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Neuropathological differences by race from the National Alzheimer's Coordinating Center

Neill R. Graff-Radford^a, Lilah M. Besser^b, Julie E. Crook^c, Walter A Kukull^b, and Dennis W. Dickson^d

^aDepartment of Neurology, Mayo Clinic, Jacksonville, FL

^bDepartments of Epidemiology, School of Public Health, University of Washington and the National Alzheimer's Coordinating Center, Seattle, WA

^cDepartment of Statistics, Mayo Clinic, Jacksonville, FL

^dDepartment of Neuroscience, Mayo Clinic, Jacksonville, FL

Abstract

Introduction—Compared to Caucasians, African Americans (AA) have higher dementia prevalence, different genetic markers and higher vascular risk factors. However, pathological underpinnings are unknown.

Methods—We used neuropathological and clinical data on 110 AA and 2500 Caucasians who were demented before death. The groups were compared regarding demographics, cognition, apolipoprotein E (ApoE) genotype, comorbidities, and clinical and neuropathological characteristics.

Results—AA and Caucasians differed in their demographics, cognition at the last visit before death, ApoE genotype, presence of hypertension, primary clinical diagnoses, and AD, cerebrovascular disease (CVD), and other neuropathologies such as Lewy body disease (LBD).

Discussion—AD, LBD and CVD pathology were more common and TDP and FTLT-tau less common in AA than in Caucasians. ApoE accounted for most of the AD neuropathological differences. If replicated, the observed differences in underlying neuropathology by race will be important for public health policy, and recruitment for and interpreting of clinical trials.

Keywords

Brain Autopsy; African American; Dementia; Alzheimer disease

Corresponding Author: Neill R Graff-Radford, Mayo Clinic, 4500 San Pablo Road, Jacksonville, Florida 32256, graffradford.neill@mayo.edu, phone 904 9537103, fax 904 9530656.

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1. Introduction

Some studies suggest that compared to Caucasians, African Americans (AA) have a higher prevalence of dementia [1–4], different genetic markers [5–7], and higher prevalence of vascular risk factors such as diabetes [8] and hypertension [9]. Researchers from fields such as anthropology and public health have debated whether race exists as a biological concept and whether it should be considered in research studies [10–13]. Those who disagree with studying health differences by race may disagree with universally lumping together individuals who self-identify with a particular race because of the variation within the group. In addition, researchers may desire to move away from categorizing individuals based on race, which is intrinsically based on racism. We argue that race remains an important construct for dementia research, but not because of biological differences by race at birth. Instead, self-reported race may serve as a proxy measure of the complex web of interrelated social, cultural, economic, and behavioral characteristics (e.g., psychosocial stress, socioeconomic status, health behaviors) present over the lifecourse that may be associated with dementia risk [14, 15].

At this time, the pathological substrate underlying dementia in AA is unknown. This is important because some treatment trials [16] [17] [18] are targeting persons with positive amyloid beta (A β) Positron Emission Tomography (PET) scans. No known studies have examined A β PET scans among AA, who may be more or less likely to be A β positive than Caucasians. Pre-existing autopsy exam data that includes AA can be used to explore racial differences in neuropathology, given the limited availability of A β PET scan data for AA. What we know so far is related to the few autopsy studies of AA [19] [20] [21] [22] [23] [24] [25]. The study by Riudavets et al [25], is the largest published study to date; however, the clinical presence or absence of dementia among autopsied subjects was unknown. The authors described the pathological findings in 200 medical examiner autopsies among 65 to 95 year olds who were equally distributed by sex and race (half AA and half Caucasian). They found that there was no racial difference in the A β plaques; in fact, they were present in 60% of black males, 58% of white males, 74% of black females and 74% of white females. Tau lesions were present in 96% of black males, 88% of white males, 96% of black females and 96% of white females. Age and apolipoprotein e4 (ApoE 4) increased the risk of AD lesions in a similar way in whites and blacks [26].

A paper by Barnes and colleagues [27] described the Minority Aging Research study, which by 2012 had 23 African American autopsies and a cohort of 784 being followed. In 2015, they reported [28] 41 AA autopsy patients diagnosed clinically as having probable and possible AD and matched them by age, gender, education and last MMSE with 81 Caucasians. They found AD pathology in more than 93% of AA and Caucasians. AA compared to Caucasians had AD as the single dementia pathology in 19.5% versus 42.0% and were more likely to have AD mixed with an additional pathology (70.7% vs 50.6%), particularly AD pathology and Lewy body disease (LBD), and AD pathology, LBD, and infarcts.

