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Title:

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Date:

2020-01-01

Citation:

Dhiman, K., Gupta, V. B., Villemagne, V. L., Eratne, D., Graham, P. L., Fowler, C., Bourgeat, P., Li, Q. X., Collins, S., Bush, A. I., Rowe, C. C., Masters, C. L., Ames, D., Hone, E., Blennow, K., Zetterberg, H. & Martins, R. N. (2020). Cerebrospinal fluid neurofilament light concentration predicts brain atrophy and cognition in Alzheimer's disease. *Alzheimer S and Dementia Diagnosis Assessment and Disease Monitoring*, 12 (1), <https://doi.org/10.1002/dad2.12005>.

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## CEREBROSPINAL FLUID BIOMARKERS

# Cerebrospinal fluid neurofilament light concentration predicts brain atrophy and cognition in Alzheimer's disease

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### Abstract

**Introduction:** This study assessed the utility of cerebrospinal fluid (CSF) neurofilament light (NfL) in Alzheimer's disease (AD) diagnosis, its association with amyloid and tau pathology, as well as its potential to predict brain atrophy, cognition, and amyloid accumulation.

**Methods:** CSF NfL concentration was measured in 221 participants from the Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing (AIBL).

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**Results:** CSF NfL levels as well as NfL/amyloid  $\beta$  (A $\beta$ 42) were significantly elevated in AD compared to healthy controls (HC;  $P < .001$ ), and in mild cognitive impairment (MCI) compared to HC ( $P = .008$  NfL;  $P < .001$  NfL/A $\beta$ 42). CSF NfL and NfL/A $\beta$ 42 differentiated AD from HC with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.84 and 0.90, respectively. CSF NfL and NfL/A $\beta$ 42 predicted cortical amyloid load, brain atrophy, and cognition.

**Discussion:** CSF NfL is a biomarker of neurodegeneration, correlating with cognitive impairment and brain neuropathology.

#### KEYWORDS

amyloid, biomarker, dementia, diagnosis, ELISA, neurodegeneration, neurofilaments

## 1 | INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia.<sup>1</sup> The use of positron emission tomography (PET) imaging has not only led to the possibility of diagnosis pre-mortem, but also to the confirmation that AD pathology develops many years before the symptoms appear.<sup>2</sup> However, PET diagnostic methods have limited utility due to the high cost and poor accessibility. For more cost-effective diagnostic tools, a significant amount of research has been done to explore and validate cerebrospinal fluid (CSF) biomarkers.<sup>3</sup> This has led to CSF biomarkers being included in the diagnostic criteria for AD in 2011, by the National Institute on Aging (NIA) and the Alzheimer's Association (AA),<sup>4</sup> and the International Working Group (IWG) in 2014.<sup>5</sup> In addition, blood biomarkers have been investigated, as well as eye imaging; however, these approaches although promising require considerably more evidence to be as convincing as the gold standard CSF biomarkers.<sup>6-8</sup>

Evidence indicates that AD is a disease of multiple etiologies, with numerous risk factors that overlap with respect to metabolic and pathological changes they cause, yet together direct and/or accelerate the trajectory of AD dementia.<sup>3,9</sup> The multiple pathological changes are associated with specific biomolecules that might serve as biomarkers for making a diagnosis, and as indicators of changes that occur with disease progression.

This article focuses on CSF neurofilament light (NfL) chain protein and its potential as an AD biomarker. NfL has emerged as one of the most promising CSF markers of neurodegeneration, for diagnostic purposes, and in particular for studying disease neuropathological progression.<sup>10-14</sup> Elevated CSF NfL levels are linked to white matter changes in the brain, which reflects the fact that NfL is a biomarker of axonal degeneration.<sup>15</sup> Elevated levels are associated with rate of hippocampal atrophy in cognitively healthy individuals, including those at risk for AD.<sup>16</sup> In addition recent studies have reported elevated levels of NfL in the plasma of AD subjects.<sup>17,18</sup>

Neurofilaments are phosphoproteins that are synthesized in the cell bodies and then translocated to the axons.<sup>19</sup> The functions of neurofilaments depend on their state of phosphorylation.<sup>20</sup> They are hetero-polymeric proteins comprising four subunits: neurofilament

heavy (NfH), neurofilament medium (NfM), and neurofilament light (NfL) polypeptides and  $\alpha$ -internexin or peripherin.<sup>21</sup> Neurofilaments are found particularly in neuronal axons, keeping the myelinated axons structurally stable and playing an essential role in the growth and impulse conduction along the axons.<sup>21</sup> They also act as skeletal supports, helping to maintain the shape of neurons.<sup>22</sup> Neuronal damage in neurodegenerative diseases, as well as in acute brain injury, would likely result in the release of neurofilaments into the CSF.

