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The age-dependent associations of white matter hyperintensities and neurofilament light in early- and late-stage Alzheimer's disease

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ABSTRACT

Neurofilament light (NFL) is an emerging marker of axonal degeneration. This study investigated the relationship between white matter hyperintensities (WMHs) and plasma NFL in a large elderly cohort with, and without, cognitive impairment. We used the Alzheimer's Disease Neuroimaging Initiative and included 163 controls, 103 participants with a significant memory concern, 279 with early mild cognitive impairment (EMCI), 152 with late mild cognitive impairment (LMCI), and 130 with Alzheimer's disease, with 3T MRI and plasma NFL data. Multiple linear regression models examined the relationship between WMHs and NFL, with and without age adjustment. We used smoking status, history of hypertension, history of diabetes, and BMI as additional covariates to examine the effect of vascular risk. We found increases of between 20% and 41% in WMH volume per 1SD increase in NFL in significant memory concern, early mild cognitive impairment, late mild cognitive impairment, and Alzheimer's disease groups ($p < 0.02$). Marked attenuation of the positive associations between WMHs and NFL were seen after age adjustment, suggesting that a significant proportion of the association between NFL and WMHs is age-related. No effect of vascular risk was observed. These results are supportive of a link between WMH and axonal degeneration in early to late disease stages, in an age-dependent, but vascular risk-independent manner.

1. Introduction

Alzheimer's disease (AD) is pathologically complex. In addition to amyloid deposition and tau accumulation, other pathologies often coexist including vascular pathology and neuroinflammation (Schneider et al., 2007, Wyss-Coray and Rogers, 2012). Cellular damage does not only occur in the gray matter, but also in the white matter. To fully investigate AD in vivo, additional biomarkers are needed that complement the classical biomarkers of cerebrospinal fluid (CSF) amyloid beta (Aβ), total-tau, and phosphorylated-tau (Jack et al., 2018). These biomarkers may be useful in identifying early stages of disease. Understanding how different biomarkers are associated throughout the AD course is important in terms of appreciating whether they are pathologically linked throughout the disease.

Two such biomarkers that have emerged in recent years are white matter hyperintensities (WMHs) and neurofilament light (NFL). WMHs, once thought to be an inevitable consequence of aging, are now known to associate with cognitive decline (De Groot et al., 2002, Prins et al., 2005) and with incidence of AD (Yoshita et al., 2006). WMHs are widely considered to be a marker of

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cerebrovascular disease (CVD) (Wardlaw et al., 2013); however, WMHs have numerous histopathological correlates suggesting there could be multiple pathological pathways underlying their existence (Gouw et al., 2008). Indeed, recent evidence suggests that at least some WMHs may be caused by non–vascular-related neurodegeneration or tau pathology (McAleese et al., 2015, 2017). NFL is a biomarker of large-caliber axonal injury (Skillback et al., 2014); increases in CSF levels have been demonstrated in AD (Mattsson et al., 2019; Zetterberg et al., 2016), as well as other diseases, such as frontotemporal dementia, amyotrophic lateral sclerosis, and multiple sclerosis (Kuhle et al., 2013, Lu et al., 2015, Rohrer et al., 2016, Teunissen and Khalil, 2012). Recent technological developments have also enabled the analysis of NFL in blood (serum and plasma), showing good correlation with CSF levels (Zetterberg and Blennow, 2018).

Links between NFL and white matter changes in AD have been previously demonstrated. There are similarities in the timing of changes in both NFL and WMHs, with recent studies in autosomal dominant familial AD (ADAD) reporting elevations in WMHs (Lee et al., 2016) and serum NFL (Preische et al., 2019) in very early disease stages. Studies have also shown direct associations between NFL and WMHs (Osborn et al., 2018; Zetterberg et al., 2016), and NFL and diffusion tensor imaging measures (Moore et al., 2018). Other studies however found no evidence of associations between NFL and diffusion tensor imaging (Kim et al., 2019) or WMHs (Mattsson et al., 2019).

