Received: 26 June 2025 | Revised: 21 October 2025 | Accepted: 25 October 2025

DOI: 10.1002/alz.71024

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

RESEARCH ARTICLE

Evaluating the association of *apolipoprotein E* genotype and cognitive resilience in SuperAgers

Alaina Durant[1] | Shubhabrata Mukherjee[2] | Michael L. Lee[2] | Seo-Eun Choi[2] | Phoebe Scollard[2,3] | Brandon S. Klinedinst[2] | Emily H. Trittschuh[4,5] | Jesse Mez[6] | Lindsay A. Farrer[6,7,8] | Katherine A. Gifford[1,8] | Carlos Cruchaga[9,10] | Jason Hassenstab[11] | Adam C. Naj[12,13] | Li-San Wang[13] | Sterling C. Johnson[14,15] | Corinne D. Engelman[14,15] | Walter A. Kukull[16] | C. Dirk Keene[17] | Andrew J. Saykin[18,19] | Michael L. Cuccaro[20] | Brian W. Kunkle[20] | Margaret A. Pericak-Vance[20] | Eden R. Martin[20] | David A. Bennett[21] | Lisa L. Barnes[21] | Julie A. Schneider[21] | William S. Bush[22] | Jonathan L. Haines[22] | Richard Mayeux[23] | Badri N. Vardarajan[23] | Marilyn S. Albert[24] | Paul M. Thompson[25] | Angela L. Jefferson[1,26] | The Alzheimer's Disease Neuroimaging Initiative (ADNI)*Alzheimer's Disease Genetics Consortium (ADGC)The Alzheimer's Disease Sequencing Project (ADSP) | Paul K. Crane[2] | Logan Dumitrescu[1,26,27] | Derek B. Archer[1,26,27] | Timothy J. Hohman[1,26,27] | Leslie S. Gaynor[1,28]

Correspondence
Leslie S. Gaynor, Vanderbilt Memory and Alzheimer's Center, 3319 West End Ave, Rm 819, Nashville, TN 37203, USA.
Email: leslie.gaynor@vumc.org

Funding information
The ADSP Phenotype Harmonization Consortium; NIA, Grant/Award Numbers: U24 AG074855, U01 AG068057, R01 AG059716, K01 AG073584; DBA, Grant/Award Number: K24 AG046373; ALJ, Grant/Award Number: U19 AG066567; the Wisconsin Registry for Alzheimer's Prevention, Grant/Award Numbers: R01 AG021155, R01 AG0271761, R01 AG037639, R01 AG054047; the Alzheimer's Disease Neuroimaging Initiative, Grant/Award Numbers: U01 AG024904, W81XWH-12-2-0012; the National Institute on Aging; the National Institute of Biomedical Imaging and Bioengineering; following: AbbVie; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Elan

Abstract

INTRODUCTION: "SuperAgers" are oldest-old adults (ages 80+) whose memory performance more closely resembles middle-aged adults. The present study examined apolipoprotein E (*APOE*) allele frequency in non-Hispanic Black (NHB) and non-Hispanic White (NHW) SuperAgers compared to controls and Alzheimer's disease dementia cases.

METHODS: In 18,080 participants from eight cohorts, harmonized clinical diagnostics and memory, executive function, and language domain scores were used to identify SuperAgers, cases, and controls across age-defined bins.

RESULTS: NHW SuperAgers had significantly lower frequency of *APOE*-ε4 alleles and higher frequency of *APOE*-ε2 alleles compared to all cases and controls, including oldest-old controls. Similar patterns were found in a small yet substantial sample of NHB SuperAgers; however, not all comparisons with controls reached significance.

DISCUSSION: We demonstrated strong evidence that *APOE* allele frequency relates to SuperAger status. Further research is needed with a larger sample of NHB SuperAgers to determine if mechanisms conferring cognitive resilience differ across race groups.

Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd.; Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; Transition Therapeutics; Canadian Institutes of Health Research; National Institutes of Health; Northern California Institute for Research and Education; Alzheimer's Therapeutic Research Institute; Laboratory for Neuro Imaging; University of Southern California, Grant/Award Numbers: R01 AG017917, P30 AG10161, P30 AG072975, R01 AG022018, R01 AG056405, UH2 NS100599, UH3 NS100599, R01 AG064233, R01 AG15819, R01 AG067482; Illinois Department of Public Health; Alzheimer's Disease Research Fund, Grant/Award Number: U24 AG072122

KEYWORDS
Alzheimer's disease, APOE genotype, cognitive aging, cognitive resilience, SuperAgers

Highlights

- *Apolipoprotein E (APOE)* allele frequency differs between SuperAgers and cases
- *APOE* allele frequency differs between non-Hispanic White SuperAgers and controls
- The relationship of *APOE* and non-Hispanic Black SuperAger status is unclear

1 | BACKGROUND

"SuperAgers" is a term used to describe oldest-old (ages 80+) adults with episodic memory performance most closely resembling adults in their 50s to mid-60s.[1,2] It is unclear whether SuperAgers' high memory scores are due to resistance to age-related pathologic processes or high brain reserve.[3–5] Further research is needed to elucidate factors conferring optimal memory performance in SuperAgers. Moreover, research is needed to explore optimal memory performance in non-Hispanic Black (NHB) SuperAgers, as this group is largely understudied.[6]

Apolipoprotein E (APOE)-ε4 is the strongest genetic risk factor for late-onset AD.[7] The Northwestern SuperAging project reported lower *APOE*-ε4 allele frequency in SuperAgers (N = 10-12) compared to non-demented older adults.[2,8] In contrast, most studies report no differences in *APOE*-ε4 allele frequency between SuperAgers and oldest-old adults with typical memory performance, both groups having lower *APOE*-ε4 allele frequency compared to AD dementia cases.[4,5,9–12] Notably, these studies have small SuperAger samples (N = 25-64)[4,5,9–12] oftentimes drawn from the same cohort, thus limiting their generalizability and reliability. Further, these studies exclusively include non-Hispanic White (NHW) participants.[4,5,9–12] To our knowledge, only one study has been published with a NHB SuperAger sample (N = 61) and did not find a significant difference in *APOE*-ε4 allele frequency between SuperAgers and same-age controls.[6] Even fewer studies have explored the relationship of *APOE*-ε2, the protective *APOE* allele, and SuperAger status,[11–13] likely due to the low minor allele frequency of *APOE*-ε2. Studies of *APOE*-ε2 allele frequency and superior memory in the oldest-old have not found a significant relationship[11–13]; however, questions of statistical power, generalizability, and reliability remain.

The present study aims to explore *APOE*-ε4 and -ε2 allele frequency in SuperAgers compared to AD dementia cases and controls in a large, harmonized multicohort dataset from the Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium (ADSP-PHC). Using harmonized clinical diagnoses and cognitive domain scores (e.g., memory, executive function, language), we classified NHW and NHB middle-aged, old, and oldest-old adults as cases, controls, or SuperAgers, and compared *APOE*-ε4 and -ε2 allele frequency of SuperAgers to cases and controls by age bin. Although prior literature suggests that there is not a relationship between optimal memory in oldest-old age and *APOE* genotype, this is likely due to a limitation of sample size. The ADSP-PHC has enabled us to complete, to our knowledge, the largest and most racially diverse study to date of *APOE* allele frequency and SuperAger status. We hypothesize that NHW and NHB SuperAgers will possess a lower frequency of *APOE*-ε4 alleles and a higher frequency of *APOE*-ε2 alleles compared to both AD dementia cases and controls.