A study from Brazil [29], which included 202 medical examiner autopsies, found that 33% of the 112 with African heritage (via genetic testing) were cognitively impaired on the CDR.

Those with African heritage had less amyloid plaques, but APOE 4 prevalence was not significantly different between those with African or Caucasian heritage.

To date no large autopsy study has been carried out in AA using detailed data on cognitive status and clinical characteristics immediately preceding death. We used the National Alzheimer's Coordinating Center's (NACC) Neuropathology data set and Uniform Data Set (UDS) to compare the demographic, clinical, and neuropathological characteristics of AA and Caucasians who were autopsied and had dementia prior to death. We compared demographics, apolipoprotein E (APOE) genotype, and clinical characteristics between the AA and Caucasians sample, examined whether AA had more AD and vascular neuropathology than Caucasians, and explored the association between race and other neuropathologies such as Lewy body disease (LBD) and Frontotemporal lobar degeneration (FTLD).

2. Methods

2.1. Participants

We used data from NACC's Uniform Data Set (UDS) and Neuropathology (NP) Data Set, which were collected at 32 past and present U.S. Alzheimer's Disease Centers (ADC). ADCs have collected demographic, clinical, and neuropathology data on UDS participants with normal cognition, mild cognitive impairment (MCI), and dementia annually since 2005. A standardized Neuropathology Form and Coding Guidebook are used across ADCs to provide autopsy data to NACC [30, 31]. UDS participants come from clinic samples, public recruitment efforts, participant referrals, and other ongoing studies. Because recruitment methods vary, UDS participants are best described as a clinical case series of patients from each ADC. Additional details about the UDS sample are found elsewhere [32, 33]. Data collected between September 2005 and March 2015 were included in this study. Our sample consisted of AA and Caucasian subjects from NACC's UDS and Neuropathology data set [34] who had dementia at their last visit before death and went to autopsy.

2.2. Definition of race

UDS participants and co-participants are asked what the participant reports as his or her race, and up to three races can be reported. The originally collected race categories include White, Black or African American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Asian, Other (with a write-in field), and Unknown. NACC has developed a variable that collapses the three reported races into a single race variable (NACCNHR) that was used in this study to determine the participant's self-reported race. The NACCNHR variable includes the categories originally collected plus a multiracial category for participants who reported more than one race. AA and Caucasians reporting Hispanic ethnicity, as well as any participants reporting a race other than AA and Caucasian were excluded from the sample.

2.3. NACC's Neuropathology data

UDS participants who died and previously consented to autopsy had neuropathological evaluations completed at the ADCs. Although the methods of staining and evaluation may

vary by center, the neuropathological criteria and noted features are based on consensus guidelines and follow NACC's Neuropathology Data Set Coding Guidebook [24]. Centers record and send the neuropathological findings to NACC using a standardized form.

We used data on Braak stage to describe neurofibrillary degeneration (stage 0: no neurofibrillary degeneration; stage VI: pathology observed all brain regions associated with AD), and collapsed the stages into four categories (Stages 0, I/II, III/IV, and V/VI). Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores of A β plaque frequency (none, sparse, moderate, frequent) were used to describe neuritic and diffuse plaques. Alzheimer's disease neuropathologic change (ADNC), according to the current National Institute of Aging-Alzheimer's Association (NIA-AA) criteria, was added to NACC's Neuropathology Form in January 2014; however, these data were excluded due to the small sample size with ADNC data to date. As a surrogate measure of ADNC, we created a new variable that defined the presence of AD neuropathology as having moderate to frequent neuritic plaques and Braak stage III–VI, and the absence as none to sparse neuritic plaques and Braak stage 0–II.

Acute and old cerebrovascular disease neuropathology were assessed together in older versions of the NP Form, and were evaluated separately for the newest form version. Thus, we combined acute and old findings to allow for us to include all NP data collected over time. Infarcts and lacunes (observed grossly) were grouped together in the most recent version of the NP Form, but were assessed separately in earlier versions; therefore, they were grouped together for our analysis (i.e. 1 infarct or lacune). Hemorrhages were defined as 1 cerebral hemorrhages. Microinfarcts were defined as infarcts not observed only through a microscope, and were counted as present if 1 were found in the cortical areas. Subcortical arteriosclerotic leukoencephalopathy was defined as the presence of multifocal or diffuse white matter pathology attributable to arteriosclerotic small vessel disease.