What is not understood is whether NFL and WMHs are associated across the full range of normal aging to AD. Our study aimed to establish this and to appreciate whether any relationship was altered with age adjustment. We hypothesized that WMHs would show associations with NFL and that this relationship would change depending on disease stage. This is because WMHs are thought to have a heterogeneous pathological basis (Gouw et al., 2008) and, although we have shown that WMHs have consistent relationships with CSF Aβ1-42 across the disease course from this data set (Walsh et al., 2020), other studies from other data sets have shown that relationships can vary depending on disease stage (Barnes et al., 2013; Fiford et al., 2017; McAleese et al., 2017; Zhou et al., 2009). Because NFL increases with axonal degeneration, which is likely to become more prominent with the development of AD pathology, we considered the relationship would be stronger at later disease stages. We further considered that the relationship between WMHs and NFL could be mediated by vascular risk factors.

2. Methods

2.1. Cohort

Participants newly recruited into the Alzheimer's Disease Neuroimaging Initiative (ADNI) GO and 2 phases with normal cognition, early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI), a significant memory concern (SMC), and AD were used for this study. A diagnosis of MCI was based on a memory complaint (reported by participant or informant) and a clinical dementia rating of 0.5, but a Mini-Mental State Examination (MMSE) no lower than 24. Level of MCI (early or late) was determined by the Wechsler Memory Scale Logical Memory II. The SMC group was developed by ADNI to bridge the gap between the controls and MCI participants, and is characterized by individuals who have self-reported a memory complaint but score within a normal range for cognition.

ADNI is a multicenter, longitudinal public-private funded partnership, with the primary goal of using demographic, biomarker, neuropsychological, and MRI data to monitor progression of AD. Since 2003, Principle Investigator Michael W. Weiner, MD, has overseen recruitment of healthy controls, MCI and AD subjects from over 60 sites across the United States and Canada. (For up-to-date information, see www.adni-info.org).

Ethical approval was obtained by the institutional review board at each participating center. All study participants provided written informed consent. Participants took part in the baseline and follow-up clinical, neuropsychometric, and MRI assessments. Plasma NFL data were collected from all subjects where possible.

2.2. Plasma NFL measurements

Plasma NfL level was measured at the Clinical Neurochemistry Laboratory, University of Gothenburg, Mölndal Campus, Mölndal, Sweden, using an ultrasensitive enzyme-linked immunosorbent assay on a single molecule array platform (Quanterix Corp).

2.3. Images and image processing

All sites in ADNI use a standardized protocol to obtain MRI data (3T), described in the study by Jack et al. (2015), before undergoing quality control at the Mayo Clinic (Rochester, MN) to assess protocol compliance, image quality, and any significant neurological/radiological abnormalities. Baseline T1-weighted and FLAIR images were downloaded from the ADNI database (http://adni.loni.usc.edu/).

Bayesian model selection, a fully automated lesion segmentation tool, was applied to the coregistered T1 and FLAIR image pairs at the Dementia Research Centre (London, UK). Bayesian model selection is fully described in the study by Sudre et al. (2015), but briefly, a Gaussian mixture model is used to jointly model healthy tissue and unexpected intensity observations for the different anatomical brain tissue. A split and merge strategy was used to optimize the number of Gaussian components required to appropriately model each tissue type. After fitting the model, candidate hyperintense voxels are selected and the formed connected components classified as lesion or artifacts in a post-processing step based on anatomy rules. The resultant probability map of WMHs was integrated to calculate the WMH volume. Only supratentorial WMHs were included which were located in the white matter and subcortical gray matter. All automated WMH segmentations were inspected by a rater trained on semi-automated WMH segmentation procedures (Fiford et al., 2020) and segmentations were flagged if large amounts of artifact were included or if there were significant mis-segmentations. This quality control stage was used to make improvements to the automated WMH segmentation, therefore limiting the number of unusable segmentations.

WMH analysis was carried out on 944 separate individuals newly recruited into ADNI2/GO with FLAIR and T1 imaging (Walsh et al., 2020). Twelve individuals were excluded because of poor-quality WMH segmentations and 3 individuals were excluded because of lack of clinical information, resulting in 929 individuals with good-quality WMH segmentations and demographic/diagnostic information initially being included in this study. 827 of these subjects had plasma NFL data and therefore made up the cohort used here. 2 subjects had missing information regarding history of diabetes and 3 subjects had missing information regarding their body mass index (BMI) and were therefore not included in analyses using these variables.

Total intracranial volumes (TIVs) were calculated from T1-weighted images using the Geodesic information flows label fusion framework (Cardoso et al., 2015).

2.4. Statistical analyses

All statistical analysis was performed using STATA v 16 (Stata Corp.)

