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Publication Date

2023-11-01

DOI

10.1016/j.neurobiolaging.2023.07.021

Peer reviewed

HHS Public Access

Author manuscript

Neurobiol Aging. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

Neurobiol Aging. 2023 November ; 131: 144–152. doi:10.1016/j.neurobiolaging.2023.07.021.

Biomarkers of Alzheimer's disease in Black and/or African American Alzheimer's Disease Neuroimaging Initiative participants

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CRediT authorship contribution statement:

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[*]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Disclaimer:

This article was prepared while first author, Dr. Renee C. Groechel, was at Boston University Chobanian & Avedisian School of Medicine. Dr. Groechel is now employed at the National Institute of Neurological Disorders & Stroke (NINDS) Intramural Research Program, National Institute of Health (NIH). Dr. Groechel's present address and email are stated above. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States Government.

Disclosure Statement: None of the authors part of this work have any conflicts of interests.

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Abstract

Majority of dementia research is conducted in non-Hispanic White participants despite a greater prevalence of dementia in other racial groups. To obtain a better understanding of biomarker presentation of Alzheimer's disease (AD) in the non-Hispanic White population, this study exclusively examined AD biomarker abnormalities in 85 Black and/or African American participants within the Alzheimer's Disease Neuroimaging Initiative (ADNI). Participants were classified by the ADNI into three clinical groups: cognitively normal, mild cognitive impairment, or dementia. Data examined included demographics, *APOE* ε4, cerebrospinal fluid (CSF) $A\beta_{1–42}$, CSF total tau (t-tau), CSF phosphorylated tau (p-tau), 3T magnetic resonance imaging (MRI), and measures of cognition and function. Analyses of variance and covariance showed lower cortical thickness in five of seven selected MRI regions, lower hippocampal volume, greater volume of white matter hyperintensities, lower measures of cognition and function, lower measures of CSF $A\beta_{1–42,}$ and greater measures of CSF t-tau and p-tau between clinical groups. Our findings confirmed greater AD biomarker abnormalities between clinical groups in this sample.

Keywords

amyloid-beta; biomarkers; Black or African American; cerebrospinal fluid; cognition; dementia; magnetic resonance imaging; mild cognitive impairment; race; tau

1. Introduction

An overwhelming number of participants in studies of dementia identify as non-Hispanic White yet older Black adults (including but not limited to those of African or Caribbean descent) are reported to be nearly twice as likely to develop dementia (Canevelli et al, 2019; Mayeda et al, 2016; Raman et al, 2021).This disparity has been attributed to social determinants of health, racial inequities in access to education and health care, and other risk factors such as the apolipoprotein E *(APOE)* ε4 genotype and the prevalence of cardiovascular diseases (Canevelli et al, 2019, Carvalho et al., 2015; Walker et al, 2021). It remains unclear how these factors interact and ultimately lead to dementia (Barnes, 2022; Fleishman et al, 2022; Shin & Doraiswamy, 2016).

An example of the underrepresentation of Black and/or African American individuals in dementia research studies is illustrated in the multisite Alzheimer's Disease Neuroimaging Initiative (ADNI). This initiative consists of 59 sites across North America and has been successful in obtaining data from thousands of older adults yet less than 5% of ADNI data collected thus far has come from Black and/or African American participants (Gianattasio et al., 2021). This discrepancy is not an isolated problem of the ADNI study as it is commonly

seen in other large datasets and clinical trials intended for Alzheimer's disease (AD) research advancement (Franzen et al., 2022; Saiyasit et al., 2022). Similarly, recruitment and retainment efforts in Black and/or African American participants and other racial minority groups has been unsuccessful in broader long-term health outcomes research. Altogether, this precludes our understanding of the effectiveness of clinical interventions in racial minority groups (Babulal et al., 2022; Saiyasit et al., 2022; Taylor et al., 2022; Webb et al., 2022).

Recent studies have sought to compare the presentation of AD biomarkers such as amyloid beta (Aβ), tau, or neurodegeneration in older adults that identify as non-Hispanic White or Black and/or African American to better understand why there is an increased prevalence of dementia in older Black and/or African American adults (Garrett et al, 2019; Howell et al., 2017; McDonough, 2017; Morris et al., 2019). These studies have helped increase awareness of the underrepresentation of racial minority groups in research studies and highlighted the significant need for understanding what racial disparities exist in diseases such as AD and/or dementia. However, a shortcoming of such comparisons stems from selection and ascertainment bias in enrollment which can translate to Black and/or African American participants in such studies not being representative of the broader US Black population (Deters et al., 2021; Fleischman et al., 2021; Manly et al, 2021). This is commonly reflected in factors such as educational attainment, socioeconomic status, and cardiovascular disease risk. For instance, many Black and/or African American participants enrolled in the ADNI have roughly 16 years of schooling, (the equivalent of a college education) whereas data from the US Census Bureau shows that only 25% of all Black Americans aged 25 and older have a college degree (US Census Bureau, 2020). Meanwhile, selection and ascertainment bias still exist in the non-Hispanic White population but are less prominent because this group has greater enrollment in dementia research studies, thus allowing non-Hispanic White participants to represent a wider breath of the total population. Ultimately, making comparisons between the two racial groups, particularly when one is not as representative as the other, can lead to skewed or biased interpretations (Deters et al., 2021; Fleischman et al., 2021).

