JAMA Neurology | Original Investigation

Amyloid-Beta Pathology and Cognitive Performance in Centenarians

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IMPORTANCE Older individuals without dementia often have amyloid-beta (Aβ) Thal phases similar to patients with Alzheimer disease (AD), suggesting that Aβ pathology may be a benign consequence of aging.

OBJECTIVE To explore whether Aβ pathology in centenarians is associated with cognitive performance.

DESIGN, SETTING, AND PARTICIPANTS This longitudinal cohort study used cross-sectional data on antemortem cognitive performance and postmortem neuropathology of participants in the Dutch 100-plus Study. Cognitive performance was measured a median of 10 (IQR, 3-13) months before postmortem brain donation. From January 2013 to July 2022, 1187 centenarians who self-reported being cognitively healthy, confirmed by proxy, were approached: 406 were included and 95 donated their brain. Centenarians were compared with patients with clinicopathologically confirmed AD from the Netherlands Brain Bank. Data were analyzed from June 2022 to October 2024.

MAIN OUTCOMES AND MEASURES Aβ pathology was assessed with the Thal phase for Aβ progression and by determining quantitative Aβ loads (percentage positive area) in the frontal, parietal, temporal, and occipital neocortices, 3 parahippocampal, and 5 hippocampal subregions. Aβ pathology was associated with performance on 13 neuropsychological tests assessing memory, fluency, attention/processing speed, and executive functioning, as well as 4 measures of global cognition.

RESULTS This study evaluated Aβ pathology in 95 centenarians (median age at brain donation, 103.5 [IQR, 102.3-104.7] years; 71 female [75%] and 24 male [25%]) and 38 patients with AD (median age, 84 [IQR, 78-90] years; 18 female [47%] and 20 male [53%]). Global cognition parameters were available for all 95 centenarians and complete cognitive assessment for 72 centenarians (76%). A fraction of the centenarians had no Aβ load (9 of 95 [9%]), most had low Aβ load (53 of 95 [56%]) and, despite high Thal phases, about one-third (33 of 95 [35%]) had high Aβ load comparable with patients with AD. Centenarians with no or low Aβ load had significantly higher cognitive performance than centenarians with high Aβ loads. Higher Aβ loads across all 4 neocortical regions, cornu ammonis 3, cornu ammonis 1/subiculum, and the entorhinal cortex specifically affected executive functioning. Interestingly, 5 resilient centenarians maintained high cognitive performance despite having high Aβ loads; they had significantly less tau pathology compared with centenarians with high Aβ loads and low cognitive performance.

CONCLUSIONS AND RELEVANCE These results indicate that Aβ pathology is not a benign consequence of aging. Even in the oldest individuals, Aβ and tau pathology interaction was consistent with the amyloid cascade hypothesis.

Supplemental content

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JAMA Neurol. 2025;82(8):837-847. doi:10.1001/jamaneurol.2025.1734
Published online June 30, 2025.

Alzheimer disease (AD) is characterized by cognitive decline, including memory and learning impairment, and changes in behavior and personality.[1] Neuropathological hallmarks of AD consist of amyloid-β (Aβ) plaques and hyperphosphorylated tau proteins accumulated in neurofibrillary tangles (NFTs).[2] The amyloid-cascade hypothesis postulates Aβ pathology as an initiator of downstream NFT pathology, neuronal dysfunction and death, and eventually dementia.[3] Aβ can accumulate in plaques, including diffuse and cored plaques, in vessel walls as cerebral amyloid angiopathy (CAA), and in subpial deposition.[4,5] The widely accepted standard for assessing Aβ pathology in the postmortem brain is the Thal phase, which evaluates the progressive spatiotemporal deposition of Aβ into 5 phases: neocortex (phase 1), allocortex (phase 2), diencephalon and striatum (phase 3), brainstem (phase 4), and cerebellum (phase 5).[6]

Typically, patients with AD have a Thal phase of 3 or higher, while individuals without dementia younger than 70 years exhibit minimal or no Aβ pathology (Thal phase lower than 3).[6-8] However, with increasing age, the average Thal phase in individuals without dementia increases and reaches Thal phases observed in patients with AD, converging at around 100 years.[7,8] These observations suggest that Aβ pathology may not inevitably lead to neurodegeneration and dementia, challenging the amyloid-cascade hypothesis.[9,10] However, whereas the Thal phase reflects the spatiotemporal progression of Aβ accumulation across brain regions, it does not consider the actual abundance of Aβ pathology (ie, Aβ load) in affected regions.

In this study, we quantified Aβ load in 4 neocortical areas, 3 parahippocampal regions, and 5 hippocampal subregions in the medial temporal lobe (MTL) in 95 centenarians from the longitudinal 100-plus Study. We examined whether Aβ distribution patterns (Thal phase) and abundance in centenarians differ from 38 patients with AD, and whether these measures correlate with cognitive performance close to death. The short interval between cognitive testing and brain donation, as available in the 100-plus Study, provides a unique opportunity to assess whether Aβ pathology in older adults should be considered a benign consequence of aging.

Key Points

Question Older individuals without dementia often have Thal phases for amyloid-beta (Aβ) distribution similar to those observed in patients with Alzheimer disease; raising the question whether Aβ pathology in older individuals without dementia is a benign consequence of aging.

Findings In this observational study of centenarian brains, higher Aβ loads were associated with lower cognitive performance measured approximately 10 months prior to brain donation, which particularly affected executive functioning.

Meaning Accumulation of Aβ should not be regarded as a benign consequence of aging; these findings support the amyloid-cascade hypothesis and suggest that therapies aimed at reducing Aβ may be of relevance for the older population.

Methods

The 100-plus Study

The 100-plus Study includes self-reported cognitively healthy Dutch centenarians (median Mini-Mental State Examination [MMSE] score at baseline, 26/30; IQR, 23-28).[11] At baseline and annual follow-up house visits, we: (1) collect lifetime history, including educational history; (2) assess cognitive performance; (3) collect blood samples, allowing apolipoprotein E (APOE) genotyping (detailed in the eMethods in Supplement 1); and (4) discuss optional postmortem brain donation. The study was approved by the VUmc Medical Ethics Committee (registration 2016.440) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. All participants provided written informed consent.

