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REFERENCES

1. Disease GBD, Injury I, Prevalence C; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017; 390(10100):1211-1259. doi:10.1016/S0140-6736(17)32154-2

2. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders: 3rd edition. *Cephalalgia*. 2018;38(1):1-211. doi:10.1177/0333102417738202

3. Stewart WF, Wood C, Reed ML, Roy J, Lipton RB; AMPP Advisory Group. Cumulative lifetime migraine incidence in women and men. *Cephalalgia*. 2008;28(11):1170-1178. doi:10.1111/j.1468-2982.2008.01666.x

4. Victor TW, Hu X, Campbell JC, Buse DC, Lipton RB. Migraine prevalence by age and sex in the United States: a life-span study. *Cephalalgia*. 2010; 30(9):1065-1072. doi:10.1177/0333102409355601

5. Buse DC, Silberstein SD, Manack AN, Papapetropoulos S, Lipton RB. Psychiatric comorbidities of episodic and chronic migraine. *J Neurol*. 2013;260(8):1960-1969. doi:10.1007/s00415-012-6725-x

6. Kurth T, Rohmann JL, Shapiro RE. Migraine and risk of cardiovascular disease. *BMJ*. 2018;360:k275. doi:10.1136/bmj.k275

7. Facchinetti F, Allais G, Nappi RE, et al. Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. *Cephalalgia*. 2009;29(3):286-292. doi:10.1111/j.1468-2982.2008.01704.x

8. Fagherazzi G, El Fatouhi D, Fournier A, et al. Associations between migraine and type 2 diabetes in women: findings from the E3N cohort study [published online December 17, 2018]. *JAMA Neurol*. doi:10.1001/jamaneurol.2018.3960

9. Li TP, Guo Z, Liu CJ, Sun T, Chen L, Zhao X. Association of down-regulation of calcitonin gene-related peptide and substance P with increase of myocardial vulnerability in diabetic neuropathic rats. *Peptides*. 2017;96:1-7. doi:10.1016/j.peptides.2017.08.007

10. Liu T, Kamiyoshi A, Sakurai T, et al. Endogenous calcitonin gene-related peptide regulates lipid metabolism and energy homeostasis in male mice. *Endocrinology*. 2017;158(5):1194-1206. doi:10.1210/en.2016-1510

11. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. *Physiol Rev*. 2017;97(2):553-622. doi:10.1152/physrev.00034.2015

12. Stewart WF, Roy J, Lipton RB. Migraine prevalence, socioeconomic status, and social causation. *Neurology*. 2013;81(11):948-955. doi:10.1212/WNL.0b013e3182a43b32

13. Aamodt AH, Stovner LJ, Hagen K, Bråthen G, Zwart J. Headache prevalence related to smoking and alcohol use: the Head-HUNT study. *Eur J Neurol*. 2006;13(11):1233-1238. doi:10.1111/j.1468-1331.2006.01492.x

14. Winsvold BS, Nelson CP, Malik R, et al; CARDIoGRAM Consortium and the International Headache Genetics Consortium. Genetic analysis for a shared biological basis between migraine and coronary artery disease. *Neurol Genet*. 2015;1(1):e10. doi:10.1212/NXG.0000000000000010

15. Gormley P, Kurki MI, Hiekkala ME, et al; 23andMe Research Team; International Headache Genetics Consortium (IHGC). Common variant burden contributes to the familial aggregation of migraine in 1,589 families. *Neuron*. 2018;98(4):743-753.e4. doi:10.1016/j.neuron.2018.04.014

Biomarkers for Alzheimer Dementia in Diverse Racial and Ethnic Minorities—A Public Health Priority

Lisa L. Barnes, PhD

Research on racial differences in Alzheimer dementia (AD) has increased dramatically in recent years. Older African American individuals, a rapidly growing segment of the US population, bear a disproportionate burden of AD and cognitive impairment compared with non-Hispanic white individuals, with some estimates suggesting that they may have more than a 2-fold increased risk than their white counterparts.[1] Our understanding of AD has steadily advanced owing to increasing knowledge about the underlying pathologic substrates leading to disease.[2,3] Ultimately, this knowledge has translated into clinical knowledge via biofluid and neuroimaging biomarkers of underlying pathologic characteristics, and into clinical trials of disease-modifying pharmacotherapies.[4] However, because of challenges in the recruitment of African American individuals into AD research studies in general,[5] the field has struggled to include this population in studies that involve invasive procedures such as lumbar punctures and autopsy.[6,7] As a consequence, there is an unfortunate lack of biological data on this population, causing knowledge of the drivers of the disparities to lag far behind.

