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Review article

Neuroimaging and biofluid biomarkers across race and ethnicity in older adults across the spectrum of cognition

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ABSTRACT

Neuroimaging and biofluid biomarkers provide a proxy of pathological changes for Alzheimer's disease (AD) and are useful in improving diagnosis and assessing disease progression. However, it is not clear how race/ethnicity and different prevalence of AD risks impact biomarker levels. In this narrative review, we survey studies focusing on comparing biomarker differences between non-Hispanic White American(s) (NHW), African American(s) (AA), Hispanic/Latino American(s) (HLA), and Asian American(s) with normal cognition, mild cognitive impairment, and dementia. We found no strong evidence of racial and ethnic differences in imaging biomarkers after controlling for cognitive status and cardiovascular risks. For biofluid biomarkers, in AA, higher levels of plasma Aβ42/Aβ40, and lower levels of CSF total tau and p-tau 181, were observed after controlling for *APOE* status and comorbidities compared to NHW. Examining the impact of AD risks and comorbidities on biomarkers and their contributions to racial/ethnic differences in cognitive impairment are critical to interpreting biomarkers, understanding their generalizability, and eliminating racial/ethnic health disparities.

1. Background

Alzheimer's disease (AD) is a neurodegenerative disease characterized by beta-amyloid plaques and tau-containing neurofibrillary tangles in the brain (Braak and Del Tredici-Braak, 2015). Multiple factors contribute to the development of AD and cognitive decline, such as genetics, cardiovascular risks, low educational attainment, socioeconomic status, lifestyle, psychological, and sociocultural factors, and social determinants of health (SDOH) (Alzheimer's Association, 2024; Meeker et al., 2021; Silva et al., 2019). Epidemiologic studies have found African Americans (AA) to be twice as likely, and Hispanic/Latino Americans (HLA) to be 1–1.5 times as likely, to develop AD or other dementias compared to non-Hispanic White Americans (NHW) (Alzheimer's Association, 2021; Mayeda, Glymour, Quesenberry, and Whitmer, 2017; Mehta and Yeo, 2017). Reasons for the disparities are not clear, but may include a higher frequency of AD risk factors, including cardiovascular disease, hypertension, diabetes mellitus, obesity, and lower levels of socioeconomic status (e.g., education, income, and poverty) among AA and HLA compared to NHW (Barnes and Bennett, 2014; Chen and Zissimopoulos, 2018; Gijsberts et al., 2015; Gottesman, Fornage, Knopman, and Mosley, 2015; Meeker et al., 2021; Peek, Cargill, and Huang, 2007; Prabhakaran et al., 2008).

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Imaging and biofluid biomarkers, as surrogates of underlying pathological changes in the brain, can aid disease identification and staging especially in the preclinical stage of AD (Hansson et al., 2022; Jack et al., 2018; Therriault et al., 2024). However, these biomarkers, whether specific or non-specific to AD pathology, can be influenced by the same factors associated with AD risk (Alateeq, Walsh, and Cherbuin, 2021; Franchetti et al., 2020; Lamar, Boots, Arfanakis, Barnes, and Schneider, 2020; Meng and D'Arcy, 2012; Stern, 2012). For instance, cardiovascular risks are associated with whole brain atrophy in older adults without dementia (Pase et al., 2016). Hypertension has been associated with higher frequency of severe white matter hyperintensities (WMH), which has been associated with increased global amyloid (Alban et al., 2023; Li, Wang, Sang, Zhang, and Li, 2023). So while AD risk factors vary across races/ethnicities, it is not clear how they impact brain and fluid biomarkers. Understanding whether and to what degree biomarkers are influenced by these factors will allow us to establish appropriate references for people from diverse backgrounds.

The aim of this paper is to review studies that have compared neuroimaging and biofluid biomarkers between AA, HLA, Asian Americans, and NHW across the spectrum of cognition from normal cognition to mild cognitive impairment (MCI) to dementia, and to elucidate factors that may contribute to any observed racial and ethnic differences in biomarkers. This review is organized into three parts: (1) Studies of imaging biomarkers across race and ethnicity, (2) Studies of biofluid biomarkers across race and ethnicity, and (3) Discussion.