2 | METHODS

2.1 | Study population

The ADSP-PHC was assembled in 2021 to provide large-scale harmonization of ADSP cohorts, spanning markers of cognition, neuroimaging, fluid biomarkers, and neuropathology. Cohorts that are part of ADSP-PHC and were included in the present study are: Adult Changes

RESEARCH-IN-CONTEXT

1. **Systematic review**: The authors searched PubMed for studies related to SuperAgers and apolipoprotein E (*APOE*). Our review revealed that previous studies examining *APOE-ε4* allele frequency in SuperAgers have small SuperAger samples (N = 10-64), only one study has characterized *APOE-ε4* allele frequency in non-Hispanic Black (NHB) SuperAgers, and few studies have examined *APOE-ε2* allele frequency in SuperAgers.
2. **Interpretation**: We extend this work by examining the relationship of SuperAger status and *APOE* allele frequency in a large, harmonized multicohort dataset, including 18,080 total participants and 1,623 non-Hispanic White (NHW) and NHB SuperAgers (NHW SuperAgers: $N = 1{,}412$; NHB SuperAgers: $N = 211$).
3. **Future directions**: We found that *APOE* allele frequency significantly differed between SuperAgers and Alzheimer's disease dementia cases, while differences in *APOE* allele frequency between SuperAgers and controls were only significant in NHW comparisons. Further research is needed to determine if mechanisms conferring resilience in SuperAgers differ across race groups.

in Thought (ACT),[14] Alzheimer's Disease Neuroimaging Initiative (ADNI),[15] Biomarkers of Cognitive Decline Among Normal Individuals (BIOCARD),[16] National Alzheimer's Coordinating Centers (NACC),[17] National Institute on Aging Alzheimer's Disease Family Based Study (NIA-AD FBS),[18] Religious Orders Study/Rush Memory and Aging Project/Minority Aging Research Study (ROS/MAP/MARS),[19,20,21] Knight Alzheimer's Disease Research Center (Knight ADRC),[22] and Wisconsin Registry for Alzheimer's Prevention (WRAP).[23]

Written informed consent was obtained from all participants in each cohort, and research was carried out with protocols approved by each site's institutional review board. These secondary analyses were approved by the Vanderbilt University Medical Center institutional review board.

2.2 | Cognitive domain scores

Each cohort used different neuropsychological assessment tools to measure cognition which may not be on the same scale. Using pre-established procedures,[24] we derived co-calibrated and harmonized cognitive domain scores for four domains (i.e., memory, executive function, language, and visuospatial) using confirmatory factor analysis.[25] In summary, experts carefully reviewed the neuropsychological assessments administered by each cohort and assigned item scores to a cognitive domain: memory, executive function, language, or visuospatial (see https://vmacdata.org/adsp-phc/data/data-dictionary/cognition to explore the neuropsychological item scores assigned to each cognitive domain). Rigorous quality control procedures ensured consistent data coding across cohorts. Overlapping items with identical scoring and administration across cohorts were identified as "anchor items" and were used to anchor cognitive domain scores across cohorts. Then, confirmatory factor analyses were used to model memory, executive function, language, and visuospatial domains. Full details on cognitive domain harmonization and co-calibration can be found in original papers published by Mukherjee and colleagues.[24,25]

Consistent with previous definitions of SuperAgers, only memory, executive function, and language domains were used in present analyses.[1,2] To ensure inclusion of high-quality harmonization, cognitive domain scores with a standard error of measurement > 0.6 (estimated during the co-calibration and composite generation procedure) were excluded.

For the purpose of this study, regression-based cognitive domain scores were created for participant classification. Age, years of education, sex, and cohort were regressed on cognitive domain score at each available timepoint. Residuals were used to capture cognitive performance not explained by demographic variables or cohort differences. Separate models were used for NHW and NHB participants.

2.3 | Participant classification

Participants were grouped by race (self or study reported), clinical status, and age (Figure 1A). Age bins were decided based on the age-related criteria of SuperAgers (ages 80+) and the middle-aged adults whose memory performance is compared to oldest-old adults to determine SuperAger status (ages 50-64).[26] Therefore, the age bins included middle-aged (ages 50-64), old (ages 65-79), and oldest-old (ages 80+) adults. Participant classification was determined separately for NHW and NHB adults. Of note, the demographic characteristics of the middle-aged adult participants used to determine SuperAger status (NHW: $N = 3{,}123$, age = 59 ± 4, education = 16 ± 2, sex (female%) = 68%; NHB: $N = 575$, age = 60 ± 4, education = 15 ± 3, sex (female%) = 74%) were similar to the demographic characteristics of the larger oldest-old adult sample from which our SuperAgers and other oldest-old study participants were drawn (NHW: $N = 13{,}197$, age = 83 ± 4, education = 16 ± 3, sex (female%) = 58%; NHB: $N = 1{,}797$, age = 83 ± 3, education = 14 ± 3, sex (female %) = 77%).

Given that longitudinal data were available for most participants, and some participants' ages spanned multiple age bins, participant classification was decided using a predetermined schema (Figure 1B). Firstly, participants with a clinical diagnosis of AD dementia at least once were considered cases. Across all cohorts, a diagnosis of AD dementia followed standard published criteria (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA]).[27–29] Given that the present study focused on dementia cases likely due to AD, participants with comorbid neurological disorders (e.g., stroke, traumatic brain injury with significant loss of

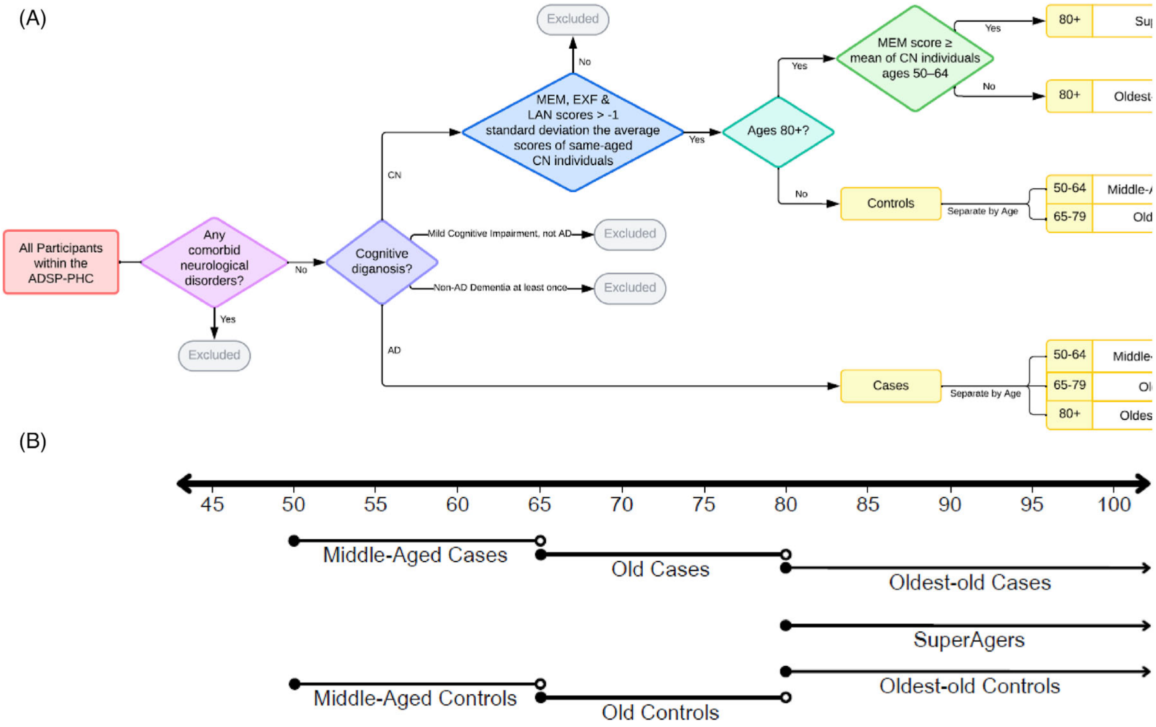

FIGURE 1 Flow diagram for participant classification of SuperAgers, cases, and controls. (A) Flowchart depicting inclusion and exclusion criteria for identifying SuperAgers, AD dementia cases, controls. (B) Flowchart depicting selection order of SuperAgers, cases, and controls. Age range of participants indicated by line segment with arrows on each end. Age of participant classification is indicated by position of shorter, labeled line segments. Closed circles at the end of line segments indicate inclusion of age, such that age range is less-than-or-equal-to or greater-than-or-equal-to the age with which the circle aligns, while open circles indicate exclusion of age, such that age range is less-than or greater-than the age with which the circle aligns. Sequence of selection is indicated by line height, higher lines indicating earlier selection. AD, Alzheimer's disease; ADSP-PHC, Alzheimer's Disease Sequencing Project – Phenotype Harmonization Consortium; CN, cognitively normal; EXF, executive functioning; LAN, language; MEM, memory.

consciousness) or primary diagnoses of non-AD dementia (e.g., dementia with Lewy bodies, vascular dementia) at any timepoint were excluded. Age bin was determined based on age at first AD dementia diagnosis.

