Received: 15 August 2025 | Revised: 25 November 2025 | Accepted: 25 November 2025

DOI: 10.1002/alz.71052

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Association between basal forebrain volume and age in the presenilin-1 E280A autosomal dominant Alzheimer's disease kindred

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Funding information
the National Institute on Aging, Grant/Award Number: R01AG077627; the National Institute of Neurological Disorders and Stroke, Grant/Award Number: RM1NS132996

Abstract

INTRODUCTION: The basal forebrain (BF), a key cholinergic hub, undergoes atrophy in Alzheimer's disease (AD), contributing to cognitive decline. However, its age-related differences and early vulnerability in autosomal dominant AD (ADAD) remain unclear.

METHODS: We studied 158 individuals from the Colombian Presenilin-1 (*PSEN1)* E280A kindred, including 80 carriers (60 cognitively unimpaired, 20 cognitively impaired). Participants underwent structural magnetic resonance imaging, blood sampling, and neuropsychological testing. Analysis of covariance and false discovery rate–corrected *t* tests assessed group differences. Correlations evaluated associations among BF volume, age, and cognitive scores. Hamiltonian Markov chain Monte Carlo modeling estimated the age at which BF volume diverged between carriers and non-carriers.

RESULTS: BF volume was comparable between cognitively unimpaired carriers and non-carriers but declined more rapidly in carriers, with divergence at ≈ 37.8 years, 6 years prior to the median age at onset of mild cognitive impairment.

DISCUSSION: BF volume changes precede the onset of clinical symptoms in ADAD, supporting its potential as an early biomarker of cholinergic degeneration and therapeutic target.

KEYWORDS
autosomal dominant Alzheimer's disease, basal forebrain, brain volume, memory, presenilin 1

Highlights

- There were not basal forebrain (BF) volume differences between *PSEN1* E280A unimpaired carriers and non-carriers.
- Age-related modeling revealed a faster BF volume decline in carriers vs non-carriers.
- Age-related differences first emerged at 37.8 years, about 6 years before clinical onset.
- BF volume was related to age, cognition, and plasma phosphorylated tau 217 levels.
- BF changes may be early indicators of Alzheimer's disease–related neurodegeneration.

1 | BACKGROUND

The basal forebrain (BF) is a critical brain region composed of several interconnected anatomical structures, including the diagonal band of Broca, the nucleus basalis of Meynert (NbM), the ventral striatum, and cholinergic cell groups located beneath the globus pallidus.[1–3] Rich in cholinergic neurons, the BF serves as the primary source of acetylcholine (ACh) for the cortex and hippocampus.[4,5] ACh plays a key role in attention, memory, and learning,[6,7] and the decline of ACh levels is a hallmark of Alzheimer's disease (AD) pathology.[8–10] Consistent evidence from *post mortem* and in vivo neuroimaging studies in sporadic AD has demonstrated that BF atrophy and cholinergic dysfunction are strongly associated with cognitive decline.[11–15] Therefore, acetylcholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, are widely used to treat symptoms of AD by enhancing cholinergic neurotransmission and cognitive function[16–18].

A prior study in autosomal dominant AD (ADAD) revealed findings that differ from those observed in sporadic AD.[19,20] Using Bayesian analysis of covariance (ANCOVA) with Bayes factor hypothesis testing, the authors examined data from the Alzheimer's Prevention Initiative (API) Colombia ADAD cohort, including *Presenilin-1* (*PSEN1)* E280A carriers over the age of 30, and found no evidence of reduced BF volume in non-demented mutation carriers compared to non-carriers[21]. They proposed that this absence of volume differences may reflect distinct trajectories of disease progression between familial and sporadic AD.

Our understanding of the role of BF degeneration in cognitive decline within ADAD is still emerging. ADAD provides a unique model for studying preclinical disease mechanisms due to its predictable progression and earlier onset [22]. Importantly, ADAD mutation carriers are typically younger and less likely to have age-related comorbidities such as vascular disease, offering a cleaner window to examine neurodegenerative changes. ADAD provides the opportunity to track the progression of cholinergic disruption, help identify early neurodegenerative markers, and potentially expand the window for therapeutic intervention before the onset of irreversible cognitive decline.