Atherosclerosis in the circle of Willis was assessed as none, mild, moderate, or severe. Arteriolosclerosis was defined as hyaline thickening of the media of arterioles, and was categorized as none, mild, moderate, or severe. ADC neuropathologists were asked to provide a semi-quantitative assessment of the presence of overall neocortical amyloid angiopathy. In the earlier versions of the NP Form, the guidelines for neuropathologists were less specific (i.e., ranked subjectively as none, mild, moderate, severe). However, in the most recent version of the NP Form implemented in January 2014, neuropathologists were provided additional details on how to assess amyloid angiopathy, as follows: None/absent; Mild (scattered positively in the parenchymal and/or leptomeningeal vessels, possible in only one brain area); Moderate (intense positivity in many parenchymal and/or leptomeningeal vessels); Severe (Widespread (more than one brain area) intensive positivity in parenchymal and leptomeningeal vessels). For our study, we dichotomized the atherosclerosis, arteriosclerosis, and amyloid angiopathy variables as present (mild, moderate, or severe) or absent in order to assess overall differences by race, and to accommodate differences in assessment of mild, moderate, or severe by Center.

Lewy body (LB) pathology is preferably assessed with alpha-synuclein immunohistochemistry, and follows the Dementia with Lewy Bodies Consortium

semiquantitative evaluation and categorization of no pathology, or brainstem predominant, limbic or neocortical LB pathology. The likelihood that the dementia was due to AD, determined by the NIA-Reagan and CERAD criteria, was no longer collected starting with the newest version of the NP Form. Corticobasal degeneration (CBD), Pick's disease, progressive supranuclear palsy (PSP), and hippocampal sclerosis were assessed according to the standardized NACC definitions. FTLN-TDP was not specifically assessed in earlier versions of NACC's NP form; therefore, we defined FTLN-TDP pathology as having FTLN with ubiquitin positive inclusions or FTLN with no distinctive histopathology as defined in previous form versions. These FTLN pathologies are almost always TDP positive. Finally, we defined a variable for other major pathological disorder, which could include one or more pathologies not already specified: white matter rarefaction, laminar necrosis, acute neuronal necrosis, vascular malformation, aneurysm, vasculitis, CADASIL, mineralization of blood vessels, other ischemic/vascular pathology, other angiopathy, neuron loss in substantia nigra, prion disease, pigment spheroid degeneration/neuron degeneration with brain iron accumulation, multiple system atrophy, trinucleotide disease, malformation of cortical development, metabolic/storage disorder of any type, white matter disease, acute or chronic contusion/traumatic brain injury, primary or metastatic neoplasm, infectious process of any type, herniation at any site, or other pathologic diagnosis.

2.4. Clinical Measures

The CDR [35] was assessed at each UDS visit by a clinician and was based primarily on neurological exam and informant report. The global CDR ranges from 0 (no impairment) to 3 (severe dementia). The CDR sum of boxes (CDR-SB) is a summary measure of the participant's scores for each of the six major categories assessed: memory, orientation, judgment, community affairs, home and hobbies, and personal care, and ranges from 0 (no impairment) to 18 (severe dementia). The MMSE ranges from 0 (severely impaired) to 30 (no impairment). Unlike the CDR, which is never missing at a UDS visit, the MMSE was missing among approximately 20% of the sample.

ApoE genotype was missing in 32% of AA and 18% of whites. History of hypertension, diabetes, heart attack, atrial fibrillation, stroke, hypercholesterolemia, parkinsonism, and years smoking was obtained from report by the participant and/or co-participant at the most recent UDS visit. Body mass index (kg/m^2) was calculated from height and weight measured at the most recent UDS visit using the standardized calculation[36], and was categorized as $<25\text{kg}/\text{m}^2$ (underweight or normal weight); $25\text{--}29.9\text{ kg}/\text{m}^2$ (overweight), and $30\text{ kg}/\text{m}^2$ (obese). Systolic and diastolic blood pressure were measured at the most recent UDS visit. Clinicians determined if DLB and parkinsonian symptoms (hallucinations and REM sleep behavior disorder) were present among participants as of the most recent UDS visit. The Unified Parkinson's Disease Rating Scale (UPDRS), a voluntary instrument in the earlier versions of the UDS, was available for approximately 40% of AA and Caucasians.