The present study aimed to investigate the utility of CSF NfL levels in the diagnosis of AD and in the assessment of brain amyloid load, atrophy, and cognition. The study was conducted by using baseline CSF samples from participants in the Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing (AIBL). The aims of the present study were as follows: (1) to assess the diagnostic utility of NfL in distinguishing AD from mild cognitive impairment (MCI) and healthy controls (HCs); (2) to assess the diagnostic accuracy of NfL (alone or in combination with CSF amyloid  $\beta$  [A $\beta$ 42], CSF total tau [T-tau], or phosphorylated tau [P-tau]) in differentiating AD from controls using receiver operating characteristic (ROC) curve analysis; (3) to assess whether there is an association between CSF NfL levels and amyloid levels, tau pathology, and/or brain volumes; (4) to assess whether CSF NfL levels predict baseline brain amyloid load, brain atrophy, and cognition; and (5) to assess whether NfL predicts change in brain amyloid burden.

## 2 | MATERIALS AND METHODS

### 2.1 | Participants

This study reports on data and samples obtained from 221 participants recruited as a part of the AIBL study (<http://aibl.csiro.au/>), who had their CSF collected at baseline between 2009 and 2016. Among these, 100 were recruited at the time of the study inception and the remaining participants were recruited during enrichment of the cohort. The AIBL is a prospective, longitudinal study that assesses the participants at 18-month intervals, investigating changes in biomarkers, cognition, and other parameters. The study was initiated in 2006 to investigate

potential biomarkers, cognitive parameters, and lifestyle factors associated with AD. The study consists of individuals categorized as AD, MCI, and HC.<sup>23</sup> The classification of AD is based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria<sup>24</sup> and MCI based on the protocol defined by the criteria given by Winblad et al.,<sup>25</sup> which is informed by Petersen et al. criteria.<sup>26</sup> Exclusion criteria include heavy alcohol consumption, past serious head injury, history of non-AD dementia, current clinical depression, schizophrenia, bipolar disorder, epilepsy, Parkinson disease, cancer (other than basal cell skin carcinoma), history of stroke, untreated obstructive sleep apnea, and withdrawal of consent.<sup>23</sup> The AIBL has been approved by the institutional ethics committees of Austin Health, St. Vincent's Health, Hollywood Private Hospital, and Edith Cowan University. All volunteers provided written informed consent before participating in the study. The study participants (n = 221) were clinically classified as HC (n = 159), MCI (n = 34), and AD (n = 28). Age, gender, and apolipoprotein E (APOE) genotype data were assessed as part of the cohort demographic characterization. The AIBL has more than 2400 participants, and lumbar punctures (LPs) have been done on over 200 participants only, because about one in 10 agreed to have one.

## 2.2 | Brain imaging and cognitive assessment

Cognitive assessment was done using a neuropsychological battery comprising various tests, which cover the main domains of cognition.<sup>23</sup> Of interest, in this article were the baseline Mini-Mental State Exam (MMSE) scores. Most of these participants (n = 195) underwent amyloid imaging using positron emission tomography (PET) with different tracers (carbon-11 (C-11) labeled Pittsburgh compound B [<sup>11</sup>C-PiB], fluorine-18 [F-18] labeled florbetapir or F-18 labeled flutemetamol). Each amyloid tracer has a different dynamic range; therefore, to place all the standardized uptake value ratios (SUVRs) on the same continuous scale, the SUVR from the F-18 tracers were transformed into PiB-like SUVR units as described previously.<sup>27</sup> A subgroup of participants (n = 118) underwent amyloid imaging at follow-up (average follow-up interval, 18 months). A subgroup of the participants (n = 179) underwent brain magnetic resonance imaging (MRI). The methodology for MRI image acquisition, brain segmentation, and volumes has been described elsewhere.<sup>28</sup>

## 2.3 | Sample collection and storage

CSF samples were collected by lumbar puncture (LP) in the morning after overnight fasting. Collection of CSF samples was performed at two centers (Perth and Melbourne) as per the guidelines recommended by the Alzheimer's Biomarker Standardization Initiative (ABSI).<sup>29</sup> Following collection, samples were centrifuged and aliquoted into polypropylene tubes (0.5 mL) and stored at -80°C in a liquid nitrogen vapor tank. Prior to NfL analysis, all samples went through one freeze-thaw cycle to aliquot the samples further.

### HIGHLIGHTS

- Cerebrospinal fluid (CSF) neurofilament light (NfL) is a biomarker of neurodegeneration in Alzheimer's disease (AD), the levels of which are significantly elevated in AD as compared to controls, and distinguish AD from controls with a high sensitivity of 81.5%.
- CSF NfL significantly predicts cortical gray matter volume loss at baseline.
- CSF NfL significantly predicts the state of cognition at baseline.