Plasma biomarkers represent a promising non-invasive and cost-efficient approach for early detection of AD[23]. Plasma phosphorylated tau (p-tau)217 has emerged as a highly promising biomarker, with elevated levels observed in both sporadic AD[24] and ADAD[25]. Its robust association with cerebral amyloid and tau deposition underscores its sensitivity to early AD pathology[26,27]. P-tau217 has also been shown to predict longitudinal accumulation of amyloid and tau in individuals at risk for AD[28,29]. Recent evidence suggests that p-tau217 outperforms other blood-based biomarkers in diagnosing clinical AD during preclinical stages [30–32]. Importantly, recent studies suggest that elevated plasma p-tau217 levels are associated with atrophy of the BF and with spatial navigation deficits, suggesting that p-tau217 levels may contribute to BF degeneration and related cognitive impairments in older individuals[33].

This study aimed to characterize the age-related changes of BF volume among carriers of the *PSEN1* E280A mutation and examine its associations with plasma p-tau217 and cognitive performance. This Colombian kindred is known for early-onset AD, with a median age of 44 (43–45) years for mild cognitive impairment (MCI) and 49 (49–50) years for dementia onset [34–36]. In this population, age serves as a reliable proxy for disease progression, as older carriers are generally closer to clinical onset.

2 | METHODS

2.1 | Materials and methods

A total of 158 individuals from the *PSEN1* E280A kindred were enrolled through the University of Antioquia in Medellín, Colombia. The sample included 60 cognitively unimpaired (CU) carriers, 20 cognitively impaired (CI) carriers, and 78 non-carriers, as shown in Table 1. Exclusion criteria included: (1) any neurological, psychiatric, or systemic condition likely to affect cognition; and (2) medical contraindications to magnetic resonance imaging (MRI). Cognitively unimpaired status was defined by a Functional Assessment Staging (FAST)[37] score ≤ 2. All participants completed structural MRI, cognitive testing, and plasma sampling for biomarker analysis. Written informed consent was obtained from participants, with procedures approved by the local ethics committees of the University of Antioquia and Mass General Brigham, in accordance with international institutional review board regulations.

2.2 | Cognitive assessments

We administered a Spanish version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery, culturally and linguistically adapted for this population[38]. The following measures were included in our analyses: Mini-Mental State Examination (MMSE) to assess global cognition [39]; CERAD Word List Learning (WLL) task to measure memory[40]; category fluency (animals)[41] to measure verbal fluency;[42] a 15-item naming to assess confrontation naming; the Digit Symbol and Digit Span subtests from the Wechsler Adult Intelligence Scale (WAIS-IV)[43] to measure working memory and auditory attention; and the Geriatric Depression Scale (GDS) to asssess depressive symptom atology[44].

2.3 | MRI acquisition and processing

All participants underwent high-resolution anatomical MRI on a Siemens 3.0T scanner at Hospital Pablo Tobón Uribe in Medellín, Colombia. Images were acquired using a 3D T1-weighted magnetization-prepared rapid gradient echo sequence (echo time = min full, flip angle = 8°, number of excitations = 1, field of view = 22 cm, matrix = 192×192, slice thickness = 1.2 mm).

We assessed BF volumes and included hippocampal volumes as a comparison, given prior evidence linking hippocampal atrophy to early-stage AD, as well as to cognitive performance[45–47]. Volumetric analyses were performed using a pipeline implemented in Statistical Parametric Mapping (SPM12) and the CAT12 toolbox[48]. Scans were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) with a 1.5 mm isotropic voxel size, then normalized to a Montreal Neurological Institute (MNI) reference template using the DARTEL algorithm[49].

The BF volumes were calculated in the template space using a stereotactic map of the bilateral BF derived from the anatomical mask by Kilimann et al.[50] This mask was developed to align with the IXI-MNI template provided in the VBM8 and CAT12 toolboxes for SPM, which has a resolution of 1.5 mm isotropic and corresponds to a version of the MNI152 template adapted for use with SPM's high-dimensional DARTEL normalization algorithm. The atlas labels in this mask included six subregions: the posterior NbM (Ch4p), the medial septal nucleus and vertical limb of the diagonal band of Broca (Ch1/Ch2), anterior and intermediate NbM (Ch4a-i), the horizontal limb of the diagonal band (Ch3), the nucleus subputaminalis, the lateral extension of the anterior NbM (Ch4al/NSP), and the interstitial nuclei, as illustrated in Figure S1 in supporting information. Total bilateral BF volume was computed as the sum of these subregions. The hippocampal volume measure was calculated as the combined total of the left and right hippocampi, as defined by the Desikan–Killiany Atlas[51]. Total intracranial volume (TIV) was calculated as the sum of the total segmented GM, WM, and CSF volumes[49].

