

RESEARCH ARTICLE

Elevated plasma neurofilament light in aging reflects brain white-matter alterations but does not predict cognitive decline or Alzheimer's disease

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Abstract

Introduction: We investigated neurofilament light (NFL) accumulation in normal aging as well as in preclinical and clinical Alzheimer's disease (AD) and assessed individual differences in NFL load in relation to cognition and brain white-matter integrity.

Methods: We analyzed longitudinal data covering 30 years (1988–2017). Cognitive testing was done up to six times. Plasma NFL was quantified for controls and 142 cases who developed AD over time, and longitudinal changes in NFL were quantified for 100 individuals with three brain-imaging sessions.

Results: Longitudinal analyses revealed age-related NFL increases with marked variability. AD cases had elevated NFL levels, while no significant group differences were seen in the preclinical phase. Variability in NFL levels showed non-significant correlations with cognition but was associated with brain white matter.

Discussion: Our findings suggest that elevated blood NFL, likely reflecting brain white-matter alterations, characterizes clinical AD, while NFL levels do not predict age-related cognitive impairment or impending AD.

KEYWORDS

Alzheimer's disease, biomarker, brain white matter, cognition, early prediction, longitudinal, neurofilament light

1 | INTRODUCTION

The discovery of minimally invasive and cost-effective blood-based biomarkers for dementia has stimulated studies of amyloid beta ($A\beta$),^{1,2} tau,^{3,4} and neurofilament light (NFL).^{5,6} NFL is a neurofilament protein

exclusively situated in the neuronal cytoplasm. It is highly expressed in large-caliber myelinated axons and it increases in cerebrospinal fluid (CSF) and blood in proportion to central nervous system (CNS) axonal damage.⁷ Higher levels of plasma NFL levels have been found in demented individuals and individuals with mild cognitive impairment

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(MCI) than in controls, and higher NFL was related to poor cognition and brain atrophy and hypometabolism.⁶ Blood NFL concentration is increased across dementias and diseases with axonal injury, suggesting it is a general marker of neurodegeneration.⁸ However, several issues remain.

First, long-term longitudinal NFL data covering the adult life span are largely missing, but vital for characterizing the average rate as well as individual differences in NFL accumulation in aging. Second, the expression of NFL in large-caliber axons suggests that elevated NFL levels should correlate with white-matter alterations, but available findings are mixed and inconclusive.^{6,9,10} Longitudinal studies show a relation of white-matter changes with decline in speed of processing¹¹ and block design/general cognition,¹² suggesting that such tasks rather than coarse screening tests of cognitive deficits may be the most sensitive cognitive markers of an NFL effect. Third, a recent study¹³ found evidence for elevated serum NFL in the preclinical phase of familial Alzheimer's disease (AD), but related NFL data for non-familial dementias are scarce and cover a limited time segment.

Here, to address these issues we used data from the 30-year longitudinal Betula study.¹⁴ We focused on individuals with longitudinal data on blood samples, cognition, and brain imaging, as well as a case-control study of manifest and preclinical AD versus selected controls (Figure 1A, B). We predicted (1) a significant increase in NFL plasma levels in aging along with marked individual differences, (2) relation of higher NFL levels in aging with alterations in brain white matter and impaired cognitive performance, and (3) elevation of NFL levels in individuals with clinical AD and possibly also preclinical AD.

2 | METHODS

2.1 | Betula study design

Data were obtained from the Swedish longitudinal Betula study,¹⁴ a population-based prospective study on aging, memory, and dementia conducted in northern Sweden (www.umu.se/en/betula). An overview of the Betula design and the collection of health, cognitive, imaging, and biomarker data used in the present study is given in Figure 1A and B.

2.2 | Participants

The Betula study comprises 4425 study participants, randomly selected from the population registry, into six age- and sex-stratified cohorts (S1–S6). Health- and cognitive data were collected in up to six test waves (W1–W6) 5 years apart, in total 25-year follow-up time (1988–2014). In 2017, a seventh test wave (W7) was conducted, only including S1 and S3 participants with imaging data from W5 and W6 for a third magnetic resonance imaging (MRI)/function MRI (fMRI) investigation (n = 100). The participants considered for the present study were obtained from two longitudinal samples; sample 1 (S1; n = 1000) included at W1, 1988–1990, and sample 3 (S3; n = 963) included at W2, 1993–1995. Because plasma sampling was introduced at the third test