### RESEARCH IN CONTEXT

1. Systematic review: Neurofilament light (NfL) has emerged as one of the most promising cerebrospinal fluid (CSF) markers of neurodegeneration for the diagnosis and study of disease progression in Alzheimer's disease (AD). Various studies have highlighted the role of CSF NfL and plasma NfL as a potential AD biomarker.
2. Interpretation: To further validate the utility of CSF NfL as an AD biomarker, its levels were assessed in CSF samples from the Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing (AIBL). CSF NfL levels were significantly elevated in AD and demonstrated a high sensitivity in distinguishing AD from healthy controls (HCs). In addition, CSF NfL levels predicted baseline cognition and cortical gray matter volume.
3. Future directions: We further aim to evaluate the utility of CSF NfL to predict disease onset in HCs that progress to dementia, as well as its utility for predicting rate of cognitive decline in individuals with AD.

## 2.4 | Biomarker measurement

CSF NfL concentration was quantified using a commercial enzyme-linked immunosorbent assay (ELISA) (NF-light; UmanDiagnostics, Umeå, Sweden), according to the manufacturer's protocol. All samples were analyzed in duplicate and a pooled control CSF was also run to check for the interplate variation. The percentage coefficient of variance (CV) between duplicates was <8% and between plates was <12%. CSF A $\beta$ 42, T-tau, and P-tau concentrations were also analyzed in duplicate using ELISAs: INNOTEST  $\beta$ -AMYLOID<sub>(1-42)</sub> (A $\beta$ 42), INNOTEST hTAU Ag (T-tau), and INNOTEST PHOSPHO-TAU<sub>(181P)</sub> (P-tau181P) (Fujirebio, Ghent, Belgium) according to the manufacturer's protocol.

## 2.5 | Statistical analysis

Analysis of covariance (ANCOVA) was used to assess for differences in at least one pair of continuous mean CSF or brain volumetric measures between participant groups after adjustments for age, gender and APOE genotype (presence of  $\epsilon 4$  allele). The CSF measures and brain volumetric measures required natural logarithm transformation to normalize the distributions for subsequent analysis so that assumptions would be met. Chi-square tests were used to compare categorical variables and Kruskal-Wallis analysis of variance (ANOVA) was used to compare groups for MMSE. Bonferroni corrections were made for all pairwise comparisons. Linear correlations between CSF NfL and other markers, as well as brain volumetric measures were analyzed by Pearson's product moment correlation, after transforming them using the natural logarithm. ROC curve analysis was carried out to assess the diagnostic utility of various CSF markers (untransformed and continuous, ie, raw) for determination of AD versus HC. A cutoff value for the raw CSF marker was also selected, which provided similar specificity and sensitivity. Multiple regression analysis was undertaken to assess the utility of CSF NfL and other CSF measures (CSF A $\beta$ 42, T-tau, P-tau) including different ratios (NfL/A $\beta$ 42, T-tau/A $\beta$ 42, P-tau/A $\beta$ 42), for predicting the baseline amyloid load as measured by SUVR, brain atrophy (gray matter volume), and cognition (MMSE). A log transformation was applied to SUVR so that regression assumptions were met. Gray matter volume did not require transformation to meet assumptions in these models. MMSE is not normally distributed (it is left skewed) and transformations are not available that rectify this issue. All biomarkers were rescaled to have the same units (ng/mL). Standardized regression coefficients<sup>30</sup> and  $R^2$  (ie, the proportion of variability explained by a model) were used to differentiate the CSF predictors. Similarly, regression analysis was used to assess the utility of CSF NfL and other measures to predict change in brain amyloid load, by using log SUVR at follow-up as the outcome, and log SUVR at baseline and the time interval between the amyloid scans as additional predictors. All analyses controlled for the covariates: age, gender and apolipoprotein E (APOE) genotype (presence of  $\epsilon 4$  allele). For each of the regression and ANCOVA models, all variables were entered at the same time in a single step. For all regression analyses, assumptions were checked in the usual way (ie, via histograms of the residuals, scatterplots of the residuals vs fitted values) and deemed reasonable unless otherwise stated. For all the tests a  $P$  value  $<0.05$  was considered statistically significant. Statistical analysis was performed using IBM SPSS version 25 (for Microsoft Windows).