RESEARCH IN CONTEXT

1. **Systematic review**: Literature searches (e.g., PubMed, Google Scholar) showed inconsistent findings on basal forebrain (BF) volume changes in sporadic Alzheimer's disease (AD), while a recent study in autosomal dominant AD (ADAD) reported no early structural alterations. These relevant works are appropriately cited. No study has yet quantified the earliest age at which BF volume begins to diverge in ADAD or integrated magnetic resonance imaging, cognitive measures, and phosphorylated tau (p-tau)217 data in the *PSEN1* E280A cohort.
2. **Interpretation**: Findings showed no difference in BF volume between cognitively unimpaired carriers and non-carriers. However, age-related modeling revealed a faster decline in carriers, with divergence occurring at37.8 years, about 6 years before the median age at onset of cognitive impairment. BF volume correlated with both p-tau217 and cognitive performance, supporting its potential as an early biomarker of AD-related neurodegeneration.
3. **Future directions**: Longitudinal studies are needed to characterize BF volume trajectories in preclinical AD stages and to validate its utility as an early biomarker.

2.4 | Plasma p-tau217

Blood samples were collected in three ethylenediaminetetraacetic acid tubes for plasma extraction without anticoagulant. Samples were then centrifuged at 1200 × g for 5 minutes. Concentrations of plasma p-tau217 were analyzed using the Lumipulse immunoassay (Fujirebio) at the Michael T. Zuendel Family Biomarker Laboratory at Banner Sun Health Research Institute, as previously described.

2.5 | Statistical analysis

Independent *t* tests were used to compare continuous demographic variables among CU carriers, CI carriers, and non-carriers, while chi-squared tests were used for categorical variables. Group differences in brain volumes and plasma p-tau217 levels were assessed using ANCOVA with covariates age, sex, years of education, and TIV. Post hoc pairwise comparisons were conducted using *t* tests with false discovery rate (FDR) correction, where the magnitude of differences was assessed using Cohen *d*. [53] Partial Pearson correlations were computed, controlling for sex, years of education, and TIV to examine associations between age and neuroimaging and plasma biomarkers in the full sample and across CU carriers, CI carriers, and non-carriers. Partial Pearson correlations were computed, controlling for age, sex,

TABLE 1 Demographic and cognitive data.

	Non-carriers $N = 78$	Unimpaired carriers $N = 60$	Impaired carriers $N = 20$
Sex (F/M)	41/37	31/29	11/9
Years of education	12.44 ± 2.93	11.63 ± 3.32	8.9 ± 3.6[a,b]
Age	33.45 ± 8.87	29.88 ± 5.65[c]	48.45 ± 5.59[a,b]
Neuropsychological test score			
MMSE total (min, max)	28.79 ± 1.22 (25,30)	28.27 ± 1.53[c] (24,30)	18.85 ± 5.64[a,b] (8,26)
Word list learning recall (min, max)	8.01 ± 1.30 (4,10)	7.95 ± 1.42 (4,10)	1.4 ± 1.67[a,b] (0,5)
Word list learning total (min, max)	21.48 ± 3.18 (14,27)	20.67 ± 3.19 (13,29)	8.75 ± 4.87[a,b] (0,17)
Animal fluency (min, max)	21.31 ± 3.22 (10,31)	20.67 ± 4.28 (11,29)	12.3 ± 5.77 [a,b] (3,21)
Naming (min, max)	13.56 ± 1.01 (10,15)	13.10 ± 1.46[c] (8,15)	11.12 ± 2.95 [a,b] (6,15)
Digit symbol (min, max)	65.66 ± 17.63 (21,129)	61.36 ± 15.13 (32,59)	60 ± 20.46 [a,b] (0,49)
Digit span forward (min, max)	7.51 ± 1.85 (4,11)	7.57 ± 1.90 (4,12)	5.8 ± 1.82 [a,b] (2,9)
Digit span back (min, max)	5.19 ± 1.82 (2,11)	5.02 ± 2.09 (2,11)	4.71 ± 2.17 [a,b] (0,5)
GDS (min, max)	1.58 ± 2.21 (0,11)	2.83 ± 3.38[c] (0,13)	3.7 ± 4.38 [a] (0,15)
FAST (min, max)	1.06 ± 0.25 (1,2)	1.15 ± 0.36 (1,2)	4.15 ± 0.93 [a,b] (3,6)
Basal forebrain	694.68 ± 64.13	694.49 ± 67.91	580.79 ± 73.14 [a,b]
Hippocampus	3915.1 ± 415.8	3955.25 ± 331.32	3166.03 ± 451.04 [a,b]
P-tau217	0.08 ± 0.04	0.18 ± 0.2 [c]	1.36 ± 0.65 [a,b]