Next, SuperAgers were identified using previously published criteria.[1,2] Across all cohorts, SuperAgers were defined as oldest-old adults with (1) memory domain scores at or above the mean of middle-aged adults (ages 50-64), (2) executive function and language residual scores no more than 1 standard deviation below their same-aged peers (ages 80+) at the same visit as their superior memory performance, and (3) whose diagnosis remained "cognitively normal" for the duration of study participation.

Regarding classification as a control, given the importance of oldest-old (ages 80+) participants to our central analyses, we sequentially identified oldest-old, middle-aged, and then old controls. Criteria for controls included (1) memory, executive function, and language residual scores no lower than 1 standard deviation below their same-aged peers at a single visit, and (2) who did not meet standard published criteria for mild cognitive impairment or AD dementia and thus were given a diagnosis of "cognitively normal," for the duration of study participation.

2.4 | *APOE* genotyping

APOE haplotypes were determined from the single nucleotide variants rs7412 and rs429358 for ACT, BIOCARD, NACC, NIA-AD FBS, Knight ADRC, and WRAP and from pyrosequencing of *APOE* codons 112 and 158 for ADNI and ROS/MAP/MARS.[30,31]

2.5 | Statistical analyses

Statistical analyses were performed using R Statistical Software (v4.2.3.).[32] Logistic regression models examined differences in *APOE*-ε4 and -ε2 allele frequency of SuperAgers compared to cases and controls at all age bins. *APOE* allele positivity was determined by allele presence (0 = no allele present, 1 = one or more alleles present). Models covaried for sex and years of education due to their known modifying effects on the relationship of *APOE* and late-life cognition.[33,34] Sensitivity analyses included analyses removing individuals with *APOE*-ε2/ε4 genotype and adding *APOE* genotyping method as a covariate. Additionally, to determine whether differences in sample size explained differences in the significance of comparisons across NHW and NHB

TABLE 1 Participant characteristics by cohort.

Participant demographics	All	ACT	ADNI	BIOCARD	Knight ADRC	NACC	NIA-AD FBS	ROS, MAP, MARS	WRAP
No. of participants	18080	2188	825	51	735	11851	645	1462	323
No. of observations	78549	13016	3568	455	3314	42004	956	13931	1305
Visits, mean (SD)	4 (4)	6 (3)	4 (3)	9 (3)	5 (4)	4 (3)	1 (1)	10 (6)	4 (2)
Follow-up time, mean (SD), y	5 (5)	10 (6)	3 (3)	13 (4)	4 (5)	3 (4)	2 (3)	9 (6)	9 (5)
Baseline age, mean (SD), y	72 (10)	73 (6)	74 (7)	53 (9)	74 (8)	72 (10)	74 (12)	77 (8)	53 (6)
NHW race, no. (%)	15698 (87)	2116 (97)	753 (91)	51 (100)	635 (86)	10149 (86)	605 (94)	1086 (74)	303 (94)
Education, mean (SD), y	15 (3)	15 (3)	16 (3)	17 (2)	15 (3)	16 (3)	14 (3)	16 (4)	16 (3)
Female sex, no. (%)	11213 (62)	1295 (59)	401 (49)	30 (59)	453 (62)	7319 (62)	406 (63)	1091 (75)	218 (67)
APOE genotype									
ε2/ε2, %	0.4	0.6	0.4	0	0.3	0.4	0.6	0.5	0.3
ε2/ε3, %	8.8	12.5	8.6	13.7	8.7	7.9	5.1	12.1	7.1
ε2/ε4, %	2.6	2.3	2.4	0	2.7	2.6	3.3	2.1	3.4
ε3/ε3, %	47.0	58.8	44.8	62.7	41.9	44.2	37.7	57.9	52.6
ε3/ε4, %	33.5	24.0	33.1	19.6	38.8	35.6	43.1	24.4	32.2
ε4/ε4, %	7.8	1.7	10.7	3.9	7.6	9.4	10.2	2.9	4.3
SuperAgers, no. (%)	1623 (9)	275 (13)	59 (7)	0 (0)	53 (7)	935 (8)	16 (2)	285 (19)	0 (0)
Controls, no. (%)	7628 (42)	1207 (55)	335 (41)	49 (96)	290 (39)	4605 (39)	309 (48)	510 (35)	323 (100)
Cases, no. (%)	8829 (49)	706 (32)	431 (52)	2 (4)	392 (53)	6311 (53)	320 (50)	667 (46)	0 (0)

Abbreviations: ACT, Adult Changes in Thought; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; BIOCARD, Biomarkers of Cognitive Decline Among Normal Individuals; Knight ADRC, Knight Alzheimer's Disease Research Center at Washington University; MAP, Memory and Aging Project; MARS, Minority Aging Research Study; NACC, National Alzheimer's Coordinating Centers; NHW, non-Hispanic White; NIA-AD FBS, National Institute on Aging Alzheimer's Disease Family Based Study; ROS, Religious Orders Study; WRAP, Wisconsin Registry for Alzheimer's Prevention.

samples, we included sensitivity analyses randomly down-sampling the NHW sample by participant classification and cohort. Correction for multiple comparisons was applied using Benjamini-Hochberg false discovery rate (FDR) procedure.[35] Results tables include odds ratios (OR), confidence intervals (CI), and FDR-corrected *p*-values.

3 | RESULTS

3.1 | Participant characteristics

In total, 18,080 participants were included in the present analyses with a total of 78,549 datapoints (Table 1). Participants completed an average of 4 ± 4 visits over 5 ± 5 years. The number of follow-up visits and length of follow-up varied by cohort due to differences in study design.

Average baseline age varied by cohort ($\text{Age}_{[\text{all cohorts}]} = 72 \pm 10$); the youngest cohorts on average, BIOCARD and WRAP, primarily recruited cognitively normal participants. Generally, cohorts were highly educated ($\text{Years of Education}_{[\text{all cohorts}]} = 15 \pm 3$), mostly female (62%), and mostly NHW (87%). The frequency of each *APOE* genotype differed by cohort, with higher frequency of ε3/ε4 and ε4/ε4 genotypes in cohorts with a higher frequency of AD dementia cases.

3.2 | Participant classification

SuperAgers made up 9% of all participants (N = 1,623). The two youngest cohorts, BIOCARD and WRAP, did not contribute any SuperAgers. Cognitively unimpaired controls comprised 42% of all participants (N = 7,628), and cases made up 49% of all participants (N = 8,829).

Table 2 displays participant characteristics of NHW and NHB SuperAgers, controls, and cases in age-defined bins. On average, NHW SuperAgers (N = 1,412) were somewhat older, had more years of education, and included more males than NHB SuperAgers (N = 211). There was not a difference in the proportion of participants in each participant classification (SuperAger, control, case) across racialized groups ($\chi^2_{[2]} = 3.79$, p = 0.15). Comparing NHW and NHB participants across age-defined bins, all NHW bins had greater average years of education and a higher proportion of males than NHB bins.

3.3 | *APOE* allele frequency

In NHW comparisons (Table 3A), SuperAgers had a significantly higher frequency of *APOE*-ε2 alleles (Figure 2A; middle-aged controls:

TABLE 2 Characteristics of SuperAgers, cases, and controls by race and age bin.

