Title: Evaluating the association of *APOE* genotype and cognitive resilience in SuperAgers

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Key Points

Question: Does the frequency of *APOE*-ε4 and *APOE*-ε2 alleles explain the exceptional memory of non-Hispanic Black and non-Hispanic White SuperAgers?

Findings: In this multicohort, multiracial study, SuperAgers had significantly higher proportions of *APOE*-ε2 alleles and lower proportions of *APOE*-ε4 alleles compared to Alzheimer's disease dementia cases. Non-Hispanic White SuperAgers had significantly lower proportions of *APOE*-ε4 alleles and significantly higher proportions of *APOE*-ε2 alleles compared to all cases and controls, including oldest-old (ages 80+) controls. In contrast, non-Hispanic Black SuperAgers had significantly lower proportions of *APOE*-ε4 alleles compared to cases and younger controls, and only significantly higher proportions of *APOE*-ε2 alleles compared to cases.

Meaning: This is the largest study to date to identify differences in *APOE*-ε4 allele frequency based on SuperAger status, and the first study of SuperAgers to find a relationship between *APOE*-ε2 allele frequency and SuperAger status. As has been found in studies of middle-aged (ages 50-64) and old (ages 65-79) adults, genetic resiliency in oldest-old (80+) age likely differs by genetic ancestry.

Abstract (350 words)

Importance: "SuperAgers" are oldest-old adults (ages 80+) whose memory performance resembles that of adults in their 50s to mid-60s. Factors underlying their exemplary memory are underexplored in large, racially diverse cohorts.

Objective: To determine the frequency of *APOE* genotypes in non-Hispanic Black and non-Hispanic White SuperAgers compared to middle-aged (ages 50-64), old (ages 65-79), and oldest-old (ages 80+) controls and Alzheimer's disease (AD) dementia cases.

Design: This multicohort study selected data from eight longitudinal cohort studies of normal aging and AD.

Setting: Variable recruitment criteria and follow-up intervals, including both population-based and clinical-based samples.

Participants: Inclusion in our analyses required *APOE* genotype, that participants be age 50+, and are identified as either non-Hispanic Black or non-Hispanic White. In total, 18,080 participants were included in the present study with a total of 78,549 datapoints.

Main Outcomes and Measures: Harmonized, longitudinal memory, executive function, and language scores were obtained from the Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium (ADSP-PHC). SuperAgers, controls, and AD dementia cases were identified by cognitive scores using a residual approach and clinical diagnoses across multiple timepoints when available. SuperAgers were compared to AD dementia cases and cognitively normal controls using age-defined bins (middle-aged, old, oldest-old).

Results: Across racialized groups, SuperAgers had significantly higher proportions of *APOE*-ε2 alleles and lower proportions of *APOE*-ε4 alleles compared to cases. Similar differences were observed between SuperAgers and middle-aged and old controls. Non-Hispanic White SuperAgers had significantly lower proportions of *APOE*-ε4 alleles and significantly higher proportions of *APOE*-ε2 alleles compared to all cases and controls, including oldest-old controls. In contrast, non-Hispanic Black SuperAgers had significantly lower proportions of *APOE*-ε4 alleles compared to cases and younger controls, and significantly higher proportions of *APOE*-ε2 alleles compared only to cases.

Conclusions and Relevance: In the largest study to date, we demonstrated strong evidence that the frequency of *APOE*-ε4 and -ε2 alleles differ between non-Hispanic White SuperAgers and AD dementia cases and cognitively normal controls. Differences in the role of *APOE* in SuperAging by race underlines distinctions in mechanisms conferring resilience across race groups given likely differences in genetic ancestry.