Abbreviations: FAST, Functional Assessment Staging; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau.
[a] $p < 0.05$ impaired carriers compared to non-carriers.
[b] $p < 0.05$ impaired carriers compared to unimpaired carriers.
[c] $p < 0.05$ unimpaired carriers compared to non-carriers.

years of education, and TIV to examine associations between BF volume and cognitive scores in the full sample and across CU carriers, CI carriers, and non-carriers.

2.6 | Analysis of associations among BF, hippocampal volume, p-tau217, and age

An age-related analysis to model the difference of brain volumes across age in *PSEN1* E280A mutation carriers and non-carriers was performed. For each biomarker, curvilinear regression models, including linear, quadratic, and sigmoidal, were applied to examine their associations with age. The optimal model for each association was selected based on the coefficient of determination (R^2) and the Akaike information criterion (AIC)[35,54]. All model comparisons and statistical analyses were performed using RStudio.

Model parameters were estimated using a Bayesian framework implemented via a Hamiltonian Markov chain Monte Carlo (MCMC) approach using Stan [55]. We used restricted cubic spline modeling to capture potential non-linear age-related changes in the brain volume. This approach generated posterior distributions of parameter estimates median and 99% credible intervals for each group across the age range. It also allowed the estimation of the distribution of the differences in brain volumes between carriers and non-carriers with a 99% credible interval. Based on the difference curve and its credible interval, we then estimated the age of onset as the earliest time at which the 99% credible intervals of the group difference did not overlap.

3 | RESULTS

3.1 | Participant characteristics

CU *PSEN1* mutation carriers were significantly younger, had higher GDS scores, and had lower MMSE and naming scores compared to non-carriers. CI *PSEN1* carriers were significantly older, had fewer years