RESEARCH IN CONTEXT

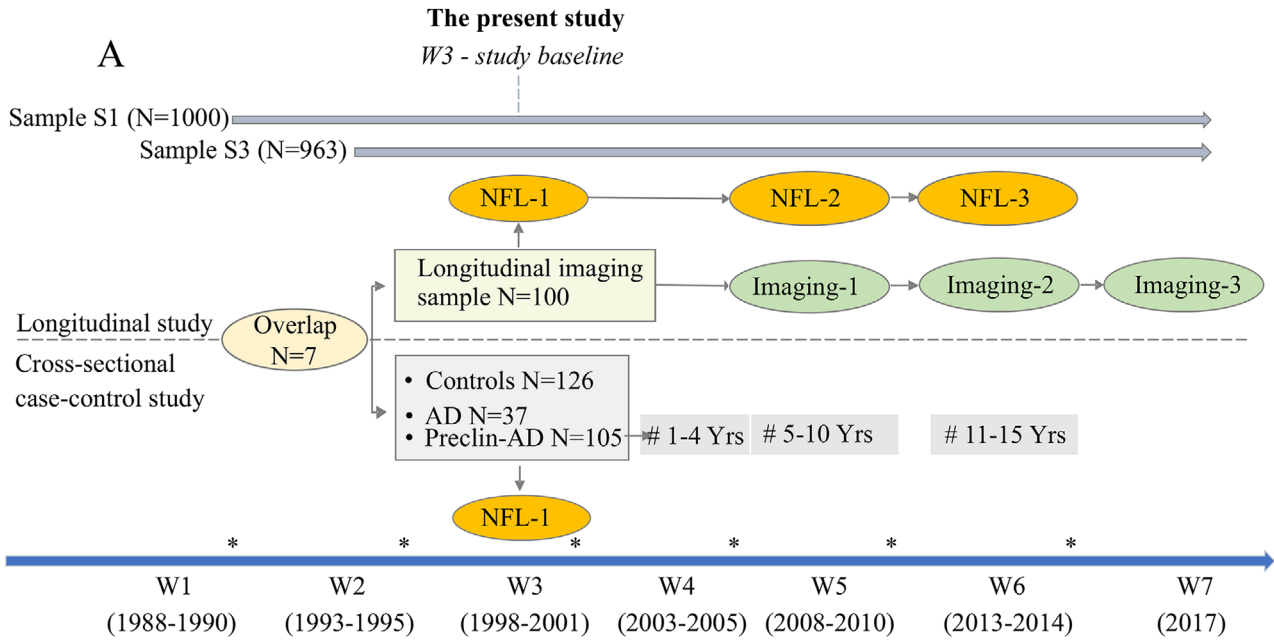
1. Systematic review: Previous studies have shown that blood neurofilament light (NFL) levels are increased in dementias and diseases with axonal injury, suggesting elevated levels could serve as a non-invasive biomarker of neurodegeneration. This work is properly cited. The longitudinal accumulation of NFL in normal aging and in preclinical Alzheimer's disease (AD) remain unclear.
2. Interpretation: Our findings link age-related increases in NFL levels in blood to brain white-matter alterations, thus validating the usefulness of measuring NFL in blood. Our findings of no correlations of NFL levels with cognition or impending AD inform current efforts at identifying early biomarkers of dementias.
3. Future directions: To investigate blood NFL levels in relation to other forms of dementia and neurodegenerative diseases.

wave, W3 constitutes study baseline both with regard to NFL measures for the AD-control dataset and the longitudinal imaging dataset.