Cognitive Assessment of Centenarians

To minimize time between assessment of cognitive performance[11] and neuropathology, we selected cognitive performance from the last study visit (median time interval, 10 [IQR, 5-13] months). Some test scores were missing due to sensory or motor difficulties, changes in the test battery over time, or fatigue, leading to missing scores for the last tests in the battery. Missing scores were imputed, as previously described and detailed in the eMethods in Supplement 1.[12,13] Aβ pathology was associated with performance on 13 tests with scores available for more than 50% of centenarians prior to imputation: Visual Association Test (VAT)[14]; Rivermead Behavioral Memory Test immediate and delayed recall[15]; Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-word list immediate and delayed recall[16]; D-A-T Letter Fluency and Animal Fluency[17]; Digit Span backward (DSB)[18] and Digit Span forward[18]; Key Search[19]; Trail Making Test A and B[20]; and Clock Drawing (CD)[21] (eTable 1 in Supplement 1). We included 72 centenarians who had more than 50% of tests and at least 1 test per domain available prior to imputation. A composite global cognition score was calculated by averaging normalized *z* scores on the 13 individual tests. Additionally, global cognition was measured for all 95 centenarians using the MMSE,[22] Researcher Impression of Dementia,[11] and ability to complete the test battery (eMethods in Supplement 1).[23]

Patients With AD

We compared Aβ pathology between 95 centenarians and 38 patients with AD obtained from the Netherlands Brain Bank. Patients with AD were selected based on: (1) clinical dementia diagnosis; (2) intermediate or high AD neuropathologic change[2]; (3) APOE genotype available; and (4) formalin-fixed paraffin-embedded tissue available for Aβ load quantification in the neocortical regions or the MTL. Because no AD case had all 4 neocortical regions and the MTL available, 2 independent AD cohorts were composed: 1 for the neocortex (n = 27) and 1 for the MTL (n = 11) (eFigure 1A in Supplement 1; **Table**).

Postmortem Brain Tissue and Neuropathological Evaluation

Brain donation, tissue processing, and neuropathological evaluation are detailed in the eMethods in Supplement 1 and

Table. Characteristics of the Centenarian and 2 Alzheimer Disease (AD) Cohorts

Characteristic	Centenarians	AD neocortex	AD MTL
No.	95	27	11
Sex, No. (%)			
Female	71 (75)	14 (52)	4 (36)
Male	24 (25)	13 (48)	7 (64)
Age at death, y, median (IQR) [minimum-maximum]	103.5 (102.3-104.7) [100.4-111.8]	86.0 (79.5-90.5) [77.0-96.0]	84.0 (71.5-86.0) [53-100]
NIA-AA amyloid score, median (IQR) [minimum-maximum]	2 (1-3) [0-3]	3 (3-3) [2-3]	3 (3-3) [2-3]
Thal phase	3 (1-4) [0-5]	5 (5-5) [3-5]	4 (3-5) [3-5][a]
Braak NFT stage, median (IQR) [minimum-maximum]	III (III-IV) [I-V]	V (V-VI) [IV-VI]	V (IV-VI) [IV-VI]
CERAD-NP score, median (IQR) [minimum-maximum]	1 (0-2) [0-3]	3 (2-3) [1-3]	3 (2-3) [1-3]
Thal CAA stage, median (IQR) [minimum-maximum]	1 (1-1) [0-3]	1 (1-2) [1-2]	1 (1-2) [0-2]
Thal CAA type, No. (%)			
NA	22 (23)	0	2 (18)
1	46 (48)	15 (56)	6 (55)
2	27 (28)	12 (44)	3 (27)
APOE ε, No. (%)			
2/2	2 (2)	0	0
2/3	18 (19)	1 (4)	0
3/3	67 (71)	10 (37)	5 (45)
2/4	2 (2)	0	1 (9)
3/4	6 (6)	12 (44)	3 (27)
4/4	0	4 (15)	2 (18)

Abbreviations: APOE, apolipoprotein E; CAA, cerebral amyloid angiopathy; CERAD-NP, Consortium to Establish a Registry for Alzheimer's Disease neuritic plaques score; MTL, medial temporal lobe; NA, not applicable; NIA-AA, National Institute on Aging and Alzheimer Association; NFT, neurofibrillary tangle.

[a] The Thal phase was unknown for 4 patients with AD in the MTL cohort, but could be extrapolated to be 4 or more based on their NIA-AA amyloid score of 3. These cases were excluded from the median and IQR calculations, which may affect the cohort's descriptive statistics.

included Thal phase (or the National Institute on Aging–Alzheimer's Association amyloid score),[2,6] Braak NFT stage,[24] CERAD neuritic plaques (NP) score,[25] Thal CAA stage and type,[5,26] TAR DNA-binding protein (TDP)-43 stage,[27] and hippocampal sclerosis (HS) (eMethods in Supplement 1).