## 3 | RESULTS

### 3.1 | Diagnostic utility of NfL for distinguishing different diagnostic groups

Levels of NfL in the CSF samples of the 221 participants were quantified. Table 1 shows the summary of the demographics and biomarker

data of the participants. Two samples were eliminated from the analysis owing to their influence in the diagnostic plots even after natural logarithm transformation of the CSF NfL. Both samples were of AD-affected participants and had very high values. Therefore, analysis was carried out using the data from the remaining 219 participants, to assess the differences between any pair of participant groups after log transformation of the CSF measures. NfL levels were significantly increased in AD as compared to HC ( $P < .001$ ), as well as in MCI compared to HC ( $P = .008$ ). Levels were not significantly different between the AD and MCI groups (Figure 1,  $P = .139$ ). The ratio of CSF NfL to CSF A $\beta$ 42 (NfL/A $\beta$ 42), was significantly elevated in AD compared to both MCI ( $P = .007$ ) and HC ( $P < .001$ ). In addition, NfL/A $\beta$ 42 was significantly elevated in MCI compared to HC ( $P < .001$ ). Similar results were observed for other biomarkers (CSF A $\beta$ 42, T-tau, P-tau) including the ratios (T-tau/A $\beta$ 42, P-tau/A $\beta$ 42), as shown in Table 1.

ROC curve analyses were undertaken for all 221 samples, to assess the ability of individual CSF measures, as well as different ratios to differentiate AD from HC (results shown in Table 2). CSF NfL differentiated AD from controls with an area under the ROC curve (AUC) of 0.84 and a sensitivity and specificity of 81.5% and 79.7%, respectively, which is comparable to the results obtained using CSF A $\beta$ 42, but higher than the biomarkers of tau pathology (Table 2). NfL/A $\beta$ 42 ratio distinguished AD from controls, with an AUC of 0.90 and a sensitivity and specificity of 81.5% and 80.4%, respectively. Among the individual measures, CSF T-tau had the highest AUC of 0.87 and among the ratios, T-tau/A $\beta$ 42 with an AUC of 0.91.

### 3.2 | Association of NfL with amyloid and tau pathology

To assess the association of NfL with amyloid pathology (via CSF A $\beta$ 42), the extent of correlation between CSF NfL and CSF A $\beta$ 42 (both transformed using natural logarithm) was evaluated. There was no significant correlation between NfL and CSF A $\beta$ 42 ( $r = -0.122$ ,  $P = .072$ ). The association of NfL with tau pathology was assessed by the extent of correlation between CSF NfL and CSF T-tau and P-tau after transformation using natural logarithm. CSF NfL was significantly correlated with CSF T-tau ( $r = 0.52$ ,  $P < .001$ ) and P-tau ( $r = 0.43$ ,  $P < .001$ ). The correlations remained significant even after controlling for age and gender.

### 3.3 | Association of NfL with brain atrophy

Associations between CSF NfL and brain volumes (cortical gray matter, white matter, ventricular and hippocampal volumes) were investigated, after transforming to natural logarithm. There was a significant negative moderate correlation between cortical gray matter volume and NfL ( $r = -0.38$ ,  $P < .001$ ) and a significant weak negative correlation between hippocampal volume and NfL ( $r = -0.27$ ,  $P < .001$ ). CSF NfL levels were not associated significantly with either white matter

**TABLE 1** Summary of demographics and biomarker data at baseline

	Participant groups		
	HC	MCI	AD
<b>Demographics</b>			
Number of participants (n = 221)	159	34	28
Gender M/F (% females)	75/84 (53%)	21/13 (38%)	16/12 (43%)
Age at LP (years)	72.8 (5.54)	74.1(7.62)	74.6 (7.54)
APOE $\epsilon$ 4 allele not present/present (% present)	121/38 (24%)	19/15 (44%)*	11/17 (61%)*
<b>Cognitive scores</b>			
MMSE	29 (1.45)	27 (2.15)*	21 (4.95)*,†
<b>CSF measures</b>			
CSF A $\beta$ 42 (pg/mL) (n = 219)	872 (268.84)	714 (207.44)#	588 (198.41)*,‡
CSF T-tau (pg/mL) (n = 219)	249 (112.98)	334 (177.47)#	488 (252.70)*,‡,¶
CSF P-tau (pg/mL) (n = 219)	54 (18.92)	61 (27.28)	73 (25.78)#
CSF NfL (pg/mL) (n = 219)	1506 (510.59)	1977 (908.44) <sup>§</sup>	2201 (626.96)*
T-tau/A $\beta$ 42 (n = 219)	0.31 (0.19)	0.51 (0.31) <sup>§</sup>	0.95 (0.69)*,†
P-tau/A $\beta$ 42 (n = 219)	0.07 (0.03)	0.09 (0.05)	0.14 (0.08)*,¶
NfL/A $\beta$ 42 (n = 217)	1.89 (0.87)	2.96 (1.60)*	4.09 (1.82)*,¶
<b>MRI brain volumetric measures (n = 179)</b>			
Cortical gray matter volume (cm <sup>3</sup> )	460.11 (19.47)	446.91 (22.29)#	430.48 (28.35)*,‡
Cortical white matter volume (cm <sup>3</sup> )	392.34 (20.17)	391.38 (27.46)	377.50 (24.38) <sup>‡</sup> ,#
Ventricular volume (cm <sup>3</sup> )	35.71 (15.25)	44.16 (21.47)	58.67 (30.69)*,‡
Hippocampal volume (cm <sup>3</sup> )	2.95 (0.29)	2.77 (0.41)	2.32 (0.52)*,†

AD, Alzheimer's disease; APOE, apolipoprotein E; A $\beta$ , amyloid beta; CSF, cerebrospinal fluid; HC, healthy control; LP, lumbar puncture; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; NfL, neurofilament light; P-tau, phosphorylated tau; T-tau, total tau.