Introduction

"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] Studies suggest that resilience to Alzheimer's disease (AD) pathological changes and neurodegeneration may explain SuperAgers' high memory scores.[3-6] Further research is needed to elucidate factors conferring resilience to AD-related brain changes and subsequent cognitive decline in SuperAgers. Moreover, research is needed to explore resiliency factors in non-Hispanic Black (NHB) SuperAgers, as this group is largely understudied.[7]

APOE-ε4 is the strongest genetic risk factor for late-onset AD.[8] The Northwestern SuperAging project reported lower *APOE*-ε4 allele frequency in SuperAgers (N = 10-12) compared to non-demented older adults.[2,9] 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.[4-6,10-12] Notably, these studies have small SuperAger samples (N = 25-64)[4-6,10-12] oftentimes drawn from the same cohort, thus limiting their generalizability and reliability. Further, these studies exclusively include NHW participants.[4-6,10-12] To our knowledge, only one study has been published characterizing NHB SuperAgers (N = 61) and did not find a significant difference in *APOE*-ε4 allele frequency between SuperAgers and same-aged controls.[7] 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 a residual approach to evaluate harmonized cognitive domains (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 SuperAgers will possess a higher frequency of *APOE*-ε4 alleles and a lower frequency of *APOE*-ε2 alleles compared to both AD dementia cases and controls.

Methods

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 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.

Cognitive Domain Scores. Each cohort used different neuropsychological assessment tools to measure cognition which may not be on the same scale. We derived co-calibrated and harmonized cognitive domain scores for four domains (i.e., memory, executive function, language, and visuospatial) using confirmatory factor analysis.[24] 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. Visit the data dictionary at https://vmacdata.org/adsp-phc to explore the cognitive variables from each cohort that make up each cognitive domain.

For the purposes of this study, regression-based normative 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.

Participant Classification. Participants were grouped by race, clinical status, and age (**Figure 1A**). Age bins were decided based on the age-related criteria for SuperAgers (ages 80+) and the adults whose memory performance is compared to oldest-old adults to determine SuperAger status (ages 50-64).[25] 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. 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, or NINCDS-ADRDA).[26-28] 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 consciousness) or non-AD dementia (e.g., Dementia with Lewy Bodies, Vascular Dementia) diagnosed 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 score at or above the mean of middle-aged adults (ages 50-64), (2) executive function and language domain scores no lower 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 domain scores no lower than 1 standard deviation below their same-aged peers at a single visit, and (2) whose diagnosis remained "cognitively normal" for the duration of their study participation.

***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.[29,30]

Statistical Analyses. Statistical analyses were performed using R Statistical Software (v4.2.3.).[31] 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) and did not consider the additive effect of homozygosity. Models covaried for sex and years of education due to their known modifying effects on the relationship of *APOE* and late-life cognition.[32,33] Sensitivity analyses included analyses removing individuals with *APOE*-ε2/ε4 genotype and individuals with data from only a single timepoint. Correction for multiple comparisons was applied using Benjamini-Hochberg false discovery rate (FDR) procedure.[34] Results tables include odds ratios (OR), confidence intervals (CI), and FDR-corrected *p*-values.

Results

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; for example, while participants from BIOCARD completed an average of 9 ± 3 visits over 13 ± 4 years, participants from NIA-AD FBS completed an average of 1 ± 1 visits over 2 ± 3 years.

Average baseline age varied by cohort ($Age_{[all\ cohorts]}$ = 72 ± 10); the youngest cohorts on average, BIOCARD and WRAP, primarily recruited cognitively normal participants. Generally, cohorts were highly educated ($Years\ of\ Education_{[all\ cohorts]}$ = 15 ± 3), mostly female (62.9%), and mostly NHW (85.4%). The proportion of each *APOE* genotype differed by cohort, with higher proportions of ε3/ε4 and ε4/ε4 genotypes in cohorts with a higher proportion of AD dementia cases.

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.

***APOE* Allele Frequency.** In NHW comparisons (**Table 3A**), SuperAgers had a significantly higher frequency of *APOE*-ε2 alleles (**Figure 2A**) and a significantly lower frequency of *APOE*-ε4 alleles compared to all cases and controls (**Figure 2B**). In contrast, NHB SuperAgers (**Table 3B**) had a significantly higher frequency of *APOE*-ε2 alleles only compared to cases (**Figure 2C**), and a significantly lower frequency of *APOE*-ε4 alleles compared to all cases and controls except oldest-old controls (**Figure 2D**).

Sensitivity Analyses. Analyses were repeated removing individuals with an *APOE*-ε2/ε4 genotype. Given their low frequency, very few participants were removed (**Supplementary Table 1;** NHW SuperAgers: N = 1,393; NHB SuperAgers: N = 200) and findings were preserved (**Supplementary Table 2**).