2.5. Data analysis

We compared AA and Caucasians by their demographics, age of onset of cognitive decline, test scores at their last visit before death, ApoE genotype, and comorbidities. We then compared the two groups by their clinical characteristics and clinical diagnoses at their last

visit before death. AD neuropathology was compared in the two groups, specifically their Braak stage for neurofibrillary degeneration, CERAD scores for neuritic and diffuse plaques, and a summary measure of AD neuropathology (moderate to frequent neuritic plaques and Braak stage III–VI). We also compared the two groups on how many met the NIA-Reagan or CERAD criteria for AD neuropathology, two frequently used Alzheimer's disease criteria that were used by ADCs until January 2014 when the newest NP form was implemented.

AA and Caucasians were compared by the presence of any ischemic/vascular/hemorrhagic pathology, large artery infarcts or lacunes, hemorrhages, microinfarcts, subcortical arteriosclerotic leukoencephalopathy, atherosclerosis of the circle of Willis, arteriolosclerosis, and amyloid angiopathy. The two groups were also compared by the presence of LB pathology, FTLT-Tau (CBD, Pick's disease, and PSP), FTLT-TDP, hippocampal sclerosis, and other major neuropathology disorders.

For all of the unadjusted analyses, the two groups were compared using Pearson chi-square tests (Fisher's exact test if a cell included <5 participants) for unordered categorical variables, t-tests for continuous variables, and Wilcoxon-Mann-Whitney tests for ordinal variables. An alpha level of 0.05 determined statistical significance.

Eight multivariable logistic regression models were run, using generalized estimating equations to account for Center clustering, to examine the association between race and the eight separate outcomes of interest (AD neuropathology, infarcts or lacunes, hemorrhages, microinfarcts, subcortical arteriosclerotic leukoencephalopathy, atherosclerosis of the circle of Willis, arteriolosclerosis, and amyloid angiopathy). The multivariable model with AD neuropathology as the outcome was first run controlling for age at death, education, and CDR sum of boxes score at the last visit before death, and then ApoE genotype was added to the model to investigate whether it was a mediator in the relationship between race and AD neuropathology. The models with vascular pathologies as the outcomes controlled for age at death, education, and presence of hypertension. To account for multiple comparisons, a Bonferroni correction was applied resulting in a statistically significant p-value of 0.006 (i.e., 0.05/8 outcomes).

3. Results

A total of 110 AA and 2500 Caucasians met our criteria (Supplemental Figure 1). Compared to Caucasians, AA had less education, fewer males, greater cognitive impairment, more with 1 ApoE 4 allele and hypertension, and fewer with atrial fibrillation (Table 1). AA had significantly higher levels of systolic BP, less often self-reported parkinsonism, more often had a primary clinical diagnosis of AD, and more often had a contributing diagnosis of vascular dementia/stroke than Caucasians (Table 2).

Compared to Caucasians, AA had higher Braak stage, higher CERAD scores for neuritic and diffuse plaques, more often had AD neuropathology, and more often met the NIA/Reagan and CERAD neuropathological criteria for AD (Table 3, Supplemental Table 1). Additionally, compared to Caucasians, AA more often had infarcts or lacunes, hemorrhages, microinfarcts, atherosclerosis, and amyloid angiopathy (Table 4). Lewy body pathology was

more frequent, and FLTD-tau and FTLTD-TDP pathology were less frequent in AA compared to Caucasians (Table 5). AA and Caucasians did not differ according to their primary neuropathological diagnosis, but more AA than Caucasians had LBD as their contributing neuropathological diagnosis (Supplemental Table 2).

In the multivariable analyses (Table 6), AA were more likely than Caucasians to have AD neuropathology after controlling for age at death, education, and CDR-SB (OR 2.69; 95% CI: 1.37–5.23). Controlling for ApoE genotype reduced the association between race and AD neuropathology and it was no longer statistically significant (OR: 1.86; 95% CI: 0.80–4.28). After controlling for age at death, education, and hypertension, AA were more likely to have hemorrhages and microinfarcts than Caucasians, and there were no other statistically significant differences in vascular neuropathologies by race

