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# Impact of *APOE* ε4 and ε2 on plasma neurofilament light chain and cognition in autosomal dominant Alzheimer's disease

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## Abstract

**Background** Apolipoprotein E (*APOE*) genotypes have been suggested to influence cognitive impairment and clinical onset in presenilin-1 (*PSEN1*) E280A carriers for autosomal dominant Alzheimer's disease (ADAD). Less is known about their impact on the trajectory of biomarker changes. Neurofilament light chain (NfL), a marker of neurodegeneration, begins to accumulate in plasma about 20 years prior to the clinical onset of ADAD. In this study we investigated the impact of *APOE* ε4 and ε2 variants on age-related plasma NfL increases and cognition in *PSEN1* E280A mutation carriers.

**Methods** We analyzed cross-sectional data from *PSEN1* E280A mutation carriers and non-carriers recruited from the Alzheimer's Prevention Initiative Registry of ADAD. All participants over 18 years with available *APOE* genotype, plasma NfL, and neuropsychological evaluation were included in this study. *APOE* genotypes and plasma NfL concentrations were characterized for each participant. Cubic spline models using a Hamiltonian Markov chain Monte Carlo method were used to characterize the respective impact of at least one *APOE* ε4 or ε2 allele on age-related log-transformed plasma NfL increases. Linear regression models were estimated to explore the impact of *APOE* ε4 and ε2 variants and plasma NfL on a composite cognitive test score in the ADAD mutation carrier and non-carrier groups.

**Results** Analyses included 788 *PSEN1* E280A mutation carriers (169 *APOE* ε4 +, 114 ε2 +) and 650 mutation non-carriers (165 *APOE* ε4 +, 80 ε2 +), aged 18–75 years. *APOE* ε4 allele carriers were distinguished from ε4 non-carriers by greater age-related NfL elevations in the ADAD mutation carrier group, beginning about three years after the mutation carriers' estimated median age at mild cognitive impairment onset. APOE ε2 allele carriers had lower plasma NfL concentrations than ε2 non-carriers in both the ADAD mutation carrier and non-carrier groups, unrelated to age, and an attenuated relationship between higher NfL levels on cognitive decline in the ADAD mutation carrier group.

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**Conclusions** *APOE* ε4 accelerates age-related plasma NfL increases and *APOE* ε2 attenuates the relationship between higher plasma NfL levels and cognitive decline in ADAD. NfL may be a useful biomarker to assess clinical efficacy of *APOE*-modifying drugs with the potential to help in the treatment and prevention of ADAD.

**Keywords** Autosomal dominant Alzheimer's disease, PSEN1, APOE, Blood biomarkers, Neurodegeneration

## Background

Apolipoprotein E (*APOE*) genotype is the largest genetic component of sporadic Alzheimer's disease (AD) risk. The ε4 allele (*APOE* ε4+) is associated with increased disease risk and earlier disease onset, whereas presence of the ε2 allele (*APOE* ε2+) confers protection [1, 2], and each additional copy of the ε4 or ε2 allele is associated with a higher and lower risk respectively [3]. Although autosomal dominant AD (ADAD) is genetically determined by mutations on the Presenilin-1 (*PSEN1*), *PSEN2*, or amyloid precursor protein genes, similar risk and protective effects of *APOE* observed in sporadic AD have been found in ADAD [4–6]. Previously, we showed that age-related trajectories of cognitive impairment are influenced by *APOE* ε4 and ε2 in members of the world's largest kindred with ADAD due to a single mutation, *PSEN1* E280A [4]. Mutation carriers who were also *APOE* ε4+had accelerated onset of cognitive impairment, whereas those who were *APOE* ε2+had delayed onset of cognitive impairment [4]. The underlying mechanisms of this relationship between *APOE* and cognition in ADAD remain to be further examined.

AD-associated neurodegeneration is closely related to clinical and cognitive impairment [7, 8]. A review of *APOE* genotype and neurodegeneration found consistent evidence that *APOE* ε4+variants are associated with more extensive atrophy and neurodegeneration, typically measured through structural MRI measures [9]. However, biofluid markers of neurodegeneration are becoming increasingly common due to the lower cost and accessibility to broader populations. Neurofilament light chain (NfL) is a marker of axonal loss and neurodegeneration that can be measured through biofluids and is elevated in neurodegenerative diseases, including AD [10, 11]. Similarly to MRI markers of neurodegeneration, higher levels of NfL are associated with worse cognition and proximity to disease onset [12–14]. Plasma NfL levels distinguish *PSEN1* E280A carriers from non-carriers more than two decades prior to clinical disease onset [15] and are associated with worse cognition and clinical progression [16].