A	SuperAgers	Middle-Aged controls	Old controls	Oldest-old controls	Middle-Aged cases	Old cases	Oldest-old cases
No. of participants	1412	1622	3202	1213	1101	3528	3258
No. of observations	5640	6698	11320	3505	2534	8833	7255
Visits, mean (SD)	4 (3)	4 (3)	4 (3)	3 (2)	2 (2)	3 (2)	2 (2)
Follow-up time, mean (SD), y	4 (4)	5 (5)	4 (3)	3 (3)	1 (2)	2 (2)	1 (2)
Baseline age, mean (SD), y	83 (3)	58 (4)	71 (4)	84 (4)	59 (5)	74 (4)	87 (5)
Education, mean (SD), y	16 (3)	16 (2)	16 (3)	15 (3)	15 (3)	15 (3)	15 (3)
Female sex, No. (%)	953 (67)	1119 (69)	1964 (61)	661 (54)	618 (56)	1905 (54)	1989 (61)
APOE-ε2 frequency, No. (%)	246 (17)	216 (13)	467 (15)	179 (15)	50 (5)	184 (5)	321 (10)
APOE-ε4 frequency, No. (%)	276 (20)	647 (40)	981 (31)	270 (22)	639 (58)	2495 (71)	1425 (44)
B	**SuperAgers**	**Middle-Aged controls**	**Old controls**	**Oldest-old controls**	**Middle-Aged cases**	**Old cases**	**Oldest-old cases**
No. of participants	211	296	752	145	85	413	444
No. of observations	864	1017	3017	426	164	1009	1052
Visits, mean (SD)	4 (3)	3 (3)	4 (3)	3 (2)	2 (1)	2 (2)	2 (2)
Follow-up time, mean (SD), y	4 (4)	3 (4)	4 (3)	2 (3)	1 (1)	2 (2)	2 (2)
Baseline age, mean (SD), y	82 (3)	60 (4)	70 (4)	83 (3)	60 (4)	74 (4)	86 (4)
Education, mean (SD), y	15 (3)	15 (3)	15 (3)	13 (3)	14 (3)	14 (4)	13 (4)
Female sex, No. (%)	177 (84)	222 (75)	564 (75)	115 (79)	58 (68)	283 (69)	331 (75)
APOE-ε2 frequency, No. (%)	56 (27)	68 (23)	155 (21)	27 (19)	8 (9)	36 (9)	53 (12)
APOE-ε4 frequency, No. (%)	54 (26)	125 (42)	261 (35)	39 (27)	65 (76)	307 (74)	216 (49)

(A) Non-Hispanic White participants; (B) Non-Hispanic Black participants.
Abbreviations: APOE apolipoprotein E;

TABLE 3 Logistic regression model results comparing *APOE-ε2* and -*ε4* allele frequency among SuperAgers, cases, and controls.

	APOE-ε2		***APOE-ε4***	
A	**OR (CI)**	P_{FDR}	**OR (CI)**	P_{FDR}
SuperAgers vs. Middle-Aged controls	1.38 (1.13, 1.68)	*0.002*	0.37 (0.31, 0.43)	*<0.001*
SuperAgers vs. Old controls	1.24 (1.05, 1.47)	*0.015*	0.55 (0.47, 0.64)	*<0.001*
SuperAgers vs. Oldest-Old controls	1.28 (1.03, 1.59)	*0.035*	0.81 (0.67, 0.99)	*0.044*
SuperAgers vs. Middle-Aged cases	4.55 (3.30, 6.27)	*<0.001*	0.18 (0.15, 0.21)	*<0.001*
SuperAgers vs. Old cases	4.02 (3.26, 4.96)	*<0.001*	0.09 (0.08, 0.11)	*<0.001*
SuperAgers vs. Oldest-Old cases	2.03 (1.68, 2.44)	*<0.001*	0.32 (0.27, 0.37)	*<0.001*
	APOE-ε2		***APOE-ε4***	
B	**OR (CI)**	P_{FDR}	**OR (CI)**	P_{FDR}
SuperAgers vs. Middle-Aged controls	1.19 (0.79, 1.80)	0.423	0.48 (0.33, 0.71)	*0.001*
SuperAgers vs. Old controls	1.41 (0.99, 2.01)	0.079	0.66 (0.47, 0.94)	*0.035*
SuperAgers vs. Oldest-Old controls	1.63 (0.93, 2.85)	0.115	1.18 (0.70, 1.98)	0.564
SuperAgers vs. Middle-Aged cases	3.59 (1.60, 8.06)	*0.005*	0.12 (0.07, 0.22)	*<0.001*
SuperAgers vs. Old cases	4.56 (2.75, 7.55)	*<0.001*	0.12 (0.08, 0.18)	*<0.001*
SuperAgers vs. Oldest-Old cases	2.73 (1.75, 4.25)	*<0.001*	0.39 (0.27, 0.57)	*<0.001*

(A) Non-Hispanic White; (B) Non-Hispanic Black.
Abbreviations: APOE apolipoprotein E; CI, confidence interval (95%); FDR, false discovery rate; OR, odds ratio; P_{FDR}, FDR-corrected *p*-value.