In hopes to better understand *why* one racial group is more at risk to develop AD and/or dementia than the other, we elected to focus analyses in the present study on data we have from Black and/or African American participants currently enrolled in the ADNI. Exclusively examining biomarker presentation in Black and/or African American participants may provide insight as to how links between brain structure, cognitive performance, and neuropathology within this racial minority group relate to dementia prevalence. Equally pertinent to our understanding of dementia in this population is the study of *APOE* ε4, the strongest risk gene that has been identified for late-onset AD (Rajabli et al., 2018). Recent studies have shown that both the prevalence and impact of this genotype on AD risk may vary between racial groups and perhaps have less impact in Black and/or African Americans individuals than in non-Hispanic White individuals (Berg et al., 2019; Deters et al., 2021; Qin et al., 2021; Rajabli et al., 2018; Ren et al., 2021). Altogether, understanding these associations between morphometry, cognition, pathology, and genetics could be essential to the development of successful interventions and appropriate clinical trials (Fleischman et al., 2021). Our hypothesis was that there would be a greater number

of AD biomarker abnormalities between the clinical groups (dementia > mild cognitive impairment (MCI) > cognitively normal). Differences were assessed using a framework of biomarkers commonly used in AD research such as magnetic resonance imaging (MRI) data, cognitive and functional measures, cerebrospinal fluid (CSF) measures of amyloid beta 1–42 peptide ($A\beta_{1-42}$) and tau, and *APOE* ε4 carrier status.

2. Material and Methods

2.1 Participants

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biomarkers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

After carefully examining all demographic data within the ADNI Image and Data Archives, we identified 85 individuals who self-identified as “Black or African American,” “not Hispanic/Latino,” and had a 3T MRI scan. Data were downloaded from the ADNI database in August 2020 and CSF data were updated in April 2021. All participants were scanned between 2006 – 2020 at 41 different ADNI sites. Three clinical groups (cognitively normal (CN), MCI, and AD) were defined by the ADNI Clinical Core (Petersen et al., 1999; Petersen et al., 2014). Per guidelines of the ADNI Clinical Core, participants diagnosed as CN must have been free of memory complaints (beyond what would be expected for aged adults) and those with MCI must have abnormal memory function or a subjective memory concern with otherwise preserved functional performance in other cognitive domains. Participants diagnosed as “having” AD were required to have abnormal memory function and performance further diminished on neuropsychological testing such as the Clinical Dementia Rating (CDR ®) and Logical Memory Delayed Recall (for further details, see ADNI Study protocols). In the present study, the AD group will be referred to as the dementia group. Demographic and *APOE* ε4 data are listed in Table 1. Imaging, cognitive and functional assessments, and CSF data for each participant were obtained within ~3 months of each other. Written informed consent or assent was obtained from all participants, and study procedures were approved by the institutional review board at each of the ADNI participating sites.

2.2 Imaging Assessments

The neuroimaging methods and parameters utilized by ADNI for T1 and fluid attenuated inversion recovery (FLAIR) scans have been described (Jack et al., 2008; Wyman et al., 2013). Visual inspection for artifact and unexpected neuropathology by the ADNI MRI core was completed at the time of image upload to the ADNI. Upon downloading, we also visually inspected the images for artifacts that could have impaired image processing. All scans downloaded from the ADNI database were in their native DICOM format and obtained from baseline visits except in the case of 7 participants for whom 3T MRI data were not available at baseline and later scans were used.

2.2.1 T1 Scans—T1 scans from all 85 participants were processed using Freesurfer version 6.0 (https://surfer.nmr.mgh.harvard.edu/) on a Mac Pro 2013 running OS version 10.14.5 to obtain cortical parcellations and subcortical segmentation of anatomical regions (Desikan et al., 2006; Iglesias et al., 2015). Regions of interest (ROI) were parcellated using the Desikan-Killiany atlas and included the entorhinal cortex, inferior parietal lobule, middle temporal gyrus, parahippocampal gyrus, posterior division of the cingulate cortex, precuneus, and insula. These regions were chosen based on previous studies which have shown these ROI are commonly implicated in the progression of AD (Fennema-Notestine et al., 2009; Zhou et al., 2016). The average thickness of each ROI was calculated between the right and left hemispheres and used in statistical analyses. Estimated total intracranial volume (eTIV), total hippocampal volume (right and left hemispheres added together), and total cerebral white matter volume were also generated by Freesurfer.

