African Americans have differences in CSF soluble TREM2 and associated genetic variants

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African Americans Have Differences in CSF Soluble TREM2 and Associated Genetic Variants

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Abstract

Objective
To evaluate for racial differences in triggering receptor expressed on myeloid cells 2 (TREM2), a key immune mediator in Alzheimer disease, the levels of CSF soluble TREM2 (sTREM2), and the frequency of associated genetic variants were compared in groups of individuals who self-reported their race as African American (AA) or non-Hispanic White (NHW).

Methods
Community-dwelling older research participants underwent measurement of CSF sTREM2 concentrations and genetic analyses.

Results
The primary cohort included 91 AAs and 868 NHWs. CSF sTREM2 levels were lower in the AA compared with the NHW group (1,336 ± 470 vs 1,856 ± 624 pg/mL, p < 0.0001). AAs were more likely to carry TREM2 coding variants (15% vs 3%, p < 0.0001), which were associated with lower CSF sTREM2. AAs were less likely to carry the rs1582763 minor allele (8% vs 37%, p < 0.0001), located near MS4A4A, which was associated with higher CSF sTREM2. These findings were replicated in an independent cohort of 23 AAs and 917 NHWs: CSF sTREM2 levels were lower in the AA group (p = 0.03), AAs were more likely to carry coding TREM2 variants (22% vs 4%, p = 0.002), and AAs were less likely to carry the rs1582763 minor allele (16% vs 37%, p = 0.003).

Conclusions
On average, AAs had lower CSF sTREM2 levels compared with NHWs, potentially because AAs are more likely to carry genetic variants associated with lower CSF sTREM2 levels. Importantly, CSF sTREM2 reflects TREM2-mediated microglial activity, a critical step in the immune response to amyloid plaques. These findings suggest that race may be associated with risk for genetic variants that influence Alzheimer disease–related inflammation.
Alzheimer disease (AD) dementia affects people of all races and ethnicities. Recent studies have found that key proteins associated with AD, including CSF total tau (tTau) and phosphorylated tau 181 (pTau), vary between groups of individuals by self-reported race. Importantly, race is a social identity and does not always segregate with genetic markers of ancestry. Associations with race are affected by numerous nongenetic influences, including factors that affect health such as socioeconomic status, education, and stress. However, when individuals are grouped by self-reported race, African Americans (AAs) and non-Hispanic Whites (NHWs) have different frequencies of some gene variants known to modify risk for AD dementia.

In the brain, triggering receptor expressed on myeloid cells 2 (TREM2) is expressed by microglia and is a key mediator of the innate immune response to amyloid plaques. Multiple coding variants in the TREM2 gene have been associated with increased AD risk and are hypothesized to impair TREM2 function. The p.R47H and p.R62H variants, which are associated with AD risk in individuals of European ancestry, are less frequent in AA. CSF soluble TREM2 (sTREM2) is a biomarker of TREM2-mediated microglial activity and CSF sTREM2 concentrations have been associated with some variants in TREM2 and MS4A4A, a gene that is also associated with AD risk. It is unknown whether average CSF sTREM2 levels vary in individuals grouped by racial identity.

We evaluated whether CSF sTREM2 and genetic variants known to be associated with CSF sTREM2 levels vary between AA and NHW groups. CSF sTREM2 concentrations, the frequencies of TREM2 coding variants, and the frequencies of 2 single nucleotide polymorphisms in or near MS4A4A were compared in AA and NHW groups.

Methods
Participants
The primary cohort for this study was from the Knight Alzheimer Disease Research Center (ADRC), which includes one of the largest groups of AA in AD research with both CSF biomarker and genetic data. This cohort consists of community-dwelling older adults, including participants with and without cognitive impairment, enrolled in research studies of memory and aging at Washington University in St. Louis. The cohort was recruited for research participation only and was not clinic-based. Most participants lived in the greater St. Louis metropolitan area, which is approximately 18% AAs and 77% NHWs. Recruitment methods included word of mouth from individuals who were already participants, community presentations and other outreach efforts, and occasionally physician referral. Eligibility criteria included the absence of major medical conditions (e.g., metastatic cancer) that could interfere with longitudinal participation, but common chronic medical conditions (e.g., hypertension, diabetes, and depression) were permitted. The participants underwent annual clinical and cognitive assessments using the Uniform Data Set that includes the Clinical Dementia Rating (CDR) and Mini-Mental State Examination. The CDR and etiologic diagnosis of the cause(s) of dementia when present was made by the clinician in accordance with standard criteria and methods without reference to the participant’s performance on neuropsychological tests, the results of prior assessments, or biomarker results. Race, sex, and family history of AD were self-reported. Data were used for research purposes only.