2. PET imaging biomarkers

2.1. Racial and ethnic difference in amyloid burden

Table 1 summarizes studies that examined the effect of race and ethnicity on amyloid burden on PET scans. The results suggest that Apolipoprotein E (*APOE*) ε4 status and cognition contribute to differences in amyloid burden between races and ethnicities. For people without dementia, AA were found to have higher amyloid SUVRs as compared to NHW after controlling for hypertension, educational

Table 1
Studies examining racial and ethnic differences in amyloid burden using PET imaging in normal cognition, MCI, and dementia. Independent variables other than race/ethnicity included in the model(s) are listed under "AD risks/ factors". Dependent variables are listed under "Outcome". "Covariates" list factors that were accounted for in the statistical model(s).

Study	Study cohort	Clinical diagnosis	AD risks/ factors	Outcome	Covariates	Main findings
(Gottesman et al., 2016)	NHW (n = 188) AA (n = 141)	Subjects without dementia			0,6,15 4,9,18,19	AA had higher SUVRs, but the race effect did not survive after stratified by cognition.
(Gottesman et al., 2017)	NHW (n = 183) AA (n = 139)	Subjects without dementia	2		0,4,9,12,15	Increasing number of midlife vascular risks were associated with elevated SUVRs. Race did not modify this association.
(McDonough, 2017)	NHW (n = 43) AA (n = 232)	Subjects without dementia (MMSE > 25)			0,1,6,19	(1) No difference in amyloid SUVRs between AA and NHW without covariates. (2) After including covariates, significant interaction effects of race and amyloid status on cortical volume and thickness was found.
				Predicted age	0,1,19	AA had an older brain than NHW.
(Morris et al., 2019)	NHW (n = 889) AA (n = 143)	Subjects without dementia (CDR 0–1)			0,6,10,12, 15	No racial difference in amyloid SUVRs in AD regions between NHW and AA.
(Gu et al., 2015)	NHW (n = 40) AA (n = 53) HLA (n = 22)	Subjects without dementia		Cognitive decline	0,6,15	AA had higher global and regional amyloid SUVRs, which were associated with faster cognitive decline. This association was not observed in NHW.
(Duara et al., 2019)	NHW (n = 65) HLA (n = 94)	Normal cognition, MCI, dementia			0,1,15	No ethnic differences in SUVRs across frontal, temporal, parietal, anterior and posterior cingulate cortex regions between HLA and NHW.
			15		0,1,15	NHW with *APOE* ε4 carriers had greater amyloid burden than HLA *APOE* ε4 carriers.
(O'Bryant, Petersen, Hall, and Johnson, 2022)	NHW (n = 150) HLA (n = 105)	Normal cognition, MCI, dementia	15		0,1,6	The models were stratified by ethnicity. The presence of *APOE* ε4 was associated with significantly higher global and regional cerebral amyloid levels in both NHW and HLA groups.
(Xiong et al., 2022)	NHW (n = 374) AA (n = 47)	Normal cognition at baseline (biomarker or cognitive assessments)			0, 6,7,12, 15	A lower baseline amyloid PET centiloid and slower rate of amyloid accumulation was found in AA.
(Meeker et al., 2021)	NHW (n = 317) AA (n = 55)	Cognitively normal			0,15	No significant race effect on amyloid centiloid was found between AA and NHW.
(Bonomi et al., 2024)	NHW (n = 976) AA (n = 157)	All levels of cognition			0,1,2,6,15	(1) There is a trend toward lower amyloid centiloid in AA as compared to NHW (2) No racial differences in correlations between amyloid centiloid and global cognitive composite between AA and NHW.