4. Discussion

There are several important findings in this study. AA and Caucasians differed in their primary clinical diagnoses but not their primary pathological diagnoses. Importantly, AA had more AD-related pathology, measured as meeting the NIA/Reagan and CERAD criteria and through AD neuropathological features (Braak Stage, CERAD neuritic and diffuse plaque scores). AA more frequently had ApoE 4 than Caucasians, which has been reported clinically in previous studies [37, 38]. Our findings suggests that ApoE 4 is a mediator of the association between race and AD neuropathology and makes an important contribution to AD pathology in AA. A history of hypertension and higher systolic BP levels were found in AA, which are in keeping with the increased pathological vascular disease findings. Cultural, social, and behavioral factors such as diet and psychosocial stress may help account for the racial differences in vascular neuropathology after controlling for hypertension. Because AA have greater vascular pathology, intervening early to treat vascular risk factors could have a larger effect on brain health in AA compared to Caucasians.

LB pathology was more common in AA than Caucasians, but the number with a primary clinical LBD diagnosis (DLB or PD) was not significantly different by race. If our findings are replicated by many future studies, clinical LBD diagnoses may become more common in AA due to increased awareness of LBD as a prevalent pathology among AA. However, regardless of race, clinical LBD diagnosis was much less frequent than the number with LBD pathology at autopsy. Therefore, future studies are needed to determine the accuracy of clinical LBD diagnosis and whether it varies by race and the presence of AD and vascular disease. Unlike the study by Barnes and colleagues [39], which focused on cases with a clinical AD diagnosis, our study included all AA with dementia regardless of their clinical diagnosis. Nonetheless, both studies have similar findings with overlapping AD, LBD and vascular disease accounting for most of the dementia burden. Our sample demonstrated a wide array of other pathologies and suggested that FTD spectrum diseases with tau and TDP pathology may be less common in AA. This study also differed from the Brazil study[29] in that the majority of their medical examiner sample were non-demented. Additionally, while they focused on genetic racial differences, our focus was on racial differences that cannot be solely explained by genetics and that may be related to the culture of race in the United

States. As such, the results from our paper are not easily comparable to studies focused on Africans or those with African genetic heritage.

Our study found that ApoE 4 homozygotes were more common in AA, suggesting that any prevention trials focused on ApoE 4 homozygotes could be enriched by including AA. Alzheimer studies targeting either A β or tau proteins, which are as common or more common in AA, may also be enriched by including more AA. However, Barnes and colleagues point out that comorbidities of LBD and vascular disease are more common in AA, which could dampen the effect of such targeted treatments. In studies directed against FTD pathology, AA populations may have less affected individuals and thus may contribute less to those studies. Our findings may not be generalizable because the ADC participants are usually not derived from population-based cohorts and have different enrollment and consenting practices. However, we can speculate that the African Americans who consented to autopsy are more educated than the overall US population of African Americans, as is usually observed among Caucasian study volunteers. Greater participation by educated individuals is not restricted to the NACC sample, and the number of ADCs contributing neuropathology data on African Americans can be considered a strength of this study. Similar studies based on a particular population-based cohort conducted in a single city may not be generalizable to the United States because of differences in regional immigration patterns by race. Thus, one strength of the NACC data is that it contains participants from a wide variety of US regions that may each include AA of differing origins. Additional weaknesses of our study include potential subjectivity in the neuropathological exam (e.g., vascular pathology assessment), lack of information on socioeconomic status beyond education, and missing APOE genotype data (missing 32% of AA and 18% of Caucasians). Major strengths of the study are that: 1) the NACC data are collected using standardized data collection protocols used by the ADCs; 2) the NACC data are routinely audited to ensure data quality and completeness; and 3) the dataset includes numerous demographic, clinical, and neuropathological characteristics with which to examine the differences among AA and Caucasians.

4.1. Conclusions

This is the largest pathological brain autopsy series among demented AA. In our sample, we found that AD, LBD and vascular pathologies were more frequent in AA than in Caucasians. The difference in the number with 1 ApoE 4 allele accounted for the observed differences in AD neuropathology by race. AA more frequently had hemorrhages and microinfarcts than Caucasians, whereas Caucasians more often had FTLD pathologies than AA. Additionally studies are needed to replicate and expand upon findings, such as further studies that investigate whether AA are less likely than Caucasians to have FTLD pathologies. Similarities and differences in neuropathology by race are important in public health policy and in recruitment for and interpreting of clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Context

To date there have been no large autopsy studies carried out in AA patients with known cognitive status and detailed data on clinical characteristics immediately preceding death. Many of the previous studies have been small, not used antibody stains for α -synuclein or TAR DNA binding protein 43 (TDP-43) and not included a wide array of pathological diagnoses. The National Alzheimer's Coordinating Center's (NACC) Neuropathology data set and Uniform Data Set (UDS) were used to compare the demographic, clinical, and neuropathological characteristics of AA and Caucasians who were autopsied and had dementia prior to death.