After analyses of the Knight ADRC cohort were complete, an independent cohort was examined to determine whether the major findings could be replicated (racial differences in CSF sTREM2 and associated genetic variants). Data used for the replication cohort were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. For a full description of the ADNI cohort and protocols, see adni-info.org.

Participants in both the Knight ADRC and ADNI cohorts met the following criteria: (1) race was self-reported as either AA or NHW and (2) CSF sTREM2, Aβ42, tTau, and pTau measurements were available within 1 year of a clinical assessment. No participants were represented in both cohorts.

Standard Protocol Approvals, Registrations, and Patient Consents
Written informed consent was obtained from all participants and their study partners. All procedures were approved by Washington University’s Human Research Protection Office.

Sequencing and Genotyping
The APOE genotype was determined by genotyping rs7412 and rs429358 using TaqMan genotyping technology. TREM2 variants were determined by pooled DNA sequencing. The rs1582763 and rs6591561 polymorphisms associated with MS4A4A were genotyped using Illumina arrays.
Principal components were computed using genome-wide genotyping data. Estimates of African ancestry for each individual were established with the first principal component (PC1) which differentiates European and African ancestry. A higher PC1 value corresponds to greater African ancestry.

**CSF Collection and Analysis**

Methods for the Knight ADRC cohort are described here; for the ADNI cohort, the methods were similar and are described in detail online at adni-info.org. Lumbar puncture was performed as previously described. For CSF samples collected before October 11, 2016, Aβ42, tTau, and pTau were measured with the corresponding Elecsys assays on a Roche Cobas e 601 analyzer. Elecsys data and Tauer were measured with the corresponding Elecsys assays on a Roche Cobas e 601 analyzer. Elecsys data were not available for samples collected more recently (October 13, 2016, through February 12, 2019), but Aβ42, tTau, and pTau were measured with the corresponding INNOTEST (Fujirebio) assays. Neurofilament light chain (NfL) was measured with an immunoassay kit manufactured by Uman Diagnostics. Concentrations of sTREM2 were measured with the same immunoassay in both the Knight ADRC and ADNI cohorts. To decrease plate-to-plate variability due to potential matrix effects, sTREM2 values were normalized using high and low pooled controls and bridging samples.

**Statistical Analysis**

For analyses involving CSF Aβ42, tTau, and pTau, only values obtained with Elecsys assays (87% of samples) were used because it is unclear whether INNOTEST values are comparable to those measured by Elecsys. CSF biomarker concentrations were transformed with the natural logarithm for visualization, analysis, and covariate adjustment. Characteristics of AA and NHW groups were compared using Student t tests for continuous variables and χ² tests or Fisher exact tests for categorical variables. The significance of differences in CSF biomarker values between AA and NHW groups was calculated by Mann-Whitney tests for unadjusted raw values and Student t tests for natural logarithm-transformed values. Comparisons of CSF biomarkers were performed with Student t tests of the natural logarithm-transformed value unless otherwise specified. Spearman correlations were performed between natural logarithm-transformed CSF biomarker concentrations and PC1 because PC1 was not normally distributed.

Analysis of covariance (ANCOVA) models were implemented using natural logarithm-transformed CSF biomarker concentrations as the outcome variable. Predictors in the ANCOVA models were based on previously published models and included the following: race (AA or NHW), centered age (the age at CSF collection minus the mean age for the cohort [69.0 years]), sex, years of education (dichotomized as ≤12 and >12 years of education), history of dementia status (positive or negative, only available for the Knight ADRC cohort), APOE ε4 status (carrier or noncarrier), dementia status (CDR = 0 or CDR > 0), and every 2-way interaction among these variables. Genetic variant status (carrier or noncarrier) and the interaction of genetic variant status with all other covariates were entered into the CSF sTREM2 model to obtain covariate-adjusted p values for each genetic variant. In the model incorporating both TREM2 coding variant status and rs1582763 minor allele (A) carrier status, the interaction between these variants was also included.