Analyses were also repeated including only individuals with longitudinal data. Across racialized groups, SuperAgers' sample size was more substantially reduced (**Supplementary Table 3;** NHW SuperAgers: N = 1,053; NHB SuperAgers: N = 160). Findings were relatively similar; however, differences in *APOE*-ε2 and -ε4 allele frequency between NHW SuperAgers and oldest-old controls were no longer significant (**Supplementary Table 4**).

Discussion

Mechanisms conferring resilience to memory decline in oldest-old age are yet unknown. This is the largest study to date of *APOE*-ε4 and -ε2 allele frequency in both NHW and NHB SuperAgers. Across 8 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 proportion of *APOE*-ε2 alleles and a lower proportion of *APOE*-ε4 alleles compared to individuals with AD dementia. Unlike 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, NHW oldest-old adults with ≥1 ε4 allele were 0.81 less likely to be a SuperAger, and those with ≥1 ε2 allele were 1.28 more likely to be a SuperAger. This finding held when ε2/ε4 carriers were removed from analyses. *APOE* genotype did not significantly differentiate NHB SuperAgers and oldest-old controls. Differences in the relationship of *APOE* allele frequency and SuperAger status across racialized group suggests differences in the role of genetics in resilience to memory decline in oldest-old age.

APOE-ε4 is the strongest genetic risk factor for late-onset AD,[8] and has been shown to be related to increased entorhinal and hippocampal atrophy[35] and amnestic cognitive impairment.[36,37] Our data are supportive of these findings, such that AD dementia cases had a greater proportion of *APOE*-ε4 alleles compared to controls.[38] Unlike most studies of genetic resilience in SuperAgers, we found that NHW SuperAgers had a lower proportion of *APOE*-ε4 alleles compared to oldest-old adults with typical memory performance. This was found in one previous study published by Rogalski and colleagues,[2] but was not replicated by subsequent studies with larger samples of SuperAgers.[4-6,10-12] This finding is relatively unexpected. Across racialized groups, the effect of *APOE*-ε4 is most impressive prior to age 70.[39,40] Additionally, *APOE*-ε4 carriership is related to increased mortality.[41,42] 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.

The protective *APOE*-ε2 allele is related to lower likelihood of late-onset AD dementia[13, 43] and better cognitive performance in older adults even in the presence of AD neuropathology.[44] 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.[43] Despite this, 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.[43]

Genetic factors underlying the superior memory performance of NHB SuperAgers, a critically under-diagnosed and understudied group, are relatively unknown.[7] Previous research suggests that, while NHB individuals have higher proportions 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.[40,47-49] The effect is 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.[40] Similar to *APOE*-ε4, NHB individuals have higher proportions 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.[40] In fact, a recent study from the MARS cohort found that NHB older adults (ages 65+) with more *APOE*-ε2 alleles had slower cognitive decline over a 10-year study period.[50] Additionally, *APOE*-ε2 carriership was related to better survival in a sample of NHB and NHW individuals from NACC with and without AD neuropathology.[46] In the present study, NHB SuperAgers had significantly lower proportions of *APOE*-ε4 alleles compared to cases and younger controls, and significantly higher proportions of *APOE*-ε2 alleles compared only to cases. The lack of difference in APOE allele carriership between NHB SuperAgers and oldest-old controls may be explained by survivorship bias; recent research indicates that NHB adults have higher probability of survival from ages 70 and 80 to 100 compared to NHW adults.[51] NHB SuperAgers and other oldest-old adults may share environmental and genetic factors, including *APOE*-ε2 allele carriership, that support survival and reduced mortality risk in older age.

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.[7] 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.

Strengths and Limitations. The present study has several strengths, including being the largest and most racially diverse of its kind to explore the relationship of *APOE* genotype and optimal memory performance in both NHW and NHB SuperAgers. Our study also has several limitations. Firstly, the smaller sample size of NHB SuperAgers compared to NHW SuperAgers makes it difficult to interpret differences in the statistical significance of the relationship of *APOE* allele frequency and SuperAger status across racialized groups. As mentioned previously, targeted recruitment of NHB SuperAgers is required to clarify the contribution of genetics to the superior memory performance of NHB adults in old age. Additionally, studies have identified other genetic factors that may confer greater AD risk in NHB older adults compared to *APOE*, including *ABCA7*.[52,53] Future studies will need to consider other genetic factors that may be more 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.[40] Subsequent research leveraging advanced genetic analyses to consider admixture may further our understanding of genetic profiles underlying AD risk.