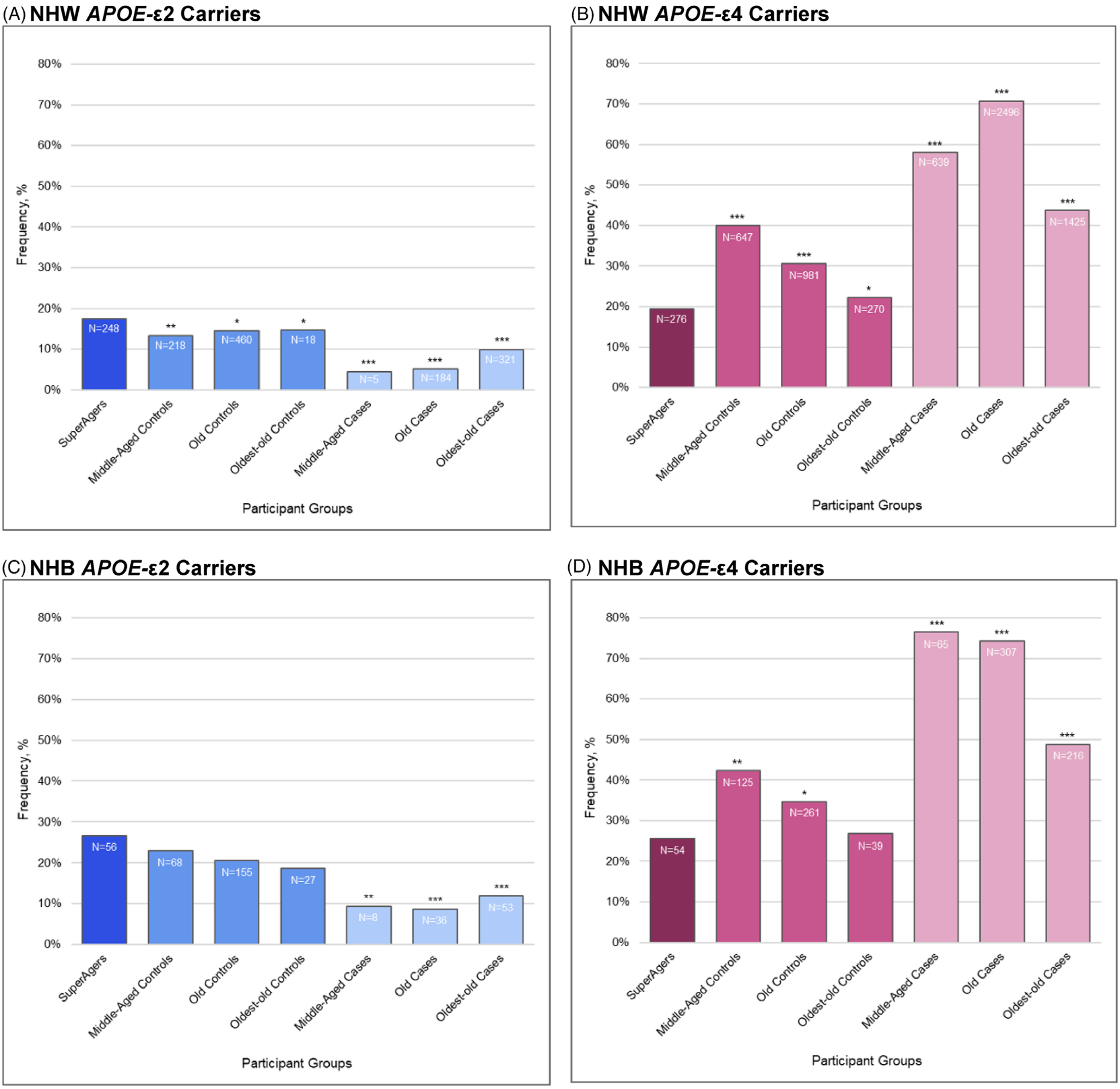

FIGURE 2 *APOE* allele frequency in NHW and NHB SuperAgers compared to cases and controls. Bar charts depicting *APOE*-ε2 and *APOE*-ε4 allele frequency for SuperAgers, cases, and controls across age-defined subgroups. Participant classification is indicated by the X-axis, while percent frequency is indicated by the Y-axis. (A) *APOE*-ε2 allele frequency in NHW participants. (B) *APOE*-ε4 allele frequency in NHW participants. (C) *APOE*-ε2 allele frequency in NHB participants. (D) *APOE*-ε4 allele frequency in NHB participants. Asterisks denote significant differences in allele frequency compared to SuperAgers determined by logistic regression models covarying for sex and years of education (* ≤ 0.05, ** ≤ 0.01, *** ≤ 0.001). APOE, apolipoprotein E; NHW, non-Hispanic White; NHB, non-Hispanic Black.

OR = 1.38, 95%CI[1.13, 1.68], $P_{FDR} = 0.002$; old controls: OR = 1.24, 95%CI[1.05, 1.47], $P_{FDR} = 0.015$; oldest-old controls: OR = 1.28, 95%CI[1.03, 1.59], $P_{FDR} = 0.035$; middle-aged cases: OR = 4.55, 95%CI[3.30, 6.27], $P_{FDR} < 0.001$; old cases: OR = 4.02, 95%CI[3.26, 4.96], $P_{FDR} < 0.001$; oldest-old cases: OR = 2.03, 95%CI[1.68, 2.44], $P_{FDR} < 0.001$) and a significantly lower frequency of *APOE*-ε4 alleles (Figure 2B; middle-aged controls: OR = 0.37, 95%CI[0.31, 0.43], $P_{FDR} < 0.001$; old controls: OR = 0.55, 95%CI[0.47, 0.64], $P_{FDR} < 0.001$; oldest-old controls: OR = 0.81, 95%CI[0.67, 0.99], $P_{FDR} = 0.044$; middle-aged cases: OR = 0.18, 95%CI[0.15, 0.21], $P_{FDR} < 0.001$; old cases: OR = 0.09, 95%CI[0.08, 0.11], $P_{FDR} < 0.001$; oldest-old cases: OR = 0.32, 95%CI[0.27,0.37], $P_{FDR} < 0.001$) compared to all cases and controls. In contrast, NHB SuperAgers (Table 3B) had a significantly higher frequency of *APOE*-ε2 alleles only compared to cases (Figure 2C; middle-aged cases: OR = 3.59, 95%CI[1.60, 8.06], $P_{FDR} = 0.005$; old cases: OR = 4.56, 95%CI[2.75, 7.55], $P_{FDR} < 0.001$; oldest-old cases:

OR = 2.73, 95%CI[1.75, 4.25], $P_{FDR} < 0.001$), and a significantly lower frequency of *APOE*-ε4 alleles compared to all cases and controls except oldest-old controls (Figure 2D; middle-aged controls: OR = 0.48, 95%CI[0.33, 0.71], $P_{FDR} = 0.001$; old controls: OR = 0.66, 95%CI[0.47, 0.94], $P_{FDR} = 0.035$; middle-aged cases: OR = 0.12, 95%CI[0.07, 0.22], $P_{FDR} < 0.001$; old cases: OR = 0.12, 95%CI[0.08, 0.18], $P_{FDR} < 0.001$; oldest-old cases: OR = 0.39, 95%CI[0.27, 0.57], $P_{FDR} < 0.001$).

3.4 | Sensitivity Analyses

Analyses were repeated removing individuals with an *APOE*-ε2/ε4 genotype. Given their low frequency, very few participants were removed (Supplementary Table S1; NHW SuperAgers: N = 1,393; NHB SuperAgers: N = 200) and findings were preserved (Supplementary Table S2).

Findings were also preserved when *APOE* genotyping method was included as a covariate (Supplementary Table S3).

To determine the impact of sample size on the significance of NHB comparisons, we randomly down-sampled the NHW sample by participant classification and cohort (Supplementary Table S4). In the smaller sample, differences in *APOE*-ε2 and -ε4 allele frequency between NHW SuperAgers and controls were no longer significant, except for the comparison between NHW SuperAgers and middle-aged controls (Supplementary Table S5).

4 | DISCUSSION

Mechanisms conferring cognitive resilience in oldest-old age are yet unknown. This is the largest published sample of SuperAgers and the largest study to date of the relationship of *APOE*-ε4 and -ε2 allele frequency and SuperAger status. Across eight national aging cohorts, we identified 1,623 NHW and NHB SuperAgers with *APOE* genotyping using longitudinal harmonized cognitive and clinical data. As expected, we found that SuperAgers had a higher frequency of *APOE*-ε2 alleles and a lower frequency of *APOE*-ε4 alleles compared to individuals with AD dementia. Unlike most previous studies of *APOE* genotype in NHW SuperAgers, we found significant differences in *APOE* genotype compared to controls of all ages, including oldest-old controls. Specifically, the odds of having 1 ε4 allele was about 20% lower in NHW SuperAgers compared to same-age controls, and the odds of having 1 ε2 allele was about 30% higher in NHW SuperAgers compared to same-age controls. This finding held when ε2/ε4 carriers were removed from analyses and when *APOE* genotyping method was added as a covariate. Although NHB SuperAgers also had a higher frequency of *APOE*-ε2 alleles and a lower frequency of *APOE*-ε4 alleles compared to oldest-old controls, comparisons did not rise to the level of significance. Sensitivity analyses down-sampling NHW SuperAgers suggest that sample size likely impacted the significance of comparisons with NHB SuperAgers.

APOE-ε4 is the strongest genetic risk factor for late-onset AD,[7] and has been shown to be related to increased entorhinal and hippocampal atrophy[36] and amnestic cognitive impairment.[37,38] Our data are supportive of these findings, such that AD dementia cases had a higher frequency of *APOE*-ε4 alleles compared to controls and SuperAgers.[39] Unlike most studies of genetic resilience in SuperAgers, we found that NHW SuperAgers had a lower frequency of *APOE*-ε4 alleles compared to oldest-old adults with typical memory performance. This was found in two previous studies published from the same cohort (N = 10-12),[2,8] but was not replicated in subsequent studies with larger samples of SuperAgers.[4,5,9–12] This finding is relatively unexpected. Across racialized groups, the effect of *APOE*-ε4 is most impressive prior to age 70.[40,41] Additionally, *APOE*-ε4 carriership is related to increased mortality.[42,43] In line with these studies, we found lower *APOE*-ε4 allele frequency in oldest-old compared to middle-aged and old controls. Despite NHW oldest-old controls being older than NHW SuperAgers on average, we found that SuperAgers had a significantly lower frequency of *APOE*-ε4 alleles compared to oldest-old controls, indicating that *APOE*-ε4 allele carriership influences memory even in adults who live past age 80. Moreover, dementia incidence increases exponentially with age,[44] suggesting that the oldest-old control group also represents exceptional aging. We found that NHW SuperAgers had a significantly lower frequency of *APOE*-ε4 alleles compared to same-age peers, thus underscoring the utility of the SuperAgers phenotype for uncovering factors conferring resilience in cognitive aging.