Statistical analyses were implemented using SAS 9.4 (SAS Institute Inc., Cary, NC). Plots were created with GraphPad Prism version 7.04 (GraphPad Software, La Jolla, CA). All p values were from 2-sided tests, and results were deemed statistically significant at p < 0.05.

**Data Availability**

Data are available to qualified investigators on request to the Knight ADRC (knightadrc.wustl.edu/Research/ResourceRequest.htm) and ADNI (adni.loni.usc.edu/data-samples/access-data/).

**Results**

**Participants**

The Knight ADRC cohort consisted of 959 participants who met the inclusion criteria: 91 AAs and 868 NHWs (table 1). The AA group was younger than the NHW group (66.1 ± 8.2 vs 69.3 ± 9.2 years, p = 0.001), less likely to have dementia (13% vs 25%, p = 0.01), less likely to have a family history of dementia (44% vs 56%, p = 0.03), and reported slightly fewer years of education (15.2 ± 2.9 vs 15.9 ± 2.7, p = 0.02). The ADNI cohort consisted of 940 participants who met the inclusion criteria: 23 AAs and 917 NHWs (table 2). The AA group reported fewer years of education compared with the NHW group (14.9 ± 2.5 vs 16.1 ± 2.8, p = 0.04), but did not differ significantly by age or dementia status.

**Differences in CSF Biomarkers by Self-Reported Race or Genetic Ancestry**

Concentrations of CSF biomarkers including sTREM2 were examined as a function of race. In the Knight ADRC cohort, there was no difference in CSF Aβ42 concentrations (figure 1A) between AA and NHW groups. However, CSF tTau, pTau, NfL, and sTREM2 levels were lower in the AA compared with the NHW group (p < 0.0001 for all) (figure 1, C, E, G, and I). CSF biomarker levels were also examined as a function of the PC1 measure of African genetic ancestry. PC1 was not correlated with CSF Aβ42 (figure 1B), but was correlated with CSF tTau, pTau, NfL, and sTREM2 (p < 0.0001 for all) (figure 1, D, F, H, and J), with lower levels of these biomarkers associated with higher African genetic ancestry. Even after adjusting for age, sex, years of education, family history of dementia, APOE ε4 status, dementia status, and every 2-way interaction among these variables, there were highly significant reductions in CSF tTau, pTau, NfL, and sTREM2 in the AA compared with the NHW group (p <
Race did not interact significantly with APOE e4 in these models, but among APOE e4 carriers, pTau and tTau concentrations were lower in the AA compared with the NHW group (p = 0.0001 and p < 0.0001, respectively). In contrast, among APOE e4 noncarriers, there were no significant racial differences in pTau and tTau concentrations.

Because the AA and NHW groups in the Knight ADRC cohort had significant differences in some major covariates (age, years of education, presence of dementia, and family history of AD), an alternative approach was performed to evaluate whether differences in CSF biomarker levels as a function of race were a result of inadequate statistical correction for covariates. A computer algorithm matched each AA participant, if possible, with 1 NHW participant by closest age (within 3 years), years of education (within 2 years), presence of dementia (CDR = 0 or CDR > 0), and family history of AD. NHW matches were available for 86 of 91 AA participants (table e-6, links.lww.com/NXG/A399). In this subcohort where there were no significant differences between the AA and NHW groups, pTau and tTau concentrations were analyzed.

### Table 1

| Characteristic                              | African American participants | Non-Hispanic White participants | p Value |
|---------------------------------------------|-------------------------------|---------------------------------|---------|
| Age at CSF collection, y                    | 91                            | 66.1 ± 8.2                      | 868     | 69.3 ± 9.2 | 0.002 |
| Sex, n (% female)                           | 91                            | 50 (55)                         | 868     | 473 (55)  | N.S.  |
| Years of education                          | 91                            | 15.2 ± 2.9                      | 868     | 15.9 ± 2.7 | 0.02  |
| APOE e4 status, n (% carrier)               | 90                            | 39 (43)                         | 863     | 348 (40)  | N.S.  |
| CDR 0/0.5/1/2 (% >0)                        | 91                            | 79/8/4/0 (13)                   | 868     | 647/177/39/5 (25) | 0.01  |
| MMSE (of 30)                                | 91                            | 28.5 ± 2.5                      | 868     | 28.3 ± 2.5 | N.S.  |
| Family history, n (% positive)              | 91                            | 40 (44)                         | 868     | 489 (56)  | 0.03  |
| TREM2 variant carriers, n (%)               | 91                            | 14 (15)                         | 868     | 28 (3)    | <0.0001|
| rs1582763 genotype AA/AG/GG (minor allele [A] frequency) | 89 | 1/13/75 (8) | 843 | 106/407/330 (37) | <0.0001 |
| rs6591561 genotype GG/AG/AA (minor allele [G] frequency) | 88 | 9/31/48 (28) | 851 | 73/355/423 (29) | N.S. |