Current research is inconclusive as to the relationships between *APOE* and plasma NfL concentrations in AD. In studies combining participants from various disease stages, one reported that *APOE* ε4+participants had higher levels of NfL than those who were ε4- [17] and another that plasma NfL did not differ by *APOE* ε4, nor did *APOE* ε4 relate to NfL or progression from MCI to AD dementia [18]. Effects of *APOE* may differ depending on disease stage, such that including persons at all stages of disease may mask these effects. In support of this idea, a study examining cognitively unimpaired older adults found that plasma NfL was higher in *APOE* ε4+than ε4- participants only after adjusting for age, sex, and education, and plasma NfL levels increased as a function of age most quickly in *APOE* ε4 homozygotes, with particularly steep accumulation between ages 75 and 85 [19]. Although most research has focused on the effects of *APOE* ε4, one study found that, compared to individuals with *APOE* ε3/ε3 variants, those who were *APOE* ε2+had lower levels of plasma NfL, whereas *APOE* ε4+individuals had similar levels of NfL compared to the ε3/ε3 group [20]. Thus, there is a need for additional research into the effects of both *APOE* ε4 and ε2 variants on plasma NfL concentrations, particularly examining accumulation across age. Further, these relationships have yet to be explored in ADAD populations.

In this study, we sought to examine the associations among plasma NfL, *APOE* variants, and cognition in carriers and non-carriers of the *PSEN1* E280A mutation for ADAD. We hypothesized that mutation carriers who were also *APOE* ε4+would have increased plasma NfL levels, whereas *APOE* ε2+mutation carriers would have reduced levels. In addition, we hypothesized that *APOE* variant would moderate the effects of NfL on cognitive performance, such that ε4+carriers would show a stronger NfL-cognition relationship and ε2+carriers would have a weaker NfL-cognition relationship.

## Methods

### Participants

Participants were identified through the Alzheimer's Prevention Initiative (API) Registry, consisting of family members of a Colombian kindred with a high incidence of the *PSEN1* E280A mutation for ADAD. Participants were unaware of their own genetic status but had a parent who was known to carry the *PSEN1* E280A mutation. All participants with plasma NfL and *APOE* genotyping above the age of 18 were included in this study, resulting in 788 *PSEN1* E280A mutation carriers and 650 mutation non-carriers. A subset of these participants (674 *PSEN1* E280A carriers, 594 mutation non-carriers) also had cognitive data.

### Procedures and measures

Investigators were blind to participant genetic status during all collection and processing procedures.

Genomic DNA was extracted from the blood using standard protocols. *PSEN1* E280A characterization was conducted at the University of Antioquia as described previously [21]. Genomic DNA was amplified with the primers *PSEN1*-S 5′ AACAGCTCAGGAGAGGAATG 3′ and *PSEN1*-AS 5′ GATGAGACAAGTNCCNTGAA 3′. We used the restriction enzyme *Bsm*I for restriction fragment length polymorphism analysis. Each participant was classified as a *PSEN1* E280A carrier or non-carrier. *APOE* genotyping was performed using a Kompetitive Allele Specific PCR – KASP™ assay [22] (LGV Genomics, Beverly, MA). *APOE* ε4 carriers were defined as individuals with at least one ε4 allele (*APOE* ε4+), while non-carriers had no *APOE* ε4 alleles (*APOE* ε4-). *APOE* ε2 carriers had at least one ε2 allele (*APOE* ε2+), while non-carriers had no *APOE* ε2 alleles (*APOE* ε2-). Sixteen *PSEN1* carriers and 16 non-carriers who were *APOE* e2/e4 were included in both the e2+ and e4+ groups. The distribution of *APOE* variants is provided in Supplementary Table S1.

Three aliquots of 1 ml of plasma were collected in the morning (not fasting). Samples were stored at −80°C. One plasma aliquot was shipped on dry ice to the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital, Mölndal, Sweden for NfL analysis. NfL concentration was measured using an in-house Single molecule array (Simoa) assay, as previously described (manufacturer: Quanterix, Billerica, MA) [23]. The measurements were performed by board-certified laboratory technicians. One batch of reagents and one instrument was used to analyze the whole study.