The protective *APOE*-ε2 allele is related to lower likelihood of late-onset AD dementia[13,45] and better cognitive performance in older adults even in the presence of AD neuropathology.[46] Unlike *APOE*-ε4, *APOE*-ε2 carriership was previously shown to affect cognition after age 80; more precisely, although oldest-old *APOE*-ε2 carriers were as likely as *APOE*-ε4 carriers to meet neuropathologic criteria for AD, they were less likely to be diagnosed with dementia.[45] Nonetheless, no previous studies have found a relationship of *APOE*-ε2 allele frequency and SuperAger status.[11–13] The present study is the first to find that NHW SuperAgers had a significantly higher frequency of *APOE*-ε2 alleles compared to controls. Our results suggest that *APOE*-ε2 not only reduces the likelihood of dementia in oldest age but increases the likelihood one will possess optimal memory in oldest age. Future studies are needed to determine whether SuperAgers have similar levels of AD neuropathology compared to AD dementia cases as was previously found in oldest-old *APOE*-ε2 carriers without dementia.[45]

Genetic factors underlying the superior memory performance of NHB SuperAgers, a critically under-diagnosed and understudied group, are relatively unknown.[6] Previous research suggests that, while NHB individuals have a higher frequency of *APOE*-ε4 alleles compared to NHW individuals, *APOE*-ε4 carriership is associated with attenuated risk for late-onset AD, yet similar mortality risk, in NHB individuals compared to NHW individuals.[41,47–49] The effect is likely related to global population ancestry; more specifically, *APOE*-ε4 carriership is associated with a greater risk of AD in NHB older adults with decreased global African ancestry or increased global European ancestry.[41] Similar to *APOE*-ε4, NHB individuals have a higher frequency of *APOE*-ε2 alleles compared to NHW individuals.[47] Unlike *APOE*-ε4, researchers did not detect differences in the protective effect of *APOE*-ε2 alleles related to global population ancestry.[41] In fact, a recent study from the MARS cohort found that NHB older adults (ages 65+) with more

*APOE-ε*2 alleles had slower cognitive decline over a 10-year study period.[50] Additionally, *APOE-ε*2 carriership was related to better survival in a sample of NHB and NHW individuals from NACC with and without AD neuropathology.[51] In the present study, NHB SuperAgers had a significantly lower frequency of *APOE-ε*4 alleles compared to cases and younger controls, and a significantly higher frequency of *APOE-ε*2 alleles compared only to cases. Importantly, the present study included a substantially smaller sample of NHB SuperAgers compared to NHW SuperAgers, although the sample was still far larger than has been previously reported. Sensitivity analyses suggest that sample size likely impacted the significance of comparisons with NHB SuperAgers. It is also possible that the lack of significant difference in *APOE* allele carriership between NHB SuperAgers and oldest-old controls is partially explained by survivorship bias; recent research indicates that NHB adults have a higher probability of survival from ages 70 and 80 to 100 compared to NHW adults.[52] Thus, NHB SuperAgers and cognitively normal oldest-old adults may share environmental and genetic factors, including *APOE-ε*2 allele carriership, that support survival and reduced mortality risk in older age, resulting in a lack of significant difference in *APOE* genotype between these two, very similar, exceptional aging groups.[6] Still, more research and targeted recruitment of high-performing NHB oldest-old adults is necessary to determine the role of *APOE* genotype in their sustained optimal memory performance.

The present study has several strengths, including being the largest of its kind to explore the relationship of *APOE* genotype and optimal memory performance in both NHW and NHB SuperAgers. This is the largest study to date to identify differences in *APOE-ε*4 allele frequency based on SuperAger status, and the first study of SuperAgers to find a relationship between *APOE-ε*2 allele frequency and SuperAger status. Our study also has several limitations. Across cohorts, participants were highly educated, limiting generalizability to lower-educated or socioeconomically diverse populations. Additionally, studies have identified other genetic factors that may confer greater AD risk in NHB older adults compared to *APOE*, including *ABCA7*.[53,54] Future studies will need to consider other genetic factors that may also be relevant to exceptional aging in NHB older adults. Moreover, differences in the effect of genetic factors on AD risk have been associated with genetic ancestry, which was only available for a subset of participants in our sample.[41] Subsequent research leveraging advanced genetic analyses to consider admixture may further our understanding of genetic profiles underlying AD risk.

The present study reveals important information about genetic factors associated with SuperAger status. While significant findings were restricted to NHW comparisons, study results importantly direct our attention to the need for targeted recruitment of high-performing NHB oldest-old adults to more definitively determine the role of genetics in sustained optimal memory performance in oldest-old age across racialized groups. There is an ongoing initiative that intends to answer complex questions about brain aging, resilience, and resistance in a well-characterized SuperAging cohort through longitudinal, multimodal data collection.[55,56] SuperAging research will contribute tremendously to our understanding of factors conferring cognitive resilience in oldest-old age, such as preserved regional brain volume, differences in lifestyle factors, and resistance to neuropathology.

AFFILIATIONS

[1]Vanderbilt Memory & Alzheimer's Center, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[2]Department of Medicine, University of Washington, Seattle, Washington, USA

[3]Bordeaux Population Health Research Center, University Bordeaux, Inserm, Bordeaux, France

[4]Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, Washington, USA

[5]VA Puget Sound Health Care System, GRECC, Seattle, Washington, USA

[6]Department of Neurology, Boston University Chobanian & Avedisian School of Medicine, Boston University Medical Center, Boston, Massachusetts, USA

[7]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA

[8]Department of Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston, Massachusetts, USA

[9]Department of Psychiatry, Washington University in St. Louis, St. Louis, Missouri, USA

[10]NeuroGenomics and Informatics Center, Washington University in St. Louis, St. Louis, Missouri, USA

[11]Department of Neurology and Department Psychological & Brain Sciences, Washington University in St Louis, St. Louis, Missouri, USA

[12]Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[13]Penn Neurodegeneration Genomics Center, Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

[14]Alzheimer's Disease Research Center, University of Wisconsin-Madison, School of Medicine and Public Health, Madison, Wisconsin, USA

[15]Department of Population Health Sciences, University of Wisconsin-Madison, School of Medicine and Public Health, Madison, Wisconsin, USA

[16]Department of Neurology, WashU Medicine, St. Louis, Missouri, USA

[17]Department of Laboratory Medicine and Pathology, University of Washington, St. Seattle, Washington, USA

[18]Department of Radiology and Imaging Services, Indiana University School of Medicine, Indianapolis, Indiana, USA

[19]Department of Medical and Molecular Genetics, School of Medicine, Indiana University, Indianapolis, Indiana, USA

[20]John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, Florida, USA

[21]Rush Alzheimer's Disease Center, Rush University Medical Center, St. Chicago, Illinois, USA

[22]Cleveland Institute for Computational Biology, Department of Population and Quantitative Health Sciences, School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA

[23]Department of Neurology, The Taub Institute for Research on Alzheimer's Disease and The Aging Brain, Columbia University Medical Center and The New York Presbyterian Hospital, New York, New York, USA

[24]Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[25]Keck School of Medicine, University of Southern California, Los Angeles, California, USA

[26]Department of Neurology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[27]Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[28]Division of Geriatric Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