While most participants in the present study had longitudinal data to support their participant classification, many participants did not. Sensitivity analyses with only individuals with longitudinal data included only 1,053 NHW SuperAgers and 160 NHB SuperAgers, likely affecting our ability to detect significance. Defining SuperAgers using longitudinal data is likely more robust, as it is unclear whether participants with a single timepoint of cognitive data and clinical diagnoses will remain within their participant classification over time.[54] 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] This research will contribute tremendously to our understanding of factors conferring resilience in oldest-old age.

Conclusions. We have limited knowledge of the genetic factors that contribute to optimal memory performance in oldest-old age. This is the largest study to date to identify differences in *APOE*-ε4 allele frequency based on SuperAger status, and the first study of SuperAgers to find a relationship between *APOE*-ε2 allele frequency and SuperAger status. The present study reveals important information about potential differences in the genetic factors associated with exceptional memory in oldest-old adults, a group at the highest risk for AD neuropathologic accumulation and dementia. While significant findings were restricted to NHW comparisons, study results importantly direct our attention to other genetic risk factors that may be more important to the cognitive resilience of NHB oldest-old adults.

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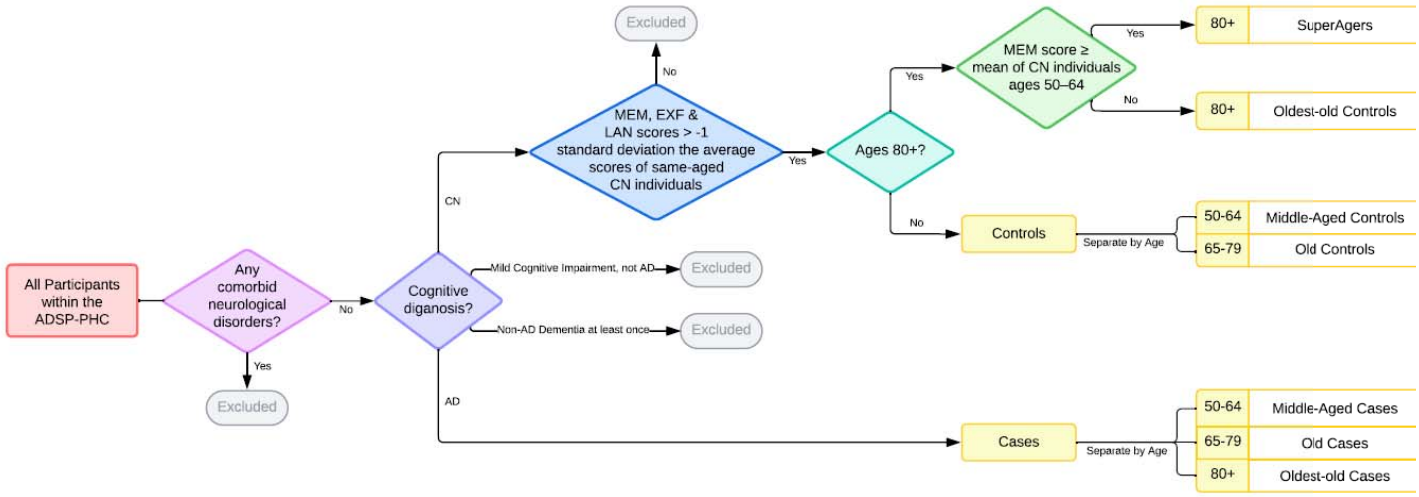
A