Table 1

Demographics, test scores, ApoE genotype, and comorbidities

Characteristic [*]	NH African Americans n=110	NH Caucasians n=2500	p-value [†]
Age at death, mean (SD)	79.6 (10.5)	78.6 (11.6)	0.36
Education (years), mean (SD)	13. (3.7)	15.3 (3.0)	<.0001
Male, n (%)	39 (35.5%)	1438 (57.5%)	<.0001
Age of onset of cognitive decline, mean (SD)	70.2 (9.7)	69.6 (12.2)	0.60
Months between last visit and death, mean (SD)	16.8 (19.6)	14.9 (15.3)	0.22
Last MMSE score before death, mean (SD)	9.8 (8.5)	14.2 (8.6)	<.0001
Last global CDR score before death, mean (SD)	2.3 (0.8)	2.1 (0.9)	0.01
Last CDR sum of boxes score before death, mean (SD)	13.7 (4.9)	12.4 (5.1)	0.01
Apolipoprotein E genotype, n (%)			
No e4 alleles	24 (31.6%)	1037 (50.2%)	
1 e4 allele	39 (51.3%)	822 (39.8%)	0.001
2 e4 alleles	13 (17.1%)	207 (10.0%)	
Hypertension, n (%)	87 (79.8%)	1321 (53.1%)	<.0001
Diabetes, n (%)	15 (13.6%)	260 (10.4%)	0.28
Heart attack, n (%)	12 (10.9%)	243 (9.7%)	0.69
Atrial fibrillation, n (%)	7 (6.4%)	337 (13.5%)	0.03
Stroke, n (%)	16 (14.7%)	264 (10.6%)	0.71
Hypercholesterolemia, n (%)	60 (55.6%)	1272 (51.4%)	0.40
Lifetime cigarette smoking of one year or more, n (%)	45 (47.4%)	1053 (44.3%)	0.56

Abbreviation: NH, non-Hispanic; SD, standard deviation; MMSE, Mini Mental State Exam; CDR, Clinical Dementia Rating

^{*} Missing data (African American: Caucasian): Education (n=2; n=31); MMSE (n=20; n=499); Age of onset (n=4; n=41); APOE genotype (n=34; n=434); hypertension (n=1; n=10); diabetes (n=0; n=3); heart attack (n=0; n=4); atrial fibrillation (n=0; n=8); stroke (n=1; n=18); hypercholesterolemia (n=2; n=26); smoking one year or more (n=15; n=124)

[†] Obtained from Pearson chi-square test, t-test, or Wilcoxon-Mann-Whitney test as appropriate

Table 2

Clinical characteristics and diagnoses

Characteristic at last visit before death [*]	NH African Americans n=110	NH Caucasians n=2500	p-value [†]
Body mass index (kg/m ²), n (%)			
<25	35 (39.8%)	706 (36.5%)	
25–29.9	14 (15.9%)	521 (26.9%)	0.63
30	39 (44.3%)	708 (36.6%)	
Systolic blood pressure (mmHg), mean (SD)	135.1 (25.6)	128.2 (19.5)	0.003
Diastolic blood pressure (mmHg), mean (SD)	74.4 (13.7)	72.1 (11.1)	0.08
Visual hallucinations, n (%)	26 (25.7%)	453 (19.3%)	0.11
Auditory hallucinations, n (%)	9 (9.2%)	181 (7.8%)	0.57
REM sleep behavior disorder, n (%)	4 (5.6%)	161 (9.6%)	0.40
Parkinsonism, self-reported, n (%)	5 (4.6%)	331 (13.3%)	0.01
UPDRS, total score, mean (SD)	19.8 (20.5)	19.2 (16.2)	NC
Primary clinical diagnosis [‡]			
Alzheimer's disease	94 (85.5%)	1639 (65.6%)	
Dementia with Lewy bodies	6 (5.5%)	205 (8.2%)	
Parkinson's disease	0 (0.0%)	38 (1.5%)	0.001
bvFTD/PPA	6 (5.5%)	326 (13.0%)	
Vascular dementia/Stroke	1 (0.9%)	55 (2.2%)	
Other	3 (2.7%)	237 (9.5%)	
Contributing diagnosis(es) (not mutually exclusive) [‡]			
No contributing diagnosis	70 (63.6%)	1692 (67.7%)	0.38
Alzheimer's disease	4 (3.6%)	136 (5.4%)	0.52
Dementia with Lewy bodies	7 (6.4%)	88 (3.5%)	0.12
Parkinson's disease	4 (3.6%)	52 (2.1%)	0.30
bvFTD/PPA	0 (0.0%)	75 (3.0%)	0.07
Vascular dementia/Stroke	16 (14.6%)	188 (7.5%)	0.01
Other	19 (17.3%)	438 (17.5%)	NC