ACKNOWLEDGMENTS

The authors have nothing to report. The ADSP Phenotype Harmonization Consortium (ADSP-PHC) is funded by NIA (U24 AG074855, U01 AG068057 and R01 AG059716). This study was also funded by several additional funding sources, including K01 AG073584 (DBA) and K24 AG046373 (ALJ). The data contributed from the Adult Changes in Thought study was supported by NIA U19 AG066567. The data contributed from the Wisconsin Registry for Alzheimer's Prevention was supported by NIA R01 AG021155, R01 AG0271761, R01 AG037639, and R01 AG054047. Data collection and sharing for this project was funded (in part) by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (NIA U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. Data contributed from MAP/ROS/MARS was supported by NIA R01 AG017917, P30 AG10161, P30 AG072975, R01 AG022018, R01 AG056405, UH2 NS100599, UH3 NS100599, R01 AG064233, R01 AG15819 and R01 AG067482, and the Illinois Department of Public Health (Alzheimer's Disease Research Fund). Data can be accessed at www.radc.rush.edu. The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADRCs: P30 AG062429 (PI James Brewer, MD, PhD), P30 AG066468 (PI Oscar Lopez, MD), P30 AG062421 (PI Bradley Hyman, MD, PhD), P30 AG066509 (PI Thomas Grabowski, MD), P30 AG066514 (PI Mary Sano, PhD), P30 AG066530 (PI Helena Chui, MD), P30 AG066507 (PI Marilyn Albert, PhD), P30 AG066444 (PI David Holtzman, MD), P30 AG066518 (PI Lisa Silbert, MD, MCR), P30 AG066512 (PI Thomas Wisniewski, MD), P30 AG066462 (PI Scott Small, MD), P30 AG072979 (PI David Wolk, MD), P30 AG072972 (PI Charles DeCarli, MD), P30 AG072976 (PI Andrew Saykin, PsyD), P30 AG072975 (PI Julie A. Schneider, MD, MS), P30 AG072978 (PI Ann McKee, MD), P30 AG072977 (PI Robert Vassar, PhD), P30 AG066519 (PI Frank LaFerla, PhD), P30 AG062677 (PI Ronald Petersen, MD, PhD), P30 AG079280 (PI Jessica Langbaum, PhD), P30 AG062422 (PI Gil Rabinovici, MD), P30 AG066511 (PI Allan Levey, MD, PhD), P30 AG072946 (PI Linda Van Eldik, PhD), P30 AG062715 (PI Sanjay Asthana, MD, FRCP), P30 AG072973 (PI Russell Swerdlow, MD), P30 AG066506 (PI Glenn Smith, PhD, ABPP), P30 AG066508 (PI Stephen Strittmatter, MD, PhD), P30 AG066515 (PI Victor Henderson, MD, MS), P30 AG072947 (PI Suzanne Craft, PhD), P30 AG072931 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P30 AG086401 (PI Erik Roberson, MD, PhD), P30 AG086404 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), P30 AG072959 (PI James Leverenz, MD). NACC data can be accessed at naccdata.org. The recruitment and clinical characterization of research participants at Washington University were supported by NIH P30 AG066444 (JCM), P01 AG03991 (JCM), and P01 AG026276 (JCM). The National Institute on Aging-AD Family Based Study (NIA-AD FBS; https://www.neurology.columbia.edu/research/research-centers-and-programs/national-institute-aging-alzheimers-disease-family-based-study-nia-ad-fbs) collected the samples used in this study and is supported by National Institute on Aging (NIA) grant U24 AG056270. Additional families were contributed to the NIA-AD FBS through NIH grants: R01 AG028786, R01 AG027944, R01 AG027944, RF1 AG054074, U01 AG052410. This work was supported by access to equipment made possible by the Hope Center for Neurological Disorders, the Neurogenomics and Informatics Center (NGI: https://neurogenomics.wustl.edu/) and the Departments of Neurology and Psychiatry at Washington University School of Medicine. Data contributed from the Wisconsin Registry for Alzheimer's Prevention were supported by R01 AG027161.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants provided informed consent in their respective cohort studies.

ORCID

Leslie S. Gaynor https://orcid.org/0000-0003-1121-4365

REFERENCES

1. Harrison TM, Weintraub S, Mesulam M, Rogalski E. Superior memory and higher cortical volumes in unusually successful cognitive aging. *J Int Neuropsychol Soc*. 2012;18:1081-1085. doi:10.1017/S1355617712000847
2. Rogalski EJ, Gefen T, Shi J, et al. Youthful memory capacity in old brains: anatomic and genetic clues from the northwestern superaging project. *J Cogn Neurosci*. 2013;25:29-36. doi:10.1162/jocn_a_00300
3. de Godoy LL, Alves CAPF, Saavedra JSM, et al. Understanding brain resilience in superagers: a systematic review. *Neuroradiology*. 2021;63:663-683. doi:10.1007/s00234-020-02562-1

4. Gefen T, Peterson M, Papastefan ST, et al. Morphometric and histologic substrates of cingulate integrity in elders with exceptional memory capacity. *J Neurosci*. 2015;35:1781-1791. doi:10.1523/JNEUROSCI.2998-14.2015
5. Harrison TM, Maass A, Baker SL, Jagust WJ. Brain morphology, cognition, and β-amyloid in older adults with superior memory performance. *Neurobiol Aging*. 2018;67:162-170. doi:10.1016/j.neurobiolaging.2018.03.024
6. Trammell AR, Goldstein FC, Parker MW, Hajjar IM. Characterization of African-American Super-Agers in the national Alzheimer's coordinating center cohort. *J Am Geriatr Soc*. 2024;72:1995-2005. doi:10.1111/jgs.18882
7. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261:921-923. doi:10.1126/science.8346443
8. Rogalski E, Gefen T, Mao Q, et al. Cognitive trajectories and spectrum of neuropathology in SuperAgers: the first 10 cases. *Hippocampus*. 2019;29:458-467. doi:10.1002/hipo.22828
9. Mapstone M, Lin F, Nalls MA, et al. What success can teach us about failure: the plasma metabolome of older adults with superior memory and lessons for Alzheimer's disease. *Neurobiol Aging*. 2017;51:148-155. doi:10.1016/j.neurobiolaging.2016.11.007
10. Dekhtyar M, Papp KV, Buckley R, et al. Neuroimaging markers associated with maintenance of optimal memory performance in late-life. *Neuropsychologia*. 2017;100:164-170. doi:10.1016/j.neuropsychologia.2017.04.037
11. Spencer BE, Banks SJ, Dale AM, et al. Alzheimer's polygenic hazard score in SuperAgers: superGenes or SuperResilience?. *Alzheimer's & Dementia: Transl Res Clin Interv*. 2022;8:e12321. doi:10.1002/trc2.1232
12. Garo-Pascual M, Gaser C, Zhang L, Tohka J, Medina M, Strange BA. Brain structure and phenotypic profile of superagers compared with age-matched older adults: a longitudinal analysis from the Vallecas project. *Lancet Healthy Longev*. 2023;4:e374-e385. doi:10.1016/S2666-7568(23)00079-X
13. Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat Genet*. 1994;7:180-184. doi:10.1038/ng0694-180
14. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol*. 2002;59:1737-1746. doi:10.1001/archneur.59.11.1737
15. Jack CR, Bernstein MA, Fox NC, et al. The Alzheimer's disease neuroimaging initiative (ADNI): mRI methods. *J Magn Reson Imaging: Off J Int Soc Magn Reson Med*. 2008;27:685-691. doi:10.1002/jmri.21049
16. Sacktor N, Soldan A, Grega M, et al. The BIOCARD index: a summary measure to predict onset of mild cognitive impairment. *Alzheimer Dis Assoc Disord*. 2017;31:114-119. doi:10.1097/WAD.0000000000000194
17. Beekly DL, Ramos EM, van Belle G, et al. The national Alzheimer's coordinating center (NACC) database: an Alzheimer disease database. *Alzheimer Dis Assoc Disord*. 2004;18:270-277. doi:https://lww/alz/88441/03-070R
18. Lee JH, Cheng R, Graff-Radford N, Foroud T, Mayeux R, National Institute on Aging Late-Onset Alzheimer's Disease Family Study Group. Analyses of the national institute on aging late-onset Alzheimer's disease family study: implication of additional Loci. *Arch Neurol*. 2008;65:1518-1526. doi:10.1001/archneur.65.11.1518
19. Bennett DA, Buchman AS, Boyle PA, Barnes LL, Wilson RS, Schneider JA. Religious orders study and rush memory and aging project. *J Alzheimer's Dis*. 2018;64:S161-S189. doi:10.3233/JAD-179939
20. A Bennett D, A Schneider J, S Buchman A, L Barnes L, A Boyle P, S Wilson R. Overview and findings from the rush memory and aging project. *Curr Alzheimer Res*. 2012;9:646-663. doi:10.2174/156720512801322663
21. L Barnes L, C Shah R, T Aggarwal N, A Bennett D, A Schneider J. The minority aging research study: ongoing efforts to obtain brain donation in African Americans without dementia. *Curr Alzheimer Res*. 2012;9:734-745. doi:10.2174/156720512801322627
22. Fernandez MV, Liu M, Beric A, et al. Genetic and multi-omic resources for Alzheimer disease and related dementia from the knight Alzheimer disease research center. *Sci Data*. 2024;11:768. doi:10.1038/s41597-024-03485-9
23. Johnson SC, Koscik RL, Jonaitis EM, et al. The Wisconsin registry for Alzheimer's prevention: a review of findings and current directions. *Alzheimer's & Dement (Amst. Neth.)*. 2018;10:130-142. doi:10.1016/j.dadm.2017.11.007
24. Mukherjee S, Mez J, Trittschuh EH, et al. Genetic data and cognitively defined late-onset Alzheimer's disease subgroups. *Mol Psychiatry*. 2020;25:2942-2951. doi:10.1038/s41380-018-0298-8
25. Mukherjee S, Choi S, Lee ML, et al. Cognitive domain harmonization and cocalibration in studies of older adults. *Neuropsychology*. 2023;37:409. doi:10.1037/neu0000835
26. Harrison TM, Weintraub S, Mesulam MM, Rogalski E. Superior memory and higher cortical volumes in unusually successful cognitive aging. *J Int Neuropsychol Soc*. 2012;18:1081-1085. doi:10.1017/S1355617712000847
27. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group* under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology*. 1984;34:939-944. doi:10.1016/j.jalz.2011.03.005
28. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers & Dement: The J Alzheimer's Assoc*. 2011;7:263-269. doi:10.1016/j.jalz.2011.03.005
29. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol*. 2007;6:734-746. doi:10.1016/S1474-4422(07)70178-3
30. Yu L, Lutz MW, Farfel JM, et al. Neuropathologic features of TOMM40 '523 variant on late-life cognitive decline. *Alzheimer's & Dementia*. 2017;13:1380-1388. doi:10.1016/j.jalz.2017.05.002
31. Naj AC, Jun G, Beecham GW, et al. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nat Genet*. 2011;43:436-441. doi:10.1038/ng.801
32. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing; 2021.
33. Lee M, Hughes TM, George KM, et al. Education and cardiovascular health as effect modifiers of APOE $\varepsilon 4$ on Dementia: the atherosclerosis risk in communities study. *J Gerontol Biol Sci Med Sci*. 2022;77:1199-1207. doi:10.1093/gerona/glab299
34. Hohman TJ, Dumitrescu L, Barnes LL, et al. Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of tau. *JAMA Neurol*. 2018;75:989-998. doi:10.1001/jamaneurol.2018.0821
35. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol*. 1995;57:289-300. doi:10.1111/j.2517-6161.1995.tb02031.x
36. Juottonen K, Lehtovirta M, Helisalmi S, Sr PJR, Soininen H. Major decrease in the volume of the entorhinal cortex in patients with Alzheimer's disease carrying the apolipoprotein E $\varepsilon 4$ allele. *J Neurology, Neurosurgy, and Psychiatry*. 1998;65:322-327. doi:10.1136/jnnp.65.3.322