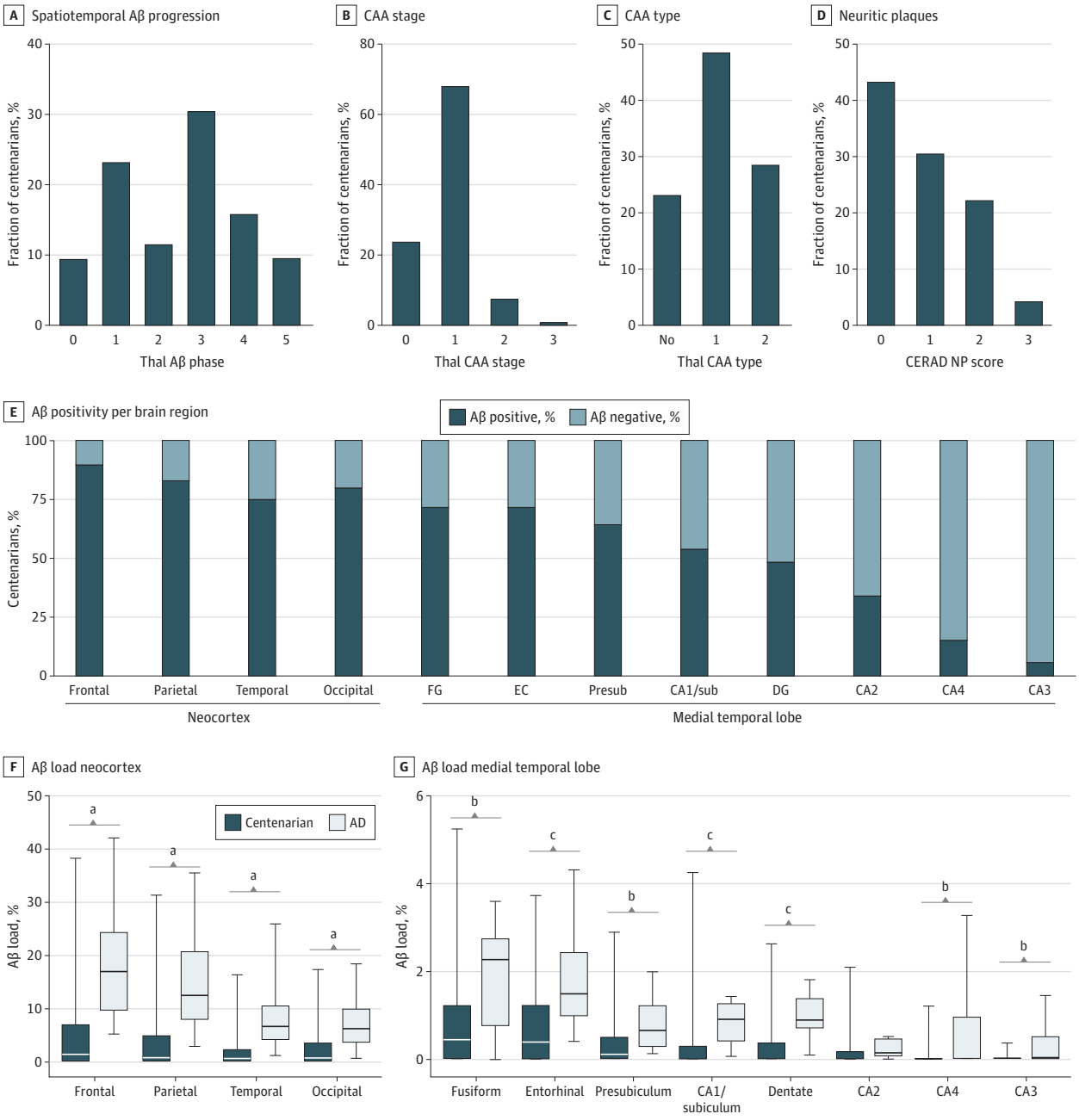
Quantitative Aβ Load

Formalin-fixed paraffin-embedded sections of middle frontal gyrus, inferior parietal lobe, temporal pole, occipital pole (all 8 µm), and the MTL at the level of the lateral geniculate nucleus (6 µm) were stained for Aβ (eMethods and eFigure 1A in Supplement 1), scanned at 20 × magnification (Olympus VS200 slide scanner and software version 3.3), and analyzed in QuPath version 0.4.2.[28] The MTL was segmented in 5 hippocampal and 3 parahippocampal subregions: dentate gyrus, cornu ammonis (CA) 4, CA3, CA2, CA1/subiculum, presubiculum, entorhinal cortex (EC), and fusiform gyrus cortex (eFigure 1B, eFigure 2, and eMethods in Supplement 1). In the neocortical sections, all gray matter was annotated as a single region of interest (eFigure 1C in Supplement 1). A pixel classifier was trained to accurately detect different types of Aβ deposition with varying intensities (eFigures 1D through H and eMethods in Supplement 1). Aβ load was calculated as the percentage of region of interest positive for Aβ immunoreactivity (eFigure 3 in Supplement 1) and further categorized into Aβ negative (0%) or Aβ positive (more than 0%). Moreover, the centenarian cohort was divided into no, low, or high load using the minimum observed Aβ load in the frontal cortex of the AD cohort, the most frequently and severely affected region.

Statistical Analysis

Analyses were performed in Rstudio version 4.3.2 (Posit PBC) and GraphPad Prism version 10.2.0 (GraphPad Software). Aβ loads in centenarians and patients with AD were compared using Kruskal-Wallis tests with Dunn multiple comparisons version 1.3.6. χ^2 Test compared APOE genotypes (grouped as protective [ε2/2 and ε2/3], neutral [ε3/3], or risk increasing [ε2/4 and ε3/4]) across centenarians with no, low, or high Aβ load, and across centenarians with no CAA, CAA type 1, or CAA type 2. Associations between Aβ pathology and cognitive scores were examined using robust linear regression models (MASS version 7.3-60) to reduce outlier impact and address nonnormal residuals, with estimated *P* values extracted from *t* values (sfsmisc v1.1.19). Models were adjusted for sex, age at death, and education (years). All variables were normalized to *z* scores to ensure comparability of regression coefficients across different associations. Additional models included copathologies (Braak NFT stage, TDP-43 stage, and HS) as covariates, since these are known to associate with cognitive performance in centenarians.[12] Lastly, resilient centenarians were defined as those with high Aβ load (described above) and cognition scores in the top 25% of all centenarians in this study (eTable 1 in Supplement 1). All *P* values were corrected for multiple testing using the Benjamini-Hochberg method, significance was set at $P < .05$.