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In this issue of *JAMA Neurology*, Morris and colleagues[8] address an important question of whether African American individuals differ from non-Hispanic white individuals regarding molecular biomarkers of Alzheimer disease. Using previously collected biomarker data from 1215 adults age 43 years or older (14.2% African American) enrolled in longitudinal studies at the Knight Alzheimer Disease Research Center in St Louis, Missouri, they compared African American and white individuals who had undergone a magnetic resonance imaging study of the brain, and/or a positron emission tomography scan of the brain with Pittsburgh compound B (radioligand for aggregated amyloid-β), and/or

cerebrospinal fluid (CSF) assays for the concentrations of amyloid-β42, total tau (t-tau), and tau phosphorylated at position 181 (p-tau$_{181}$). Primary outcomes examined were hippocampal volume, global cerebral amyloid burden, and CSF concentrations of amyloid-β42, t-tau, and p-tau$_{181}$ using well-established and standardized methods.[9-11]

Interestingly, although African American individuals had greater vascular risk factors (ie, higher body mass index and hemoglobin A$_{1c}$) than white individuals, the groups did not differ in the frequency of ischemic lesions or in the volume of white matter hyperintensities, in contrast with what has been reported in population-based studies.[12,13] The primary finding in the report by Morris and colleagues[8] is that African American individuals had reduced CSF levels of t-tau and p-tau$_{181}$ and lower hippocampal volumes for those reporting a family history of dementia, but no racial differences in amyloid burden. Furthermore, the lower levels of both t-tau and p-tau$_{181}$ among African American individuals were seen only in those with an apolipoprotein E (*APOE*) ε4 allele (n = 37 African American individuals). Although this study had the largest number of African American individuals with fluid biomarkers, the numbers of persons from both racial groups varied significantly across the different biomarker categories. Interestingly, African American individuals (143 of 173 [82.7%]) were as likely to have magnetic resonance imaging data as white individuals (889 of 1082 [82.2%]), but consistent with what has been reported in previous studies, they were less likely to have CSF data (African American individuals, 87 [50.3%] vs white individuals, 816 [75.4%]). In contrast with the racial differences in numbers of individuals with magnetic resonance imaging and CSF data, frequency of participation in positron emission tomography imaging was equally low for both racial groups (African American individuals, 65 [37.6%] vs white individuals, 504 [46.6%]).

Molecular biomarker data in minority populations are rare and, as a consequence, few studies are able to examine racial differences in AD biomarkers. Thus, the study by Morris and colleagues,[8] among the first to examine racial differences in molecular biomarkers of AD in which the cohort contributed both amyloid concentrations as measured by positron emission tomography and data on CSF concentrations of amyloid-β42, t-tau, and p-tau$_{181}$, takes an important step in addressing a question that has garnered increased attention from the scientific community: what underlies the racial disparities in AD? The study has a number of important strengths, including the use of uniform and standard diagnostic classification for cognitive impairment across race, blinding of biomarker assessment to the clinical status of participants, and statistical adjustment for vascular and genetic risk factors known to differ between African American and white individuals (eg, presence of an *APOE* ε4 allele, body mass index, and hemoglobin A$_{1c}$ concentration). The authors conclude that racial differences in AD biomarkers suggest possible race-dependent biological mechanisms that contribute to expression of disease.