Abbreviation: NH, non-Hispanic; NC, Not calculated; SD, standard deviation; bvFTD, behavioral variant frontotemporal dementia; PPA, primary progressive aphasia; REM, rapid eye movement; UPDRS, Uniform Parkinson's Disease Rating Scale

^{*} Missing data (African American; Caucasian): body mass index (n=22; n=565); systolic blood pressure (n=23, n=819); Diastolic blood pressure (n=23, n=820); visual hallucinations (n=9; n=157); auditory hallucinations (n=12; n=183); REM sleep behavior disorder (n=39; n=827); parkinsonism (n=1; n=331); UPDRS score (n=67; n=1444)

[†] Obtained from Pearson chi-square test, Fisher's exact test, t-test, or Wilcoxon-Mann Whitney test as applicable

[‡] AD: possible and probable AD; VaD: possible and probable VaD and stroke; Other category includes any other specified primary diagnoses such as Corticobasal Degeneration, Progressive Supranuclear Palsy, Huntington's disease, and cognitive impairment due to medications.

Table 3

Alzheimer's disease neuropathology

AD neuropathology [*]	Unadjusted comparison		p-value [†]
	NH African Americans	NH Caucasians	
	n (%)	n (%)	
Braak stage for neurofibrillary degeneration			
Stages V–VI	80 (74.1%)	1425 (57.8%)	0.0004
Stages III–IV	18 (16.7%)	493 (20.0%)	
Stages I–II	6 (5.6%)	364 (14.8%)	
Stage 0	4 (3.7%)	182 (7.4%)	
CERAD score for density of neuritic plaques			
Frequent	76 (69.7%)	1380 (55.4%)	0.001
Moderate	18 (16.5%)	443 (17.8%)	
Sparse	7 (6.4%)	219 (8.8%)	
None	8 (7.3%)	448 (18.0%)	
CERAD semi-quantitative score for diffuse plaques			
Frequent	64 (68.8%)	1379 (60.8%)	0.03
Moderate	20 (21.5%)	369 (16.3%)	
Sparse	4 (4.3%)	210 (9.3%)	
None	5 (5.4%)	309 (13.6%)	
Alzheimer's disease neuropathology [‡]			
Present	92 (91.1%)	1720 (79.3%)	0.003
Absent	9 (8.9%)	448 (20.7%)	

Abbreviations: NC, Not calculated; NH, non-Hispanic

^{*} Missing data (African American; Caucasian): Braak stage (n=2; n=36); Density of neuritic plaques (n=1; n=10); Diffuse neuritic plaques (n=17; n=233), Alzheimer's disease neuropathology (n=9; n=332)

[†] Fisher's exact test or Wilcoxon-Mann-Whitney test as applicable

[‡] Alzheimer's disease neuropathology: Present = Moderate to frequent neuritic plaques and Braak stage III–VI; Absent = No or sparse neuritic plaques and Braak stage 0–II

Table 4

Vascular neuropathology

Neuropathology*	NH African Americans	NH Caucasians	p-value [†]
	n (%)	n (%)	
Any ischemic/vascular/hemorrhagic pathology	107 (99.1%)	2382 (96.5%)	0.27
Large artery infarcts or lacunes (old/acute/subacute)	35 (32.1%)	516 (20.7%)	0.005
Hemorrhages (old/acute/subacute)	14 (12.8%)	124 (5.0%)	0.0003
Microinfarcts (old/acute/subacute)	30 (27.5%)	424 (17.0%)	0.005
Subcortical arteriosclerotic leukoencephalopathy	18 (19.0%)	338 (15.3%)	0.34
Atherosclerosis of the Circle of Willis	93 (87.7%)	1887 (76.2%)	0.006
Arteriolosclerosis	88 (83.8%)	1668 (76.9%)	0.10
Amyloid angiopathy	66 (74.2%)	1552 (63.0%)	0.03