‡ Indices for AD risks and covariates: 0:Gender/age, 1:Baseline cognition, 2:Cardiovascular risks, 3:Cardiovascular disease, 4:Hypertension, 5:Smoking,6:Educational attainment, 7:Socioeconomic factor, 8:Head size, 9:Diabetes, 10:Clinical diagnosis (e.g. cognitive normal, MCI, AD), 11:Peripheral inflammation, 12:Body mass index (BMI)/ obesity, 13:Low- and High-density lipoprotein (LDL/HDL), 14:Alcohol assumption, 15:Genetics (APOE genotype), 16:Family history of dementia, 17:Functional activities, 18:Total intracranial volume (TIV or ICV), 19:Other brain biomarkers (WMH, cortical infarcts, cortical thickness) 20: Depression/depressive symptoms

attainment, diabetes, *APOE* genotype, and WMH burden (Gottesman et al., 2016). However, racial differences were absent when the analysis was stratified by cognition (normal vs MCI). Two studies with larger sample sizes found no significant effect of race on amyloid accumulation between AA and NHW after controlling for BMI, *APOE* ε4 status, cognition, and education in those without dementia (Gottesman et al., 2017; Morris et al., 2019). However, a significant interaction between ethnicity and *APOE* genotype on amyloid burden has been evidenced in NHW and HLA (Duara et al., 2019; Gu et al., 2015). Duara et el. showed that NHW *APOE* ε4 carriers had greater amyloid burden than HLA *APOE* ε4 carriers across normal, MCI, and dementia status, suggesting a weaker influence of *APOE* ε4 on amyloid load in HLA (Duara et al., 2019).

Other evidence shows lower odds of amyloid positivity in Asian American, AA, and HLA compared to NHW after controlling for age, sex, education, living arrangement, cardiovascular risks (history of hypertension and diabetes), family history of dementia, and level of impairment (MCI vs dementia) (Wilkins et al., 2022). Although *APOE* ε4 genotyping was not reported in this study, a potential explanation of this finding is that a differential frequency of the *APOE* ε4 allele across race/ethnicity might account for the different odds of amyloid positivity in these groups.

2.2. Racial and ethnic difference in Tau deposition

To the best of our knowledge, two studies have examined racial and ethnic differences in tau accumulation in the brain (Meeker et al., 2021; Royse et al., 2024). Meeker et al. compared accumulation of tau on PET between AA (n=34) and NHW (n=262) participants aged 45 years and older with normal cognition. Tau accumulation was calculated by averaging tau SUVRs across amygdala, entorhinal cortex, the inferior temporal region, and the lateral occipital region. The results showed no difference in tau deposits between AA and NHW after controlling for age, sex, *APOE* ε4 status, and polygenic risk score. However, the results of this study should be interpreted with caution due to the small sample size in AA. With a larger sample size, Royse et al. found lower tau SUVRs in a study cohort that included greater proportion of AA compared to another study cohort of primarily NHW participants. However, this comparison did not adjust for age and education, which were significantly different between the two study cohorts. Future studies in cognitively impaired older adults from underrepresented racial and ethnic groups are needed.

3. MR imaging biomarkers

3.1. Racial and ethnic difference in cortical atrophy

Numerous studies have found no association between race/ethnicity and cortical volume in AA, HLA, or in Asians (Brickman et al., 2008; Choi et al., 2020; Fan et al., 2019; Liu et al., 2015; Morris et al., 2019; Stickel et al., 2021)(Table 2). Notably, the study by Morris et al. showed that for individuals without a family history of dementia, no effect of race on hippocampal volume was found between AA and NHW after adjusting for age, sex, education level, *APOE* ε4 status, clinical dementia rating, and BMI. However, AA participants reporting a family history of dementia had smaller total hippocampal volumes as compared to NHW counterparts (Morris et al., 2019). Other studies have shown differences in cortical volume in AD-susceptible brain regions between AA (DeCarli et al., 2008; Meeker et al., 2021) and HLA (Arruda et al., 2020) compared to NHW with normal cognition, MCI, and dementia. Specifically, for cognitively normal individuals and individuals with dementia, both AA and HLA had smaller hippocampal volumes than NHW, while for those with MCI, HLA and AA had larger hippocampal volumes as compared to NHW after adjusting for age, sex, education, and vascular risks (DeCarli et al., 2008), which may suggest a non-linear relationship between race/ethnicity and cortical volume. Arruda et al. showed that independent of diagnosis, HLA individuals were more likely to have larger hippocampal and entorhinal volumes compared to NHW after controlling for demographic factors, including education, and cognition (Arruda et al., 2020). The discrepancies in these findings may be due to the inclusion of different covariates. Meeker et al. found that area-based socioeconomic status significantly mediated the relationship between race and cortical volume, with AA from more disadvantaged neighborhoods (based on the Area Deprivation Index (ADI)(Kind et al., 2014) showing significantly reduced cortical volumes in AD susceptible regions compared to NHW participants (Meeker et al., 2021). In summary, mixed findings have been reported and it appears that clinical diagnosis of the study population, family history of dementia, and area-based socioeconomic status are potentially important factors contributing to racial and ethnic differences in cortical atrophy. In addition, studies that found no differences in cortical volume were primarily from participants without dementia (except for (Meeker et al., 2021)) whereas significant racial and ethnic differences were from the studies that included participants across a broader range of cognitive status. Other potential explanations for these mixed findings are differences in the covariates included, assessment of whole brain vs. regional brain volumes, and absolute vs. normalized values (e.g. relative to total intracranial volume).