Figure 1. Amyloid-Beta (Aβ) Pathology in Centenarians



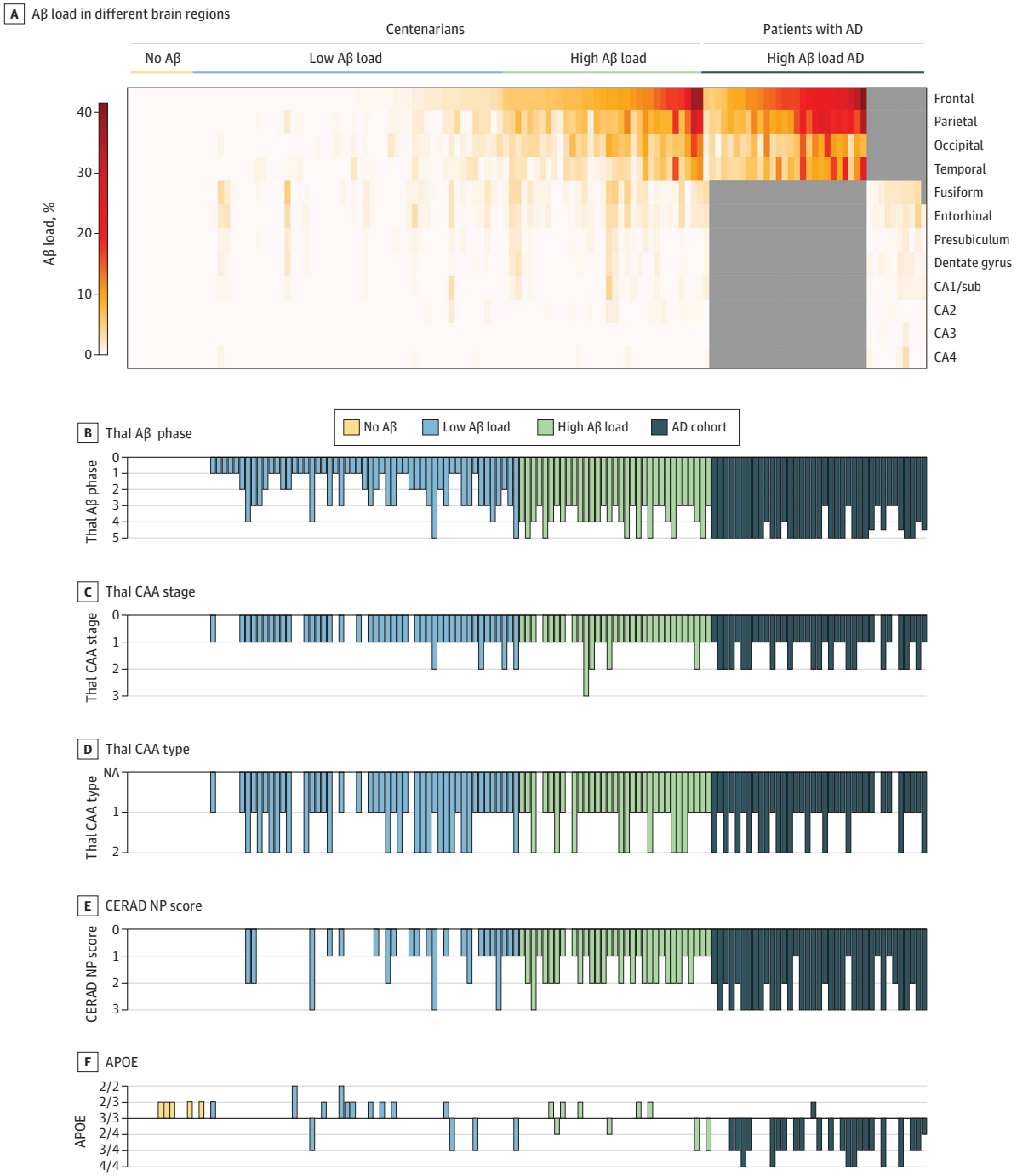
Thal amyloid-β (Aβ) phase (A), Thal CAA stage (B), Thal CAA-type (C), and CERAD-neuritic plaque (NP) score in 95 centenarians (D). Proportion of the centenarian cohort (n = 95) exhibiting Aβ positivity (Aβ load > 0%) vs Aβ negativity (Aβ load = 0%) in a given brain region (E). Quantitative Aβ load across different brain regions. Boxplots illustrate median, IQR, and the minimum and maximum observed Aβ load values. Kruskal-Wallis tests with Dunn multiple comparisons test were performed to test differences between centenarians and patients with Alzheimer disease (AD). Images representative for the first quartile, median, and third quartile of Aβ load in the frontal cortex in both the centenarian and AD cohorts are given in eFigure 3 in Supplement 1. Note that different AD cohorts were used for panel F (n = 27) and panel G (n = 11) (see the **Table**). CA1/sub indicates cornu ammonis 1/subiculum; CA2, cornu ammonis 2; CA3, cornu ammonis 3; CA4, cornu ammonis 4; DG, dentate gyrus; EC, entorhinal cortex; FG, fusiform gyrus; Presub, presubiculum.

[a] $P \leq .001$.

[b] $P \leq .05$.

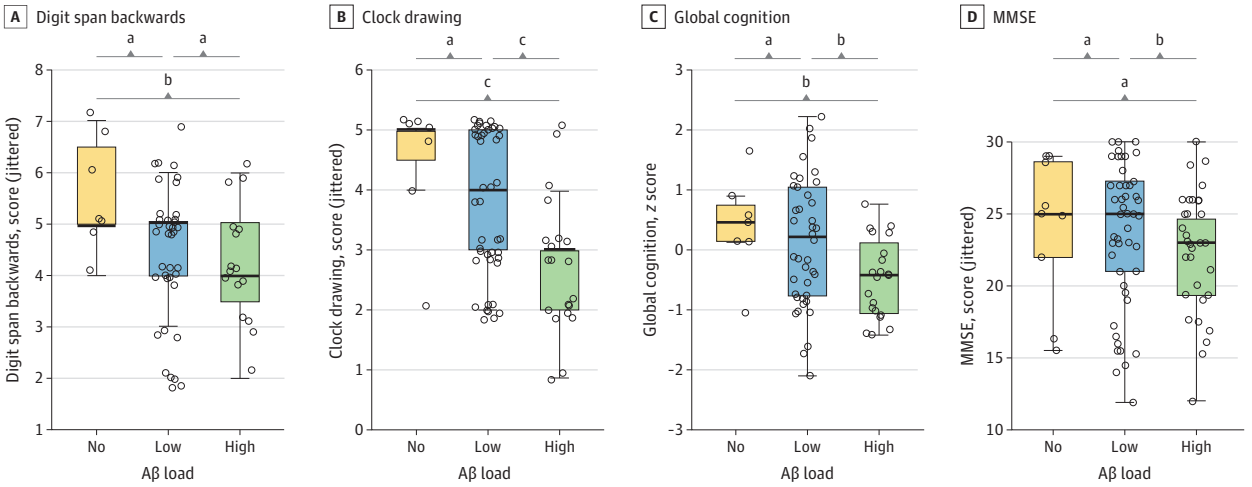
[c] $P \leq .01$.