Neuropsychological assessments were administered at the University of Antioquia in Spanish. Cognition was assessed using the API cognitive composite, a composite score derived from 5 neuropsychological tests that has been shown to be sensitive to early cognitive changes due to AD in this Colombian kindred [24]. The API composite includes CERAD Word List Recall, CERAD Boston Naming Test (high frequency), MMSE Orientation to Time, CERAD Constructional Praxis, and Ravens Progressive Matrices (Set A). The total cognitive composite score was calculated out of 100 with higher scores indicating better performance. Neuropsychological testing was performed within three months of the plasma collection.

### Statistical analysis

All analyses were conducted in R (version 4.2.3). Effects of *APOE* were examined by comparing *APOE* ε4+ versus ε4- groups, and separately, *APOE* ε2+ versus ε2- groups. To address heavy skewness, log-transformed plasma NfL values were used in analyses. Differences in continuous demographic variables between *APOE* groups were conducted using two-sample *t*-tests (Levene's test used to compare equality of variances). Chi-squared tests were used to examine differences in sex distribution. Group differences in plasma NfL were assessed using a factorial ANOVA, with *PSEN1* and *APOE* group as independent variables, run with and without age and sex as covariates. Age-related trajectories of plasma NfL were modeled using a cubic spline model as a function of *APOE* group. Hamiltonian Markov chain Monte Carlo (MCMC) was used to model parameters with a 99% credible interval. Linear regression was used to examine *APOE*, plasma NfL, and their interaction in predicting API Composite scores. Regressions were run with and without age and sex as covariates. Supplementary analyses for plasma NfL group differences and linear regression were run comparing three *APOE* groups, excluding *APOE* ε2/ε4 participants: *APOE* e3/4 & ε4/4 versus ε3/ε3 versus ε2/ε3 & ε2/ε2 (Supplementary Tables S2, S3, Supplementary Figures S1, S2). Results were consistent with the two group comparisons reported in the main text.

## Results

### Participant characteristics

Participant demographics are provided in Table 1. A total of 788 *PSEN1* E280A mutation carriers (169 *APOE* ε4+, 609 *APOE* ε4-; 154 cognitively impaired carriers) and 650 mutation non-carrier family members (165 *APOE* ε4+, 485 *APOE* ε4-) had plasma NfL and *APOE* genotype data collected. One *PSEN1* E280A mutation carrier and 4 mutation non-carriers did not have education data available. Age, sex distribution, and education did not differ by *APOE* ε4 group. A subset of 674 *PSEN1* E280A carriers (141 *APOE* ε4+, 533 *APOE* ε4-) and 594 non-carriers had cognitive data (148 *APOE* ε4+, 446 *APOE* ε4-). Within this subset, the *APOE* ε4+ group had higher years of education.

Among *PSEN1* non-carriers, 650 (165 *APOE* ε4+, 485 *APOE* ε4-) had plasma NfL and *APOE* collected, and a subset of 594 (148 *APOE* ε4+, 446 *APOE* ε4-) also had cognitive data. Age, education, and sex distribution did not differ as a function of *APOE* ε4 group either in the full sample or subset with cognitive data (Table 1). Participant demographics as a function of *APOE* ε2 group are provided in Supplementary Table S4.