As to whether race/ethnicity modifies the link between cortical atrophy and cognition, mixed findings have also been observed in individuals with or without dementia. A close relationship between cortical atrophy and cognition has been demonstrated in NHW individuals without dementia (Pase et al., 2016). In contrast, weaker associations have been found between cortical atrophy and cognitive decline in AA and HLA both with and without dementia (Avila et al., 2021; Zahodne et al., 2015). For instance, Zahodne et al. found hippocampal volume was a weaker predictor of memory function in HLA without dementia compared with corresponding NHW, after controlling for demographics, cardiovascular risks, cortical infarcts, WMH, and cortical thickness (Zahodne et al., 2015). Other studies showed no effect of race or ethnicity on the associations between cortical atrophy and cognitive performance in normal cognition, MCI, and dementia (Aggarwal et al., 2010; DeCarli et al., 2008).

3.2. Racial and ethnic difference in cortical thickness

No differences in cortical thickness in AD susceptible brain regions were found between NHW and HLA, and between NHW and Chinese with varying degrees of cognitive function (Avila et al., 2021; Fan et al., 2019) (Table 3). However, Avila et al. showed that both NHW and HLA had significantly greater cortical thickness compared to AA after controlling for gender and sex in people with varying levels of cognitive function (Avila et al., 2021). Controlling for cognitive level, *APOE* ε4 status, education, and cardiovascular factors will be necessary in future studies to confirm these results. Studies have also demonstrated that race/ethnicity modifies the effect of cortical thickness on cognition (Avila et al., 2021; McDonough, 2017). For instance, Avila et al. (Avila et al., 2021) found that for NHW and HLA, cortical thickness was a stronger predictor of performance on language tests than for AA after controlling for age. Furthermore, more years of education attenuated the impact of cortical thinning in AD susceptible brain regions on language performance for NHW, but not for AA or HLA.

3.3. Racial and ethnic difference in WMH and cortical infarcts

Converging evidence suggests no racial or ethnic difference in WMH levels and cortical infarcts after controlling for cardiovascular risks. For example, numerous studies have found no significant differences in WMH between AA and NHW after controlling for cardiovascular risks, hypertension, BMI, diabetes, and education, (Boots et al., 2020; Liu et al., 2015; Power et al., 2015) (Table 4). Although no significant differences were found between Chinese Americans and NHW in WMH

Table 2
Studies examining racial and ethnic differences in cortical atrophy using T1 weighted MRI in normal cognition, MCI, and dementia.