Their findings are intriguing and consistent with those in an earlier report that found race-associated differences in CSF tau markers.[14] Although the overall number of African American individuals in the study by Morris and colleagues[8] is relatively small in comparison with the number of white individuals, this study represents the largest sample size of African American individuals with positron emission tomography and CSF data to date. In St Louis, a Midwestern city in which African American individuals are the largest minority group, representing 18% of the metropolitan statistical area and 13% of those age 65 years or older, the authors worked for more than a decade (2004-2015) to obtain a sample size of 173 African American individuals with biomarker data. It is clear from these efforts how much harder it is to recruit minority participants in invasive studies of this nature. The work is not only challenging, it is labor intensive and requires extensive community outreach and relationship building. In a perfect world, we would be able to conduct studies with fluid biomarkers in population-based samples of diverse racial and ethnic individuals. However, in reality, very few studies have been successful at obtaining these data from population-based studies of the majority white population.[15] Therefore, just as many successful initiatives combine data from several centers and projects to examine important research questions in the majority white population, it is likely that similar strategies will need to be implemented for biomarker studies of older African American individuals and other racial and ethnic minority populations for which the data are much more limited and the work is more challenging.

One interesting aspect of the study by Morris and colleagues[8] was the reported interaction of race by *APOE* ε4 status in which the finding of lower tau markers among African American individuals was seen only in those with an *APOE* ε4 allele. There were no racial differences in tau markers for those who did not carry an *APOE* ε4 allele. The data on *APOE* ε4 and AD have been mixed in African American individuals, with most, but not all, studies showing a weaker effect of *APOE* ε4 in this population despite the allele being much more frequent. In fact, the authors speculate that their finding may be similar to the observed weaker association of *APOE* ε4 with AD in African American individuals. The *APOE* ε4 allele has been found to be the most robust driver of AD pathologic characteristics in white individuals.[16] Given the weaker association of *APOE* ε4 with risk of AD in African American individuals, however, one would have expected the association with pathologic characteristics to be weaker as well, consistent with what the study by Morris and colleagues[8] reported. Interestingly, one previous study demonstrated that *APOE* ε4 was related to a faster rate of decline in episodic memory in African American individuals similar to that seen in white individuals, but not to any other cognitive domains,[17] suggesting that the weakened effect of this allele in African American individuals may be owing to the reliance on brief global measures that represent fewer cognitive abilities and thereby obscure the relatively specific effect on episodic memory.

The study by Morris and colleagues[8] had some limitations. It is not clear how differential participation across biomarkers may have influenced the reported results, as persons agreeing to undergo the various procedures were likely not random. In addition, as noted by the authors, there are many important social and medical factors, such

as socioeconomic status, comorbid diseases, and negative cultural experiences, that contribute to racial differences in AD and cognitive impairment that could have influenced the results,[18] but were not included as covariates in their study. Future work with biomarkers in minority populations should consider adding important sociocultural variables, such as perceived discrimination, quality of education, and experiences with social disadvantage early in life, to understand the association of biofluid biomarkers and genetics with aging and AD in older African American individuals.

Older African American individuals, a population that is rapidly growing, are at greater risk of AD than are older white individuals, but are underrepresented in clinical research studies. Inclusion of African American individuals and other minority populations in biomarker studies is challenging, even for research centers that do this work well. But as the field moves toward a biological definition of AD, the underinclusion of minority populations in AD research will significantly hinder our progress as a field and the race to end AD will not be shared with our most vulnerable, at-risk populations. There are not yet enough numbers to say anything definitive about the association of biomarkers with race. The scientific community will need many more people working in this space to obtain credible numbers. No one center can achieve this result alone; in fact, it will likely take innovative funding opportunities and large collaborative efforts of numerous centers throughout different parts of the country working together with communities to address this major public health priority.