**Table 1** Participant characteristics

| | ***All participants*** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ***PSEN1 E280A Carriers*** | | | | ***PSEN1 E280A Non-Carriers*** | | | |
| | ***APOE ε4+ (n = 169)*** | ***APOE ε4- (n = 609)*** | ***Group difference*** | | ***APOE ε4+ (n = 165)*** | ***APOE ε4- (n = 485)*** | ***Group difference*** | |
| *Age (years)* | *35.87 ± 12.28* | *35.92 ± 12.41* | *t (776) = -0.05* | *p = 0.961* | *36.72 ± 12.70* | *35.34 ± 12.43* | *t (648) = -1.22* | *p = 0.223* |
| *Sex (% female)* | *55.62%* | *56.32%* | $\chi^2(1) = 0.03$ | *p = 0.871* | *60.60%* | *55.05%* | $\chi^2(1) = 1.545$ | *p = 0.214* |
| *Education (years)* | *7.80 ± 4.04* | *7.15 ± 4.50* | *t (776) = 1.74* | *p = 0.082* | *8.51 ± 4.93* | *8.26 ± 4.66* | *t (648) = 0.585* | *p = 0.559* |
| *Log10 NfL levels* | *1.06 ± 0.43* | *1.03 ± 0.39* | *t (776) = 0.89* | *P = 0.374* | *0.84 ± 0.32* | *0.83 ± 0.26* | *t (648) = 0.317* | *p = 0.751* |
| | ***Subset of participants with cognitive data*** | | | | | | | |
| | ***PSEN1 E280A Carriers*** | | | | ***PSEN1 E280A Non-Carriers*** | | | |
| | ***APOE ε4+ (n = 141)*** | ***APOE ε4- (n = 533)*** | ***Group difference*** | | ***APOE ε4+ (n = 148)*** | ***APOE ε4- (n = 446)*** | ***Group difference*** | |
| *Age (years)* | *33.70 ± 10.89* | *34.23 ± 11.27* | *t (672) = -0.50* | *p = 0.616* | *35.53 ± 11.78* | *34.83 ± 12.07* | *t(592) = 0.615* | *p = 0.539* |
| *Sex (% female)* | *55.32%* | *54.60%* | $\chi^2(1) = 0.02$ | *p = 0.878* | *60.12%* | *54.48%* | $\chi^2(1) = 1.44$ | *p = 0.230* |
| *Education (years)* | *8.01 ± 3.96* | *7.25 ± 4.47* | *t(672) = 2.06* | *p = 0.040* | *8.44 ± 4.76* | *8.17 ± 4.68* | *t(592) = 0.608* | *p = 0.544* |
| *API Composite* | *57.28 ± 22.85* | *57.12 ± 21.18* | *t(672) = 0.08* | *p = 0.938* | *65.08 ± 14.76* | *63.89 ± 13.31* | *t(592) = 0.916* | *p = 0.360* |

Means ± standard deviations given for continuous variables

Years of education was unavailable for 1 *PSEN1* carrier and 4 *PSEN1* non-carriers

### Associations between *APOE* ε4 and plasma NfL

We first examined the effects of *PSEN1* and *APOE* ε4 on plasma NfL collapsing across age. Plasma NfL was higher in *PSEN1* E280A carriers than in non-carriers (Table 1) [F (1, 1424) = 86.84, $p < 0.001$]. There was no main effect of *APOE* ε4 nor an interaction between *APOE* ε4 and *PSEN1* genotypes on plasma NfL concentrations (Fig. 1A). Similar negative results were observed when including age and sex as covariates.

We then examined the accumulation of plasma NfL across age as a function of *APOE* ε4 using a restricted cubic spline model. Among *PSEN1* E280A carriers, those who were also *APOE* ε4 + had greater age-related accumulation of plasma NfL beginning around age 47.5 compared to those who were *APOE* ε4- (Fig. 1B, C), the typical age between the onset of MCI and dementia in this cohort [25]. Age-related plasma NfL accumulation did not differ by *APOE* ε4 group in *PSEN1* E280A mutation non-carriers in the sample's specified age range (Fig. 1D, E).

Within the subset of *PSEN1* E280A mutation carriers with cognitive data, higher plasma NfL was associated with lower scores on the API cognitive composite (ß = -0.60, $p < 0.001$). There was no main effect of *APOE* ε4 nor an interaction between *APOE* ε4 and plasma NfL on cognitive scores (Fig. 1F). When including age and sex as covariates, there was a non-significant trend for the NfL-cognition association to be stronger in *APOE* ε4 + carriers (NfL: ß = -0.24, $p < 0.001$; *APOE* ε4: ß = 0.17, $p = 0.059$; NfL x *APOE* ε4 interaction: ß = -0.18, $p = 0.054$).

In *PSEN1* E280A mutation non-carriers, there was no main effect of *APOE* ε4, but plasma NfL was inversely associated with API composite scores (ß = -0.11, $p = 0.031$), and *APOE* ε4 moderated the association between NfL and cognition (ß = 0.29, $p = 0.033$; Fig. 1G). These relationships did not remain statistically significant when including age and sex as covariates.

### Associations between *APOE* ε2 and plasma NfL

Collapsing across age, plasma NfL accumulation was higher in *PSEN1* E280A mutation carriers than non-carriers, but there were no group differences by *APOE* ε2 nor an interaction between *PSEN1* and *APOE* genotypes (Fig. 2A). When including age and sex in the model, however, the main effect of *APOE* ε2 was significant, such that participants who were *APOE* ε2 + had lower levels of plasma NfL than those who were *APOE* ε2-, in both the *PSEN1* mutation carrier and non-carrier groups [*PSEN1*: F(1, 1422) = 198.43, $p < 0.001$); *APOE* ε2: F(1, 1422) = 5.92, $p = 0.015$; *PSEN1* x *APOE* ε2 interaction: F(1, 1422) = 1.70, $p = 0.192$; age: F(1, 1422) = 1204.31, $p < 0.001$; sex: F(1, 1422) = 10.97, $p = .\ 001$]. The age-related trajectories of plasma NfL accumulation did not differ by *APOE* ε2 group in *PSEN1* E280A mutation carriers or non-carriers (Fig. 2B-E).