Figure 2. Majority of the Centenarians Resistant to Alzheimer Disease (AD)–Associated Levels of Amyloid-Beta (Aβ) Load



Each column represents 1 brain donor and their Aβ load in different brain regions (A), Thal Aβ phase (B), Thal cerebral amyloid angiopathy (CAA) stage (C), Thal CAA type (D), Consortium to Establish a Registry for Alzheimer's Disease neuritic plaques score (CERAD NP) score (E), and apolipoprotein E (APOE) genotype (F). Donors were sorted per cohort (centenarians and AD) and within cohorts on Aβ load in the frontal cortex, or the fusiform gyrus for the AD cases with missing Aβ load in the frontal cortex. The minimum Aβ load in the frontal cortex of the AD cohort was set as a threshold, dividing the centenarians into 9 (9%) centenarians with no Aβ, 53 (56%) centenarians with low Aβ load, and 33 (35%) centenarians with high Aβ load. The exact Thal phase was unknown for 4 patients with AD. Based on the National Institute on Aging amyloid stage being 3, the Thal phase could be extrapolated to be 4 or more. In this plot, their Thal phase was plotted as 4.5. Gray cells indicate missing Aβ load information. CAA indicates cerebral amyloid angiopathy; CA1/sub, cornu ammonis 1/subiculum; CA2, cornu ammonis 2; CA3, cornu ammonis 3; CA4, cornu ammonis 4; CERAD-NP, Consortium to Establish a Registry for Alzheimer's Disease neuritic plaques score; NA, not applicable.

Figure 3. Lower Cognitive Performance in Centenarians With High Amyloid-Beta (Aβ) Load



Comparison of cognitive performance between 7 centenarians with no Aβ pathology, 45 centenarians with low Aβ load, and 20 centenarians with high Aβ load in the frontal cortex (Figure 2A). Performance on the digit span backward, clock drawing test, global composite cognition, and Mini-Mental State Examination (MMSE) were compared between groups with Kruskal-Wallis test (all $P < .05$). For the MMSE, all 95 centenarians were included: 9 had no Aβ load, 53 had low Aβ load, and 33 had high Aβ load.

[a]Not significant.

[b]$P \leq .05$, after Bonferroni correction.

[c]$P \leq .01$, after Bonferroni correction.

Results

Aβ Pathology in Centenarians

The 95 centenarians (Table) spanned all Thal phases (median, 3; IQR, 1-4). Remarkably, only 9 centenarians (9%) had Thal phase 0, while most had at least some Aβ pathology (91%) (**Figure 1**A). CAA was present in 73 centenarians (77%), mainly at stage 1 (68%; median, 1; IQR, 1-1; Figure 1B), of which 46 centenarians had CAA type 1 (48%) and 27 centenarians had CAA type 2 (28%) (Figure 1C). Moreover, 54 centenarians had NPs (57%) (median CERAD-NP score, 1, IQR, 0-2; Figure 1D).

In Aβ-positive centenarians (ie, Thal phase equal to or more than 1), a similar spatiotemporal distribution of cortical Aβ load was observed as in patients with AD: Aβ load was the highest and most frequent in the frontal cortex, followed by the parietal, temporal, and occipital cortices (Figure 1E and F). In the MTL, Aβ loads were on average 10-fold lower compared with the neocortex (Figure 1F and G). Specifically, the fusiform gyrus and EC (affected in Thal phase 2) were most severely and frequently affected, followed by CA1/subiculum (phase 2), presubiculum (phase 3), dentate gyrus (phase 3), and CA2 (no defined phase), while CA4 (phase 4) and CA3 (no defined phase) were rarely affected. All Aβ measures, except CAA type 2, strongly intercorrelated (eFigure 4 in Supplement 1). Compared with patients with AD, centenarians had lower Aβ loads across all neocortical and MTL subregions, except in CA2.