2.2.2 FLAIR Scans—Of the 85 participants in this study, 78 had FLAIR scans available for download from the same imaging session as the T1 scans. Six of the participants without FLAIR scans had imaging conducted prior to when the FLAIR sequence became part of ADNI protocol and images for one participant failed to process correctly and were excluded. Thirty-six participants had FLAIR scans completed with 3D acquisition and the other forty-two were completed using 2D acquisition. Scans were processed using the Lesion Segmentation Toolbox (LST) running on MatlabR2019b on a Mac Pro 2013 running OS version 10.14.5 (Ribaldi et al., 2021; Schmidt et al., 2012). The Lesion Prediction Algorithm was used to perform a dual channel form of segmentation using both T1 and FLAIR scans. The kappa threshold used was the default measure (0.5) and only lesions > 0.015 mL were identified. The output measure obtained through LST was volume of white matter hyperintensity (WMH) lesions which were consequently log-transformed to reduce skewness (Barnes et al., 2013; DeCarli et al., 2008).

2.3 Assessment of Cognition and Function

All 85 participants performed testing in English at one of the ADNI sites. Details pertaining to ADNI testing procedures have been described previously (Aisen et al., 2010; Aisen et al., 2015). Data from the following eight measures were used in our between-clinical group analyses: (1) Functional Activities Questionnaire (FAQ), (2) Logical Memory Immediate Recall (modified from the Wechsler D. Wechsler Memory Scale-Revised, San Antonio, Texas: Psychological Corporation; 1987), (3) Category Fluency (Animals), (4) Boston Naming Test, (5) Number of Trials Learned on and (6) Sum of Total Trials on the Rey Auditory Verbal Learning Test (RAVLT), (7) Part A and (8) Part B of the Trailmaking Test. None of these eight measures are used by the ADNI Clinical Core to determine clinical groups. To standardize the data, raw scores were converted to z-scores. Direction of scores was not altered.

2.4 CSF Sampling and Analysis

Of the 85 participants in this study, 48 consented to undergo CSF sampling and had CSF measures generated by ADNI. Standard practice of the ADNI is to measure concentrations of the $A\beta_{1–42}$, total tau (t-tau), and tau phosphorylated at threonine 181 (p-tau) in collected

CSF samples. Samples were obtained at the various ADNI sites via lumbar puncture as described previously (Shaw et al., 2009).

2.5 Statistical Analysis

All analyses were performed in JMP Pro V15.2 on a MacBook Pro 2015 running OS version 10.15.7. Analyses of variance (ANOVAs) were used to assess differences between the CN, MCI and dementia clinical groups in age and years of education. Chi-square testing was used to assess the distribution in categorical variables such as sex and *APOE* ε4 carrier status. Statistical significance was set at $p < 0.05$ without correction.

The means and standard deviations of MRI measures, CSF samples, and cognition and functional z-scores between clinical groups are shown in Tables 1–2. Models assessing the main effect of clinical group were completed within each group of dependent variables (cortical thickness of selected ROI, hippocampal volume, WMH volume, measures of cognition and function, CSF sampling). Prior to creating models, linear regressions were used to determine whether covariates such as age and years of education influenced the measures. For MRI measures of hippocampal and WMH volume, additional linear regressions were conducted to determine whether covariates such as eTIV, total cerebral white matter, and FLAIR acquisition (2D or 3D) influenced these measures. Post hoc Tukey's Honestly Significant Difference (HSD) test was performed for all significant results and pairwise significant group differences, *p* values, and 95% confidence intervals (CI) are shown (Tables 3–5). For models including measures of cortical thickness and cognition/function, multiple comparisons were corrected for by use of the Benjamini-Hochberg method (Benjamini & Hochberg, 1995). Secondary analyses were run assessing the main effect of *APOE* ε4 carrier status and the interaction of clinical group (CN, MCI, and dementia) and *APOE* ε4 carrier status on each set of dependent variables (Table 6). The purpose of theses analyses was to better understand if being an *APOE ε4* carrier modifies the effect clinical group has on any of the examined outcome measures. To account for missing data in features such as CSF, *APOE* ε4, and FLAIR (WMH) data, we conducted sensitivity analyses to further assess potential demographic differences in those with missing measures. All statistical analyses used in this study assume missingness at random.

3. Results

Demographic data is shown in Table 1. Clinical groups (CN, MCI, and dementia) did not differ in age nor years of education ($p > 0.05$). Chi-square testing showed there were significantly more females (n = 57) than males (n = 28) in the study ($p = 0.002$), but that the number of males and females in the CN, MCI and dementia clinical groups was not significantly different ($p = 0.36$). Years of education was not significantly different between males and females ($p = 0.50$).

Of the 85 participants in this study, 74 had *APOE* ε4 genotyping (Table 1). Those with 1 or 2 ε4 alleles were classified as "carriers" (n = 33; 44.6%) and participants with 0 ε4 alleles were classified as "non-carriers" (n = 41; 55.4%). Chi-square testing revealed a significant difference between the clinical groups in proportion of *APOE* ε4 carriers (p = 0.02) but no sex difference in the number of carriers ($p = 0.23$). Follow-up pairwise chi-square testing

revealed differences in carrier status between CN-MCI clinical groups ($p = 0.002$) and CN-dementia clinical groups ($p = 0.007$).

