormalized volume.

3.5  |  Associations stratified by presence of Aβ pathology

Participants (n = 287) were stratified depending on the presence or absence of Aβ pathology (+/−) (Table 3).

In participants with Aβ pathology, P-NFL was associated with dementia and CKD. There were also negative associations with BMI that did not persist after adjustment for age and sex. Furthermore, P-NFL was positively associated with age- and sex-adjusted volume of WMLs and CSF-NFL, and negatively with Aβ42, Aβ42/40, and Aβ42/t-tau (Table 3). P-NFL did not differ by sex, age, education, stroke, APOE ε4 carriership, hypertension, diabetes, MMSE score, or any other MRI-variables and CSF markers among individuals with Aβ pathology.
When participants with dementia from the group with A\(\beta\) pathology were excluded (Table S4), the results were the same as for the original sample with a few exceptions. After exclusion of participants with dementia, there was a positive association between P-NfL and years of education. The observed associations between P-NfL and WML volume was no longer significant.

In participants without A\(\beta\) pathology, P-NfL yielded negative associations with a diagnosis of stroke, BMI, and hippocampus volume. P-NfL showed positive associations with age- and sex-adjusted lateral ventricle volumes, WML volume, age- and sex-adjusted number of WMLs, and CSF-NfL.

There were no associations with sex, age, education, APOE \(\varepsilon4\) carriership, hypertension, diabetes, MMSE score, MRI variables, or CSF markers. Because all participants with a dementia diagnosis also presented with A\(\beta\) pathology, no association analysis was possible between P-NfL and dementia diagnosis in the group without A\(\beta\) pathology.

Associations between CSF-NfL and clinical variables revealed similar results as previously shown in the full sample (Table 2) after stratification on A\(\beta\) pathology (Table S5). The closest associations were between CSF-NfL and t-tau, p-tau, Q_{\text{aib}}, and P-NfL. In participants with A\(\beta\) pathology, CSF-NfL also was associated with sex, and in participants without A\(\beta\) pathology, CSF-NfL was positively associated with neurogranin and negatively with A\(\beta_{42}/t\)-tau.

### 4 | DISCUSSION

We examined P-NfL and CSF-NfL in relation to MRI measurements and CSF markers in a well-characterized small-scale community-based sample of 70-year-olds. Although CSF-NfL and P-NfL were associated, they presented independent profiles. P-NfL, but not CSF-NfL, was associated with smaller hippocampal volume and larger ventricular volumes, and CSF markers of A\(\beta_{42}\), whereas CSF-NfL was related to t-tau and p-tau. Furthermore, associations between P-NfL and A\(\beta\) were only observed in participants with A\(\beta\) pathology.

CSF-NfL, but not P-NfL, was slightly higher in men, and previous studies report conflicting results,\(^{10,14,32,33}\) possible due to differences in age and clinical context. We confirm previous studies demonstrating that P-NfL decreases with increased BMI, due to dilution effects.\(^{34,35}\) P-NfL was associated with a diagnosis of dementia, as described previously in other settings.\(^ {14,36,37}\) However, it must be emphasized that our study only had five participants with mild dementia.

The correlation between P-NfL and CSF-NfL in this study was quite modest, in line with reports from generally healthy individuals,\(^{4,6-8}\) unlike the established clinical correlation. The exact relationship between P-NfL and CSF-NfL is not known, although it could be proposed that P-NfL levels are determined by a passive transport over the blood-brain barrier.\(^ {4,38}\) Our results align with this concept, as there is a close association between CSF-NfL and P-NfL in all study subgroups. Furthermore, the levels of CSF-NfL were more than 10 times higher than in plasma, indicating that the main production of NfL stemmed from the central nervous system (CNS). Finally, although distinctly different, NFL in plasma and CSF were both associated with other established markers of neurodegeneration in CSF.

Previously, associations for NFL in CSF and plasma have been compared in relation to neuroimaging variables in other community-based samples.\(^ {4,39}\) We extend these studies, by adding findings on several CSF markers including CSF-NfL. P-NfL was associated with both hippocampal volume and lateral ventricle volumes, whereas CSF-NfL differed in hippocampal volume only in its highest quartile. Although P-NfL was associated with A\(\beta_{42}, \ A\beta_{42/40}\), and A\(\beta_{42}/t\)-tau, CSF-NfL was associated with t- and p-tau, and neurogranin. Previous studies of CSF-NfL in cognitively normal individuals have reported associations with tau while not finding associations with A\(\beta\) pathology or hippocampal volumes.\(^ {40,41}\) However, the distinctly different association pattern in plasma has not been reported.