Most Centenarians Had Low Aβ Load

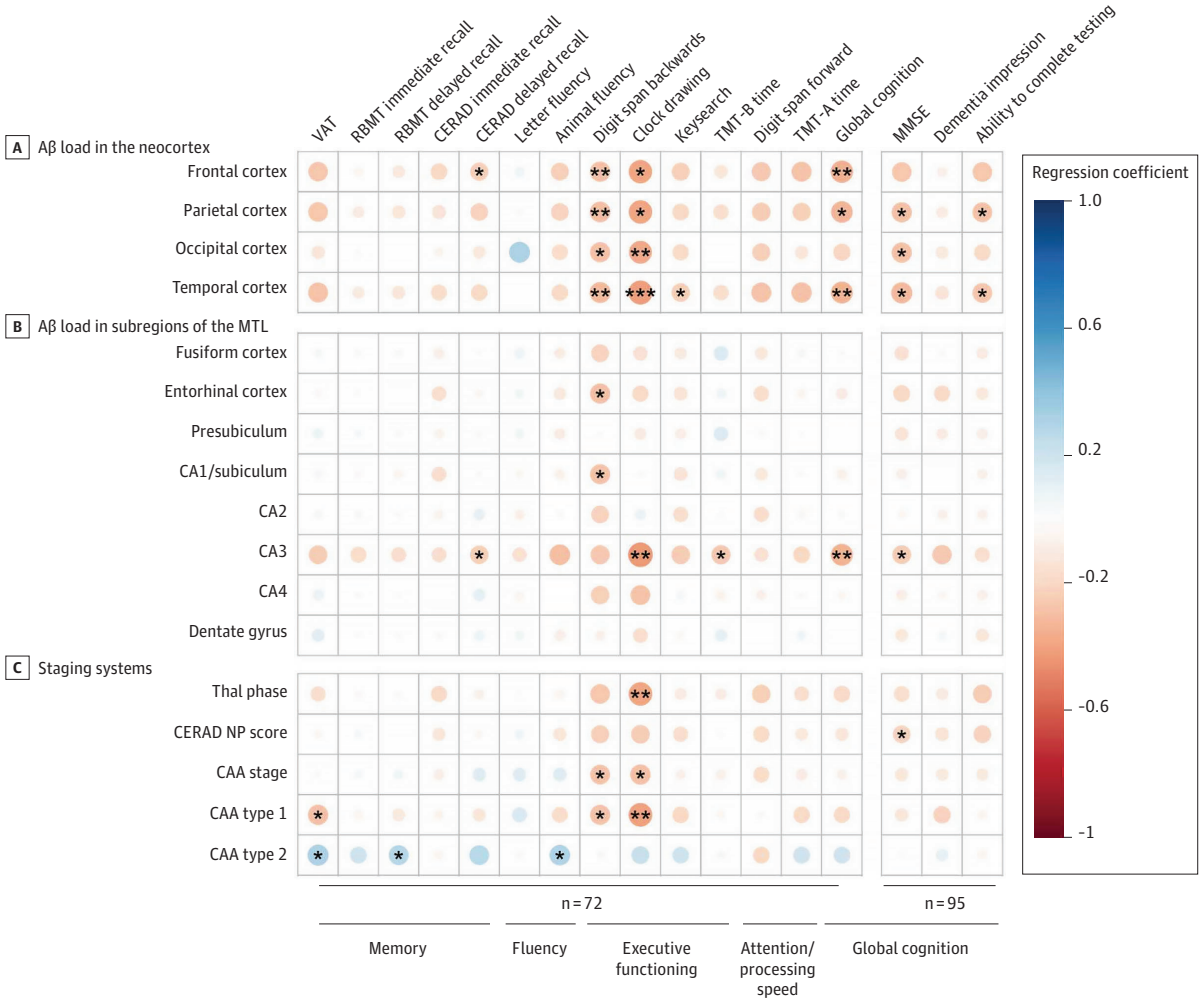
Using the minimum Aβ load in the frontal cortex of the AD cohort (5.17%) as a threshold, centenarians were divided into those with (1) no Aβ load (9 of 95 [9%]), (2) low Aβ load (53 of 95 [56%]), and (3) high Aβ load (33 of 95 [35%]) (**Figure 2**A). By definition, centenarians with no Aβ load had Thal phase 0, Thal CAA stage 0, and a CERAD-NP score of 0 (Figure 2B-E). Of the 53 centenarians with low Aβ load, 20 had a Thal phase of 3 or more (38%), 42 had a CAA stage of 1 or more (79%), and 22 had a CERAD-NP score of 1 or more (42%). Nearly all centenarians with high Aβ loads had a Thal phase of 3 or more (100%), a CAA stage of 1 or more (94%), and a CERAD-NP score of 1 7 or more (97%).

APOE genotype (Table) was similarly distributed between low and high Aβ-load centenarians, but centenarians with no Aβ load were enriched for protective APOE-ε2 genotypes (Figure 2F; eTable 2 in Supplement 1). Moreover, centenarians with a protective APOE-ε2 genotype (n = 20) were either not affected by CAA (n = 8; 40%) or affected with predominantly CAA type 1 (n = 10; 50%), while all ε4-positive centenarians (n = 8) were affected by CAA type 1 (n = 5; 63%) or CAA type 2 (n = 3; 38%) (eTable 3 in Supplement 1).

Aβ Pathology Association With Lower Cognitive Performance in Centenarians

Cognitive performance was available for 72 centenarians (eTable 1 in Supplement 1). Centenarians with no (n = 7) or low (n = 45) Aβ load had higher executive functioning (DSB and CD) and global cognition (MMSE and composite global cognition) compared with centenarians with high Aβ load in the frontal cortex (n = 20; **Figure 3**). The median level of cognitive performance was highest in the 7 centenarians with no Aβ pathology. Similar to the frontal cortex, higher Aβ load across the other neocortical regions associated with lower executive functioning (DSB, CD, and Key Search tests) and global cognition (composite global cognition, MMSE, and ability to complete the test battery (**Figure 4**A; eFigure 5A and B in Supplement 1 and eTable 4 in Supplement 2).

Figure 4. Amyloid-Beta (Aβ) Pathology Association With Cognitive Performance in Centenarians



Robust regression analysis between Aβ pathology. Color and size of the circles indicate the direction and strength of the regression coefficient. All variables were standardized (*z* scores) to ensure comparability between the regression coefficients. Models were corrected for covariates of age at death, sex (0 female, 1 male), and years of education. *P* values were corrected for false discovery rates using the Benjamini and Hochberg method. The associations with the 14 tests on the left included 72 centenarians, and the association with the 3 global cognition measurements on the right included the entire cohort of 95 centenarians. Numerical regression coefficients and *P* values can be found in eTable 4 in Supplement 2. CAA indicates cerebral amyloid angiopathy; CA1, cornu ammonis 1; CA2, cornu ammonis 2; CA3, cornu ammonis 3; CA4, cornu ammonis 4; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CERAD-NP, Consortium to Establish a Registry for Alzheimer's Disease neuritic plaques score; MMSE, Mini-Mental State Examination; MTL, medial temporal lobe; RBMT, Rivermead Behavioral Memory Test; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; VAT, Visual Association Test.