Age had a significant effect on all MRI measures (cortical thickness, hippocampal volume, and log-transformed WMH volume) and was included in all models assessing MRI measures as a covariate. FLAIR acquisition had a significant effect on log-transformed WMH volume and was included as a covariate in this model. The results of ANCOVA models assessing the main effect of clinical group and significant pairwise group differences following Tukey's HSD test for MRI measures are shown in Table 3. The main effect of clinical group remained significant for all five cortical regions after correction for multiple comparisons using the Benjamini-Hochberg method. Age had a significant effect ($p < 0.02$) in the negative direction on average cortical thickness of the entorhinal cortex, middle temporal gyrus, and insula and on volume of the hippocampus and WMH. The effect of acquisition (2D or 3D) on log-transformed WMH volume was significant ($p = 0.03$). Two-way ANCOVAs exploring the interaction of *APOE* ε4 carrier status and clinical group (with aforementioned covariates) on all MRI measures were not significant.

Age had a significant effect on cognitive and functional z-scores and was included in cognitive and functional models as a covariate. The results of ANCOVAs models assessing the main effect of clinical group and significant pairwise group differences following Tukey's HSD test for measures of cognition and function are shown in Table 4. The main effect of clinical group remained significant for all eight measures following correction for multiple comparisons using the Benjamini-Hochberg method. Age showed a significant effect ($p < 0.04$) in the negative direction on performance of Parts A and B of the Trailmaking Test and the Boston Naming Test.

Two-way ANCOVAs exploring the interaction of *APOE* ε4 carrier status and clinical group (with age as a covariate) on z-scored measures of cognition and function showed a significant interaction on the FAQ. Tukey's HSD test showed the mean z-scored performance on the FAQ was significantly different between *APOE* ε4 carriers and non-carriers with dementia (Table 6). The main effects of *APOE* ε4 carrier status ($p < 0.001$) and clinical group ($p < 0.001$) were significant for this model. The interaction failed to reach significance on the seven other measures of cognition and function.

Neither age nor education influenced CSF measures. The results of ANOVAs models assessing the main effect of clinical group and significant pairwise group differences following Tukey's HSD test for CSF measures are shown in Table 5. Two-way ANOVAs showed a significant interaction of *APOE* ε4 carrier status and clinical group on t-tau and p-tau. Tukey's HSD test showed significant differences between MCI *APOE* ε4 carriers and non-carriers for both CSF t-tau and p-tau (Table 6). The main effects of clinical group (t-tau: $p < 0.001$, p-tau: $p < 0.001$) and *APOE* ε4 carrier status (t-tau: $p = 0.03$, p-tau: $p = 0.05$) were significant for this model. The interaction failed to reach significance on CSF $A\beta_{1–42}$. Lastly, sensitivity analyses conducted to assess demographic differences in participants with missing CSF measures, *APOE* ε4, or FLAIR (WMH) data were not statistically significant (Supplemental Tables 1–3).

4. Discussion

The goal of this study was to examine AD biomarkers in Black and/or African American ADNI participants with diagnoses ranging from CN to MCI to dementia. Focusing on biomarker presentation exclusively in older Black and/or African American participants may aid our understanding of how brain structure, cognitive performance, and neuropathology are linked and related to the development of dementia within this underrepresented group (Babulal et al., 2019; Fleischman et al., 2021; Garrett et al., 2019; Howell et al., 2017; McDonough, 2017; Morris et al., 2019; Shin & Doraiswamy, 2016). Our hypothesis was that there would be greater AD biomarker abnormalities between the clinical groups (dementia > MCI > CN). Findings from T1 and FLAIR MRI measures, cognition and function, and CSF measures of $A\beta_{1-42,}$ t-tau, and p-tau supported this hypothesis. An interaction was shown when we examined the influence of *APOE* ε4 carrier status and clinical group on the FAQ, CSF t-tau, and CSF p-tau. Age also influenced all MRI variables and measures of cognition and function.

Our study and previous AD studies in diverse and non-Hispanic White populations have continually shown that dementia clinical groups typically have a greater proportion of *APOE* ε4 carriers than MCI or CN clinical groups (Cacciaglia et al., 2018; Powell et al., 2021). In comparison to existing studies that have analyzed the proportion of *APOE* ε4 in Black or African American participants, the prevalence of *APOE* ε4 (44.6%) was slightly higher in this sample than is typically reported in pooled reviews or large samples (see review by Qin et al., 2021; Powell et al., 2021) yet consistent with other reports from clinical research studies (Morris et al., 2019). It can be noted that within this sample, 7 out of 9 participants with dementia and available *APOE* genotype data were ε4 carriers whereas the proportion of carriers who were MCI or CN was much lower. The variation in prevalence of carriers in different research cohorts has been previously discussed. It is possible this variation may reflect differences in target populations that are recruited through clinical cohorts versus community- based samples among other factors (Gianattasio et al., 2021).