Study	Study cohort	Clinical diagnosis	AD risks/ factors	Outcome	Covariates	Main findings
(Liu et al., 2015)	NHW (n = 168) AA (n = 115)	All levels of cognitive status			0,1,4,6,9,12,14	No racial difference in total gray matter volume between NHW and AA.
(DeCarli et al., 2008)	NHW (n = 191) AA (n = 103) HLA (n = 107)	Normal cognition, MCI, dementia	10		0,2,6	(1) Both AA and HLA with normal cognition and dementia had smaller hippocampal volumes than NHW. (2) Significant reduced hippocampal volume in NHW with MCI but not in HLA with MCI.
(Morris et al., 2019)	NHW (n = 889) AA (n = 143)	Subjects without dementia (CDR 0–1)	16		0,6,10,12,15	(1) No racial difference in hippocampal volume between NHW and AA. (2) For individuals with a reported family history of dementia, AA had lower hippocampal volumes than NHW.
(Stickel et al., 2021)	NHW (n = 92) HLA (n = 86)	Subjects without dementia	6		0	(1) For both NHW and HLA, *APOE* ε4 carriers had smaller white matter volumes in bilateral temporal regions compared to non-carriers. (2) For HLA, *APOE* ε4 carriers who primarily spoke Spanish had larger total brain white matter volumes than those who primarily spoke English.
(Arruda et al., 2020)	NHW (n = 137) HLA (n = 89)	Normal cognition, MCI, dementia			0,1,6,17	Younger Hispanic females with fewer years of education, higher global mental status, and better functioning, were more likely to have a larger hippocampal volume.
(Choi et al., 2020)	NHW (n = 342) Korean (n = 1008)	Cognitively normal			0,6,18	(1) Koreans had bigger cortical volumes in frontal, temporal, parietal, occipital, cingulate, insular cortices than NHW. (2) NHW had bigger ventricles and caudate than Koreans.
			15		0,6,18	NHW *APOE* ε4 carriers had significantly steeper slope of aging with decreasing cortical volume than those with Korean *APOE* ε4 carriers in women.
(Fan et al., 2019)	NHW (n = 46) Chinese (n = 48)	Normal cognition, MCI, AD			0,8,18,scan type	No racial difference in GM atrophy between Chinese and NHW across the AD spectrum.
(Meeker et al., 2021)	NHW (n = 317) AA (n = 55)	Cognitively normal			0,15	(1) AA had significantly smaller AD signature volume compared to NHW. (2) Socioeconomic status mediated the relationship between race and cortical volumes.
(Brickman et al., 2008)	NHW (n = 203) AA (n = 243) HLA (n = 256)	Subjects without dementia			0,2	AA and HLA had larger relative brain volumes but no significant differences in hippocampal volumes and entorhinal cortex volume across groups.
(Wong et al., 2020)	Chinese (n = 262) Malays (n=276) Indian (n=254)	Cognitive impairment no dementia (CIND)			0,4,5,9,12, 13,15,18	Indians had smaller subcortical structures compared to Chinese and Malays.
(Yokoyama et al., 2015)	NHW (n= 71) Chinese living in the US (n = 41) Chinese living in Shanghai (n = 30)	Cognitively normal	15		0,6,18, scan type, site of data collection	Being Chinese and *APOE* ε4 carriers had significantly lower cortical volumes than NHW regardless of residence.
(Aggarwal et al., 2010)	NHW (n = 240) AA (n = 335)	Subjects with and without dementia	19	Cognitive performance	0,6	(1) For normal cognition and MCI, WMH, total brain volume (TBV), and cerebral infarcts were associated with cognition. (2) For AD, only TBV was associated with cognition. (3) Race did not modify any of these associations.
(Zahodne et al., 2015)	NHW (n = 184) AA (n = 229) HLA (n = 225)	Subjects without dementia		Cognitive performance	0,2,19	HLA had a weaker association between larger hippocampal volume and better memory than NHW.
(Xiong et al., 2022)	NHW (n = 374) AA (n = 47)	Normal cognition at baseline (biomarker or cognitive assessments)		Cognitive performance	0, 6,7,12,15	(1) Smaller hippocampal volumes and cortical thickness were found in AA as compared to NHW (2) A lower cognitive composite score was found in AA as compared to NHW.
(Bygrave et al., 2022)	NHW (n = 97) AA (n = 68)	Normal cognition			0,2,4,20	After stratified by race, social support was significantly associated with gray matte hippocampal volume in AA, but not in NHW.
(Ofori et al., 2023)	HLA (n = 61) NH* (n = 47)	Normal cognition, MCI, AD			0,6,15	No ethnic effect or ethnicity x group interaction effect were found.
(Bonomi et al., 2024)	AA (n = 254) NHW (n = 1295)	All levels of cognition			0,1,2,6,15	(1) AA had significantly smaller hippocampal volumes than NHW. (2) No racial difference in the significant correlation between hippocampal volume and global cognitive composite between AA and NHW.

* NH: Non-Hispanic individual (including AA)

Table 3
Studies examining racial and ethnic differences in cortical thickness using T1 MRI in normal cognition, MCI, and dementia.