Abbreviations: CDR = Clinical Dementia Rating, where CDR = 0 indicates cognitive normality and CDR = 0.5, 1, 2, or 3 indicates very mild, mild, moderate, or severe dementia, respectively; MMSE = Mini-Mental State Examination, where a score of 30 is “best” and a score of 0 is “worst”; N.S. = not significant. Continuous measures are presented as the mean ± SD. The significance of differences between groups was determined by Student t tests for continuous variables and by χ² or Fisher exact tests for categorical variables. See figure 2 for a listing of specific TREM2 variants by race.

### Table 2

| Characteristic                              | African American participants | Non-Hispanic White participants | p Value |
|---------------------------------------------|-------------------------------|---------------------------------|---------|
| Age at CSF collection, y                    | 23                            | 73.8 ± 7.4                      | 917     | 73.3 ± 7.2 | N.S.  |
| Sex, n (% female)                           | 23                            | 13 (57)                         | 917     | 393 (43)  | N.S.  |
| Years of education                          | 23                            | 14.9 ± 2.5                      | 917     | 16.1 ± 2.8 | 0.04  |
| APOE e4 status, n (% carrier)               | 23                            | 11 (48)                         | 917     | 441 (48)  | N.S.  |
| CDR 0/0.5/1/2 (% >0)                        | 23                            | 9/11/3 (61)                     | 917     | 265/551/101 (71) | N.S.  |
| TREM2 variant carriers, n (%)               | 23                            | 5 (22)                          | 917     | 35 (4)    | 0.002 |
| rs1582763 genotype AA/AG/GG (minor allele [A] frequency) | 22 | 0/7/15 (16) | 913 | 130/424/359 (37) | 0.003 |
| rs6591561 genotype GG/AG/AA (minor allele [G] frequency) | 23 | 3/9/11 (33) | 917 | 83/402/432 (31) | N.S. |

Abbreviations: CDR = Clinical Dementia Rating, where CDR = 0 indicates cognitive normality and CDR = 0.5, 1, 2, or 3 indicates very mild, mild, moderate, or severe dementia, respectively; N.S. = not significant. Continuous measures are presented as the mean ± SD. The significance of differences between groups was determined by Student t tests for continuous variables and by χ² or Fisher exact tests for categorical variables. See figure 2 for a listing of specific TREM2 variants by race.
and NHW groups by major covariates, the AA group had lower CSF tTau, pTau, and sTREM2 compared with the NHW group ($p < 0.0001$ for all).

In the ADNI cohort, the power to detect racial differences in CSF biomarkers was much lower because of the smaller size of the AA group ($n = 23$ AA in the ADNI cohort vs $n = 91$ AA in

Figure 1 Differences in CSF Biomarker Concentrations by Self-Reported Race
the Knight ADRC cohort). There were no significant racial differences in concentrations of CSF Aβ42, tTau, pTau, or NfL, likely because the cohort was insufficiently powered to see these smaller effects. However, even with such a small AA group, CSF sTREM2 concentrations were significantly lower in the AA compared with the NHW group (p = 0.001), and PC1 was correlated with CSF sTREM2 (p = 0.0005) (table 4). After adjusting for covariates, the racial difference in CSF sTREM2 remained significant (p = 0.03). In the ADNI cohort, the AA and NHW groups were relatively well matched for covariates, so no matching secondary analysis was performed.