Average thickness of five of seven cortical ROI and total hippocampal volume differed between the clinical groups. Not surprisingly, the greatest differences in cortical regions and hippocampal volume were found when comparing CN-dementia clinical groups. We further saw differences in thickness of the entorhinal cortex and parahippocampal gyrus and volume of the hippocampus when comparing MCI-dementia clinical groups. Average thickness of the posterior division of the cingulate cortex was also different between CN-MCI clinical groups. Few studies have reported on cortical thickness findings in Black and/or African American participants but these specified ROI findings align with abnormalities observed in non-Hispanic White participants (Fennema-Notestine et al., 2009; Zhou et al., 2016).

Analysis of MRI data further showed a significant difference in log-transformed volume of WMH between CN-dementia clinical groups. This finding is consistent with a previous study conducted in a sample of older Black participants which showed WMH volume was increased in frontal and parietal lobes in MCI participants and even more so in participants with dementia relative to controls (Meier et al., 2012). Other studies examining the relationship between WMH, cardiovascular health, and dementia risk in cohorts with

diverse representation have shown findings that align with the present study (Carmichael et al., 2012; DeCarli et al., 2008; Walker et al., 2021).

Our findings examining cognition and function further supported our hypothesis as performance on all eight measures differed between the clinical groups. These findings are consistent with previous studies conducted in two other Black and/or African American cohorts showing lower performance (on many of the same cognitive measures examined) in participants with dementia followed by MCI and CN participants (Gamaldo et al., 2010; Meier et al., 2012). Similar to previous studies, our analysis showed that memory function, the hallmark clinical symptom of dementia, was worst in participants with dementia and differences in memory function were apparent between the pre-dementia (CN-MCI) clinical groups as well. Cognitive tests that assessed language and executive function, such as the Boston Naming Test and Trailmaking Test, showed significant differences between MCI-dementia clinical groups. These findings are consistent with dementia research in non-Hispanic White participants which have shown that language and executive function are typically affected after memory impairment and in later development of AD (Joubert et al., 2016; Toepper, 2017). Our study further showed a unique interaction between the *APOE* ε4 genotype and the FAQ. In these analyses, *APOE* ε4 carriers with dementia had an increased FAQ score, which indicates greater dependency on others to assist with daily activities, in comparison to non-carriers with dementia. This interaction was not shown with other cognitive measures.

CSF findings in this sample of Black and/or African American ADNI participants were also supportive of our hypothesis. Observing differences in CSF $A\beta_{1–42}$ limited to the CN-dementia groups, whereas changes in CSF t-tau and p-tau were also apparent between MCI-dementia groups, was noteworthy because previous studies in predominantly non-Hispanic White participants have shown that changes in CSF Aβ1–42 occur prior to changes in CSF measures of tau (Jack et al., 2013; Selkoe & Hardy, 2016). Since our study design is cross-sectional, we are unable to infer about the timeline in which these changes are occurring, but it is possible that this discordance between previous literature and the present findings suggests that the rate at which amyloid and tau biomarkers are accumulating is different in the two racial groups (Xiong et al., 2022).

We further saw an interaction between *APOE* ε4 genotype with CSF t-tau and p-tau. These analyses showed that *APOE* ε4 carriers with MCI had greater concentrations of CSF t-tau and p-tau relative to non-carriers with MCI. Many previous studies have primarily shown differences in *APOE* ε4 limited to the concentration of CSF $A\beta_{1–42}$ and WMH (Fouquet et al., 2014; Sudre et al., 2017). Interestingly, a previous cross-sectional study assessing racial disparities in molecular AD biomarkers showed findings similar to the *APOE* ε4 and tau interaction we observed. Through use of data collected through the Knight Alzheimer Disease Research Center data, Morris and colleagues observed lower CSF p-tau and t-tau in Black and/or African Americans participants (compared to non-Hispanic White participants) that appeared to be driven by the presence of *APOE* ε4 (Morris et al., 2019). Altogether, our work and previous studies assessing racial differences in biomarkers allude to a potentially meaningful interaction between tau and *APOE* ε4. Other factors, such as amyloid, may remain an important factor in understanding this interaction as well (Ramanan

et al., 2019). Altogether, future longitudinal work in larger, unique Black and/or African American populations is needed. Such work could be very significant to elucidating whether the influence of *APOE* ε4 on tau pathogenesis is particularly influential in the development of dementia in this population (Morris et al., 2019; Shi et al., 2017; Xiong et al., 2022).

Lastly, we saw an effect of age on all MRI variables and measures of cognition and function. As expected, this effect reflected that with increased age, there was lower hippocampal volume and cortical thickness, greater WMH volume, and lower measures of cognition and function. This finding is consistent with a recent study conducted in the Washington Heights-Inwood Columbia Aging Project (WHICAP) and the Offspring Study of Racial and Ethnic Disparities in Alzheimer's Disease cohorts which showed similar associations between age with MRI markers across participants with diverse racial and ethnic backgrounds (Turney et al., 2023). The study by Turney and colleagues further had the opportunity to explore how this association varied by racial and ethnic groups in mid-life and reported accelerated brain aging in middle-aged Black individuals (Turney et al., 2023). Paired with the present study, these findings suggest that studying changes in morphometry, neuropathology, and cognitive function through the lifespan may also provide valuable insight as to the progression of dementia in the Black and/or African American population.