37. Snowden JS, Stopford CL, Julien CL, et al. Cognitive phenotypes in Alzheimer's disease and genetic risk. *Cortex*. 2007;43:835-845. doi:10.1016/s0010-9452(08)70683-x
38. Mukherjee S, Mez J, Trittschuh EH, et al. Genetic data and cognitively defined late-onset Alzheimer's disease subgroups. *Mol Psychiatry*. 2018;25:2942-2951. doi:10.1038/s41380-018-0298-8
39. Poirier J, Bertrand P, Poirier J, et al. Apolipoprotein E polymorphism and Alzheimer's disease. *The Lancet*. 1993;342:697-699. doi:10.1016/0140-6736(93)91705-q
40. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer disease meta analysis consortium. *JAMA*. 1997;278(16):1349-1356. doi:10.1001/jama.1997.03550160069041
41. Belloy ME, Andrews SJ, Le Guen Y, et al. APOE genotype and Alzheimer disease risk across age, sex, and population ancestry. *JAMA Neurol*. 2023;80:1284-1294. doi:10.1001/jamaneurol.2023.3599
42. Rosvall L, Rizzuto D, Wang H, Winblad B, Graff C, Fratiglioni L. APOE-related mortality: effect of dementia, cardiovascular disease and gender. *Neurobiol Aging*. 2009;30:1545-1551. doi:10.1016/j.neurobiolaging.2007.12.003
43. McKay GJ, Silvestri G, Chakravarthy U, et al. Variations in apolipoprotein E frequency with age in a pooled analysis of a large group of older people. *Am J Epidemiol*. 2011;173:1357-1364. doi:10.1093/aje/kwr015
44. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology*. 1998;51:728-733. doi:10.1212/wnl.51.3.728
45. Berlau DJ, Corrada MM, Head E, Kawas CH. APOE ε2 is associated with intact cognition but increased Alzheimer pathology in the oldest old. *Neurology*. 2009;72:829-834. doi:10.1212/01.wnl.0000343853.00346.a4
46. Shinohara M, Kanekiyo T, Yang L, et al. APOE2 eases cognitive decline during aging: clinical and preclinical evaluations. *Ann Neurol*. 2016;79:758-774. doi:10.1002/ana.24628
47. Rajan KB, Barnes LL, Wilson RS, et al. Racial differences in the association between apolipoprotein E risk alleles and overall and total cardiovascular mortality over 18 Years. *J Am Geriatr Soc*. 2017;65:2425-2430. doi:10.1111/jgs.15059
48. Beydoun MA, Weiss J, Beydoun HA, et al. Race, APOE genotypes, and cognitive decline among middle-aged urban adults. *Alzheimers Res Ther*. 2021;13:120. doi:10.1186/s13195-021-00855-y
49. Tang MX, Stern Y, Marder K, et al. The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and hispanics. *JAMA*. 1998;279(10):751-755. doi:10.1001/jama.279.10.751
50. Nsor NA, Bourassa KJ, Barnes LL, Brown CL. The effects of APOE alleles, cognitive activities, and social activities on cognitive decline in African Americans. *J Gerontol B, Psychol sci soci sci*. 2024;80(1):gbae172. doi:10.1093/geronb/gbae172
51. Shinohara M, Kanekiyo T, Tachibana M, et al. APOE2 is associated with longevity independent of Alzheimer's disease. *eLife*. 2020;19:e62199. doi:10.7554/eLife.62199
52. Ouellette N, Perls T. Race and ethnicity dynamics in survival to 100 years in the United States. *J Intern Med*. 2025;297:2-21. doi:10.1111/joim.20031
53. Logue MW, Dasgupta S, Farrer LA. Genetics of Alzheimer's disease in the African American population. *J Clin Med*. 2023;12:5189. doi:10.3390/jcm12165189
54. Reitz C, Jun G, Naj A, et al. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E ε4,and the risk of late-onset Alzheimer disease in African Americans. *JAMA*. 2013;309:1483-1492. doi:10.1001/jama.2013.2973
55. Rogalski EJ, Huentelman MJ, Roberts AC, et al. Enrollment and scientific progress of the multisite SuperAging research initiative. *Alzheimer's Dement*. 2023;19:e078625. doi:10.1002/alz.078625
56. Rogalski EJ, Huentelman MJ, Roberts AC, et al. The SuperAging research initiative: a multisite consortium focused on identifying factors promoting extraordinary cognitive aging. *Alzheimer's Dement*. 2022;18:e066407. doi:10.1002/alz.066407

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: Durant A, Mukherjee S, Lee ML, et al. Evaluating the association of *apolipoprotein E* genotype and cognitive resilience in SuperAgers. *Alzheimer's Dement*. 2026;22:e71024. https://doi.org/10.1002/alz.71024