Abbreviations: NH, non-Hispanic; NC, not calculated

* Missing data (African American; Caucasian): Any ischemic/vascular/hemorrhagic pathology (n=2; n=32); Infarcts (n=1; n=12); hemorrhages (n=1; n=8); microinfarcts (n=1; n=9); subcortical arteriosclerotic leukoencephalopathy (n=15; n=297); atherosclerosis (n=4; n=23); arteriolosclerosis (n=5; n=331); amyloid angiopathy (n=21; n=34)

[†] Obtained from Pearson chi-square test or Fisher's exact test, as applicable

Table 5

Other neuropathology

Neuropathology*	NH African Americans		NH Caucasians	
	n (%)	n (%)	p-value [§]	
Lewy body pathology				
None	60 (55.1%)	1603 (64.6%)		
Brainstem predominant	9 (8.3%)	84 (3.4%)		
Limbic (transitional)	3 (2.8%)	221 (8.9%)	0.001	
Neocortical (diffuse)	27 (24.8%)	372 (15.0%)		
Amygdala predominant/olfactory bulb/not further specified	10 (9.2%)	203 (8.2%)		
FTLD-Tau (CBD, Pick's and PSP combined)	1 (1.5%)	170 (7.7%)	0.009	
CBD	1 (1.5%)	41 (1.8%)	NC	
Pick's disease	0 (0.0%)	39 (1.7%)	NC	
PSP	0 (0.0%)	71 (2.8%)	NC	
TDP				
FTLD-TDP [‡]	5 (5.1%)	272 (13.1%)	0.02	
Mesial temporal sclerosis/hippocampal sclerosis	16 (16.5%)	280 (11.5%)	0.14	
Other major pathological disorder [‡]	45 (40.9%)	603 (24%)	NC	

Abbreviations: NH, non-Hispanic; NC, not calculated; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; TDP, transactive response DNA binding protein

* Missing data (African American; Caucasian): Lewy body disease (n=1, n=17); CBD (n=15; n=273); Pick's disease (n=12; n=255); PSP (n=0; n=0); FTLD-TDP (n=12; n=418); hippocampal sclerosis (n=13; n=73)

[‡] Subjects assessed with version 1–9 of the NP form, before TDP was examined specifically, are defined as having FTLD-TDP if they had FTLD with ubiquitin positive inclusion or FTLD with no distinctive histopathology, as these pathologies are almost always TDP positive

[‡] Includes other neuropathologies not already included in the tables that are collected on the form

[§] Obtained from Pearson chi-square test or Fisher's exact test, as applicable

Table 6

Multivariable analysis of association between race and Alzheimer's and vascular neuropathology

Model outcome	OR (95% CI)	
	Without APOE	With APOE
Alzheimer's disease neuropathology [*]	2.69 (1.37–5.23) ^{*, †}	1.86 (0.80–4.28) [§]
Large artery infarcts or lacunes (old or acute/subacute) [‡]	1.51 (1.01–2.25) [‡]	NC
Hemorrhages (old or acute/subacute) [‡]	2.55 (1.30–5.02) ^{‡, †}	NC
Microinfarcts (old or acute/subacute) [‡]	1.86 (1.24–2.82) ^{‡, †}	NC
Subcortical arteriosclerotic leukoencephalopathy [‡]	1.43 (0.81–2.51) [‡]	NC
Atherosclerosis of the Circle of Willis [‡]	1.61 (0.89–2.91) [‡]	NC
Arteriolosclerosis [‡]	1.29 (0.88–1.89) [‡]	NC
Amyloid angiopathy [‡]	1.57 (0.95–2.61) [‡]	NC

Abbreviations: NC = not calculated; APOE, apolipoprotein E

^{*} Model for Alzheimer's disease neuropathology adjusted for age at death, CDR sum of boxes score at last visit before death, and education[†] Statistically significant using Bonferroni corrected p-value of 0.006 (i.e., 0.05/8)[‡] Model adjusted for age at death, education, and presence of hypertension[§] In addition to controlling for age at death, CDR-SB at last visit before death, and education, also controlled for presence of 1 APOE e4 alleles