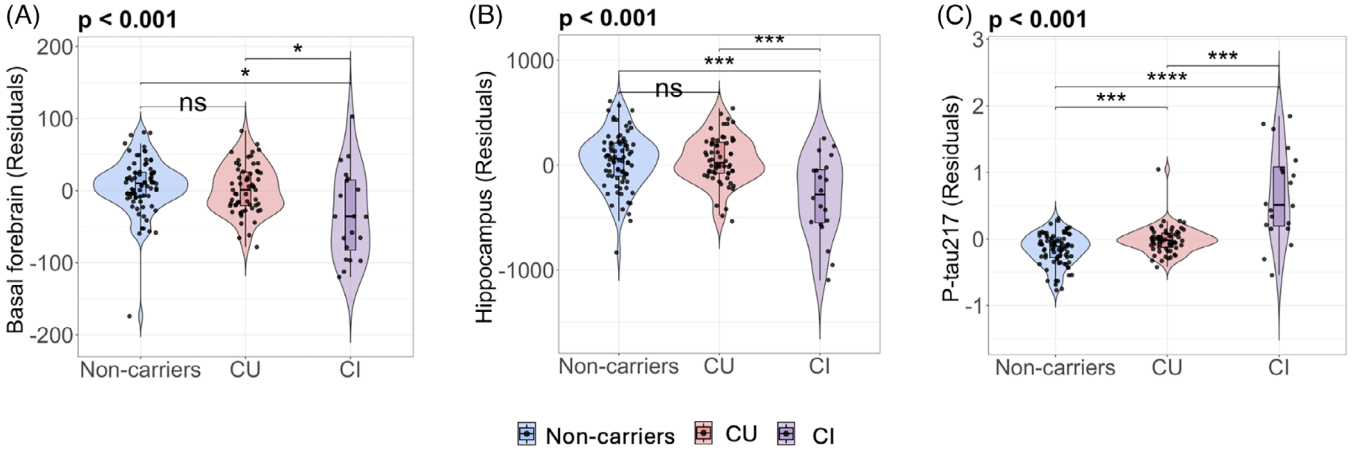

FIGURE 1 Group differences for basal forebrain, hippocampal volumes, and plasma p-tau217 levels in *PSEN1* E280A mutation carriers and non-carriers. Violin plots show residualized values for (A) basal forebrain volume residual values, (B) hippocampal volume residual values, and (C) plasma p-tau217 residual values across three groups: non-carriers (blue), cognitively unimpaired carriers (red), and cognitively impaired carriers (purple). Global *p* values are from analysis of covariance, and pairwise comparisons are false discovery rate corrected (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ns = not significant). CI, cognitively impaired; CU, cognitively unimpaired; p-tau, phosphorylated tau.

of education, had higher GDS scores, and had lower performance on most cognitive measures compared to CU carriers and non-carriers (see Table 1).

3.2 | Group differences in brain volumes and p-tau217

ANCOVA revealed significant group differences in BF ($p < 0.001$), hippocampal volumes ($p < 0.001$), and plasma p-tau217 levels ($p < 0.001$) among all carriers and non-carriers. Post hoc FDR-corrected *t* tests indicated no significant group differences in BF (*P*.fdr = 0.37, $d = 0.15$) or hippocampal volumes (*P*.fdr = 0.93, $d = 0.02$) between CU carriers and non-carriers. However, CI carriers had smaller BF (*P*.fdr = 0.049, $d = 0.7$; *P*.fdr = 0.031, $d = 0.79$) and hippocampal (*P*.fdr = 0.002, Cohen $d = 1.33$; *P*.fdr = 0.002, $d = 1.07$) volumes than CU carriers and non-carriers (Figure 1A, B).

Plasma p-tau217 levels differed significantly across groups, with CU *PSEN1* E280A mutation carriers showing higher levels than non-carriers (*P*.fdr < 0.001, $d = 0.62$), and CI carriers exhibiting the highest concentrations overall, significantly exceeding both CU carriers (*P*.fdr < 0.001, $d = 1.35$) and non-carriers (*P*.fdr < 0.001, $d = 1.6$). These findings are consistent with prior reports of elevated plasma p-tau217[29,56] levels in CU mutation carriers and support its sensitivity to disease progression (Figure 1C). Based on the established cutoff for abnormal plasma p-tau217 levels (> 0.42 pg/mL),[57] none of the non-carriers, 5% of CU carriers, and 95% of CI carriers exhibited abnormal values.

Group comparisons of BF subregional volumes revealed significant reductions in CI carriers relative to both CU carriers and non-carriers across all major cholinergic nuclei, whereas CU carriers did not differ significantly from non-carriers (Table S1 in supporting information).

3.3 | Associations among BF, hippocampal volume, p-tau217, and age

In the full sample, age showed a strong association with smaller BF ($r = -0.523$, $p < 0.001$) and hippocampal volumes ($r = -0.447$, $p < 0.001$) and higher plasma p-tau217 levels ($r = 0.420$, $p < 0.001$). Regression models revealed that a linear regression model best fit the association between age and BF, hippocampal volume, and a quadratic model best fit plasma p-tau217 in the mutation carriers (Figure S2 in supporting information). Among CU carriers, older age was significantly associated with reduced BF volume ($r = -0.408$, $p = 0.002$), but no significant associations were observed with hippocampal volumes or p-tau217 levels. Among CI carriers, age was associated only with reduced hippocampal volumes ($r = -0.689$, $p = 0.002$). In non-carriers, age was negatively correlated with BF volume ($r = -0.287$, $p = 0.012$) and with plasma p-tau217 levels ($r = -0.267$, $p = 0.02$; Figure S3 in supporting information and Table 2).

The hierarchical Bayesian MCMC with restricted cubic spline modeling estimated a divergence point at the age of 37.8 years between the mutation carriers and non-carriers (Figure 2B), the point at which the 99% credible intervals between groups no longer overlapped. A comparable divergence pattern was observed for the hippocampus, also at 37.8 years (Figure S4 in supporting information). Notably, both divergence points precede the median age of MCI onset in the cohort by ≈ 6 years.

3.4 | Associations between brain volumes with p-tau 217

In the full sample, both BF and hippocampal volumes showed significant negative correlations with plasma p-tau217 levels (BF: $r = -0.389$,

TABLE 2 Partial Pearson correlations between age and biomarkers.