Concordance of Self-Reported Race and Genetic Ancestry

Genetic ancestry data were available for 937 of 959 individuals (98%) in the Knight ADRC cohort and all individuals in the ADNI cohort. In both cohorts, only 1 individual was discordant; in both cases, the individual identified as NHW but had a PC1 consistent with high African genetic ancestry. Because self-reported race and genetic ancestry were almost completely concordant in these 2 cohorts (99.9%), analyses using either measure resulted in nearly identical findings. Self-reported race was used as the primary categorical measure of race because race is a social rather than a genetic categorization. In addition, most individuals (patients and potential research participants) cannot provide a quantitative measure of their genetic ancestry (e.g., PC1), but they can report their racial identity. Most clinical trials for AD recruit racial and ethnic groups based on self-reported race, not on GWAS data. Therefore, self-reported race is more broadly relevant to individuals and to other research studies.

Differences in TREM2 Coding Variants and MS4A4A Polymorphisms by Self-Reported Race

The frequency of TREM2 coding variant status (any coding variant vs wild-type sequence) in the AA and the NHW groups was compared. AAs were more likely than NHWs to carry a TREM2 coding variant in both the Knight ADRC cohort (15% vs 3%, p < 0.0001) and the ADNI cohort (22% vs 4%, p = 0.002). This difference was primarily driven by a higher frequency of the p.T96K, p.L211P, and p.W191X variants in the AA group; these variants were in linkage disequilibrium.

The frequencies of 2 polymorphisms in the MS4A4A gene region that have been associated with CSF sTREM2 concentrations were evaluated. The minor allele (A) of rs1582763, an intergenic variant located near MS4A4A, was less frequent in the AA than the NHW group in both the Knight ADRC cohort (minor allele frequency 8% vs 37%, p < 0.0001) and the ADNI cohort (16% vs 37%, p = 0.003). In contrast, the frequency of the rs6591561 minor allele (G) in MS4A4A was not significantly different in the AA and NHW groups in the Knight ADRC cohort (28% vs 29%) or the ADNI cohort (33% vs 31%).

Effects of Coding TREM2 Variants and rs1582763 on CSF sTREM2 Concentrations

As detailed above, AAs were more likely to carry a TREM2 coding variant and less likely to carry the rs1582763 minor allele (A). We examined how these genetic factors affected concentrations of CSF sTREM2 in the better-powered Knight ADRC cohort. Individuals carrying a TREM2 coding variant had lower CSF sTREM2 concentrations (figure 2A) (p < 0.0001 before and p = 0.02 after covariate adjustment), and individuals carrying the minor allele (A) of rs1582763 had higher sTREM2 concentrations (figure 2B) (p < 0.0001 before and after covariate adjustment).

We hypothesized that the difference between AA and NHW groups in CSF sTREM2 concentrations was largely explained by the different frequencies of TREM2 coding variants and rs1582763 (A). The effects of carrying a TREM2 coding variant and/or rs1582763 (A) were additive such that TREM2 coding variant carriers and rs1582763 (A) noncarriers had the lowest CSF sTREM2 levels (figure 2C). In the Knight ADRC cohort, a model for CSF sTREM2 was implemented that included race, TREM2 coding variant carrier status, rs1582763 (A) carrier status, and all covariates and interactions. After accounting for these 2 genetic factors and covariates, concentrations of CSF sTREM2 were not significantly different in AA and NHW groups (table e-7, links.lww.com/NXI/A399), implying that racial differences in the frequencies of coding TREM2 variants and rs1582763 (A) were a major driver of racial differences in CSF sTREM2 levels. Similar trends were seen in the ADNI cohort (figure e-1), although the small size of the AA cohort did not provide adequate power for a complex analysis. In summary, the lower average concentrations of CSF sTREM2 in AA may be related to the higher frequency of coding TREM2 variants and the lower frequency of the rs1582763 minor allele (A).

Discussion

In the Knight ADRC cohort, which includes one of the largest groups of AA in AD research with both CSF biomarker and genetic data, we found that the AA group had lower average CSF sTREM2 levels compared with the NHW group. Our analyses suggested that the lower CSF sTREM2 levels in AA could be related to differences in genetic variant frequencies between AA and NHW groups: AAs had a higher frequency of TREM2 coding variants, which were associated with lower CSF sTREM2; and AAs had a lower frequency of rs1582763 (A), which was associated with higher CSF sTREM2. After these differences were found in the Knight ADRC cohort, the ADNI cohort was evaluated specifically to determine whether these differences could be replicated, reducing the possibility of false discovery. Although the sizes of the AA groups in both cohorts were relatively small, the findings in both the Knight ADRC and ADNI cohorts were similar and highly statistically significant. Identification of differences in even small cohorts is important, as it may justify larger and more comprehensive studies.