2.4.1. Variables used in analyses

Demographic and biological data were downloaded from the ADNI database (http://adni.loni.usc.edu/). The participant information downloaded and used in this study included: age, gender, MMSE scores, *APOE*-ε4 status, plasma NFL values, height and weight, smoking status, hypertension history, and diabetes history. BMI was calculated from height and weight variables. Smoking status was coded as (1) never smoked; (2) previous smoker; (3) current smoker, using the information downloaded on smoking history.

2.4.2. Data transformation

Analyses involving WMHs were carried out on $\log_e$-transformed values to reduce skewness. NFL values were standardized using the pooled within-group SD, calculated using a linear regression that allowed for differences in mean levels by group. The use of standardized variables enabled comparisons with previous work assessing other CSF-based AD biomarkers to be made. As WMHs were analyzed on a logarithmic scale, the coefficients from regression models were back-transformed and expressed as percentage increases or decreases in WMHs for each 1SD change in plasma NFL.

2.4.3. Group demographics and biomarker summary

For estimates of differences in means across control, EMCI, LMCI, SMC, and AD groups in demographic, imaging, and plasma NFL continuous data, linear regression models were used. For $\log_e$WMH, linear regression models were used with group as the predictor of interest and adjustment for TIV. Differences among the 5 groups were tested with joint Wald tests. Analogous comparisons were performed for categorical variables, with Fisher's exact tests used for gender, *APOE*-ε4 status, and hypertension, and a chi-square test for smoking status.

2.4.4. WMH and NFL relationships

To explore the relationships between WMHs and plasma NFL within each diagnostic group, scatter plots of WMHs (on a log scale) against plasma NFL in each group were generated to show unadjusted associations. After inspection of the plots, 1 outlier from the control group and 1 from the SMC group with very high plasma NFL were identified and removed from the subsequent main analysis of the NFL/WMH relationship. These outliers were included in a separate sensitivity analysis (see the following). The standardization of NFL values described previously was therefore performed twice: once with these 2 outliers excluded (used in main analyses) and once with the 2 outliers included (used in sensitivity analyses). Separate linear regression models for each group were then fitted. The dependent variable used in all models was $\log_e$WMH, with standardized plasma NFL as the predictor variable of primary interest, and adjusted for TIV. To investigate differences in slope between diagnostic groups, a separate model was fitted to the combined data from all 5 groups with an interaction term between diagnostic group and plasma NFL. Differences among the 5 groups were tested with joint Wald tests. All of the aforementioned models were then refitted with participant age at the baseline as an additional covariate. Analyses including age were secondary because age at the baseline may be on the causal pathway (theoretically a proxy for the number of vascular events that may have happened to an individual and a resultant increase in axonal degeneration).

Partial R^2 values were calculated for the 5 separate diagnostic group models of $\log_e$WMH, and plasma NFL. Partial R^2 values from 2 models for each diagnostic group were calculated from models adjusting for (1) TIV; (2) TIV and age.

To investigate potential mechanisms involved in NFL-WMH relationships, the analysis in each of the separate diagnostic groups was extended to assess the effect of 4 additional covariates: smoking history; history of hypertension; history of diabetes; and current BMI. The new variables were all added as covariates into a combined linear regression model, as specified previously. This allowed us to assess whether the addition of these vascular risk factors influenced the NFL-WMH relationship in any manner.

2.4.5. Sensitivity analysis

A sensitivity analysis was carried out that repeated the regression models assessing the WMH/NFL relationship in each group, but with the inclusion of the one outlier from each of the control and SMC groups, respectively. The models were all adjusted for TIV and were carried out with and without age adjustment. Partial R^2 values were again calculated, as previously performed.

2.4.6. Supplementary analyses

Supplementary analyses were performed assessing the relationship between age and plasma NFL, with plasma NFL being the dependent variable and age the predictor. This was performed in each diagnostic group separately with an additional model fitted to the combined data including interactions between group and plasma NFL. Scatter plots of plasma NFL against age in each group were also generated.

3. Results

3.1. Group demographics and biomarker summary

In ADNI2/GO newly recruited individuals, who were given a diagnostic label of control, SMC, EMCI, LMCI, or AD, there were 827 subjects with both useable WMH volumes and available NFL data. Table 1 shows demographic, imaging, and biomarker summary statistics for each diagnostic group. There were statistically significant ($p < 0.05$) between group differences in age, with the youngest participants seen in the EMCI group and the oldest in the AD group. Differences were also seen in MMSE, APOE-ε4 status, and WMH volume with worsening scores, increasing proportion of ε4 carriers, and increasing WMH volumes from controls to EMCI to LMCI though to AD. For BMI, the highest values were seen in the SMC and EMCI groups and the lowest values in the AD group. For plasma NFL, the highest levels were seen in the AD group, followed by the LMCI and then EMCI, control and SMC groups.