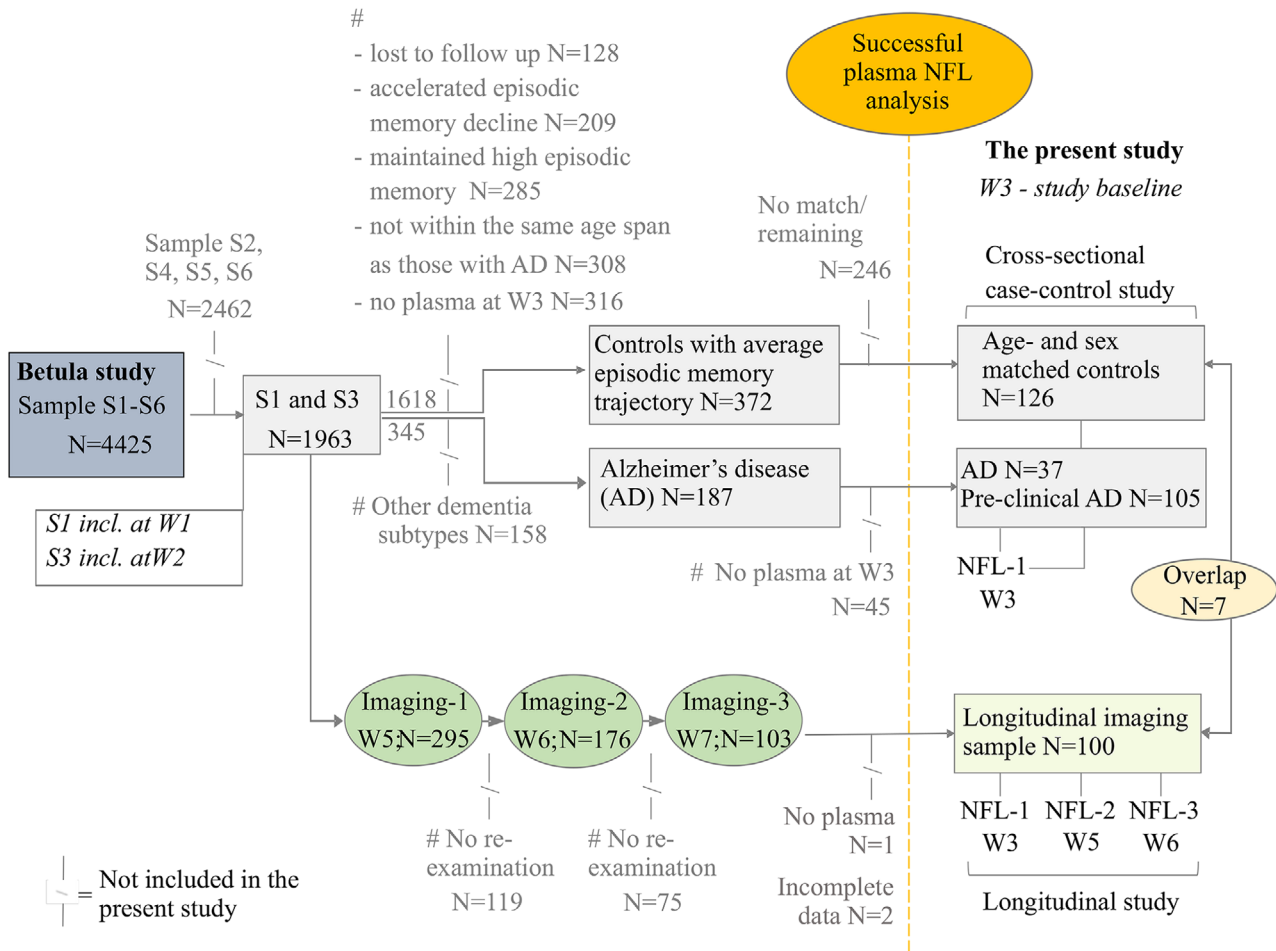
All individuals in cohorts S1 and S3 with either manifest or preclinical AD at W3 and available W3 plasma constitute the basis for the case-control sample. Preclinical AD is denoted as individuals who subsequently developed AD 1–4, 5–10, and 11–15 years after W3. The controls remained non-demented throughout the studied period (until 2017) and were classified as having an average episodic memory decline relative to their age.^{15,16} Considering only controls within the same age span as the AD population (birth year 1909–1939), the number of potential controls was limited to N = 372. After matching for age (year of birth \pm 1 year), sex, and cohort (S1, S3), 126 controls remained, of which N = 8 were not possible to match by cohort. For 16 AD cases, there were no eligible controls. The sex distribution among the AD cases showed more women than men (109/33). Seven controls included in the case-control sample were also included in the longitudinal imaging dataset. The longitudinal imaging dataset include Betula individuals from cohorts S1 and S3 with imaging data obtained at three MRI/fMRI examinations; W5 (2008–2010), W6 (2013–2014), and W7 (2017). The final sample comprises 100 non-demented participants; 43 females and 57 males, 45 to 70 years of age at W3. The Betula study was approved by the Regional Ethical Review Board in Umeå; Dnr: 2018-480-32M; 2018-12-20. Written consent for study participation was obtained for each participant.

2.3 | Diagnosis assessments

Clinical diagnoses were determined from multiple sources of information with an emphasis on written and computerized medical records over the time span from adulthood to the end of the study period.



B



Hereby a timeline was constructed, including socioeconomic, medical, psychiatric, neurological, neuroradiological, and pharmacological data from in- and out-patient care to be integrated in the dementia diagnostic process. The information obtained was sufficient for applying criteria-based systems, namely, the Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV) classification.¹⁷ The diagnosed AD cases all showed a progressive decline as evidenced by symptoms attributable to AD. Individuals with cardiovascular burden accompanied with neurological signs and a fluctuating course were diagnosed as vascular dementia (VaD). In some instances, a “mixed” condition was evident and denoted dementia NOS. Less common dementia disorders such as frontotemporal dementia (FTP), Parkinson dementia (PD), Lewy body dementia (LBD), corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP) were extensively examined within the Departments of Geriatric Medicine and Neurology, and diagnosed with established criteria (<https://medlineplus.gov/degenerativediseases.html>). Symptoms of cognitive impairment close to death, often accompanied by severe somatic conditions and delirious episodes, were not included in the dementia group, nor were individuals exhibiting a long-term low cognitive capacity after, for example, trauma, stroke, tumor, or subarachnoid hemorrhage.