The differences we reported were between racial groups, but there are likely numerous individual-level factors that modify
Significant and reproducible differences in the frequencies of genetic variants between AA and NHW groups are unlikely to be explained by nonbiological factors, but the effects of these genetic differences on CSF sTREM2 concentrations could be susceptible to many nonbiological influences. Reasons for racial differences may include differences in social, geopolitical, and environmental factors, some of which may be related to systemic racism. These include disparities in socioeconomic status, education, and stress. Differences in medical comorbidities and physiology, such as the prevalence of cerebrovascular disease, may also contribute. Notably, some of these conditions may affect risk for AD dementia. The effects of these factors on CSF sTREM2 are unknown. Neither the Knight ADRC nor the ADNI data set currently includes detailed information about social determinants of health such as economic stability, access to healthy foods, neighborhood safety, and quality of education. Studies are needed that include much larger numbers of AA with detailed sociocultural and environmental data.

The role of TREM2 in AD has been an active area of investigation because TREM2 variants were found to be associated with the risk of symptomatic AD. TREM2 is a microglial receptor that binds amyloid with high affinity and may mediate the inflammatory response to amyloid plaques. Higher TREM2 levels may ameliorate the effects of AD pathology, potentially by decreasing neuritic dystrophy and limiting spreading of pathologic tau seeds. CSF sTREM2 concentrations are not linearly associated with AD brain pathology, but are thought to peak

### Table 3 CSF Biomarker Values of Individuals in the Knight Alzheimer Disease Research Center Cohort

| Characteristic | AA participants | NHW participants | p Value |
|----------------|----------------|-----------------|--------|
|                | n              | n               |        |
| **Unadjusted raw concentrations (±SD)** |                |                |        |
| Elecsys Aβ42, pg/mL | 81 | 1,271 ± 703 | 758 | 1,277 ± 647 | N.S. |
| Elecsys tTau, pg/mL | 81 | 182 ± 77 | 758 | 253 ± 120 | <0.0001 |
| Elecsys pTau, pg/mL | 81 | 16.6 ± 7.3 | 758 | 23.6 ± 13.4 | <0.0001 |
| INNOTEST Aβ42, pg/mL | 10 | 893 ± 315 | 110 | 927 ± 340 | N.S. |
| INNOTEST tTau, pg/mL | 10 | 253 ± 123 | 110 | 411 ± 248 | 0.02 |
| INNOTEST pTau, pg/mL | 10 | 46.2 ± 18.2 | 110 | 66.5 ± 32.1 | 0.02 |
| NfL, pg/mL | 90 | 1,363 ± 755 | 853 | 1,837 ± 1,281 | <0.0001 |
| sTREM2, pg/mL | 91 | 1,336 ± 470 | 868 | 1,856 ± 624 | <0.0001 |
| **Unadjusted natural logarithm-transformed values (±SD)** |                |                | N.S. |
| Elecsys Aβ42 | 81 | 7.00 ± 0.56 | 758 | 7.02 ± 0.53 |        |
| Elecsys tTau | 81 | 5.12 ± 0.39 | 758 | 5.44 ± 0.43 | <0.0001 |
| Elecsys pTau | 81 | 2.73 ± 0.39 | 758 | 3.04 ± 0.48 | <0.0001 |
| NfL | 90 | 7.10 ± 0.48 | 853 | 7.37 ± 0.51 | <0.0001 |
| sTREM2 | 91 | 7.13 ± 0.40 | 868 | 7.47 ± 0.32 | <0.0001 |
| **Covariate-adjusted natural logarithm-transformed values (±SE)** |                |                |        |
| Elecsys Aβ42 | 81 | 6.79 ± 0.08 | 758 | 6.92 ± 0.03 | 0.10 |
| Elecsys tTau | 81 | 5.28 ± 0.07 | 758 | 5.53 ± 0.03 | <0.0001 |
| Elecsys pTau | 81 | 2.87 ± 0.08 | 758 | 3.12 ± 0.04 | <0.0001 |
| NfL | 90 | 7.21 ± 0.08 | 853 | 7.44 ± 0.03 | 0.0005 |
| sTREM2 | 91 | 7.38 ± 0.07 | 868 | 7.66 ± 0.03 | <0.0001 |