NOTE. The values in the table represent raw means (standard deviation, SD) unless otherwise indicated. Demographic and clinical characteristics were compared among the groups using analysis of covariance (ANCOVA) or chi-square tests. CSF measures and cortical brain volumetric measures were transformed using the natural logarithm for ANCOVA analyses, and differences in means were assessed after controlling for age, gender, and APOE genotype. MMSE was analyzed using Kruskal-Wallis nonparametric ANOVA.

\* $P < .001$  versus HC.

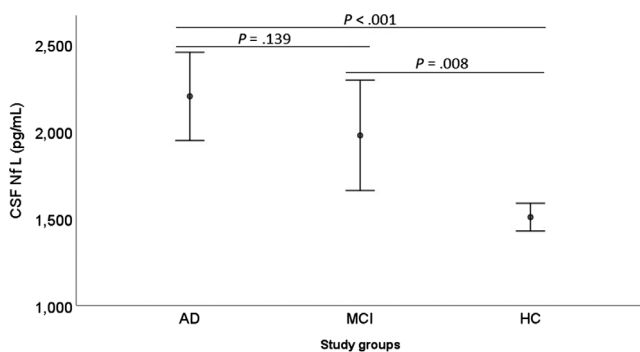
† $P < .001$  versus MCI.

‡ $P < .05$  versus MCI.

§ $P < .01$  versus HC.

¶ $P < .01$  versus MCI.

# $P < .05$  versus HC.



**FIGURE 1** Comparison of the mean NfL concentration with 95% confidence interval, among the study groups AD (n = 26), MCI (n = 34), HC (n = 159). AD, Alzheimer's disease; CSF, cerebrospinal fluid; HC, healthy control; MCI, mild cognitive impairment; NfL, neurofilament light

volume ( $r = 0.03$ ,  $P = .687$ ) or ventricular volume ( $r = 0.104$ ,  $P = .166$ ). Because there was a significant moderate correlation between CSF NfL and cortical gray matter volume, the utility of CSF NfL as a predictor of baseline gray matter volume was assessed further.

### 3.4 | Utility of CSF NfL levels as an indicator of amyloid burden, brain atrophy, and cognition

Individually, each of the CSF biomarkers significantly predicted baseline amyloid load as measured by log SUVR, brain atrophy (measured by cortical gray matter volume), as well as baseline cognition (measured by MMSE), while controlling for covariates in a linear regression (Table 3). Higher levels of CSF NfL ( $\beta = 0.11$ , standardized  $\beta = 0.24$ ,  $P = .001$ ) and the larger NfL/A $\beta$ 42 ratio ( $\beta = 0.10$ , standardized  $\beta = 0.51$ ,  $P < .001$ ) were associated with significantly higher baseline

**TABLE 2** ROC curve analysis data for AD versus HC for continuous CSF variables and ratios

Variable	AUC (95% CI)	Cutoff	Sensitivity	Specificity
AD versus HC				
CSF A $\beta$ 42 (pg/mL)	0.84 (0.75–0.93)	642	81.5%	82.3%
CSF T-tau (pg/mL)	0.87 (0.81–0.93)	308	74.1%	75.9%
CSF P-tau (pg/mL)	0.73 (0.64–0.82)	57	66.7%	63.9%
CSF NfL (pg/mL)	0.84 (0.76–0.92)	1825	81.5%	79.7%
T-tau/A $\beta$ 42	0.91 (0.85–0.97)	0.47	85.2%	84.8%
P-tau/A $\beta$ 42	0.87 (0.79–0.94)	0.09	81.5%	80.4%
NfL/A $\beta$ 42	0.90 (0.84–0.97)	2.53	81.5%	80.4%

AD, Alzheimer's disease; AUC, area under the receiver operating characteristic (ROC) curve; A $\beta$ , amyloid beta; CI, confidence interval; CSF, cerebrospinal fluid; HC, healthy control; NfL, neurofilament light; P-tau, phosphorylated tau; T-tau, total tau.