The diagnostic procedure was performed repeatedly with start at baseline and thereafter every 5 years. To increase diagnostic precision, follow-up assessments using the computerized medical record system were performed without the responsible physician having access to previously determined status with regard to possibly dementia, subtype, and disease onset. Inconsistencies between previous and current determined status resulted in a re-assessment at a separate occasion to establish conclusive status. Disease onset was defined as the time at which the clinical symptoms became sufficiently severe to interfere with social functioning and instrumental activities of daily living, that is, when the core criteria of dementia were met.¹⁸ The diagnostic evaluation was, throughout the study period, coordinated by the same research geropsychiatrist (co-author Rolf Adolfsson). An essential part of the identification of individuals with cognitive impairment and decline was neuropsychological assessments every 5 years. Particular attention was given to those who met one or several of the following pre-defined criteria: low score (≥ 1.8 standard deviations below age-based norms) on a composite score based on memory and cognitive tests, with a decline in cognitive performance from a previous test occasion (from high to average or low, or from average to low); a low score (≤ 23) or a drop by three points compared to previous scores on the Mini-Mental State Examination (MMSE¹⁹); self-reported mem-

ory impairment, or evident clinical signs of neurocognitive dysfunction observed in the test situations.

2.4 | Plasma NFL

Plasma NFL concentration was measured using the NF-LIGHT Simoa kit on an HD-1 Analyzer, following the instructions by the manufacturer (Quanterix Corp., Billerica, MA, USA). The samples were analyzed by board-certified laboratory technicians following strict procedures for quality control. A single batch of reagents were used for the analyses. Calibrators were run in duplicates, while samples (diluted four-fold) were run as singlicates. Two quality control (QC) samples (aliquots of two plasma pools) were run in duplicate in the beginning and at the end of each plate. The QC sample with an NFL concentration of 6.1 pg/mL had a within-run coefficient of variation (CV) of 5.4% and a between-run CV of 7.0%, while the QC sample with an NFL concentration of 48.4 pg/mL had a within-run CV of 3.5% and a between-run CV of 6.9%. The dynamic measuring range was 0.17 to 1800 pg/mL, and the lower limit of quantification (LLOQ) was 0.17 pg/mL.

2.5 | Cognition

Our cognitive test battery is described in Nilsson et al.¹⁴ Briefly, at each of the seven evaluations, or “waves,” we assessed episodic memory using tests of free recall of 16 learned sentences and of 12 unrelated nouns. To mitigate practice effects, we adopted a counter-balanced design using eight different versions of the sentence battery and the word list. We also administered the MMSE and the Block Design test (from the Weschler Adult Intelligence Scale [WAIS]²⁰). Beginning at Wave 3, we also used a 125-item letter-digit symbol substitution speed task.

2.6 | Neuroimaging

The acquisition of T1-weighted images, T2-weighted images, and DTI-series is thoroughly described in Gorbach et al.,²¹ along with the procedure for calculation of white matter lesions from T1/T2 and calculation of microstructure (fractional anisotropy [FA]) in the corpus callosum.

For the Voxel-Based-Morphometry (VBM) part, the T1-weighted images were segmented into gray matter, white matter, and CSF

FIGURE 1 A, Study overview: Plasma biomarker collection in the context of the 30-year longitudinal Betula design. The individuals were obtained from two samples of 1000 (S1) and 963 (S3) individuals included at Waves 1 (W1) and 2 (W2), respectively. The first collection of plasma samples at W3 forms the basis for comparing individuals with clinical (N = 37) and preclinical (N = 105) Alzheimer's disease (in figure: AD; Preclin-AD) with matched controls (N = 126). W3 was also the first of three biomarker collections (second at W5; third at W6) for the longitudinal imaging sample. Cognitive testing was done at all waves; magnetic resonance imaging was done at W5–W7. * Clinical diagnoses were assessed repeatedly with start at baseline and thereafter every 5 years. # Preclinical AD is denoting individuals who subsequently developed AD 1–4, 5–10, and 11–15 years after W3 plasma NFL analysis. B, Flow chart: Illustration of the route and decision points from the parent cohort “The Betula Study” (N = 4425) to the two present subpopulations; the cross-sectional case-control sample (N = 142; N = 126) and the longitudinal imaging sample (N = 100). See “2.2 Participants” for complementary description. # = Among those who are not included in the present study due to the specified reasons, a number of individuals were deceased prior to W3 (N = 216)

likelihood maps. For each subject a DARTEL template²² was created from the three time points they participated in. A flow-field-file mapping to subject template was achieved. The subject specific DARTEL-templates were used in a group-DARTEL process and a flow-field-file mapping from subject template to group template was achieved. A normalization in two steps, with the flow-field-maps and with a final affine registration to MNI-space, was applied on the gray-matter likelihood maps such that the amount of signal was preserved. Spatially smoothing was done with a 3 mm Gaussian kernel. A parcellation was applied on a mean anatomic image of the subjects using FreeSurfer 6.0 (<https://surfer.nmr.mgh.harvard.edu/fswiki/>). The mean VBM-value in each of the parcels for each subject and time point were extracted for further analyses. Segmentation, DARTEL template creation, and normalization were made with SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/>) using an in-house program for batching (DataZ).