4.1 Limitations

Although the study had access to data from 85 Black and/or African American participants, the sample size remains modest. A limiting factor in expanding this sample stems from the underrepresentation of Black and/or African American in dementia research studies (Canevelli et al., 2019; Shin & Doraiswamy, 2016). This is actively being addressed and more data will become available soon as the newest ADNI 4 cohort aims to recruit 50–60% of new participants from underrepresented populations (Weiner et al., 2023). Furthermore, while the use of a cross-sectional design like the present study provides insight into differences between clinical groups, it cannot capture the course of a disease progression as well as a longitudinal design.

A strength of using participants within the ADNI sample is that the database is composed of participants across North America as opposed to individuals from one local region. The disadvantage is that the ADNI sample is a clinical trials population meaning not everyone in the general population is eligible to participate. Furthermore, the education level, prevalence of *APOE* ε4, and overall health of many Black and/or African American individuals in the ADNI cohort may be greater than that of many in the general population (Gianattasio et al., 2021; Royse et al., 2021). Additionally, while the 85 Black and/or African American participants were seen at 41 different ADNI sites across North America, these site names are not available to researchers and thus we were unable to examine how location/environment may further influence our findings and the measures examined.

4.2 Conclusions

The results of this study confirmed our hypothesis that there are greater AD biomarker abnormalities between clinical groups in the Black and/or African American ADNI sample. We observed that measures of cortical thickness, volume of the hippocampus, volume of

WMH, cognition and function, and CSF measures of $A\beta_{1–42}$ and tau differed between the clinical groups. We also found interactions in this Black and/or African American sample between *APOE* ε4 carrier status and clinical groups on CSF t-tau, CSF p-tau, and the FAQ.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Data collection and sharing for this project was funded by the Boston University-Alzheimer's Disease Research Center (NIA P30-AG072978), Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant 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.

Funding

This work was supported in part by the NIH/NIA P30-AG072978, NIH U01 AG024904 and DOD W81XWH-12-2-0012.

Abbreviations:

Aβ	amyloid-beta
$A\beta_{1–42}$	amyloid-beta 1–42 peptide
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ANOVA	analysis of variance
ANCOVA	analysis of covariance
APOE	apolipoprotein E
CDR ®	Clinical Dementia Rating ®
CN	cognitively normal
CSF	cerebrospinal fluid
eTIV	estimated total intracranial volume
FAQ	Functional Activities Questionnaire

FLAIR	Fluid Attenuated Inversion Recovery
HSD	honestly significant difference
LST	lesion segmentation tool
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
PET	positron emission tomography
p-tau	tau phosphorylated at threonine 181
RAVLT	Rey Auditory Verbal Learning Test
ROI	region of interest
WMH	white matter hyperintensity

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Highlights

- Majority of dementia research has been conducted in Non-Hispanic White participants
- Examination of data from Black and/or African American participants in the ADNI
- Compared presence of AD biomarker abnormalities between clinical groups
- Expected biomarker differences were shown between the three clinical groups
- Future studies examining biomarkers exclusively in racial minority groups is necessary

Table 1.

Demographic, MRI, and CSF Data Based on Clinical Group (n = 85)

	CN (n = 46)	MCI (n = 27)	Dementia (n = 12)
Age, y	70.72 (7.38)	70.99 (7.36)	73.64 (6.97)
Sex			
Female	33 (71.7)	18 (66.7)	6 (50.0)
Male	13 (28.3)	9 (33.3)	6 (50.0)
Education, y	15.9 (2.7)	15.3 (2.3)	13.9 (3.3)
***APOE* ε4 carrier** (n = 74)	12 (29.3)	12 (50.0)	7 (77.8)
Thickness of Entorhinal Cortex, mm	3.39 (0.33)	3.31 (0.35)	2.69 (0.59)
Thickness of Inferior Parietal Lobule, mm	2.35 (0.14)	2.30 (0.15)	2.24 (0.11)
Thickness of Middle Temporal Gyrus, mm	2.74 (0.13)	2.68 (0.16)	2.59 (0.14)
Thickness of Parahippocampal Gyrus, mm	2.69 (0.24)	2.66 (0.23)	2.39 (0.44)
Thickness of Posterior Cingulate, mm	2.38 (0.12)	2.31 (0.14)	2.23 (0.08)
Thickness of Insula, mm	2.80 (0.14)	2.72 (0.18)	2.65 (0.18)
Thickness of Precuneus, mm	2.29 (0.13)	2.25 (0.12)	2.22 (0.11)
Volume of Hippocampus, mm^3	7308.60 (692.98)	6905.53 (923.82)	6032.70 (968.35)
Volume of WMH, mL (n = 78)	6.24 (9.78)	9.57 (16.41)	15.56 (11.82)
Log-transformed Volume of WMH (n = 78)	0.30 (0.69)	0.58 (0.66)	1.06 (0.40)
CSF $A\beta_{1–42}$, pg/mL (n = 48)	1325.50 (744.50)	1075.18 (591.82)	583.68 (219.32)
CSF t-tau, pg/mL (n = 48)	193.98 (110.16)	233.61 (111.32)	408.18 (199.76)
CSF p-tau, pg/mL (n = 48)	18.05 (11.43)	22.52 (11.91)	40.69 (20.49)

All continuous data reported as mean (SD), categorical data (sex, *APOE* ε4 carrier) reported as number (percent).