Abbreviations: AA = African American; Aβ42 = amyloid-β 42; NfL = neurofilament light chain; NHW = non-Hispanic White; N.S. = not significant; pTau = phosphorylated tau; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; tTau = total tau. CSF biomarker values were transformed with the natural logarithm. The significance of differences in CSF biomarker values between AA and NHW participants was calculated by Mann-Whitney tests for unadjusted raw values and Student t tests for unadjusted natural logarithm-transformed values. For each CSF biomarker, the natural logarithm-transformed value was the outcome variable in an analysis of covariance model with the following predictor variables: race (AA or NHW), centered age (the age at CSF collection minus the mean age for the cohort [69.0 years]), sex, years of education (≤12 and >12 years of education), family history of dementia (positive or negative), APOE e4 status (e4 carrier or noncarrier), dementia status (CDR = 0 or CDR >0), and every 2-way interaction among these variables. The estimated natural logarithm-transformed biomarker value for each race, adjusted for covariates, and the significance of race as a predictor variable (p value) in the model is shown.
addition, because also throughout the body in multiple myeloid cells, studies are in experiments. Given the antibody genetic deletion of TREM2 reduced antiamyloid monoclonal decrease. In our mostly cognitively normal cohort, we found shortly after AD symptom onset and then plateau or de-

| Characteristic | AA participants | NHW participants | p Value |
|---------------|-----------------|-----------------|---------|
| Elecsys CSF Aβ42, pg/mL | 23 | 1,179 ± 601 | 916 | 1,049 ± 592 | N.S. |
| Elecsys CSF tTau, pg/mL | 23 | 283 ± 141 | 914 | 292 ± 126 | N.S. |
| Elecsys CSF pTau, pg/mL | 23 | 28.1 ± 16.1 | 914 | 28.1 ± 14.1 | N.S. |
| CSF NfL, pg/mL | 8 | 1,050 ± 558 | 292 | 1,499 ± 943 | 0.09 |
| CSF sTREM2, pg/mL | 23 | 3,007 ± 1,541 | 917 | 4,128 ± 1,876 | 0.001 |
| Elecsys CSF Aβ42 | 23 | 6.92 ± 0.6 | 916 | 6.81 ± 0.5 | N.S. |
| Elecsys CSF tTau | 23 | 5.56 ± 0.4 | 914 | 5.59 ± 0.4 | N.S. |
| Elecsys CSF pTau | 23 | 3.22 ± 0.5 | 914 | 3.22 ± 0.5 | N.S. |
| CSF NfL | 8 | 6.89 ± 0.4 | 292 | 7.18 ± 0.4 | 0.07 |
| CSF sTREM2 | 23 | 7.91 ± 0.4 | 917 | 8.22 ± 0.5 | 0.001 |

Abbreviations: AA = African American; Aβ42 = amyloid-β 42; NfL = neurofilament light chain; NHW = non-Hispanic White; N.S. = not significant; pTau = phosphorylated tau181; sTREM2 = soluble triggering receptor expressed on myeloid cells 2; tTau = total tau. CSF biomarker values were transformed with the natural logarithm. The significance of differences in CSF biomarker values between AA and NHW participants was calculated by Mann-Whitney tests for unadjusted raw values and Student t tests for unadjusted natural logarithm-transformed values. For each CSF biomarker, the natural logarithm-transformed value was the outcome variable in an analysis of covariance model with the following predictor variables: race (AA or NHW), centered age (the age at CSF collection minus the mean age for the cohort [69.0 years]), sex, years of education (≤12 and >12 years of education), APOE ε4 status (ε4 carrier or noncarrier), dementia status (CDR = 0 or CDR >0), and every 2-way interaction among these variables. The estimated natural logarithm-transformed biomarker value for each race, adjusted for covariates, and the significance of race as a predictor variable (p value) in the model is shown.