*$P \leq .05$.

**$P \leq .01$.

***$P \leq .001$.

This led to the question of whether memory is more sensitive to hippocampal Aβ load, given that executive functioning is specifically sensitive to neocortical Aβ load. However, similar to the neocortex, hippocampal Aβ load also affected executive functioning and global cognition. More specifically, Aβ load in CA1/subiculum and EC was associated with lower DSB scores, while all 5 centenarians whose CA3 was Aβ positive performed poorly on the CD, Trail Making Test B, composite global cognition, and MMSE (Figure 4B; eFigure 5C in Supplement 1). Compared with the other 67 centenarians for whom cognitive performance was available, these 5 centenarians had higher Thal phase (median 5 vs 2), Braak NFT stage (median IV vs III), CERAD-NP score (median 2 vs 1), and TDP-43 stage (median 3 vs 0), and higher prevalence of HS (80% vs 17%), while CAA stage and type did not differ (eFigure 4 and eFigure 6 in Supplement 1).

Traditional staging systems correlated with several of the tests that associated with Aβ load; higher Thal phase was associated with lower CD scores, higher CAA stage was associated with lower CD and DSB scores, and higher CERAD-NP scores were associated with lower MMSE scores (Figure 4C; eFigure 7 in Supplement 1). Centenarians with CAA type 1 (n = 34) had lower memory and executive functioning, as indicated by the VAT, DSB, and CD scores (eFigure 8 in Supplement 1). Intriguingly, having CAA type 2 (n = 17) associated with higher memory and fluency performance on the VAT, Rivermead Behavioral Memory

Test–delayed recall, and Animal Fluency, also when compared with centenarians without CAA (n = 21).

Associations between lower cognitive performance and higher Aβ loads in all neocortical regions, CA1/subiculum, and CA3, as well as higher CAA stages and the presence of CAA type 1, remained after adjusting for copathologies of NFT, TDP-43, and HS (eFigure 9 in Supplement 1), despite collinearity between Aβ pathology and these copathologies (eFigure 4 in Supplement 1). After adjusting for copathologies, the associations between Thal phase and CERAD score with lower cognitive performance were no longer significant.

Resilience to Aβ Pathology Observed in 5 Centenarians

Intriguingly, 5 of the 20 centenarians with high Aβ load scored among the top 25% of all 72 centenarians on the DSB, CD, MMSE, or composite global cognition (Figure 3; eTable 5 in Supplement 1). Compared with the 15 centenarians with high Aβ load and lower cognition, these resilient centenarians had significantly lower Braak NFT (median III vs IV; $P = .05$) and TDP-43 stages (median 0 vs 2; $P = .05$), as well as depletion of CAA type 1 (20% vs 93%) and enrichment of CAA type 2 (60% vs 7%; $P = .01$). The resilient and affected centenarians had comparable Thal phase, Aβ load in the frontal cortex, CERAD-NP score, Thal CAA stage, HS, APOE genotype, age at death, sex, and education. Interestingly, the time between cognitive assessment and brain donation was significantly shorter for resilient centenarians than for affected centenarians (8 months vs 12 months; $P = .05$).

Discussion

In this study, we demonstrate that accumulation of Aβ pathology in the centenarian brain is not a benign consequence of aging. Two-thirds of the centenarians had no or negligible Aβ loads, in some cases despite high Thal phases, and maintained high cognitive performance. Overall, higher Aβ loads, especially in the neocortex, were associated with lower performance on executive functioning and global cognition, also when accounting for copathologies. Only 5 centenarians maintained high levels of cognitive performance, despite having high Aβ loads, but these individuals had lower levels of tau pathology.

Our results suggest that executive functioning may be particularly sensitive to Aβ accumulation. This aligns with previous associations between Aβ accumulation, determined by cerebrospinal fluid or positron emission tomography, and lower executive functioning in younger cohorts without dementia.[29-31] These studies suggested that Aβ-related decline in executive functioning precedes tau-related decline in memory,[30,31] possibly through changes in myelin,[32] loss of synaptic proteins,[33] or alternations in network connectivity.[31] Mouse models demonstrated that Aβ accelerates tau pathology and neuronal death, with Aβ maturation influencing disease progression.[34,35] This mechanism was recently confirmed in patients with AD, in which Aβ was found to promote tau spreading via neuronal hyperconnectivity.[36]

It is intriguing that hippocampal Aβ load, especially in the CA3 subregion, was associated with executive functioning rather than memory, as might be expected given the hippocampus's function.[37] Given the strong correlation between neocortical and hippocampal Aβ load, we cannot exclude that advanced neocortical Aβ accumulation drives the association between hippocampal Aβ load and lower executive functioning. Moreover, levels of NFT, TDP-43, and HS copathologies correlated with Aβ pathology, such that they may have contributed to changes in cognitive performance.[12] Nevertheless, the association between Aβ load and cognitive performance remained after adjusting for copathologies, which may suggest that Aβ independently affects cognition. However, this should be interpreted with caution, given that Aβ has been shown to have a disease-modifying role, for example through accelerating tau pathology.[38-40] This is supported by the 5 resilient centenarians who maintained high levels of cognition despite high Aβ loads; they had lower NFT- and TDP-43 stages. Further studies should determine whether these centenarians were assessed just before the initiation of advanced tau-accumulation, as suggested by the shorter time between cognitive testing and brain donation, or if they are resilient to high Aβ loads through other, potentially genetic, mechanisms that provide resistance against advanced tau pathology.