3.2. Plasma NFL and WMHs: main analyses

Table 2 shows percentage increases in WMHs for increases in plasma NFL estimated from diagnostic group–specific models and Fig. 1 shows corresponding scatter plots. After TIV adjustment, significant increases of between 20% and 41% in WMH volume per 1SD increase in NFL were seen in SMC, EMCI, LMCI, and AD groups ($p<0.004$). There was no evidence for differences in the slopes of the associations across groups ($p = 0.5$). These positive associations between WMHs and NFL were not significant after adjustment for age. The relationships between NFL and age are shown in the supplementary section.

Table 3 shows partial R^2 values for all covariates from the group-specific models from Table 2. In model (i) with WMHs, NFL, and TIV, NFL explained from between 2% and 10% of the variance in WMHs. In model (ii) after adjustment for age, a large decrease was observed

Table 1
Demographic and biomarker summary statistics

Characteristic	Controls	SMC	EMCI	LMCI	AD	*p* value across groups
N (total = 827)	163	103	279	152	130	
Age	73.6 (6.2)	72.3 (5.5)	71.2 (7.5)	72.1 (7.6)	74.2 (8.0)	**0.005**
Male (%)	47	43	54	55	56	0.1
MMSE/30	29.0 (1.3)	29.0 (1.2)	28.3 (1.6)	27.5 (1.8)	23.1 (2.1)	**<0.001**
APOE-ε4 positive (%)	27	34	42	57	68	**<0.001**
TIV (mL)	1407 (136)	1414 (126)	1427 (135)	1431 (133)	1422 (153)	0.5
WMH volume (mL) median (IQR)	3.4 (4.9)	3.5 (4.4)	3.9 (6.5)	3.7 (8.3)	5.8 (8.3)	**0.03**[a]
Log_eWMH (mL)	1.2 (0.9)	1.3 (0.9)	1.4 (1.0)	1.4 (1.0)	1.7 (1.0)	**0.005**[a]
Plasma NFL (pg/mL)	36.6 (24.0)	32.5 (18.2)	36.6 (19.5)	40.3 (20.0)	47.5 (22.7)	**<0.001**
History of hypertension (%)	50	47	51	46	45	0.8
Smoking:	60	51	60	65	62	0.2
Never (%)						
Previous (%)	36	47	38	32	33	
Current (%)	4	2	2	3	5	
BMI	27.4 (4.5)	28.3 (6.1)	28.2 (5.5)	27.5 (5.0)	26.3 (5.6)	**0.01**
History of diabetes (%)	7	10	11	9	14	0.4

Values are mean (SD) unless reported. Bold *p* values denote a statistically significant difference across all groups at the $p < 0.05$ level.
Key: AD, Alzheimer's disease; BMI, body mass index; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; MMSE, Mini-Mental State Examination; NFL, neurofilament light; SMC, significant memory concern; TIV, total intracranial volume; WMH, white matter hyperintensity.
[a] Adjusted for TIV.

in the percentage variance explained, with all values less than 2%. Age explained the largest proportion of variance in WMHs in each group, ranging from 4% to 20%.

3.3. Plasma NFL and WMHs: sensitivity analyses

We repeated the analyses presented in Table 2 and 3 with the addition of one outlier from both the control and SMC groups (Supplementary Table 2, outliers visible in Fig. 1). The addition of these outliers (to the regression analysis and the NFL standardization) meant that the positive association between NFL and WMHs observed in the SMC group was reduced and was no longer significant (10.6% increase in WMHs for a 1SD increase in NFL, $p = 0.3$). The borderline percentage increase in the control group was also attenuated (5% increase in WMHs for a 1 SD increase in NFL, $p = 0.4$). The inclusion of these overly influential outliers lead to a statistically significant difference in the slopes of the associations across all groups ($p = 0.007$).