Study	Study cohort	Clinical diagnosis	AD risk/ factors	Outcome	Covariates	Main findings
(Wong et al., 2020)	Chinese (n = 262) Malays (n=276) Indian (n=254)	Cognitive impairment no dementia (CIND)			0,4,5,9,12,13,15,18	Malays had reduced cortical thickness compared to Chinese and Indians.
(Avila et al., 2021)	NHW (n = 416) AA (n = 547) HLA (n = 590)	Normal cognition, MCI, dementia	6	Memory & language performance	0	Cortical thickness was positively associated with current memory and language performance for Whites and Hispanics, but not for AA
(McDonough, 2017)	NHW (n = 43) AA (n = 232)	Subjects without dementia (MMSE > 25)			0,1,6,19	Amyloid positive AA had decreased cortical thickness in most of the AD signature regions as compared to amyloid positive NHW.
(Fan et al., 2019)	NHW (n = 46) Chinese (n = 48)	Normal cognition, MCI, AD			0,8,18, scan type	No racial difference between Chinese and NHW across the AD spectrum.
(O'Bryant, Zhang, et al., 2022)	HLA (n = 688) NHW (n = 617)	Normal cognition, MCI, dementia			0,6	No interaction effect between ethnicity and household income, social support, chronic stress, acculturation, depression, duration of diabetes/ dyslipidemia/ diabetes/ hypertension on the composite cortical thickness.
(Bonomi et al., 2024)	AA (n = 254) NHW (n = 1295)	All levels of cognition			0,1,2,6,15	(1) AA had significantly decreased cortical thickness than NHW. (2) No racial differences in the significant correlations between cortical thickness and global cognitive composite between AA and NHW.

Table 4
Studies examining racial and ethnic differences in WMH and cortical infarcts using T2 weighted MRI in normal cognition, MCI, and dementia.

Study	**Study cohort**	**Clinical diagnosis**	**AD risks/ factors**	**Outcome**	**Covariates**	**Main findings**
WMH						
(Avila et al., 2021)	NHW (n = 416) AA (n = 547) HLA (n = 590)	Normal cognition, MCI, dementia	6	Memory & language performance	0	Significant association between WMH and cognition for AA but not for NHW or HLA.
				Memory & language decline	0	Stratified analyses suggested that education attenuated the negative impact of WMH burden on memory and language decline for NHW but not for AA and HLA.
(Brickman et al., 2008)	NHW (n = 203) AA (n = 243) HLA (n = 256)	Subjects without dementia			0,2	(1) AA and HLA had more severe WMH burden than NHW. (2) Greater association between WMH and vascular disease in AA as compared to NHW and HLA.
(Aggarwal et al., 2010)	NHW (n = 240) AA (n = 335)	Subjects with and without dementia	19	Cognitive performance	0,6	Race did not modify the association between WMH and cognition.
(Liu et al., 2015)	NHW (n = 168) AA (n = 115)	All levels of cognitive status			0,1,4,6,9,12,14	No difference in WMH volume between NHW and AA.
(Howell et al., 2017)	NHW (n = 65) AA (n = 70)	Normal cognition, MCI, AD		Cognitive performance	0,1,4,9,10,15	AA was associated with greater cognitive impairment than NHW for every unit of WMH change.
(Power et al., 2015)	NHW (n = 38) AA (n = 67)	Subjects without dementia			0,3,4,9,12	Increasing pack-years of smoking was associated with a greater risk of WMH progression and race did not modify this association.
(Yokoyama et al., 2015)	NHW (n= 71) Chinese living in America (n = 41) Chinese living in Shanghai (n = 30)	Cognitively normal	15		0,6,18, scan type, site of data collection	Shanghai Chinese had significantly higher WMH compared to American Chinese and NHW.
(Walker et al., 2021)	AA (n = 139) NHW (n = 183)	All levels of cognition	19	Elevated cortical amyloid	0,,3,4,5,6,9,12,15,18,19 (cerebral infarct), study center,	(1) Although increases in WMH volume significantly increased the odds of elevated cortical amyloid. AA race did not modify this relationship. (2) Midlife vascular risk significantly accounted for the WHM-amyloid relationship in AA.
Cortical infarcts						
(Wong et al., 2020)	Chinese (n = 262) Malays (n=276) Indian (n=254)	Cognitive impairment no dementia (CIND)			0,4,5,9,12,13,15,18	Malays had greater lesions compared to Chinese and Indians.
(Prabhakaran et al., 2008)	NHW (n = 144) AA (n = 171) HLA (n = 552)	Subjects without dementia			0,2,3,4,5,6,9	A significant interaction between race and age was found- younger AA had greater odds of having subclinical brain infarcts.