NOTE. Cutoffs were determined by keeping specificity and sensitivity approximately equal. The cutoffs have been rounded to the nearest whole number for CSF A $\beta$ 42, CSF T-tau, CSF P-tau, and CSF NfL. This analysis used untransformed (raw) data.

amyloid load even upon controlling for covariates such as age, gender, and APOE genotype (presence of  $\epsilon$ 4 allele). Among the individual CSF measures, CSF A $\beta$ 42 (standardized  $\beta = -0.53$ ) was the strongest predictor of baseline amyloid as measured by log SUVR (Table 3), whereby smaller CSF A $\beta$ 42 values were associated with significantly higher baseline amyloid loads. The different independent variables were combined as ratios, to determine whether they could predict baseline brain amyloid load better when evaluated together. A model including the ratio of CSF NfL and A $\beta$ 42 accounted for 40% variability in baseline amyloid load. The models including the ratio of CSF T-tau or P-tau and CSF A $\beta$ 42 explained more of the variability in baseline amyloid load (50% and 52%, respectively).

Among the CSF measures, the individual measures and derived ratios were all significantly associated with predicted baseline brain volume or brain atrophy, as measured by cortical gray matter volume, upon controlling for covariates, except CSF P-tau (Table 3). CSF NfL ( $\beta = -10.15$ , standardized  $\beta = -0.29$ ,  $P < .001$ ) and NfL/A $\beta$ 42 ratio ( $\beta = -6.99$ , standardized  $\beta = -0.43$ ,  $P < .001$ ) correlated significantly with smaller baseline cortical gray matter volume. The ratio of CSF NfL and A $\beta$ 42 levels ( $R^2 = 32\%$ ) was a better predictor of cortical brain atrophy than either of these measures individually. Among the individual measures, CSF NfL, and among the ratios, NfL/A $\beta$ 42, were the best predictors of brain atrophy.

All CSF measures and the ratios derived from these measures significantly predicted baseline cognition as measured by MMSE, even after controlling for covariates (Table 3). CSF NfL ( $\beta = -1.06$ , standardized  $\beta = -0.25$ ,  $P < .001$ ) and the ratio of NfL/A $\beta$ 42 ( $\beta = -0.84$ , standardized  $\beta = -0.41$ ,  $P < .001$ ) were associated significantly with baseline MMSE scores; however, CSF T-tau (standardized  $\beta = -0.34$ ) and T-tau/A $\beta$ 42 (standardized  $\beta = -0.43$ ) were stronger MMSE score predictors. None

**TABLE 3** Regression results to estimate the effect of CSF measures for predicting baseline amyloid load, brain volume/atrophy (cortical gray matter volume) and baseline cognitive scores

Predictor	Unstandardized $\beta$ (SE)	Standardized $\beta$	R <sup>2</sup>	P value
Baseline amyloid load (n = 188)				
CSF NfL (ng/mL)	0.11 (0.03)	0.24	0.23	0.001
CSF A $\beta$ 42 (ng/mL)	-0.56 (0.06)	-0.53	0.44	<0.001
CSF T-tau (ng/mL)	0.91 (0.12)	0.46	0.38	<0.001
CSF P-Tau (ng/mL)	5.08 (0.83)	0.39	0.32	<0.001
NfL/A $\beta$ 42	0.10 (0.01)	0.51	0.40	<0.001
T-tau/A $\beta$ 42	0.50 (0.05)	0.58	0.50	<0.001
P-tau/A $\beta$ 42	3.49 (0.31)	0.60	0.52	<0.001
Cortical gray matter volume (n = 176)				
CSF NfL (ng/mL)	-10.15 (2.56)	-0.29	0.24	<0.001
CSF A $\beta$ 42 (ng/mL)	21.75 (5.98)	0.26	0.23	<0.001
CSF T-tau (ng/mL)	-29.32 (11.31)	-0.19	0.20	0.010
CSF P-Tau (ng/mL)	-88.14 (78.27)	-0.082	0.17	0.262
NfL/A $\beta$ 42	-6.99 (1.11)	-0.43	0.32	<0.001
T-tau/A $\beta$ 42	-23.26 (4.72)	-0.33	0.27	<0.001
P-tau/A $\beta$ 42	-139.28 (32.53)	-0.30	0.25	<0.001
MMSE (n = 214)				
CSF NfL (ng/mL)	-1.06 (0.29)	-0.25	0.13	<0.001
CSF A $\beta$ 42 (ng/mL)	2.51 (0.68)	0.25	0.13	<0.001
CSF T-tau (ng/mL)	-6.12 (1.18)	-0.34	0.18	<0.001
CSF P-Tau (ng/mL)	-26.58 (8.12)	-0.22	0.12	0.001
NfL/A $\beta$ 42	-0.84 (0.13)	-0.41	0.22	<0.001
T-tau/A $\beta$ 42	-3.61 (0.52)	-0.43	0.25	<0.001
P-tau/A $\beta$ 42	-20.86 (3.58)	-0.38	0.20	<0.001

A $\beta$ , amyloid beta; CSF, cerebrospinal fluid; MMSE, mini-mental state examination score; NfL, neurofilament light; P-tau, phosphorylated tau; SE, standard error; T-tau, total tau. Baseline amyloid as measured by SUVR was transformed using the natural logarithm for regression analyses.

of the predictors explained more than 26% of the variability in MMSE scores. Because MMSE scores are left skewed, no simple transformation can be used to normalize the scores. As such, the assumption of normality of the errors was not met and the results should be treated with caution.

