Alzheimer disease

https://doi.org/10.1038/s41582-024-00930-6

Navigating complexities of racial disparities in Alzheimer disease biomarkers

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An analysis based on datasets from four studies of memory and ageing reveals differences in the relationship of cognition with cerebrospinal fluid, but not imaging, biomarkers for Alzheimer disease between self-identified Black and White participants. These findings highlight the importance of precision medicine to address Alzheimer disease disparities across diverse populations.

Refers to Bonomi, S. et al. Relationships of cognitive measures with cerebrospinal fluid but not imaging biomarkers of Alzheimer disease vary between Black and White individuals. *Ann. Neurol.* https://doi.org/10.1002/ana.26838 (2023).

The worldwide prevalence of Alzheimer disease (AD) is growing rapidly in the ageing population and is expected to double by 2050 (ref. 1). Notably, some racial groups exhibit an elevated risk of AD or related dementias (ADRD): Black older adults are twice as likely, and Hispanic older adults are about 1.5 times more likely, to have ADRD as compared with White older adults[1]. The higher risk of ADRD among Black and Hispanic individuals is probably attributed to dementia risk factors, such as cardiovascular health, as well as social and structural inequalities, and is exacerbated by delays in diagnosis, limited access to specialists and biases in neuropsychological testing that disproportionately affect these communities[1].

The recent emergence of novel US Food and Drug Administration (FDA)-approved anti-amyloid therapies for AD that change the underlying course of the disease emphasizes the importance of early disease diagnosis with biomarker confirmation of AD pathology[2]. Over the past decade, technological innovations have permitted the development of various biomarkers — including brain imaging and fluid-based tests — that reflect AD brain pathology with high accuracy. PET and cerebrospinal fluid (CSF) measures offer well-established AD biomarkers with excellent diagnostic properties and emerging blood-based biomarkers hold promise in revolutionizing AD diagnosis and improving clinical trial design[3,4]. Despite these ground-breaking advancements, AD biomarkers have largely been studied in White individuals and inclusion of racially diverse groups has been limited. This represents a critical knowledge gap that hampers how biomarker findings translate to diverse populations, and could have substantial therapy implications in the context of novel anti-amyloid therapies. A recent study by Samuele Bonomi and colleagues[5] published in the *Annals of Neurology* examined whether the relationship among biomarkers or between biomarkers and cognitive measures varies between Black and White individuals, and thereby offers insights and further scrutiny into biomarker utility across racially diverse groups.

The Bonomi et al. study leveraged data from the Study of Race to Understand Alzheimer Biomarkers (SORTOUT-AB), which is a multi-centre study based on harmonized data collected across four major AD biomarker studies in the USA[5]. A total of 495 Black and 2,600 White participants (mean age of 70.94 ± 8.95 years) with biomarker data encompassing CSF and brain imaging, centrally harmonized at Washington University, were included[5]. The study revealed significant racial differences in how biomarkers correlate with each other and with cognition. Specifically, the study showed discrepancies in the correlations among CSF biomarkers between Black and White participants, whereas imaging biomarkers showed consistent results. Notably, no racial differences were observed in the correlation between imaging biomarkers and cognition, but CSF biomarkers showed significant differences[5].

The SORTOUT-AB study findings suggest that the CSF biomarker modality does not have the same degree of ability to detect AD pathology across various racial groups, as compared with imaging modalities. This disparity could stem from differences between PET and CSF modalities in reflecting pathology accumulation over time versus real-time protein dynamics at the time of testing, possibly influenced by race-related factors. However, owing to a number of limitations, caution is warranted in interpreting the study results, their generalizability, and their implications for diagnosis and clinical trials. The limitations include a relatively small sample size (especially among Black individuals), the potential for selection bias and the lack of representativeness of racial diversity, as rightly pointed out by the authors[5]. In addition, the study's cohort consisted of highly educated individuals, and Black individuals were more cognitively unimpaired than White individuals, which is not representative of the general population.

The mere identification of correlations or biomarker differences in a cross-sectional study does not imply a direct link to underlying causative mechanisms. Why race-related factors influence CSF but not imaging biomarkers is unknown and needs further research; these observations might not result from causal biological factors in the groups. If the SORTOUT-AB study results are rigorously validated and replicated in future longitudinal studies, this finding could constitute a major milestone that highlights the crucial need for reassessment of AD diagnostic protocols and clinical-trial recruitment criteria tailored to the specific nuances observed across racially diverse populations.

Determining differences in plasma biomarkers compared with both CSF and imaging markers will be important.

The SORTOUT-AB study also showed lesser abnormality of CSF biomarkers and lower amyloid burden by PET in Black compared with White participants[5], consistent with other reports[6–8]. Notably, the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study[8], a national cohort of community-dwelling Medicare beneficiaries with mild cognitive impairment or dementia, revealed a notable trend. Despite disproportionally higher rates of dementia and clinical AD among both Hispanic and Black people, significantly lower odds of amyloid-positive PET scans were found among these individuals, as compared with White individuals[8]. Collectively, these findings suggest race-associated differences in the aetiology of cognitive impairment that could be attributed to dementia risk factors, such as vascular risk factors and social determinants of health (SDOH)[1,7,8]. For example, Black individuals in the SORTOUT-AB study had higher rates of hypertension and diabetes, consistent with the increased role of vascular risk factors and associated cerebral small vessel disease pathologies in cognitive impairment among Black individuals.

Race is a social construct with little to no genetic or biological support. On a population level, considerable gaps exist between Black and White individuals in the USA in terms of life experiences, socioeconomic factors and health conditions that might directly or indirectly alter dementia risk[1]. Indeed, several studies suggest that racial and ethnic differences in dementia risk do not persist after accounting for health and socioeconomic factors[1]. The SORTOUT-AB study, however, did not have detailed information on SDOH. Despite attempts to adjust for these factors, the influence of SDOH on the results is not fully accounted for. Future longitudinal studies equipped with comprehensive data on SDOH are needed to address this question.

The differences in biomarker levels between racial groups in studies such as the SORTOUT-AB study raise the question of whether cut-offs or criteria in AD diagnosis and clinical trials need to be adjusted on the basis of race. Although setting a race-specific biomarker threshold might enhance the representation of racially diverse individuals in AD trials, it could introduce bias by including individuals with AD pathology that is less responsive to treatments, and potentially skew study outcomes and lead to erroneous conclusions[7–9]. Instead, a holistic understanding of individual health trajectories and factors that underlie racial differences in biomarkers, such as SDOH and comorbidities, could pave the way for tailoring diagnostic and clinical trial criteria more effectively, without risking unintended consequences across diverse groups.

Overall, the study by Bonomi et al. extends upon previous research by highlighting how race might affect various AD biomarkers, and emphasizes the importance of precision medicine for a more integrated and comprehensive understanding of ADRD disparities across diverse populations. To achieve this goal, future longitudinal studies including diverse and representative cohorts with detailed information on SDOH are eagerly needed. The recently launched New IDEAS study is one such study, and is focused on leveraging a multi-pronged approach to improve the representation of under-represented populations with a specific focus on recruiting Black and Hispanic Medicare beneficiaries. The New IDEAS study will evaluate the clinical use of amyloid PET and its relation to SDOH in a diverse population of people with cognitive impairment and will be able to compare amyloid PET with plasma markers[10]. More work remains to be done, but the field has never been at a more hopeful period — where research is starting to deliver its promise to diverse communities in the clinic.

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Published online: 23 January 2024

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