In *PSEN1* E280A mutation carriers with cognitive data, both higher plasma NfL and being *APOE* ε2- were associated with lower API Composite scores (Fig. 2F; NfL: ß = -0.67, $p < 0.001$; *APOE* ε2-: ß = -0.26, $p = 0.004$). Further, *APOE* ε2 moderated the effect of plasma NfL on cognition, such that the negative

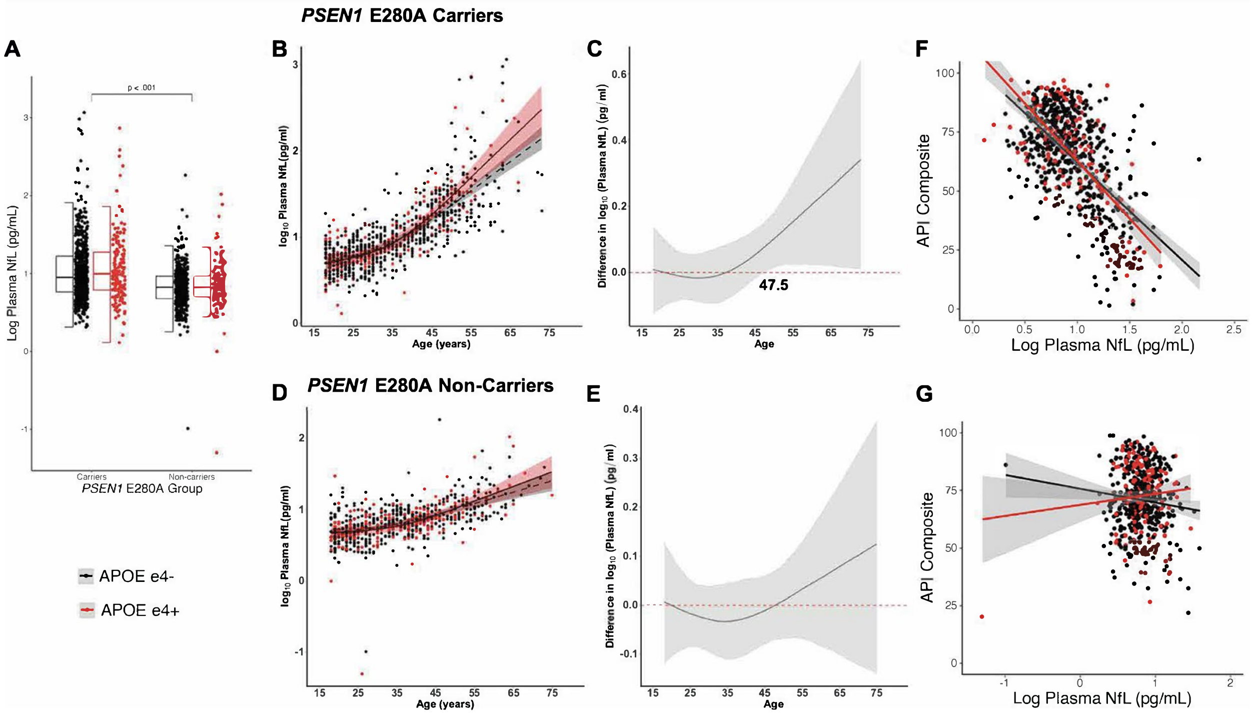

**Fig. 1** Plasma NfL as a function of *APOE* ε4. **A** Boxplot showing log-transformed plasma NfL concentrations (pg/mL) in *PSEN1* E280A carriers and non-carriers as a function of *APOE* ε4 group (black: *APOE* ε4-, red: *APOE* ε4 +). **B** Log-transformed plasma NfL concentrations of *PSEN1* E280A mutation carriers who are *APOE* ε4 + and *APOE* ε4- as a function of age. **C** Differences in NfL concentrations between *APOE* ε4 + and ε4- *PSEN1* E280A mutation carriers as a function of age. **D** Log-transformed plasma NfL concentrations of *PSEN1* E280A mutation non-carriers who are *APOE* ε4 + and *APOE* ε4- as a function of age. **E** Differences in NfL concentrations between *APOE* ε4 + and ε4- *PSEN1* E280A mutation non-carriers as a function of age. **F** API composite score plotted by log-transformed plasma NfL concentrations in *PSEN1* E280A mutation carriers stratified by *APOE* ε4 group. **G** API composite score plotted by log-transformed plasma NfL concentrations in *PSEN1* E280A mutation non-carriers stratified by *APOE* ε4 group. In panels **C** and **E**, the shaded areas of each plot represent the 99% credible intervals around the model estimates drawn from the distributions of model fits derived by the Hamiltonian Markov chain Monte Carlo analyses. In panels **F** and **G**, plots show regression line with shaded standard error bands

association between plasma NfL and cognition