2.7 | Statistical analyses

The longitudinal analyses were performed in the mixed model framework, using either linear²³ or generalized additive²⁴ mixed models (LMM and GAMM, respectively). Unless otherwise stated, the linear mixed models were specified using age as a time-varying covariate, NFL group (above/below the median NFL at the sixth wave), an age-group interaction, and the (non-time-varying) covariates education in years and baseline age. As a control analysis for the VBM data, LMM/GAMM models were specified using time in years from baseline, NFL group, a time-group interaction, baseline age and a baseline age-group interaction, and finally education in years. The generalized additive mixed model was specified using a smooth function of time-varying age as covariate. Results for the LMM models were obtained using the R software,²⁵ more specifically the lme4, lmerTest, and gamm4 packages. We also investigated our cognitive measures' relation to age cohort and NFL group at each test wave separately, for W1–W5, using analysis of variance (ANOVA). Comparison of NFL levels between cases and controls was performed using paired one-sided t-tests. For cases for which no control was identified, we performed analyses in two ways. Disregarding the non-matched cases or imputing the control age group median as control observation for that case. When analyzing the imaging sample, two subjects with observations above 35 pg/mL at one or more time points were removed as outliers, leaving us with 98 subjects and 294 observations in total. In the case-control sample, three subjects with NFL levels above 100 pg/mL were considered to be outlying and discarded.

2.8 | Data availability

Anonymized data will be shared upon request from qualified investigators for the sole purpose of replicating procedures and results presented here, and as long as data transfer is in agreement with European Union legislation on the General Data Protection Regulation.

3 | RESULTS

3.1 | NFL increase in aging: Average pattern and individual differences

Analysis of the longitudinal observations in the imaging sample ($N_{\text{OBS}} = 294$) revealed an exponential increase in NFL from the late 40s to early 80s (Figure 2A). This average pattern confirmed an average NFL increase in aging, along with marked individual differences as indicated by the individual lines. To characterize individual differences in NFL increases in aging, we split the longitudinal sample based on the median (13.1) of NFL at the last measurement (W6). Individuals with high levels at W6 tended to have high levels also 5 (W5) and 15 (W3) years earlier. A categorical analysis of NFL levels above/below the median at Waves 3 and 6, respectively, revealed a significant (Chi-square[1] = 21.16, $P < .0001$) NFL association over 15 years (W3–W6). ANOVA of longitudinal NFL changes as a function of NFL group (high/low) revealed higher increases with age in the high NFL group (Figure 2B; a significant group by age interaction, $F[1255] = 6.75$ $P < .0001$). The sex (females/males) and apolipoprotein E (APOE)- (e3/e4-carriers) distributions were comparable in the high (22/28; 34/16) and low (21/29; 31/19) NFL groups.

3.2 | NFL levels in relation to brain white matter

We first conducted a whole-brain VBM analysis and tested for NFL group (high/low) by age interactions, with focus on the brain white matter. In line with our predictions, both VBM models (see the Statistical Analyses section) identified significant interaction effects in white-matter loci in the posterior and mid-anterior corpus callosum (CC). These effects reflected a greater reduction in white-matter volume with increasing age in the high NFL group. Other significant VBM interaction effects were located in the gray matter of the left temporal cortex (Table S1 in supporting information for all significant VBM interaction effects, P 's $< .01$).

Analyses of the integrity of white-matter microstructure (DTI-FA) in the CC revealed a significant ($F[1,120] = 4.376$, $P = .039$) group-by-age interaction in the posterior CC (splenium; Figure 2C). Similar but non-significant trends toward reduced white-matter integrity with advancing age in the high NFL group were seen in the body and genu (ie, mid-anterior CC). Third, analysis of the fluid attenuation inversion recovery (FLAIR) images revealed white-matter hyper-intensity increases in aging, as previously reported for this sample. However, no significant NFL group by age interaction was found ($F[1, 177] = 1.633$, $P = .20$, Figure 2D).