	CU carriers (*N* = 60)	Non-carriers (*N* = 78)	CI carriers (*N* = 20)	Full sample (*N* = 158)
Basal forebrain				
R	**−0.408**	**−0.287**	−0.407	**−0.523**
P	**0.002**	**0.012**	0.104	**<0.001**
Hippocampus				
R	0.185	−0.136	**−0.689**	**−0.447**
P	0.167	0.246	**0.002**	**<0.001**
p-tau217				
R	0.247	**−0.267**	−0.237	**0.420**
P	0.063	**0.02**	0.358	**<0.001**

Note: Values shown in bold indicate statistically significant results ($p < 0.05$).
Abbreviations: CI, cognitively impaired; CU, cognitively unimpaired; P, *p* value; p-tau, phosphorylated tau; R, partial correlation coefficient.

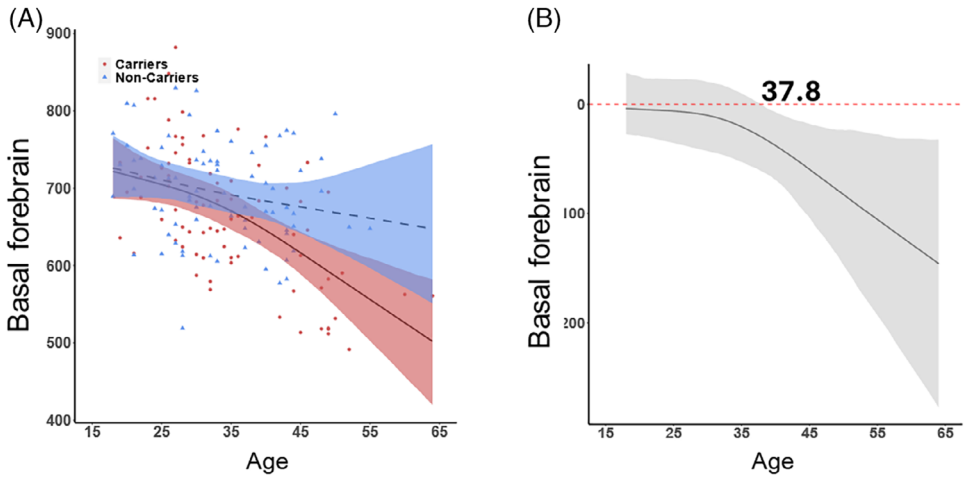

FIGURE 2 Age-related changes in basal forebrain volume among *PSEN1* E280A mutation carriers and non-carriers. A, Differences in basal forebrain volumes between mutation carriers (red circles, solid regression line) and non-carriers (blue triangles, dashed regression line) as a function of age. B, The red dashed line marks the zero-derivative threshold, with the estimated divergence age at 37.8 years. The shaded areas represent the 99% credible intervals around the model estimates.

$p < 0.001$; hippocampus: $r = -0.405$, $p < 0.001$). However, when examined within subgroups, no significant associations emerged (BF: CU: $r = -0.057$, $p = 0.676$; CI: $r = -0.400$, $p = 0.125$; non-carriers: $r = 0.123$, $p = 0.294$; hippocampus: CU: $r = -0.106$, $p = 0.434$; CI: $r = -0.341$, $p = 0.195$; non-carriers: $r = 0.207$, $p = 0.077$; Figure S5 in supporting information).

3.5 | Associations between brain volumes with cognitive performance

In the full sample, BF volume was positively associated with several cognitive measures, including MMSE ($r = 0.471$, $p < 0.001$), WLL delayed recall ($r = 0.361$, $p < 0.001$), WLL total correct ($r = 0.410$, $p < 0.001$), WAIS-IV digit symbol ($r = 0.267$, $p = 0.001$), and WAIS-IV digit backward ($r = 0.171$, $p = 0.035$; Figure S6 in supporting information). Among CI carriers, BF volume showed positive correlations with MMSE ($r = 0.651$, $p = 0.006$) and digit span backward ($r = 0.551$, $p = 0.034$). No other significant associations between BF volume and cognitive measures were observed in CU carriers or non-carriers (Table 3). In the full sample, hippocampal volume was positively associated with multiple cognitive measures, including MMSE ($r = 0.518$, $p < 0.001$), WLL delayed recall ($r = 0.405$, $p < 0.001$), WLL total correct ($r = 0.458$, $p < 0.001$), WAIS-IV digit symbol ($r = 0.355$, $p < 0.001$), digit span forward ($r = 0.272$, $p < 0.001$), and digit span backward ($r = 0.297$, $p < 0.001$; Figure S7 in supporting information). Among CI carriers, hippocampal volume showed strong positive correlations with MMSE ($r = 0.712$, $p = 0.002$) and digit span forward ($r = 0.665$, $p = 0.005$). No significant associations were observed in CU carriers or non-carriers (Table S2 in supporting information).