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REFERENCES

1. Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimers Dement*. 2016;12(3):216-224. doi:10.1016/j.jalz.2015.12.007

2. Donohue MC, Sperling RA, Salmon DP, et al; Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing; Alzheimer's Disease Neuroimaging Initiative; Alzheimer's Disease Cooperative Study. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014;71(8):961-970. doi:10.1001/jamaneurol.2014.803

3. Bennett DA, Wilson RS, Boyle PA, Buchman AS, Schneider JA. Relation of neuropathology to cognition in persons without cognitive impairment. *Ann Neurol*. 2012;72(4):599-609. doi:10.1002/ana.23654

4. Frisoni GB, Boccardi M, Barkhof F, et al. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. *Lancet Neurol*. 2017;16(8):661-676. doi:10.1016/S1474-4422(17)30159-X

5. Ejiogu N, Norbeck JH, Mason MA, Cromwell BC, Zonderman AB, Evans MK. Recruitment and retention strategies for minority or poor clinical research participants: lessons from the Healthy Aging in Neighborhoods of Diversity Across the Life Span Study. *Gerontologist*. 2011;51(suppl 1):S33-S45. doi:10.1093/geront/gnr027

6. Ighodaro ET, Nelson PT, Kukull WA, et al. Challenges and considerations related to studying dementia in Blacks/African Americans. *J Alzheimers Dis*. 2017;60(1):1-10. doi:10.3233/JAD-170242

7. Williams MM, Scharff DP, Mathews KJ, et al. Barriers and facilitators of African American participation in Alzheimer disease biomarker research. *Alzheimer Dis Assoc Disord*. 2010;24(suppl):S24-S29.

8. Morris JC, Schindler SE, McCue LM, et al. Assessment of racial disparities in biomarkers for Alzheimer disease [published online January 7, 2019]. *JAMA Neurol*. doi:10.1001/jamaneurol.2018.4249

9. Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Aβ42 in humans. *Ann Neurol*. 2006;59(3):512-519. doi:10.1002/ana.20730

10. Gordon BA, Blazey T, Su Y, et al. Longitudinal β-amyloid deposition and hippocampal volume in preclinical Alzheimer disease and suspected non-Alzheimer disease pathophysiology. *JAMA Neurol*. 2016;73(10):1192-1200. doi:10.1001/jamaneurol.2016.2642

11. Su Y, D'Angelo GM, Vlassenko AG, et al. Quantitative analysis of PiB-PET with FreeSurfer ROIs. *PLoS One*. 2013;8(11):e73377. doi:10.1371/journal.pone.0073377

12. Brickman AM, Schupf N, Manly JJ, et al. Brain morphology in older African Americans, Caribbean Hispanics, and whites from northern Manhattan. *Arch Neurol*. 2008;65(8):1053-1061. doi:10.1001/archneur.65.8.1053

13. Gottesman RF, Fornage M, Knopman DS, Mosley TH. Brain aging in African-Americans: the Atherosclerosis Risk in Communities (ARIC) experience. *Curr Alzheimer Res*. 2015;12(7):607-613. doi:10.2174/1567205012666150701102445

14. Howell JC, Watts KD, Parker MW, et al. Race modifies the relationship between cognition and Alzheimer's disease cerebrospinal fluid biomarkers. *Alzheimers Res Ther*. 2017;9(1):88. doi:10.1186/s13195-017-0315-1

15. Jack CR Jr, Vemuri P, Wiste HJ, et al; Alzheimer's Disease Neuroimaging Initiative. Shapes of the trajectories of 5 major biomarkers of Alzheimer disease. *Arch Neurol*. 2012;69(7):856-867. doi:10.1001/archneurol.2011.3405

16. Tasaki S, Gaiteri C, Mostafavi S, De Jager PL, Bennett DA. The molecular and neuropathological consequences of genetic risk for Alzheimer's dementia. *Front Neurosci*. 2018;12:699. doi:10.3389/fnins.2018.00699

17. Barnes LL, Arvanitakis Z, Yu L, Kelly J, De Jager PL, Bennett DA. *Apolipoprotein E* and change in episodic memory in blacks and whites. *Neuroepidemiology*. 2013;40(3):211-219. doi:10.1159/000342778

18. Barnes LL, Bennett DA. Alzheimer's disease in African Americans: risk factors and challenges for the future. *Health Aff (Millwood)*. 2014;33(4):580-586. doi:10.1377/hlthaff.2013.1353