3.3 | Plasma NFL levels in preclinical and clinical AD

In the AD-Control sample, individuals with manifest AD at W3 had significantly higher NFL levels than matched controls ($t[36] = 1.796$, $P = .040$, Figure 3) when using the median imputation ($t[25] = 1.218$,

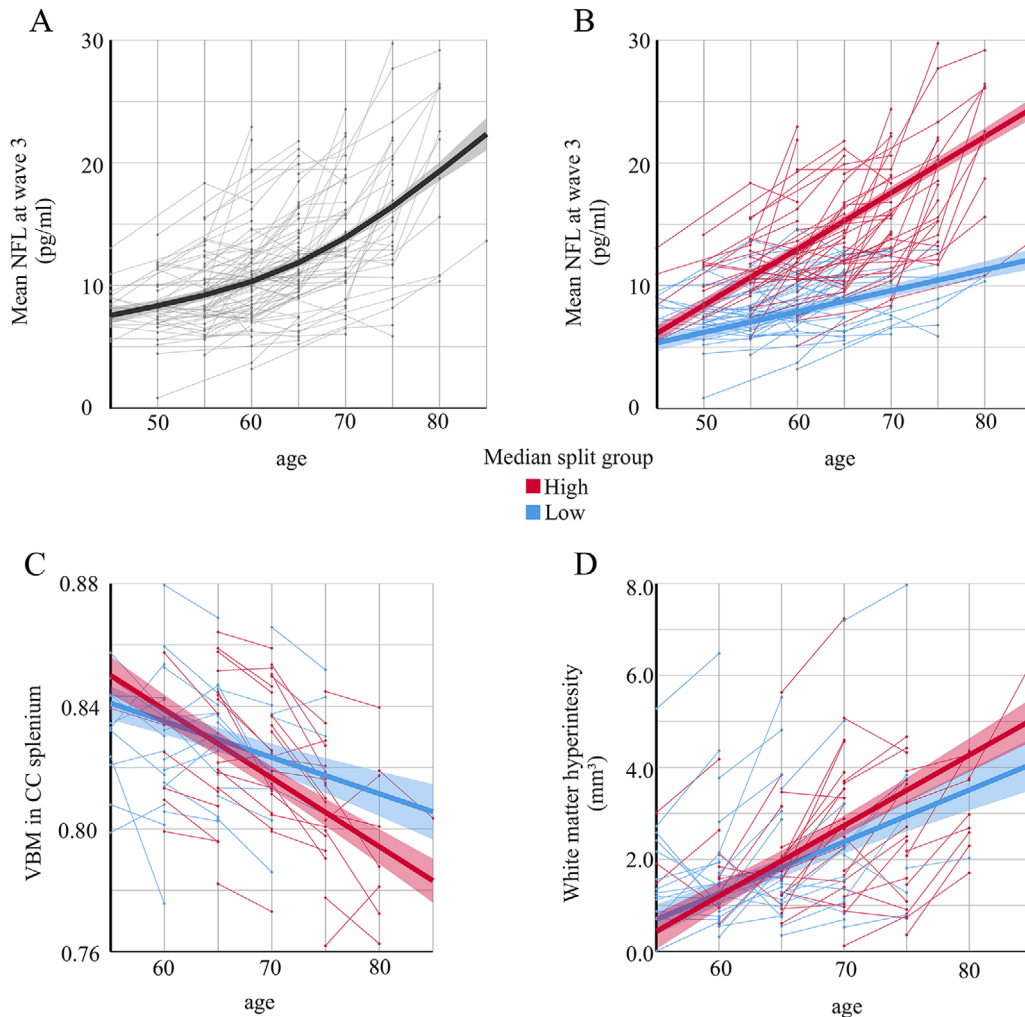


FIGURE 2 Longitudinal neurofilament light (NFL) changes. A, NFL levels increased exponentially in normal aging (thick line) with marked heterogeneity (thin lines). B, Individuals with high NFL levels (>Md at W6) had a stronger longitudinal NFL increase. C, The high NFL group had a stronger age-related decline in white-matter integrity in the splenium of corpus callosum. D, No NFL group difference was found for white-matter hyperintensities. Shaded areas represent ± 1 standard error for each line

$P = .117$ without imputation). In the preclinical phase, no significant (P 's > .1) case-control differences were seen (Figure 3) with or without imputation.

When the NFL data from the AD-Control sample were plotted as a function of age and NFL load (median-split in each age group) we replicated the pattern in the imaging sample of increased NFL levels in older age, particularly in the high NFL subgroup (Figure 4). The majority (27% or 73%) of the 37 individuals with AD diagnosis fell in the high NFL subgroup, whereas the 105 preclinical cases were evenly distributed over the high (51) and low (54) subgroups. Thus, non-demented individuals in the low NFL subgroup were as likely to develop dementia in the future as individuals with high NFL load.