B

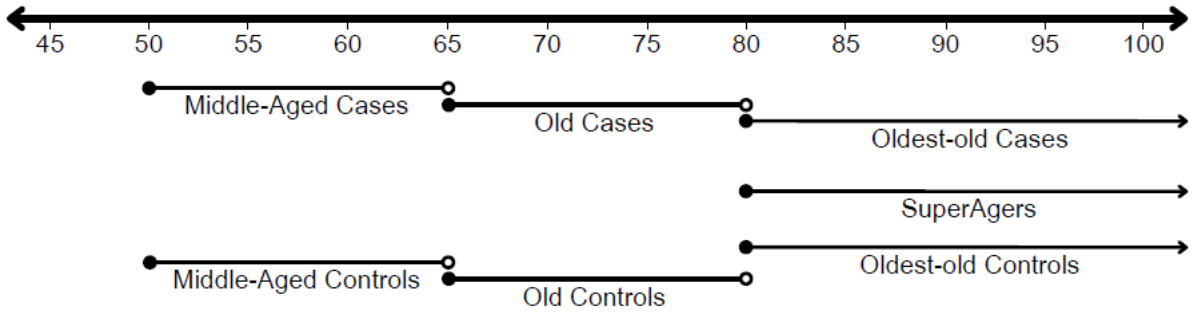
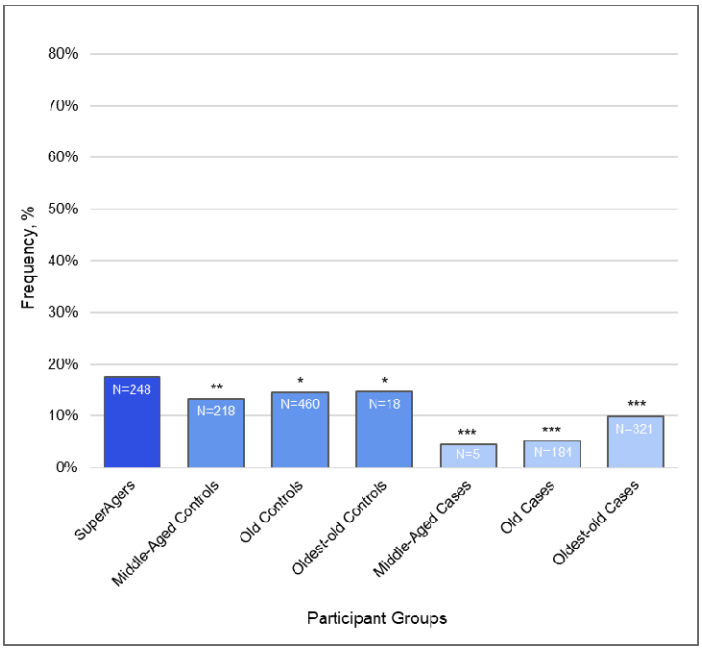
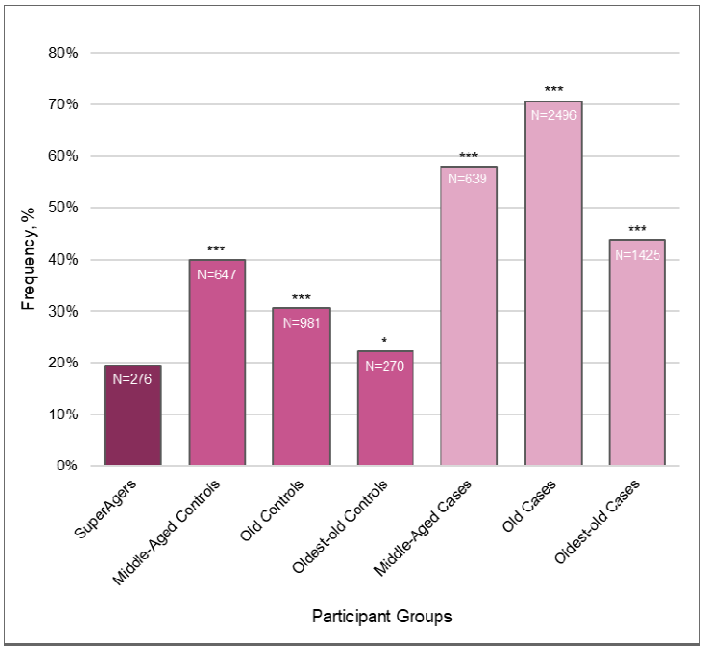


Figure 1. Flow Diagram for Participant Classification of SuperAgers, Cases, and Controls. (A) Flowchart depicting inclusion and exclusion criteria for identifying SuperAgers, AD dementia cases, controls. (B) Flowchart depicting selection order of SuperAgers, cases, and controls. Age range of participants 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. Abbreviations: ADSP-PHC, Alzheimer's Disease Sequencing Project – Phenotype Harmonization Consortium; AD, Alzheimer's Disease; CN, Cognitively Normal; MEM, Memory; EXF, Executive Functioning; LAN, Language.