3.4. Exploring the WMH and NFL relationship: the potential role for vascular risk

Table 4 shows percentage increases in WMHs for increases in plasma NFL, with adjustment for the vascular risk factors of smoking status, a history of hypertension, a history of diabetes, and BMI. With combined adjustment for the 4 vascular risk factors, there was no evidence for a marked attenuation of the association between NFL and WMHs (shown in Table 2) in any disease group.

4. Discussion

In this study, we found evidence of increased plasma NFL associating with greater WMHs in those with a significant memory concern, and from the early stages of cognitive impairment through to clinical AD. We also found a strong impact of baseline participant age, which both accounted for the most variance in WMH volumes and significantly attenuated the relationship between WMHs and NFL when included as a covariate.

These findings suggest that WMHs seen in cognitive impairment are likely to be related to axonal damage, as indicated by plasma NFL, in a manner that is dependent on age. There is previous evidence that supports a relationship between WMHs and plasma NFL. After injury to large myelinated axons, NFL has been shown to be released into the extracellular space and subsequently into the CSF (Sjogren et al., 2001). CSF NFL has been shown to be a sensitive biomarker for neurodegeneration in AD, with levels correlating with cognitive decline and brain atrophy (Mattsson et al., 2019; Zetterberg et al., 2016). Recent technological developments have enabled measurement of NFL in blood (Almeida et al., 2015), levels of which are highly correlated with CSF NFL (Zetterberg and Blennow, 2018). Recently, it was shown that plasma NFL was more strongly associated with cognitive and neuroimaging

Table 2
Results from the 2 regression models (i) TIV adjusted; (ii) TIV and age adjusted, assessing the relationship between WMHs and plasma NFL separately in each diagnostic group

Characteristic	WMHs and NFL	Controls	SMC	EMCI	LMCI	AD
i)	**TIV adjusted**	18.2 (−1.7–42.0)	36.9 (5.2–78.1)	29.5 (16.8–43.6)	41.1 (21.9–63.4)	20.6 (6.2–36.8)
	% increase in WMHs per 1SD change in NFL	0.08	**0.02**	**<0.001**	**<0.001**	**0.004**
	95% confidence intervals *p* value					
ii)	**TIV and age adjusted**	2.0 (−16.7–24.4)	16.1 (−14.8–58.1)	4.3 (−5.7–15.5)	15.5 (−1.7–35.7)	1.3 (−11.0–15.5)
	% increase in WMHs per 1SD change in NFL	0.9	0.3	0.4	0.08	0.8
	95% confidence intervals *p* value					
Between group differences in % increases per 1SD change in NFL: *p* value for differences among all groups = 0.5 (0.5 with age adjustment)						

Models assess associations between WMHs and plasma NFL in each diagnostic group, with the addition of TIV (i) and TIV and age (ii) as covariates. Estimates are percentage changes in WMH volume per one SD change (1 SD = 18.3 pg/mL) in NFL, with 95% confidence intervals. The SD is the pooled within-group SD, calculated from a linear regression model that allowed for differences in mean levels of NFL by group. The results from a model combining all 5 groups, but with a diagnostic group-NFL interaction is also displayed to investigate between group differences. Bold *p* values denote statistical significance at the $p < 0.05$ level.
Key: SMC, significant memory concern; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease; TIV, total intracranial volume; WMH, white matter hyperintensities; NFL, neurofilament light.