3.4 | NFL levels in relation to cognition

In the analyses of cognitive performance in relation to individual differences in NFL, we took advantage of the longitudinal design in which we

have data from seven (MMSE, episodic memory, block design) or five (speed) test waves, respectively (see Figure 1) and examined whether age-related cognitive decline was faster for individuals in the high NFL group of the imaging sample. However, with the exception of a significant interaction for the block-design task ($F[1,556] = 7.10$, $P = .008$, Figure 5A), the rates of cognitive decline were similar in the high and low NFL groups (P 's > .50 for group by age interactions for MMSE, episodic memory, and speed).

In the AD-Control sample, an age group by NFL load (7×2) ANOVA examined whether individuals with higher NFL levels displayed poorer cognitive performance. Consistent with the findings from the imaging study, no significant interaction effects were observed for MMSE (W1-W5), episodic memory (W1-W5), or speed (W3-W5; all 13 P -values > .10, except for speed at W4 with $P = .048$). Also, no significant effect was seen for block design (W1-W5; all three P -values > .10; Figure 5B) Thus, the NFL effect on block-design performance in the longitudinal analysis was not replicated in the cross-sectional analysis.

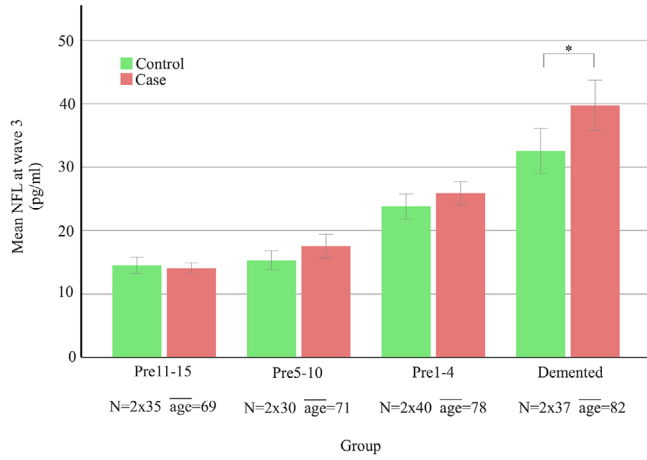


FIGURE 3 Comparison of neurofilament light (NFL) levels in preclinical and diagnosed Alzheimer’s disease versus matched controls. Case-control differences were evaluated by paired t-tests (one-tailed). Missing control data were replaced by median imputation. * $P = .040$. Error bars are ± 1 standard error (N/group, mean age in years)

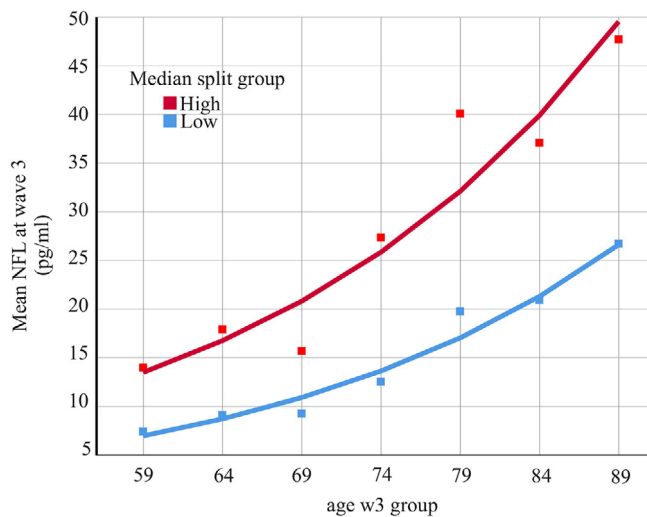


FIGURE 4 Cross-sectional age differences in the case-control sample. Individuals in each age were group median-split into low and high neurofilament light (NFL) subgroups. A marked age-related increase in NFL was observed, in particular in the high NFL subgroup. An exponential function was fitted to the means in each of the subgroups

4 | DISCUSSION

We present a large-scale study of plasma NFL changes in adulthood and aging. Consistent with our prediction, in both the longitudinal (Figure 2A) and the cross-sectional (Figure 4) analyses, we observed a marked age-related increase in NFL from the late 40s to early 80s. These observations suggest that the brain changes that underlie NFL build-up is an inherent aspect of normal aging, characterized by marked individual differences. Many brain changes accompany