Table 5
Studies examining racial differences in diffusion MRI in normal cognition, MCI, and dementia.

Study	Study cohort	Clinical diagnosis	AD risks/ factors	Outcome	Covariates	Main findings
(Boots et al., 2020)	NHW (n = 889) AA (n = 143)	Subjects without dementia	11		0,1,2,4,5,9,18	(1) No racial differences in FA, MD, and multi-component relaxometry derived myelin water fraction measure between AA and NHW.
(Liu et al., 2015)	NHW (n = 168) AA (n = 115)	All levels of cognitive status			0,1,4,6,9,12,14	AA had a lower mean diffusivity than NHW.
(Shaked et al., 2019)	NHW (n = 115) AA (n = 77)	Subjects without dementia			0,4,5,7,9,11,12,19	(1) No racial differences in FA from the frontal, temporal, parietal, and occipital lobes. (2) Individuals with low socioeconomic status had lower FA values in all brain regions.
(Ofori et al., 2023)	HLA (n = 61) NH* (n = 47)	Normal cognition, MCI, AD			0,6,15	HLA AD group had greater FW values in the temporal ROIs than the NH AD group while no differences for the CN and MCI groups between HLA and NH.

* NH: Non-Hispanic individual (including AA)

volume after controlling for covariates, WMH volume was significantly higher in Shanghai Chinese compared to Chinese Americans, yet the difference became non-significant after adjusting for the sample site, potentially suggesting that country of residence (or factors associated with different cultural contexts) may be a significant factor contributing to differences in WMH. Among Asian cohorts, Malays had a significantly higher number of cerebral microbleeds and cortical microinfarcts as compared to Chinese and Indian cohorts. However, when controlling for age, gender, *APOE* ε4 carrier status, smoking status, diabetes, hypertension, hyperlipidemia, and BMI, the differences in brain infarcts were no longer significant (Wong et al., 2020).

Although few studies have demonstrated race/ethnic differences in WMH or cortical infarcts, race seems to modify the impact of WMH and cortical infarcts on cognition and the risk of dementia. In terms of its impact on cognition, AA race modified the relationship between WMH and cognitive performance in cohorts with and without dementia (Avila et al., 2021; Howell et al., 2017; Zahodne et al., 2015). Specifically, regardless of disease stage (cognitively normal (CN), MCI, or dementia), for every unit change in WMH, AA race was associated with greater cognitive impairment than in NHW after controlling for age, sex, CSF levels of Aβ42 and total tau, *APOE* ε4 allele, and ABCA7 risk allele, suggesting that AA may be more susceptible to the consequences of WMH, resulting in worse cognitive performance (Howell et al., 2017). For the HLA cohorts, mixed findings on whether ethnicity modified the relationship between WMH and cognition have been reported (Avila et al., 2021; Zahodne et al., 2015). In a cohort of Asian individuals, for the same level of WMH and cortical infarcts, Malay and Indian cohorts had higher odds of cognitive impairment compared with Chinese after controlling for the aforementioned cardiovascular risks (Wong et al., 2020).

3.4. Racial and ethnic difference in diffusion MRI measures

Studies have found no differences in diffusion measures in white matter between AA and NHW (Boots et al., 2020; Shaked et al., 2019). One study found no effect of race on regional FA in white matter across bilateral frontal, temporal, parietal, and occipital lobes in AA and NHW without dementia after adjusting for white matter lesions, hypertension, diabetes, BMI, and smoking. However, a significant effect of socioeconomic status on FA was found, suggesting that rather than race, lower socioeconomic status contributed to poorer white matter integrity and greater diffusivity (Shaked et al., 2019). For individuals with cognitive impairments, Ofori et al. found a significant interaction effect between diagnosis (CN, MCI, and AD) and ethnicity on FW values in temporal brain regions after controlling for gender, age, education, and *APOE* ε4 status. Specifically, the HLA AD group had greater FW values compared to the non-Hispanic AD group in the left bank of the superior temporal sulcus, the left inferior and middle temporal lobes, the left supra marginal gyrus, and the right entorhinal cortex.