Abbreviations: $A\beta_{1–42}$ = amyloid beta 1–42 peptide ; APOE = apolipoprotein E; CN = cognitively normal; CSF = cerebrospinal fluid; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; p-tau = phosphorylated tau; SD = standard deviation; t-tau = total tau; WMH = white matter hyperintensities

Table 2.

Assessment of Cognition and Function (n = 85)

Cognitive and Functional Measures	CN	MCI	Dementia
FAQ (n = 82)	−0.44 (0.04)	−0.17 (0.60)	2.13 (1.09)
Logical Memory Immediate Recall	0.67 (0.72)	−0.51 (0.48)	−1.37 (0.59)
Category Fluency (n = 84)	0.51 (0.80)	−0.39 (0.75)	−1.06 (1.06)
Boston Naming Test (n = 47)	0.46 (0.57)	0.12 (0.74)	−1.43 (1.14)
Sum of Total Trials on RAVLT (n = 84)	0.55 (0.87)	−0.41 (0.68)	−1.16 (0.66)
Number of Trials Learned on RAVLT (n = 84)	0.42 (0.96)	−0.26 (0.89)	−0.96 (0.52)
Part A on Trailmaking Test (n = 84)	−0.42 (0.42)	0.13 (0.84)	1.37 (1.63)
Part B on Trailmaking Test (n = 80)	−0.47 (0.58)	0.26 (0.99)	1.30 (1.13)
CDR ®	−0.58 (0.10)	0.15 (0.41)	1.88 (1.36)
Logical Memory Delayed Recall	0.66 (0.72)	−0.53 (0.59)	−1.35 (0.42)

Values shown are mean (SD). All raw scores were converted to z-scores prior to any analyses. Performance on CDR ® and Logical Memory Delayed Recall are reported above but were **not** used in any group analyses since they were previously used by the ADNI Clinical Core to determine clinical groups. Directionality of scores was *not* altered (e.g. below the mean for FAQ indicates greater functional independence and below the mean for either part of the Trailmaking means quicker time to completion whereas below the mean for Logical Memory indicates worse recall).

Abbreviations: CDR= Clinical Dementia Rating ®; CN = cognitively normal; FAQ = Functional Activities Questionnaire; MCI = mild cognitive impairment; RAVLT = Rey Auditory Verbal Learning Test

Table 3.

Post Hoc Tukey's HSD Test for MRI Measures (n = 85)

		t ratio, *p* value 95% CI		
Variables	**ANCOVA Model, *p* value**	**CN-Dementia**	**CN-MCI**	**MCI-Dementia**
Thickness of Entorhinal Cortex	F(3,81) = 14.06, $p < 0.001$	−5.42, <0.001 [−0.94 – −0.37]	-	−4.51, <0.001 [−0.89 – −0.27]
Thickness of Middle Temporal	F(3,81) = 9.45, $p < 0.001$	−2.89, 0.01 [−0.22 – −0.02]	-	-
Thickness of Parahippocampal	F(3,81) = 4.07, $p = 0.01$	−3.18, 0.006 [−0.50 – −0.07]	-	−2.75, 0.02 [−0.49 – −0.03]
Thickness of Posterior Cingulate	F(3,81) = 6.48, $p = 0.001$	−3.45, 0.003 [−0.23 – −0.04]	2.49, 0.04 [0 – 0.14]	-
Thickness of Insula	F(3,81) = 9.20, $p < 0.001$	−2.71, 0.02 [−0.24 – −0.02]	-	-
Volume of Hippocampus	F(3,81) = 13.38 $p < 0.001$	−4.65, <0.001 [−1750.17 – −563.04]	-	−2.88, 0.01 [−1398 – −130.6]
Log-transformed Volume of WMH (n = 78)	F(4,73) = 7.15, $p < 0.001$	2.84, 0.02 [0.10 – 1.13]	-	-

Only regions with significant clinical group differences ($p < 0.05$) following post hoc Tukey's HSD test shown. Age was added as a covariate in all models. Acquisition type was also added as a covariate in volume of WMH model.

Abbreviations: ANCOVA = analysis of covariance; CN = cognitively normal; HSD = honestly significant difference; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; WMH = white matter hyperintensities

Table 4.