NPS and CAA, specifically CAA type 1 involving capillaries, also correlated with lower cognitive performance, suggesting that these pathologies may contribute to the overall association between Aβ load and lower cognitive performance. Our observation that noncapillary CAA type 2 was associated with higher cognitive performance, even compared with absence of CAA, contradicts studies linking CAA of any type to cognitive decline at old age.[41,42] Assuming that CAA type 2 itself is not protective, we speculate that it may reflect ongoing Aβ drainage, as suggested by the increase in CAA following antiamyloid immunotherapies.[43,44] In contrast to CAA type 1, which strongly correlated with increased levels of nearly all neuropathological substrates, CAA type 2 did not correlate with neuropathology, suggesting that it may be a benign or even a protective feature of healthy aging. Contradicting previous reports, CAA type 1 was enriched among APOE-ε2 carriers, suggesting a potential differential interaction between APOE genotypes and CAA type in centenarians compared with younger cohorts.[26,45,46] This warrants further investigations, especially given the growing attention to the role of APOE on the adverse effects of antiamyloid immunotherapies.[47]

Limitations

In this study, we used the 6F/3D antibody to visualize Aβ pathology, ensuring consistency with standard protocols of the Netherlands Brain Bank for assessment of Aβ pathology and Thal phase throughout the years. Although the 4G8 antibody is recommended for Thal phase assessment and has higher immunoreactivity for diffuse plaques,[6,48-50] 6F/3D has been shown to yield similar Thal phases as 4G8,[48] and we observe a substantial amount of diffuse plaques (eFigure 1E and eFigure 3 in Supplement 1). Second, in

determining Aβ loads, we did not consider specific Aβ isoforms (eg, Aβ40, Aβ42), plaque maturation (eg, AβN3pE, AβpSer8),[51] or different types of Aβ depositions (eg, CAA, cored plaques, diffuse plaques), which may differentially affect cognitive performance. Therefore, future studies should address this, especially in light of therapeutics that target specific Aβ isoforms, such as donanemab targeting AβN3pE.[52] Third, we acknowledge that collinearity among Aβ loads and the loads of copathologies, rather than staging, may affect the associations between Aβ pathology and cognitive performance. Braak NFT stage and TDP-43 stage strongly correlated with cognition in centenarians,[12] suggesting that determining quantitative loads of copathology in different brain regions might not change the results. Nevertheless, future studies should use mediation analysis to disentangle their independent and synergistic effects on cognitive decline. Lastly, to ensure that our results would not be skewed toward cognitive status of the best-performing centenarians, we used the multiple imputation by chained equations imputation method to account for missing cognitive data for those centenarians who did not finish the test battery. This is widely accepted to account for missing neuropsychological data, particularly in the context of AD research.[53,54]

Conclusions

Overall, our findings indicate that accumulation of Aβ pathology should not be considered a benign consequence of aging, and that keeping Aβ load within limits is a hallmark of maintained cognitive health until extreme ages. Increased levels of Aβ load specifically affected the executive functioning domain, which aligns with observations in younger cohorts, suggesting that the pathophysiology underlying Aβ-associated cognitive decline is preserved with increasing age. Only a small fraction of centenarians maintained high cognitive abilities, despite having high levels of Aβ pathology: these had significantly lower levels of NFTs and TDP-43 compared with centenarians with high Aβ load and lower cognitive abilities. The few centenarians in whom Aβ pathology reached even the CA3 subregion of the hippocampus had higher NFT stages and lower cognitive performance. These findings suggest an interaction between Aβ and NFT pathologies, consistent with the amyloid cascade hypothesis. Taken together, our results demonstrate that higher levels of Aβ pathology affect cognition and suggest that emerging therapies aimed at reducing Aβ accumulation may also benefit the oldest of the old.

ARTICLE INFORMATION

Accepted for Publication: February 21, 2025.

Published Online: June 30, 2025. doi:10.1001/jamaneurol.2025.1734

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Statistical analysis: Rohde, Lorenz, Fierro-Hernández, Hulsman, Zhang, Richardson.
Obtained funding: Rohde, Holstege.
Administrative, technical, or material support: Rohde, Luimes, Fierro-Hernández, Rozemuller, Zhang, Graat, van der Hoorn, Daatselaar, Sikkes, Hoozemans, Holstege.
Supervision: Scheltens, Richardson, Walker, Sikkes, Hoozemans, Holstege.

Conflict of Interest Disclosures: Dr Rozemuller received funding from Alzheimer Nederland (03.2021.06). Dr Sikkes reported grants from Zon-MW TAP-dementia (10510032120003) and The Dutch Research Council R (KICH1.GZ02.20.004) during the conduct of the study and grants from Health Holland (LSHM20084), Alzheimer Nederland (WE. 32-2022-01), and the Ministry of Health, Welfare and Sports (90001586) outside the submitted work; in addition, Dr Sikkes had a patent for Amsterdam IADL Questionnaire licensed to Amsterdam UMC; all funds were distributed to the institution. Dr Richardson reported grants from the National Institute on Aging and the Texas Alzheimer's Research and Care Consortium outside the submitted work. Dr Hoozemans reported current employment with F. Hoffmann-La Roche. Dr Holstege is supported by ABOARD, a public-private partnership receiving funding from ZonMw (73305095007) and Health Holland, Topsector Life Sciences & Health (LSHM20106), the Hans und Ilse Breuer Stiftung (2020), the HorstingStuit Foundation (2018), and the Dutch Research Council (Aspasia premie 015.016.059). No other disclosures were reported.

Funding/Support: This work was supported by BrightFocus (A2021031S), VUmc foundation, and Surf Sara (Surf 2022.031). Dr Rohde received an InterAct fellowship from Alzheimer Nederland (WE.08-2023-03).

Role of the Funder/Sponsor: The funders 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.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank and acknowledge all participating centenarians and their family members. Moreover, we would like to thank and acknowledge all other brain donors and the Netherlands Brain Bank staff for the great cooperation. Furthermore, we would like to acknowledge all former practical team member of the 100-plus Study that contributed to data collection, and Andrea B. Ganz, PhD, Genomics of Neurodegenerative Diseases and Aging, Human Genetics, Vrije Universiteit van Amsterdam, for previous contributions to neuropathological evaluations. We thank Niccolo' Tesi, PhD, and Sven van der Lee, PhD, Genomics of Neurodegenerative Diseases and Aging, Human Genetics, Vrije Universiteit van Amsterdam, for their assistance in APOE genotyping.

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