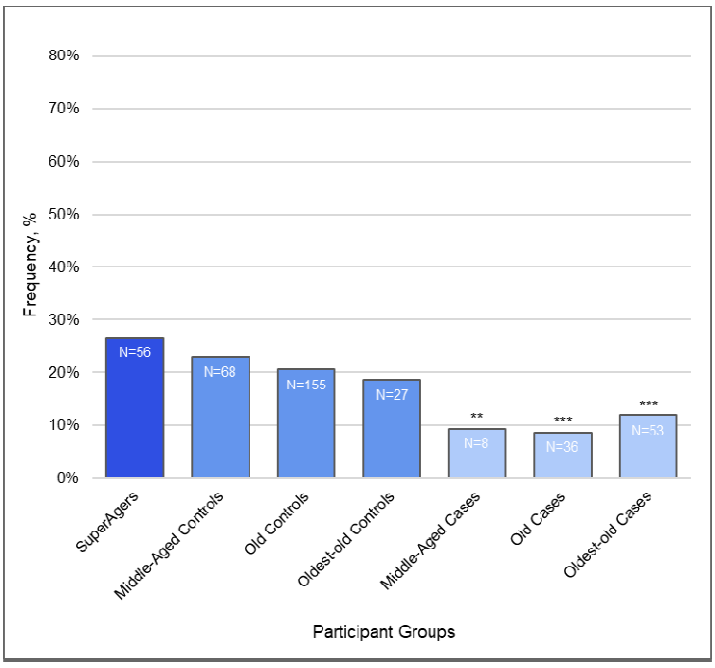
A. NHW *APOE*-ε2 Carriers



C. NHW *APOE*-ε4 Carriers



C. NHB *APOE*-ε2 Carriers



D. NHB *APOE*-ε4 Carriers

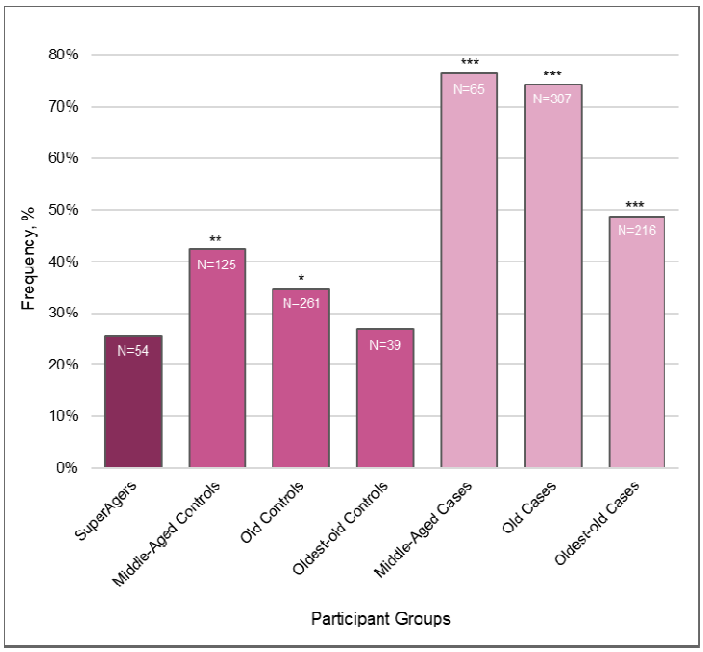


Figure 2. *APOE* Allele Frequency in Non-Hispanic White and Non-Hispanic Black SuperAgers Compared to Cases and Controls. Bar charts depicting *APOE*-ε2 and *APOE*-ε4 allele frequency for SuperAgers, cases, and controls across age-defined subgroups. Participant classification is indicated by the X-axis, 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). Abbreviations: NHW, Non-Hispanic White; NHB, Non-Hispanic Black.

Table 1. Participant Characteristics by Cohort.