Post Hoc Tukey's HSD Test for Cognitive and Functional Measures (n = 85) Only significant clinical group differences ($p < 0.05$) following post hoc Tukey's HSD test shown. Age was added as a covariate in all models.

		t ratio, *p* value 95% CI		
Variables	**ANCOVA Model, *p* value**	**CN-Dementia**	**CN-MCI**	**MCI-Dementia**
FAQ (n = 82)	F(3,78) = 74.28, *p* <0.001	14.46, <0.001 [2.12− 2.96]	-	12.22, <0.001 [1.83 − 2.72]
Logical Memory Immediate Recall	F(3,81) = 42.19, *p* <0.001	−9.71, <0.001 [−2.51 – −1.52]	7.66, <0.001 [0.81 – 1.55]	−3.78, 0.001 [−1.37 – −0.31]
Category Fluency (n = 84)	F(3,80) = 14.48, *p* <0.001	−5.45, <0.001 [−2.18 – −0.85]	4.50, <0.001 [0.42 – 1.37]	-
Boston Naming Test (n = 47)	F(3,43) = 15.65, *p* <0.001	−6.16, <0.001 [−2.54 – −1.10]	-	−4.41, <0.001 [−2.17 – −0.63]
Sum of Total Trials on RAVLT (n = 84)	F(3,80) = 19.23, *p* <0.001	−6.20, <0.001 [−2.27 – −1.01]	5.02, <0.001 [0.50 – 1.40]	−2.46, 0.04 [−1.36 – −0.02]
Number of Trials Learned on RAVLT (n = 84)	F(3,80) = 8.39, *p* <0.001	−4.46, <0.001 [−2.08 – −0.63)	3.11, 0.007 [0.16 – 1.20]	-
Part A on Trailmaking Test (n = 84)	F(3,80) = 20.04, *p* <0.001	6.43, <0.001 [1.05 – 2.29]	−2.91, 0.01 [−0.98 – −0.10]	4.09, <0.001 [0.47 – 1.79]
Part B on Trailmaking Test (n = 80)	F(3,76) = 23.02, *p* <0.001	6.11, <0.001 [0.97 – 2.22]	−3.74, 0.001 [−1.12 – −0.25]	3.32, 0.004 [0.26 – 1.58]

Abbreviations: ANOVA = analysis of covariance; CN = cognitively normal; FAQ = Functional Activities Questionnaire; HSD = honestly significant difference; MCI = mild cognitive impairment; RAVLT = Rey Auditory Verbal Learning Test

Table 5.

Post Hoc Tukey's HSD Test for CSF Measures (n = 48)

		t-ratio, *p* value 95% CI		
Variables	**ANOVA Model, *p* value**	**CN-Dementia**	**CN-MCI**	**MCI-Dementia**
CSF $A\beta_{1-42}$	F(2,45) = 3.28, $p = 0.047$	−2.50, 0.04 [−1460.52 – 23.12]	-	-
CSF t-tau	F(2,45) = 7.25, $p = 0.002$	3.81, 0.001 [77.87–350.55]	-	2.97, 0.01 [32.16 – 316.99]
CSF p-tau	F(2,45) = 7.44, $p = 0.002$	3.86, 0.001 [8.41 – 36.86]	-	2.96, 0.01 [3.31 – 33.03]

Only measures with significant clinical group differences ($p < 0.05$) following post hoc Tukey's HSD test shown. No additional covariates added to models.

Abbreviations: $A\beta_{1-42}$ = amyloid beta 1–42 peptide; ANOVA = analysis of variance; CN = cognitively normal; CSF = cerebrospinal fluid; HSD = honestly significant difference; MCI = mild cognitive impairment; p-tau = phosphorylated tau; t-tau = total tau

Table 6.

Post Hoc Tukey's HSD Test for Interaction of Group and *APOE* ε4 status

		t-ratio, *P* value 95% CI		
Variables	**ANOVA Model, *p* value**	**CN** ***APOE* ε4 carriers/non-carriers**	**MCI** ***APOE* ε4 carriers/non-carriers**	**Dementia** ***APOE* ε4 carriers/non-carriers**
FAQ (n = 82)	F(2,66) = 7.09, $p = 0.002$	-	-	−4.14, <0.001 [−2.58 – −0.44]
CSF t-tau (n = 48)	F(2,38) = 6.90, $p = 0.003$	-	−3.07, 0.04 [−352.76 – −3.89]	-
CSF p-tau (n= 48)	F(2,38) = 6.16, $p = 0.005$	-	−3.05, 0.04 [−37.17 – −0.32]	-

Only measures with significant interactions between clinical group and APOE ε4 carrier status ($p < 0.05$) following post hoc Tukey's HSD test shown. Age added as covariate in ANCOVA model for FAQ.

Abbreviations: ANOVA = analysis of variance; ANCOVA = analysis of covariance; CN = cognitively normal; CSF = cerebrospinal fluid; FAQ = Functional Activities Questionnaire; HSD = honestly significant difference; MCI = mild cognitive impairment; p-tau = phosphorylated tau; t-tau = total tau