was attenuated in *APOE* ε2 + *PSEN1* E280A mutation carriers (ß = 0.29, $p = 0.001$). Results were consistent when including age and sex as covariates. In *PSEN1* E280A mutation non-carriers, both NfL and being *APOE* ε2- were associated with lower cognitive scores (NfL: ß = -0.10, $p = 0.033$; *APOE* ε2-: ß = -0.30, $p = 0.008$), and *APOE* ε2 moderated the NfL-cognition relationship (ß = 0.24, $p = 0.037$). The main effect of NfL and the interaction between NfL and *APOE* were not statistically significant after including age and sex in the model, but being *APOE* ε2- remained associated with lower cognitive scores (ß = -0.28, $p = 0.013$) (Fig. 2G).

The findings from further analyses, which excluded three non-carrier outliers, remained consistent with the initial results and are presented in Supplementary Table S6 and Figures S4 and S5.

## Discussion

Although most carriers of the *PSEN1* E280A mutation for ADAD are genetically determined to develop AD dementia by midlife, we previously found that *APOE* influences age-related trajectories of cognitive impairment [4]. We also showed that plasma NfL levels can distinguish *PSEN1* E280A carriers from non-carriers about twenty years before symptoms appear [15]. Here, we showed that *APOE* ε4 and ε2 variants influence age-related accumulation of plasma NfL, shown previously to increase decades prior to clinical onset in this kindred [15]. Plasma NfL concentrations distinguished *PSEN1* mutation carriers who also had an *APOE* ε4 allele from those without an ε4 allele beginning at age 47, several years after the median age of onset of MCI (44 years) but prior to the estimated onset of dementia (49 years) in this kindred [25], whereas presence of the *APOE* ε2 allele was associated with lower