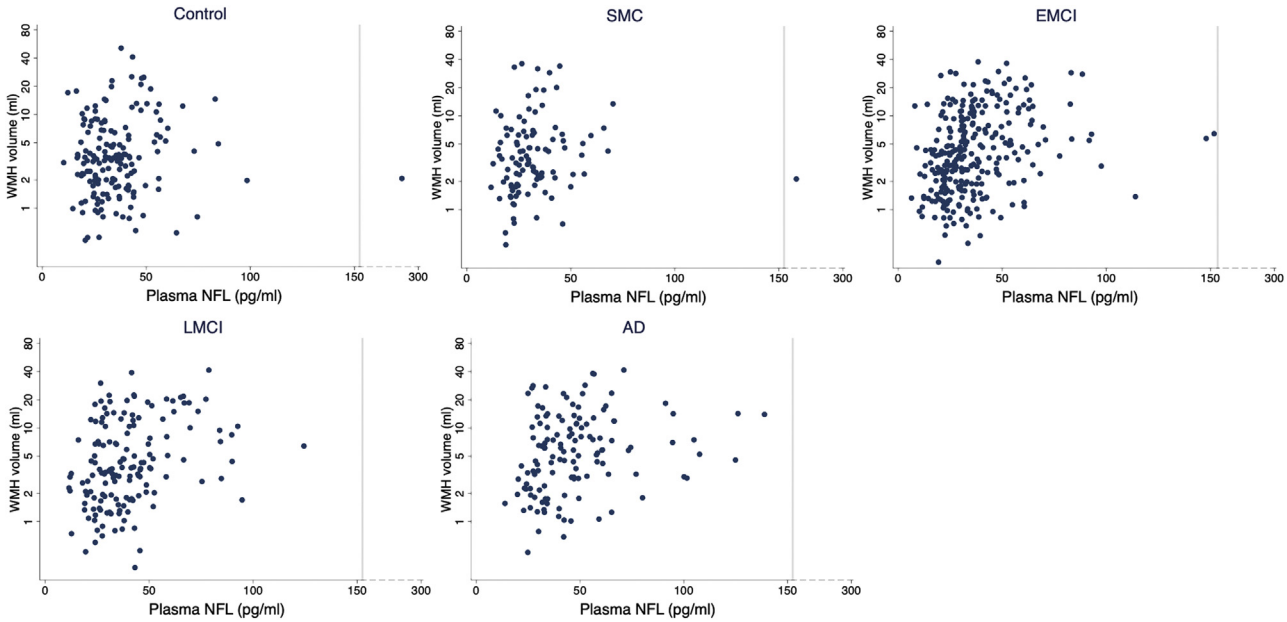

Fig. 1. Scatter plots showing the relationship between WMHs and plasma NFL in controls, significant memory concern (SMC), early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI), Alzheimer's disease (AD) groups. WMH volume is shown on a log scale and is unadjusted for any covariates. There is an x-axis break to show to show the one NFL outlier in both the control and SMC groups. Abbreviations: WMH, white matter hyperintensity; NFL, neurofilament light.

outcomes than CSF NFL (Mielke et al., 2019). Given that taking blood samples is less invasive than taking CSF, it may be that plasma NFL has great potential for widespread clinical use.

NFL levels are associated with white matter changes in multiple neurodegenerative diseases, including AD, vascular dementia, and multiple sclerosis (Sjogren et al., 2001; Teunissen and Khalil, 2012; Zetterberg et al., 2016). Previous studies have demonstrated associations of NFL with WMHs in cognitively normal and MCI (Osborn et al., 2018), and MCI and AD groups (Zetterberg et al., 2016) and with compromised white matter microstructure using diffusion imaging (Moore et al., 2018). However, a recent study by Mattsson et al. (2019) in the ADNI cohort did not find any evidence for an association of WMHs with baseline or longitudinal NFL data. The discrepancy with our study is likely partly due to differing methods used to generate WMH volumes. In addition, Mattson et al. combined 2 ADNI phases with different imaging protocols, which may have affected any associations seen.

WMHs seen in AD are often presumed to be vascular in origin, as a result of cerebral SVD (Wardlaw et al., 2013). Evidence has also suggested that NFL biomarker increases could signify damage related to vascular pathologies (Duering et al., 2018; Gattringer et al., 2017). The positive WMH-NFL relationship may be caused by either traditional Alzheimer's pathologies (Aβ deposited as plaques or in the vasculature as cerebral amyloid angiopathy, and tau) or comorbid cerebrovascular disease due to conventional risk factors, or both.

Table 3
Partial R^2 values for each covariate in both regression models i and ii from Table 2

Characteristic		Controls	SMC	EMCI	LMCI	AD
i)	NFL	0.02	0.05	0.08	0.1	0.06
	TIV	0.07	0.06	0.05	0.09	0.1
ii)	NFL	0.0002	0.009	0.003	0.02	0.0003
	TIV	0.06	0.06	0.05	0.05	0.07
	Age	0.06	0.04	0.2	0.1	0.2

Partial R^2 are shown for each covariate in both of the models i) and ii) from Table 2. Key: SMC, significant memory concern; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease; TIV, total intracranial volume; WMH, white matter hyperintensities; NFL, neurofilament light.