TABLE 3 Partial Pearson correlations between basal forebrain volumes and cognition performance.

	CU carriers (*N* = 60)	Non-carriers (*N* = 78)	CI carriers (*N* = 20)	Full sample (*N* = 158)
MMSE				
R	0.045	0.071	**0.651**	**0.471**
P	0.741	0.550	**0.006**	**<0.001**
Word list learning recall				
R	0.023	−0.010	0.336	**0.361**
P	0.865	0.934	0.202	**<0.001**
Word list learning total				
R	0.013	0.152	0.566	**0.410**
P	0.922	0.197	0.022	**<0.001**
Digit symbol				
R	0.161	0.118	0.526	**0.267**
P	0.235	0.318	0.146	**0.001**
Digit span forward				
R	−0.244	0.031	0.421	0.089
P	0.069	0.795	0.104	0.275
Digit span back				
R	−0.056	−0.004	**0.551**	**0.171**
P	0.681	0.975	**0.034**	**0.035**
GDS				
R	0.068	−0.116	0.182	−0.070
P	0.614	0.325	0.499	0.388

Note: Values shown in bold indicate statistically significant results ($p < 0.05$).
Abbreviations: CI, cognitively impaired; CU, cognitively unimpaired; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; P, *p* value; R, partial correlation coefficient.

4 | DISCUSSION

Previous volumetric MRI studies have consistently identified BF atrophy as a significant factor in cognitive decline among individuals with MCI and sporadic AD [20,58] and in Down syndrome on the continuum of the AD pathology[59]. However, its role in ADAD remains underexplored. Investigating BF alterations in ADAD mutations may provide valuable insights for the identification of early biomarkers and the development of timely intervention strategies, particularly in the context of acetylcholinesterase-based therapies[60–62].

Leveraging the world's largest ADAD kindred with the *PSEN1* E280A mutation, our study examined age-related changes in BF volume and their associations with plasma p-tau217 and cognitive decline. At the cross-sectional level, we found no significant difference in baseline BF volume between CU carriers and non-carriers, in line with previous findings[21]. However, our age-related analyses revealed a notable negative correlation between BF volume and age in CU carriers but not observed for hippocampal volume or plasma p-tau217 levels. Although BF volume did not show a statistically significant association with age among CI carriers, the effect size was moderate ($r = -0.41$, $p = 0.104$), comparable to that observed in CU carriers and the full sample. These results suggest that, even in the absence of clinical symptoms, mutation carriers experience subtle structural changes within the BF, preceding overt clinical manifestations. Specifically, Bayesian analysis identified a divergence in BF volumes between carriers and non-carriers emerging at ≈ 37.8 years, ≈ 6 years before the expected onset of MCI in this cohort. Although, the hippocampus showed a similar divergence in estimated age, its changes in carriers remained relatively flat during early adulthood, with a marked decline only beginning in the late 30s, supporting the view that hippocampal degeneration emerges closer to clinical symptoms onset [63,64]. These results suggest that the earlier and more gradual decline in BF volume suggests it may serve as a more sensitive early marker of disease progression than hippocampal changes.

Plasma p-tau217 levels were significantly higher in both CU and CI carriers compared to non-carriers, supporting its potential as an early biomarker of AD pathology.[42] Interestingly, across the entire group, BF volume was negatively associated with p-tau217 levels, potentially reflecting the impact of underlying amyloid and tau accumulation in the BF reduced volume as part of the neurodegenerative process [65]. However, no significant associations were found between p-tau217 and BF volume within subgroups, which may, in part, be due to a limited statistical power. In CI carriers, the effect size was moderate (r ≈ −0.40), comparable to the significant association in the full sample,

suggesting that the absence of statistical significance may be due to limited power in this smaller group. In contrast, effect sizes for CU carriers and non-carriers were small ($r < 0.20$), indicating weak associations. These findings suggest that the relationship between p-tau217 and BF volume may vary across disease stages, emerging more clearly at symptomatic stages, whereas in earlier stages BF volume may not yet be strongly linked to plasma p-tau217 levels. Hippocampal volume showed a comparable negative correlation with plasma p-tau217. The effect size was moderate in the full sample ($r \approx -0.40$) and in CI carriers ($r = -0.34$), and small in CU carriers and non-carriers ($r < 0.25$). These parallel findings suggest that both regions exhibit stronger associations with plasma p-tau217 during symptomatic stages, whereas such relationships are weak or absent in preclinical phases.