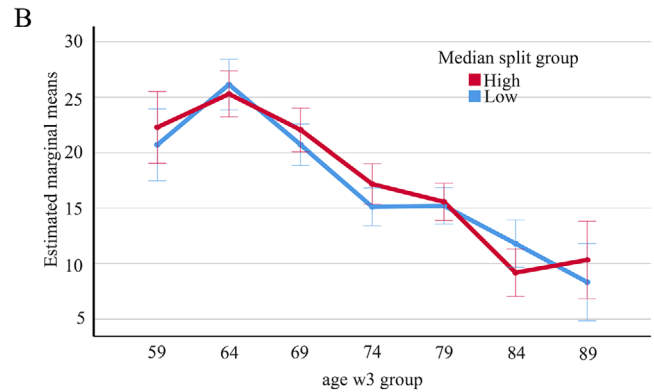
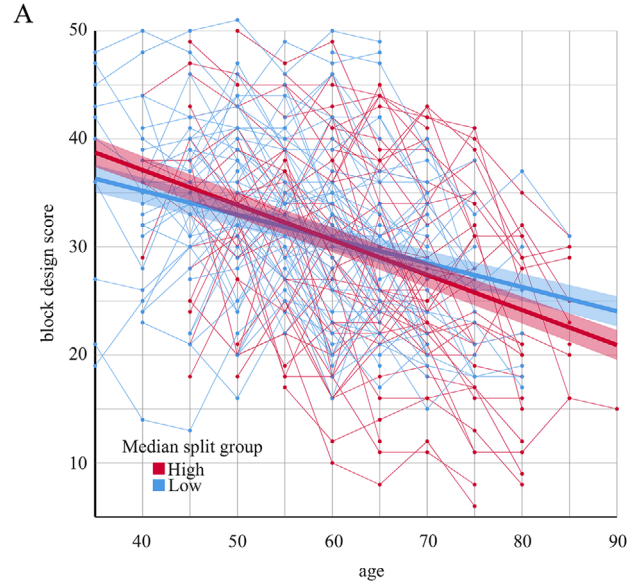


FIGURE 5 Neurofilament light (NFL) in relation to cognition. A significant NFL-group difference in block-design performance was observed for the longitudinal (A) but not for the cross-sectional (B) sample. In (B), data from W3 are presented (ie, when the serum samples were taken), but similar non-significant group effects were seen at all waves

normal aging²⁶ but given that NFL primarily is located in long myelinated axons⁸ elevated NFL should most closely reflect white-matter changes. Consistent with independent past findings,⁶ no significant group difference was seen for white-matter hyperintensities. Such abnormalities are typically of an ischemic origin²⁷ and may therefore not relate to NFL levels. Instead, we found that the high NFL group had reduced white-matter integrity (DTI) and volume (VBM) in the splenium of the corpus callosum.

The analyses of whether age-related cognitive impairment was more marked in individuals with high NFL levels provided minimal support for a relation of NFL levels with cognition. It is noteworthy that we failed to find a robust NFL link to cognitive level and change in a comparison of the low and high subgroups’ cognitive change over 25 years. On the assumption that elevated NFL reflects white-matter insult, the

absence of an NFL-cognition relation is in line with demonstrations of weak and non-significant associations between white matter and cognitive decline in aging.^{11,21} Some studies have found that high NFL levels relate to poor cognition,^{6,28,29} but observations of stronger correlations of cognition to NFL in individuals with MCI and AD than in controls suggest that a common disease factor could have influenced some previous observations of NFL–cognition relations.

The third prediction was elevated NFL levels in individuals with diagnosed AD, and possibly also in preclinical cases up to 15 years prior to diagnosis. The results showed a weak but significant NFL difference between individuals with manifest AD at W3 and their matched controls. At the individual level, most demented individuals fell in the high NFL subgroup (73%). These findings support the view that pathological brain changes in AD, likely of a white-matter origin, translate into elevation of NFL blood levels. However, no significant differences in NFL levels were found between preclinical cases and their controls—even after splitting the sample into high and low subgroups. Thus, possibly due to marked individual differences in NFL levels in normal aging, NFL levels in blood do not seem to be a reliable biomarker for future AD.

A limitation of the study is that no systematic clinical examination nor *post-mortem* neuropathological examination were conducted within the study frame. However, the diagnostic evaluation was based on long-term information obtained from largely all clinical disciplines via medical records. To minimize the risk of misclassification, diagnoses were validated by repeated assessments every 5 years.

In conclusion, we found that NFL concentration is markedly increased as a function of age, with marked individual differences. High levels of NFL were related to brain white-matter integrity, in particular in the splenium of the corpus callosum, but did not relate to cognitive decline or upcoming AD. Future studies should test whether NFL is a stronger biomarker for other forms of dementia than AD, such as white-matter dementia.³⁰

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AUTHOR CONTRIBUTIONS

Lars Nyberg, Rolf Adolfsson, Annelie Nordin Adolfsson, Anders Lundquist, Micael Andersson report no disclosures. Kaj Blennow has served as a consultant or on advisory boards for Abcam, Axon Neuroscience, Biogen, Lilly, MagQu, Novartis, and Roche Diagnostics, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. HZ has served at scientific advisory boards for Roche Diagnostics, Denali, Wave, Samumed, and CogRx; has given lectures in symposia sponsored by Biogen and Alzecure; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg.

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SUPPORTING INFORMATION

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

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