### 3.5 | Utility of baseline CSF NfL to predict change in amyloid accumulation

Baseline CSF NfL was not associated significantly with the change in amyloid accumulation as measured by log SUVR ( $\beta = -0.02$ , standardized  $\beta = -0.04$ ,  $P = .166$ ). Similar results were obtained for other individual CSF measures (Table 4). Among the ratios, only the ratio of baseline-measured P-tau/A $\beta$ 42 was associated with change in amyloid accumulation ( $\beta = 0.58$ , standardized  $\beta = 0.08$ ,  $P = .036$ ).

**TABLE 4** Regression results to estimate the effect of baseline CSF measures for predicting change in amyloid accumulation as measured by log SUVR

Predictor (n = 118)	Unstandardized $\beta$ (SE)	Standardized $\beta$	P value
CSF NfL (ng/mL)	-0.02 (0.01)	-0.04	0.166
CSF A $\beta$ 42 (ng/mL)	-0.04 (0.03)	-0.04	0.218
CSF T-tau (ng/mL)	0.04 (0.06)	0.02	0.523
CSF P-Tau (ng/mL)	0.40 (0.38)	0.03	0.283
NfL/A $\beta$ 42	-0.01 (0.01)	-0.02	0.505
T-tau/A $\beta$ 42	0.06 (0.04)	0.05	0.173
P-tau/A $\beta$ 42	0.58 (0.27)	0.08	0.036

A $\beta$ , amyloid beta; CSF, cerebrospinal fluid; NfL, neurofilament light; P-tau, phosphorylated tau; SE, standard error; T-tau, total tau.

## 4 | DISCUSSION

Consistent with findings from other studies, the current study shows that CSF NfL is a promising biomarker of AD-related neurodegeneration, demonstrating it is potentially useful in both AD diagnosis and for studying the disease's preclinical stages of pathogenic progression.<sup>10,13,14,31</sup> CSF NfL levels were significantly higher in AD patients as compared to HCs. Moreover, NfL distinguished AD from HC with reasonably high sensitivity and specificity. As seen in Table 2, the AUC of NfL can distinguish AD from HC as effectively as T-tau and CSF A $\beta$ 42, and it can distinguish AD from HC with higher AUC than P-tau levels. CSF NfL levels correlated significantly with the biomarkers of tau pathology, as well as baseline cortical gray matter volume and hippocampal volume. Baseline NfL levels significantly predicted baseline cortical gray matter volume and cognitive scores. NfL/A $\beta$ 42 was the best predictor of brain atrophy and was among the best predictors of cognitive scores. These results indicate that CSF NfL levels can be used in the assessment of cognitive decline, brain atrophy, and the stage of neurodegeneration along the disease trajectory.

There was little correlation found between CSF NfL and CSF A $\beta$ 42 levels. CSF NfL was a significant but weaker predictor of baseline amyloid load and did not predict longitudinal change in amyloid accumulation. This implies that CSF NfL levels are more likely reflective of neurodegeneration and brain atrophy than the developing amyloid pathology. Nevertheless, the ratio of CSF NfL/A $\beta$ 42 had a much higher diagnostic accuracy in distinguishing patients with AD from controls. This highlights the fact that although developing amyloid pathology and levels of axonal degeneration correlate with each other to a lesser extent than some of the other variables tested here, the two pathologies were found to develop concurrently along the disease trajectory in our cohort.

In a recent study of mouse models of neurodegenerative diseases, both CSF and plasma NfL levels increased with the onset and progression of proteopathic lesions in the brain.<sup>32</sup> These increases were seen in the models of several neurodegenerative conditions, including  $\alpha$ -synucleinopathies, tauopathies, and amyloidoses such as AD. The CSF NfL levels were elevated in the mice before neurological signs

of neurodegeneration were evident, supporting the concept that NfL changes occur early in the disease process and can act as a preclinical disease biomarker.<sup>32</sup> The study also showed that the increases in CSF NfL levels normally found in an AD mouse model (APPPS1) were much lower following 6 months of treatment with a  $\beta$ -secretase 1 (BACE1) inhibitor, indicating that NfL levels might be useful as a treatment response biomarker.<sup>32</sup> Therefore, NfL could be used as a preclinical marker of neurodegeneration (axonal degeneration), and in conjunction with the biomarkers of tau and amyloid pathology could provide specific disease diagnosis. The lack of significant difference in NfL levels between MCI and AD patients suggest that axonal degeneration is too compromised following the onset of clinical symptoms, and further studies will determine if the range of CSF NfL levels seen within the MCI group of patients reflects neurodegeneration stage.