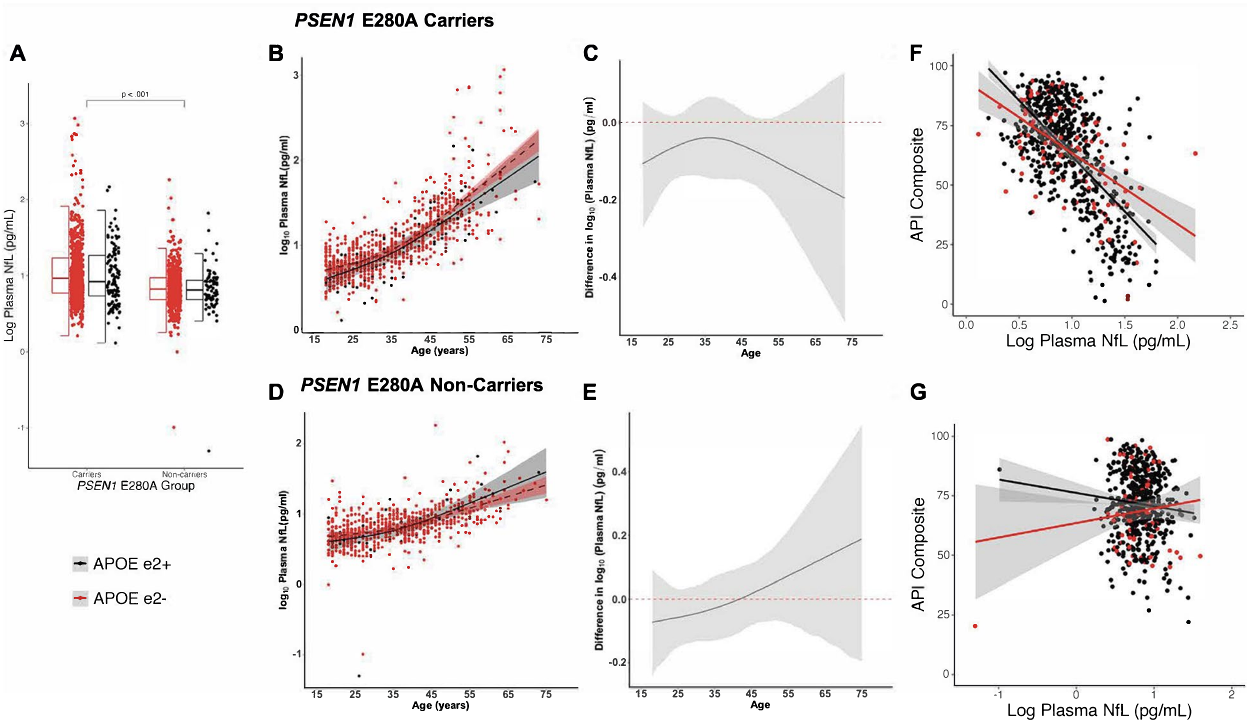

**Fig. 2** Plasma NfL as a function of *APOE* ε2. **A** Boxplot showing log-transformed plasma NfL concentrations (pg/mL) in *PSEN1* E280A carriers and non-carriers as a function of *APOE* ε2 group (black: *APOE* ε2+, red: *APOE* ε2-). **B** Log-transformed plasma NfL concentrations of *PSEN1* E280A mutation carriers who are *APOE* ε2+and *APOE* ε2- as a function of age. **C** Differences in NfL concentrations between *APOE* ε2+and ε2- *PSEN1* E280A mutation carriers as a function of age. **D** Log-transformed plasma NfL concentrations of *PSEN1* E280A mutation non-carriers who are *APOE* ε2+and *APOE* ε2- as a function of age. **E** Differences in NfL concentrations between *APOE* ε2+and ε2- *PSEN1* E280A mutation non-carriers as a function of age. **F** API composite score plotted by log-transformed plasma NfL concentrations in *PSEN1* E280A mutation carriers stratified by *APOE* ε2 group. **G** API composite score plotted by log-transformed plasma NfL concentrations in *PSEN1* E280A mutation non-carriers stratified by *APOE* ε2 group. In panels **C** and **E**, the shaded areas of each plot represent the 99% credible intervals around the model estimates drawn from the distributions of model fits derived by the Hamiltonian Markov chain Monte Carlo analyses. In panels **F** and **G**, plots show regression line with shaded standard error bands

plasma NfL concentrations regardless of age. Additionally, our findings support the possibility that *APOE* ε2 has protective effects against NfL-associated cognitive impairment.

Prior findings on the role of *APOE* genotype on NfL accumulation have been mixed. Studies of plasma and CSF concentrations of NfL report findings ranging from higher concentrations in *APOE* ε4+variants, to no difference by *APOE* genotype, and lower concentrations in *APOE* ε4+variants [17–19, 26, 27]. These inconsistent findings suggest that group-wide differences in NfL concentrations may not be consistent across age or disease stage. Our results examining effects of *APOE* ε4 across age indicate that differences emerge in prodromal disease stages, between the onset of MCI and clinical dementia. These results are consistent with a recent study showing increased NfL accumulation in *APOE* ε4+adults beginning in older adulthood [19].

Contrary to our hypotheses, and despite *APOE* ε4+*PSEN1* mutation carriers exhibiting greater age-related increases in plasma NfL, *APOE* ε4 was not associated with worse cognition nor did it moderate the relationship between NfL and cognition in this sample. These associations neared significance after adjusting for age and sex, suggesting that the effects of *APOE* ε4 on NfL-related cognitive impairment may also be age-dependent, similar to our findings characterizing group-level NfL concentrations versus age-related trajectories. Comparisons of the full study sample with the subset with cognitive data revealed that participants who had plasma NfL but not cognitive data were older and had higher levels of NfL than the subset of participants who had all available data (Supplementary Table 5). Coupled with our findings that *APOE* ε4 carriers begin to accumulate more NfL in later disease stages, *APOE* ε4 may only moderate the NfL-cognition relationship in later disease stages which is not represented in the subset of participants with cognitive data. Another possibility is that the effects of *APOE* ε4 on cognition are less evident because the *APOE* ε4 accelerated accumulation is occurring later in the disease process when there's already considerable AD pathology and possible neurodegeneration. Indeed, higher plasma NfL has been associated with higher PET-measured tau pathology and lower MRI-measured MTL volume [16, 19].