The association of WMHs with age is well documented (de Leeuw et al., 2001, Ylikoski et al., 1995) and has been shown in this cohort (Walsh et al., 2020). This relationship could be due to cerebrovascular events, disease, and risk factors, which all increase with age. In this study, however, we did not find any effect of the vascular risk factors of smoking, hypertension, BMI, or diabetes on the relationship between WMHs and NFL. These results could be interpreted as support for the growing body of evidence that WMHs represent core aspects of AD and cannot simply be attributed to concomitant CVD (McAleese et al., 2017). This evidence includes studies of ADAD, where WMH accumulation is seen in presymptomatic disease stages in young mutation carriers without comorbid CVD (Lee et al., 2016). There is also evidence of elevated NFL in ADAD cohorts (Preische et al., 2019; Weston et al., 2017).

The vascular risk factors included in this study were used as they are some of the most notable (Livingston et al., 2017) and are also consistently recorded in the ADNI cohort. However, not all vascular risk factors, vascular disease and vascular-related events will be characterized by these variables collected and a more comprehensive analysis may elucidate more of the NFL—vascular disease relationship. Osborn et al., 2019 recently assessed this relationship between systemic vascular risk and NFL and found that associations are amplified by the presence of Aβ and tau pathology. Interestingly, a previous study from the same group had found that NFL associations with vascular pathology were independent of Aβ (Osborn et al., 2018). We have recently carried out analyses looking at relationships of WMHs with CSF Aβ and tau in this ADNI cohort (Walsh et al., 2020), and it would be an interesting future study to examine any interactions between NFL, Aβ, and tau and subsequent impacts on WMHs.

One major influence on the findings we present here is likely due to the cerebrovascular exclusion criteria in ADNI (a score above 4 on the Hachinski Ischemic Scale) (https://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-procedures-manual.pdf). For example, the reason why the association between NFL and WMHs was lower in AD than the MCI groups may be due to the exclusion criteria in ADNI, whereby those patients with AD with significant cerebrovascular burden (and likely higher WMHs and NFL) may have had a Hachinski

Table 4
Regression models results for the relationship between WMHs and plasma NFL with adjustment for smoking status, history of hypertension, history of diabetes, and BMI by group

WMHs and NFL adjusted for smoking, hypertension, diabetes and BMI (N = 820)	Controls	SMC	EMCI	LMCI	AD
Adjusted for smoking, hypertension, diabetes, BMI n = 822					
% increase in WMHs per 1 SD change in NFL	18.7 (−2.1–44.1)	43.3 (8.1–90.1)	29.1 (13.6–39.9)	37.3 (17.7–60.2)	20.3 (5.1–37.8)
Confidence intervals *p* value	0.08	**0.01**	**<0.001**	**<0.001**	**0.008**

Estimates are percentage increases in WMH volume per one SD change (1 SD = 18.3 pg/mL) in NFL, with 95% confidence intervals and adjustment for TIV. The SD is the pooled within-group SD, calculated from a linear regression model that allowed for differences in mean levels of NFL by group. Bold *p* values denote statistical significance at the $p < 0.05$ level.
Key: AD, Alzheimer's disease; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; NFL, neurofilament light; SMC, significant memory concern; TIV, total intracranial volume; WMH, white matter hyperintensity.

score of greater than 4. Indeed, there appears to be a proportion of participants in the AD group with high NFL levels and low WMH volumes, but no participants both with these highest NFL levels and high WMHs (see Fig. 1). Individuals with higher numbers of vascular risk factors are likely to develop significant cerebrovascular disease and therefore be excluded from this study.

We found a strong relationship of NFL with age, with a highly significant positive relationship in each diagnostic group (see Supplementary Information). The marked reduction in the association between NFL and WMHs after age adjustment also suggests that the relationship between WMHs and NFL is largely due to their associations with age. We chose to present results with and without adjustment for age at the baseline, to be sensitive to the fact that age can be considered a proxy measure of vascular events and other comorbidities that increase over time and cause resultant degeneration. Adjusting for age cannot simply be considered as removal of the effects of normal aging on the WMH-NFL relationship. Such an approach could be achieved by the adjustment of the models with the slope of the association in healthy controls, and potentially only using the controls without evidence of amyloid pathology, in an attempt to remove the effects of normal aging.