Importantly, our findings also demonstrated cognitive implications of BF integrity, particularly in CI carriers. Across the full sample, smaller BF volume correlated with poorer global cognition, episodic memory, working memory, and processing speed, with moderate effect sizes (MMSE $r = 0.47$; WLL delayed recall $r = 0.36$; digit symbol $r = 0.27$; all $p < 0.001$). In CI carriers, BF volume showed significant positive correlations with MMSE and digit span backward, suggesting that BF atrophy may be particularly related to deficits in global cognition and working memory in this group. Moreover, although associations with WLL recall ($r = 0.336$), WLL total ($r = 0.566$), digit symbol ($r = 0.526$), and digit span forward ($r = 0.421$) were not statistically significant in CI carriers, their moderate-to-strong effect sizes indicate a meaningful relationship between BF structural integrity and cognitive performance, consistent with more pronounced cognitive decline in CI carriers. The observed cognitive associations align with the established role of BF cholinergic projections in executive function[66,67]. These findings are also consistent with a prior study showing that BF volume is associated with cognition in elderly subjects [68]. By comparison, hippocampal volume exhibited similar but generally stronger associations with cognitive measures in the full sample (e.g., MMSE $r = 0.52$; WLL delayed recall $r = 0.41$; digit symbol $r = 0.36$; all $p < 0.001$) and particularly robust correlations in CI carriers. However, in CU carriers and non-carriers, both BF and hippocampal volumes showed small or negligible correlations ($r < 0.20$), indicating that the impact of structural degeneration on cognition may emerge more prominently once clinical symptoms develop.

This study examined associations between BF volume, age, plasma p-tau217 levels, and cognitive performance to better understand early BF changes and their cognitive implications in ADAD. Certain limitations warrant consideration. The cross-sectional design restricts inferences about individual trajectories over time, and the relatively small sample size, especially within the CI carrier group, may have limited our ability to detect more subtle effects. Longitudinal studies are needed to determine whether early BF atrophy predicts clinical progression, to validate BF volume as a potential early intervention target, and to further elucidate the interplay among structural degeneration, plasma biomarkers, and cognitive decline.

Overall, our results show that BF volume does not differ in early, preclinical stages of ADAD but begins to decline years in advance of symptom onset, reaching atrophic levels by the time clinical impairment is observed. This early structural alteration underscores the BF's potential as an early biomarker of AD-related neurodegeneration. Assessing BF integrity may provide a critical opportunity for early detection and intervention, potentially delaying or mitigating cognitive decline before it becomes clinically evident.

ACKNOWLEDGMENTS

We thank the Colombian families with ADAD for contributing their time to this study and their continued commitment to this research. We also thank Dr. Alice Grazia for providing the scripts used in the extraction of basal forebrain volumes. The authors also wish to acknowledge Dr. Francisco Lopera for his lifelong commitment and dedication to studying Alzheimer's disease and other dementias, as well as his invaluable contributions to the NGF-Rita project and the Colombian ADAD kindred. Y.T.Q. received funding from the NIA (no. R01AG077627), and the National Institute of Neurological Disorders and Stroke (NINDS; grant RM1NS132996). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

Y.T.Q. has served as consultant for Biogen. All other co-authors have nothing to disclose. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Written informed consent was obtained prior to participation in the study, with procedures approved by the local ethics committees of the University of Antioquia and the Mass General Brigham, in accordance with international IRB regulations.

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SUPPORTING INFORMATION

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

How to cite this article: He B, Ospina Lopera P, Espinosa A, et al. Association between basal forebrain volume and age in the presenilin-1 E280A autosomal dominant Alzheimer's disease kindred. *Alzheimer's Dement*. 2026;22:e71052. https://doi.org/10.1002/alz.71052