Conversely, *APOE* ε2 did not influence age-related trajectories of NfL accumulation but was associated with lower levels of plasma NfL on average and attenuated cognitive impairment associated with higher levels of NfL. The protective effects of *APOE* ε2 may begin earlier in life, thereby contributing to overall group differences but not in rates of accumulation across advancing age. Additionally, the cognitive benefits of the *APOE* ε2 + variant may have been more evident in the subset of participants with cognitive data, who were on average younger than the full study sample. These results suggest the *APOE* ε2 allele may provide resilience to cognitive impairment associated with neurodegeneration. These results are consistent with prior reports of a protective effect of *APOE* ε2 in AD [4, 6, 28]; however, to our knowledge, these are the first results reporting a protective effect of *APOE* ε2 in the context of NfL-associated cognitive impairment.

Our findings suggest a role of *APOE* ε4 and ε2 alleles on biofluid markers of neurodegeneration in *PSEN1* E280A mutation carriers. Potential pathophysiological mechanisms that explain how *APOE* ε4 impacts biofluid markers of neurodegeneration, such as NfL, may include the activation of microglia to induce neuroinflammation, leading directly to neuronal degeneration, or influencing amyloid-β and tau pathology.

These results need to be interpreted with caution, as the relatively large sample size may lead to the detection of significance even with small effect sizes. Replication in independent samples is required, and further investigation is needed to determine the generalizability to sporadic AD and other ADAD mutations. However, there are several strengths of assessing these questions in ADAD. Plasma NfL concentrations increase with age and non-AD neurodegenerative diseases, making it difficult to isolate AD-specific accumulation in the general population. Because carriers of the *PSEN1* E280A are younger than their sporadic AD counterparts and are known to be developing AD-dementia, our findings are unlikely to be driven by age-related and we can more closely assess AD-specific changes. This study also has several limitations. Due to low numbers of homozygous *APOE* ε2 and ε4 carriers, we were not able to assess whether the pattern of results differ based on the number of copies of *APOE* ε2 and ε4 alleles. Additionally, this study is cross-sectional. Although *PSEN1* E280A carriers follow a well-defined disease trajectory, there are sources of individual variability. Future studies should examine longitudinal measures of plasma NfL accumulation and cognition.

In conclusion, *APOE* influences age-related accumulation of plasma NfL, and presence of the *APOE* ε2 allele may provide protection against cognitive impairment associated with neurodegeneration. These findings contribute to the growing evidence that *APOE* influences the trajectory of ADAD and provides further support for the development of *APOE*-based therapeutics for both autosomal dominant and sporadic forms of the disease. Further analyses are required to determine the number of *PSEN1* + *APOE ε4* + versus *PSEN1* + *APOE ε4-* mutation carriers showing elevated NfL levels needed to demonstrate the significant effects of AD-modifying treatments on NfL reduction. These findings will inform the design of future treatment and prevention trials within this family, potentially optimizing the size and duration of early phase trials involving this population.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01572-y.

Supplementary Material 1.

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### Authors' contributions

Y.T.Q., F.L., and E.M.R. initiated this work and supervised conduction of the study. S.L., K.B., and Y.T.Q. drafted the manuscript. Genetic data were collected and analyzed by G.G-O., C.G-M., K.K. and J.F.A.-V. Clinical information were collected and analyzed by D.A., D.V., M.G-C., A.Y.B., C.M., V.T., N.A-B, S.R-R and F.L. Statistical analyses were conducted by S.L., Y.C, V.G., J.P., P.T., and Y.S. SL and YC prepared figures. All co-authors reviewed and contributed to finalize the manuscript.

### Availability of data and materials

Anonymized clinical, genetic, and imaging data are available upon request, subject to an internal review by YTQ and FL to ensure that the participants' anonymity, confidentiality, and PSEN1 E280a carrier or non-carrier status are protected. Data requests will be considered based on a proposal review, and completion of a data sharing agreement, in accordance with the University of Antioquia and MGH institutional guidelines.

### Data availability

Source data will be available with this paper including age, log-transformed plasma NfL concentrations, API composite scores, and genetic group. The data analyzed in this study are not made publicly available in full to protect the identities of members of this kindred. The datasets will be made available from the corresponding author on request.

## Declarations

### Competing interests

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## Publisher's Note