Participant Demographics	All	ACT	ADNI	BIOCARD	Knight ADRC	NACC	NIA-AD FBS	ROS, MAP, MARS	WRAP
No. participants	18080	2188	825	51	735	11851	645	1462	323
No. 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: NHW, Non-Hispanic White; ACT, Adult Changes in Thought; ADNI, Alzheimer's Disease Neuroimaging Initiative; BIOCARD, Biomarkers of Cognitive Decline Among Normal Individuals; Knight ADRC, Knight Alzheimer's Disease Research Center at Washington University; NACC, National Alzheimer's Coordinating Centers; NIA-AD FBS, National Institute on Aging Alzheimer's Disease Family Based Study; ROS, Religious Orders Study; MAP, Memory and Aging Project; MARS, Minority Aging Research Study; WRAP, Wisconsin Registry for Alzheimer's Prevention.

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. participants	1412	1622	3202	1213	1101	3528	3258
No. observations	11528	7067	12308	6980	2692	10858	15434
Visits, mean (SD)	8 (5)	4 (3)	4 (3)	6 (4)	2 (2)	3 (2)	5 (4)
Follow-up time, mean (SD), y	10 (6)	6 (5)	4 (4)	8 (6)	2 (2)	2 (3)	5 (6)
Baseline age, mean (SD), y	77 (7)	57 (5)	70 (4)	79 (7)	59 (5)	73 (4)	83 (6)
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. participants	211	296	752	145	85	413	444
No. observations	1830	1024	3106	827	171	1300	2281
Visits, mean (SD)	9 (5)	3 (3)	4 (3)	6 (4)	2 (1)	3 (3)	5 (5)
Follow-up time, mean (SD), y	9 (6)	4 (4)	4 (4)	6 (5)	1 (1)	3 (3)	5 (6)
Baseline age, mean (SD), y	77 (6)	59 (4)	70 (4)	79 (6)	60 (4)	73 (4)	83 (6)
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; (B) Non-Hispanic Black

Table 3. Logistic Regression Model Results Comparing *APOE*-ε2 and -ε4 Allele Frequency among SuperAgers, Cases, and Controls.

A

	APOE-ε2		*APOE*-ε4	
	OR (CI)	P_{FDR}	OR (CI)	P_{FDR}
SuperAgers vs. Middle-Aged Controls	1.38 (1.13, 1.68)	*0.0023*	0.37 (0.31, 0.43)	*<0.0001*
SuperAgers vs. Old Controls	1.24 (1.05, 1.47)	*0.0148*	0.55 (0.47, 0.64)	*<0.0001*
SuperAgers vs. Oldest-Old Controls	1.28 (1.03, 1.59)	*0.0347*	0.81 (0.67, 0.99)	*0.0441*
SuperAgers vs. Middle-Aged Cases	4.55 (3.30, 6.27)	*<0.0001*	0.18 (0.15, 0.21)	*<0.0001*
SuperAgers vs. Old Cases	4.02 (3.26, 4.96)	*<0.0001*	0.09 (0.08, 0.11)	*<0.0001*
SuperAgers vs. Oldest-Old Cases	2.03 (1.68, 2.44)	*<0.0001*	0.32 (0.27, 0.37)	*<0.0001*

B

	APOE-ε2		*APOE*-ε4	
	OR (CI)	P_{FDR}	OR (CI)	P_{FDR}
SuperAgers vs. Middle-Aged Controls	1.19 (0.79, 1.80)	0.4295	0.48 (0.33, 0.71)	*0.0005*
SuperAgers vs. Old Controls	1.41 (0.99, 2.01)	0.0787	0.66 (0.47, 0.94)	*0.0353*
SuperAgers vs. Oldest-Old Controls	1.63 (0.93, 2.85)	0.1146	1.18 (0.70, 1.98)	0.5638
SuperAgers vs. Middle-Aged Cases	3.59 (1.60, 8.06)	*0.0051*	0.12 (0.07, 0.22)	*<0.0001*
SuperAgers vs. Old Cases	4.56 (2.75, 7.55)	*<0.0001*	0.12 (0.08, 0.18)	*<0.0001*
SuperAgers vs. Oldest-Old Cases	2.73 (1.75, 4.25)	*<0.0001*	0.39 (0.27, 0.57)	*<0.0001*

(A) Non-Hispanic White; (B) Non-Hispanic Black. Abbreviations: OR, Odds Ratio; CI, Confidence Interval (95%); P_{FDR}, FDR-corrected P-value.