TREM2 is a therapeutic target for AD, and an anti-TREM2 antibody is being tested in an AD clinical trial. TREM2 may also influence antiamyloid treatments for AD—1 study found that genetic deletion of TREM2 reduced antiamyloid monoclonal antibody–mediated clearance of amyloid plaques in cell culture experiments. Given the findings of this study that AAs have lower average CSF sTREM2 in AA, this suggests that AA with AD may decline more rapidly.

Some studies have found that AAs are at higher risk for AD dementia, although this is unclear, and the relationship between race and AD is likely very complex. Previous work has suggested that significant differences in AD pathophysiology exist between AA and NHW groups. In addition to our findings related to TREM2, we confirmed previous findings using more precise automated immunoassays that AAs had lower average CSF tTau and pTau. We additionally found lower average NfL in AA compared with NHW groups. CSF NfL is a nonspecific marker of neuroxonal damage, and like tTau and pTau, NfL is typically elevated in AD. The lower average levels of CSF tTau, pTau, and NfL in the AA compared with the NHW group, even when average CSF Aβ42 levels were not different between the groups, could indicate that AAs are less likely to develop neuronal damage in response to brain amyloid. It is unclear how these racial differences in CSF biomarkers relate to risk for AD dementia. A major limitation of most AD studies is the underrepresentation of racial and ethnic minorities. Our study needed to examine whether racial differences in the frequencies of TREM2 coding variants and rs1582763 (A) translate to racial differences in other inflammatory conditions.
used the Knight ADRC cohort, which includes one of the largest groups of AAs in AD research with both CSF biomarker and genetic data, but AAs were still underrepresented. Adequate representation of racial minorities in research studies is a challenge nationally due in part to historical abuses by researchers resulting in the mistrust of medical research by racial minority communities. Furthermore, deeply flawed and malignant suppositions about genetic differences between races have been used to oppress minority groups, especially AA. Race can be an uncomfortable topic for some researchers and clinicians to discuss and study. However, it is imperative to study racial differences, including racial differences related to genetics, because they may influence AD pathophysiology, diagnosis, treatment efficacy, and outcomes. For example, applying cutoffs formulated with data from NHW cohorts could increase the frequency of AD misdiagnosis in AA patients. Even more concerning, AD clinical trials with inadequate representation of AA may lead to development of AD therapies that are less likely to be safe or effective in AA as has occurred in other conditions such as

Figure 2 Differences in CSF sTREM2 Levels in the Knight Alzheimer Disease Research Center Cohort by Self-Reported Race

The natural logarithm of CSF concentrations of soluble triggering receptor expressed on myeloid cells 2 (sTREM2) was plotted as a function of TREM2 coding variant (A), MS4A4A rs1582763 genotype (B), or TREM2 coding variant status and MS4A4A rs1582763 (A) carrier status (C). For all plots, the corresponding sTREM2 concentrations in pg/mL are shown on the right axis. Red squares represent samples from African Americans (AAs), and gray circles represent samples from non-Hispanic Whites (NHWs). Horizontal dashed lines indicate the mean sTREM2 levels for AA (red) and NHW (gray) groups. Vertical dotted lines separate genetic groups. The number of individuals in each group is listed (n).
hypertension. Development of AD therapies that are less likely to be effective in AA would further compound longstanding injustices experienced by AA. This study underscores the importance of carefully evaluating the effects of race on AD pathophysiology.

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### Appendix (continued)

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African Americans Have Differences in CSF Soluble TREM2 and Associated Genetic Variants
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In the article “African Americans Have Differences in CSF Soluble TREM2 and Associated Genetic Variants” by Schindler et al., there were errors in the x-axis of figure 2C. The third label from the left should read, “TREM2 variant noncarrier rs1582763 (A) noncarrier AA (n = 63)”; the fifth label should read, “TREM2 variant carrier rs1582763 (A) carrier AA (n = 1)”; the sixth label should read “TREM2 variant carrier rs1582763 (A) carrier NHW (n = 21)”; and the eighth label should read, “TREM2 variant noncarrier rs1582763 (A) carrier NHW (n = 492).” The correct figure is published here. The editorial staff regret the errors.

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1. Schindler SE, Cruchaga C, Joseph A, et al. African Americans have differences in CSF soluble TREM2 and associated genetic variants. Neurol Genet 2021;7:e571. doi: 10.1212/NXG.0000000000000571.