Although the associations between P-NfL and A\(\beta_{42}\) as well as A\(\beta_{42/40}\) were not significant after exclusion of five participants with dementia, the change in \(P\)-value was minimal (from \(P = .043\) to \(P = .070\), and \(P = .049\) to \(P = .054\)), suggesting that dementia is not causing these associations. Furthermore, as this is a smaller sub-sample from a larger study of randomly invited 70-year-olds in Gothenburg, participants with mild dementia were not outliers in their P-NfL data. In line with this reasoning, P-NfL was associated with lower levels of A\(\beta_{42}, \ A\beta_{42/40}\), and A\(\beta_{42}/t\)-tau in the 282 participants without dementia who presented A\(\beta\) pathology, suggesting that participants with A\(\beta\) pathology drive these associations.

The reason that we only found MRI associations with P-NfL is unclear, but it is likely owing to the cognitively healthy sample. Hippocampal volumes were significantly smaller in participants with the highest quartile of CSF NfL, but no linear association was found. In line with our observations, a recent longitudinal study evaluating the associations of P-NfL with neurodegeneration in AD found that cerebral atrophy was only significantly associated with gray matter atrophy in cognitively unimpaired participants with a prevalent A\(\beta\) pathology and not in cognitively impaired participants.\(^ {42}\) This could indicate that current knowledge regarding NFL from manifest neurodegenerative conditions is not directly transferrable to generally healthy individuals.

The association between P-NfL and a reduced hippocampal volume, larger lateral ventricles, and reduced levels of A\(\beta_{42}, \ A\beta_{42/40}\), and A\(\beta_{42}/t\)-tau suggests that NFL transport from CSF to plasma was higher in the individuals with neurodegeneration related to preclinical AD. It is important to understand why, as P-NfL is more clinically accessible. In addition, associations between increases in P-NfL and cerebral amyloid plaque burden measured with PET have been reported previously.\(^ {4}\) It is well known that AD patients present specific alterations in blood-brain barrier function, possibly due to A\(\beta\) plaque formation around vessels and cerebral amyloid angiopathy. The association between NFL and CKD found only in plasma could be another indicator of a relation to microvascular dysfunction, alternatively an impaired renal clearance of NFL as suggested previously.\(^ {34}\) Unlike CSF-NFL, P-NfL is also increased in peripheral neurodegenerative conditions. However, the influence of peripheral diseases should be minimal in this study, as all outcome variables are related directly to the CNS. P-NfL and CSF-NfL were both associated with Q_{\text{aib}}, as shown previously in clinical samples.\(^ {42-45}\)
When stratifying for Aβ pathology, P-NfL was only associated with Aβ markers in participants with Aβ pathology. Conversely, most MRI measurements, including hippocampal volume only associated with P-NfL in participants without Aβ pathology. It is possible that the presence of Aβ plaques affects NFL transport over the blood brain barrier, and it is also possible that the Aβ stratification confounds results on hippocampal volumes, as both are closely related to AD. Besides the consequent reduction in sample size, stratification also separates participants at high risk for developing AD from participants with other underlying neurodegenerative pathophysiology.

A strength of this study is the comprehensive characterization of participants from a community-based sample. The random recruitment of 70-year-olds in Gothenburg limits selection bias associated with clinical cohorts. In addition, there are some limitations. Because this is a community-based sample, the number of participants with manifest cognitive deficits was relatively low. All participants from the H70 Birth Cohort Study were invited to undergo lumbar puncture. However, participants with CSF sampled were less likely to have had a stroke compared to the 867 non-participants with P-NfL analyzed. This could explain the absence of associations between CSF-NfL and WML. Second, almost all participants in the study were born in Europe, which must be considered, as ethnicity is a known risk factor in different neurodegenerative conditions.46 Third, the number of participants volunteering for CSF sampling was low in absolute numbers, thus yielding low statistical power. Furthermore, it is possible that stratification of Aβ42/40 instead of Aβ42 would have resulted in a more-specific stratification of participants with Aβ pathology.47 However, the decision to use Aβ42 was based on a previously published longitudinal study defining a reliable cut point for Aβ42 in relation to incident AD.

In conclusion, NFL in plasma and CSF presented distinctly different associations with biomarker evidence of neurodegeneration in a small-scale community-based sample of 70-year-olds in Gothenburg, Sweden. P-NfL, but not CSF-NfL, was associated to structural changes on MRI, that is, smaller hippocampal volume and larger ventricular volumes, and P-NfL was associated with CSF markers of Aβ42, whereas CSF-NfL was related to t-tau and p-tau. The implications of these different association patterns should be further explored and considered in future studies including generally healthy participants.

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CONFLICT OF INTEREST

Anna Dittrich, Nicholas J. Ashton, Fiona Geiger, Joel Simrén, Sara Shams, Alejandra Machado, Eric Westman, Ingmar Skoog and Anna Zettergren declare no conflict of interest. Henrik Zetterberg has served at scientific advisory boards for Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, and CogRX; has given lectures in symposia sponsored by Fujirebio, Alzecure, and Biogen; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. Kaj Blennow has served as a consultant, on advisory boards, or on data-monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. Michael Schöll has served on a scientific advisory board for Servier Pharmaceuticals. Silke Kern has served on the advisory board for Geras Solutions and Biogen unrelated to the present study.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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