NfL is a non-specific marker of axonal degeneration elevated in a range of neurodegenerative and neurological disorders such as synucleinopathies, amyotrophic lateral sclerosis,<sup>33</sup> frontotemporal dementia (FTD),<sup>34</sup> Creutzfeldt-Jakob disease,<sup>35</sup> and vascular dementia.<sup>36</sup> However, studies have shown that the levels vary between different disorders,<sup>36-38</sup> and further studies will evaluate the potential of NfL as a marker in differential diagnosis, when used in combination with disease-specific biomarkers, such as A $\beta$ 42. Being a non-specific neurodegeneration marker, it is not associated with amyloid accumulation. Of interest, CSF NfL levels seem to reflect the intensity of axonal degeneration in all neurodegenerative conditions, as reflected in cognition scores,<sup>31</sup> thus disease-specific research into the value of CSF NfL levels will determine the value of using this biomarker in other neurodegenerative conditions.

It can be concluded that CSF NfL, as a biomarker of neurodegeneration in AD, is of similar sensitivity to CSF A $\beta$ 42 and tau biomarkers. However, CSF NfL should be used in combination with these more disease-specific biomarkers, as it is a general biomarker of neurodegeneration and not specific to any particular neurodegenerative disease. NfL predicts cortical gray matter volume loss, as well as cognitive impairment. Therefore, NfL can be used as a marker of neurodegeneration that associates with cognitive impairment and brain atrophy, along the disease trajectory. It could serve as a better predictor of disease progression, as a surrogate marker of neurodegenerative changes, in clinical trials.

Recent studies suggest that plasma NfL levels are of diagnostic value in AD, and to a greater extent than in other conditions, such as Parkinson disease.<sup>39</sup> In familial AD cases, serum NfL levels have been shown to increase at preclinical stages, correlating with measures of disease stage and severity,<sup>40</sup> with more recent longitudinal studies by the same research group indicating serum NfL starts to increase more than a decade before symptom onset in familial AD cases.<sup>41</sup> However, blood NfL is thought to originate from the CSF, and blood levels of NfL correlate well with levels seen in the CSF, although they rise to a lesser extent and later than in the CSF.<sup>32</sup> These studies are encouraging; however, studies are still needed to evaluate the diagnostic value of both blood and CSF levels of NfL in preclinical sporadic AD cases.

## ACKNOWLEDGMENTS

The authors thank the Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing (AIBL) Study Group ([www.aibl.csiro.au](http://www.aibl.csiro.au)), Edith Cowan University (ECU) and Deakin University. The AIBL is a collaboration between the Commonwealth Scientific and Industrial Research Organisation (CSIRO), ECU, The Florey Institute of Neuroscience and Mental Health (FINMH), National Ageing Research Institute (NARI), and Austin Health. It involves support from CogState Ltd., Hollywood Private Hospital, and Sir Charles Gairdner Hospital. The initial core funding of the study was facilitated by CSIRO. The study receives funding from the National Health and Medical Research Council (NHMRC), the Dementia Collaborative Research Centres program (DCRC2), the Cooperative Research Centre (CRC) for Mental Health, and the Australian Alzheimer's Research Foundation, and Operational Infrastructure Support from the Government of Victoria. The authors also thank the participants for their assistance and commitment. K.D. also thanks ECU HDR (Higher degree by research) Scholarship. K.B. is supported by the Torsten Söderberg foundation, Sweden. H.Z. is a Wallenberg Academy Fellow supported by grants from the Swedish Research Council, the European Research Council, the Olav Thon Foundation, and the UK Dementia Research Institute at UCL. S.C. receives a NHMRC Practitioner Fellowship (#APP1105784).

## CONFLICT OF INTEREST

K. Blennow has served as a consultant or at advisory boards for Alzheon, BioArctic, Biogen, Eli Lilly, Fujirebio Europe, IBL International, Merck, Novartis, Pfizer, 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. H. Zetterberg has served at scientific advisory boards of Eli Lilly, Roche Diagnostics, Samumed, CogRx, and Wave; has received travel support from Teva; 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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**How to cite this article:** Dhiman K, Gupta VB, Villemagne VL, et al. Cerebrospinal fluid neurofilament light concentration predicts brain atrophy and cognition in Alzheimer's disease. *Alzheimer's Dement*. 2020;12:e12005. <https://doi.org/10.1002/dad2.12005>