The strong association between NFL and age is in agreement with previous studies that have demonstrated this positive association in both controls and in AD (Lewczuk et al., 2018; Vagberg et al., 2015). It is unclear what underpins this increase in NFL with age, but it is suggestive of subclinical axonal damage. Although the increase could potentially be caused by an increase in cerebrovascular pathology with increasing age (Lewczuk et al., 2018; Vagberg et al., 2015), our results do not support this notion because adjustment for most of the major vascular risk factors had little impact on the NFL and WMH relationship. This hypothesis should not be entirely discounted because the lack of support for it from our study may have been due to the nature of the vascular variables used here or the selection bias, induced by the Hachinski score cutoff, acting on this cohort. Nonetheless, our findings highlight the importance of looking beyond vascular disease and studying the role that other pathological processes may effect on axonal and white matter health in aging and in AD.

The highest levels of NFL were observed in the AD group, followed by the LMCI group, with the less cognitively impaired groups having lower levels of NFL. This suggests that NFL differs by disease stage which is a key feature of a biomarker. Further work is needed to understand whether it predicts further WMH development, serves as a good prognostic biomarker, or tracks with disease progression, particularly in the early disease stages. The strong association of NFL with age could have potential implications when considering its use as an AD biomarker. Previous reports found an age-dependent increase in the sensitivity at the cost of a decrease in the specificity, with the most marked effect seen at older ages (Lewczuk et al., 2018; Mattsson et al., 2017). Furthermore, increases in NFL are not specific to the neurodegeneration observed in AD, and have been observed in multiple sclerosis (Kuhle et al., 2013), amyotrophic lateral sclerosis (Lu et al., 2015), frontotemporal dementia (Rohrer et al., 2016), and after traumatic brain injury (Shahim et al., 2018). It may therefore be more plausible for NFL to be used as a screening tool for neurodegeneration, as opposed to a diagnostic test for any condition.

One limitation of this study is the use of the ADNI cohort for studying vascular-related pathology, as the ADNI selection criterion excludes participants with large amounts of cerebrovascular disease. As mentioned previously, although we chose important vascular risk factors for adjustment of the WMH-NFL relationship, we are unlikely to have adjusted for all vascular risks. Furthermore, we chose to collapse height and weight into the commonly used BMI measure in this analysis, but did not further collapse over all vascular risk variables to generate a points-based vascular risk score as has been carried out in other studies (D'Agostino et al., 2008, Lane et al., 2019). We felt that there was merit in entering each of these vascular risk factors separately, given the possibility that they may not all have the same relationship with WMHs or NFL levels. There are potential selection biases that affect generalization to the wider population, including a tendency toward participants of high socioeconomic status and education level. Pathological confirmation of diagnosis is not available for the ADNI cohort, leaving open the possibility of bimodal disease groups, i.e. control groups may contain individuals with early stage or atypical AD pathology and MCI groups may contain individuals that do not go on to develop AD (Jicha et al., 2006; Petersen et al., 2006). In addition, this study was only carried out using baseline data and so changes over time in the relationship between NFL and WMHs were not assessed. We have only used plasma NFL in this study due to CSF NFL not currently being available for ADNI2/GO, but it would have been interesting to compare CSF NFL as differing associations with outcome measures have been reported (Mielke et al., 2019). We also only looked at total WMH volume and therefore chose not to assess any regional associations between NFL and WMH volume. A detailed assessment of regional WMH associations would be an important future direction. An important caveat to the study design is that no causality in the WMH-NFL relationship can be inferred. We are unable to discern whether the association we observe between NFL and WMHs is induced by each biomarker's strong associations with age, or whether one biomarker causes change in the other. Further research would be necessary to reveal any causal relationship.

In summary, our study is suggestive of an association between plasma NFL and WMHs in MCI and AD, but in a manner that is largely dependent on age. This study adds to our understanding of the aging brain's vulnerability to damage, such as axonal degeneration. Plasma NFL could offer insight into white matter damage in cognitively impaired individuals in a relatively noninvasive and inexpensive manner.

Disclosure statement

The authors have no actual or potential conflicts of interest.

CRediT authorship contribution statement

Phoebe Walsh: Conceptualization, Data curation, Methodology, Writing - original draft, Writing - review & editing. **Carole H. Sudre:** Methodology, Software. **Cassidy M. Fiford:** Supervision. **Tammaryn Lashley:** Supervision. **Chris Frost:** Methodology, Data Curation, Methodology, Formal analysis, Writing - review & editing. **Josephine Barnes:** Conceptualization, Writing - review & editing, Supervision.

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The data used in this study was collected by ADNI. Ethical approval was obtained by the Institutional Review Board at each participating center. All study participants provided written informed consent.

All authors have reviewed and approve of the contents of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2020.09.008.

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