4. Biofluid biomarkers

4.1. Aβ42

4.1.1. CSF

For AA cohorts with normal cognition (Table 6), two studies (Kumar et al., 2020; Xiong et al., 2022) have found no differences in the level of Aβ42 between AA and NHW without controlling for any covariates. For studies including individuals with normal cognition and MCI, no differences in Aβ42 between AA and NHW were found after controlling for covariates such as age, sex, education, family history of AD, BMI, MoCA score, hypertension, diabetes, creatinine level, or income level (Garrett et al., 2019; Hajjar et al., 2022). For studies that included all levels of cognitive impairments (Howell et al., 2017; Morris et al., 2019; Schindler et al., 2021, 2022; Windon et al., 2022), no differences in Aβ42 between AA and NHW were reported from these studies after controlling for *APOE* ε4 and cognitive status. No difference in Aβ42 level was found when comparing HLA to NHW after adjusting for age, sex, education, MMSE scores and CDR level (Windon et al., 2022).

4.1.2. Plasma

In studies including AA, findings have been mixed. Studies have shown that AA have higher levels (Hajjar et al., 2022; Schindler et al., 2022), lower levels (J. R. Hall, Petersen, Johnson, and O'Bryant, 2022), or similar levels of plasma Aβ42 (J. R. Hall et al., 2022; Xiong et al., 2024) as compared to NHW with normal cognition and (or) all levels of cognitive impairment (Table 6). For those studies that include HLA, in those with normal cognition, a significantly lower level of Aβ42 was found when compared to NHW after adjusting for age and sex. However, when assessing ethnicity in MCI and dementia groups separately, no differences were found between HLA and NHW (J. R. Hall et al., 2022). In addition, within a sample that combined cognitively normal individuals, MCI, and dementia, no differences between HLA and NHW were found (S. E. O'Bryant, Zhang, et al., 2022). However, the O'Bryant study did not include any covariates in their analyses, despite several significant differences being reported between HLA and NHW groups including cognitive diagnosis, comorbidities (e.g. diabetes, depression), and social factors (e.g. household income, social support, acculturation). Further studies that control these factors and include additional covariates such as *APOE* ε4 status are needed.

4.2. Other modifying factors

In a predominantly white study cohort (n = 996) of cognitively unimpaired participants, hypertension, diabetes, chronic kidney disease (CKD), increases in comorbid conditions measured by Charlson Comorbidity Index (e.g chronic heart failure, peripheral vascular disease, COPD, renal disease, leukemia), and higher BMI (≥ 40) were associated with higher plasma Aβ42 levels (Syrjanen et al., 2022), while another

Table 6
Studies examining racial and ethnic differences in Aβ42 in normal cognition, MCI, and dementia.

Study	Study cohort	Clinical diagnosis	Assay /platform	Unadjusted mean pg/mL group 1 (SD/SE*/range)	Unadjusted mean pg/mL group 2 (SD/SE*/range)	Covariates	Main findings (after adjusted) (Group 1 vs Group 2)
CSF							
(Schindler et al., 2022)	AA (n = 76) NHW (n = 76)	All levels of cognitive impairment	Lumipulse G1200, Fujirebio	735 (544–971)	682 (516–883)	0,1,15	AA = NHW
(Howell et al., 2017)	AA (n = 65) NHW (n = 70)	Normal cognition, MCI, AD	INNO-BIA AlzBio3 immunoassay (Fujirebio, PA, USA)/Luminex 200 platform	212.3 (118)	207.2 (148)	0,1,10,15,19	AA = NHW
(Garrett et al., 2019)	AA (n = 152) NHW (n = 110)	Normal cognition and MCI	INNO-BIA AlzBio3/ multiplex platform (xMAP; Luminex Corp)	247.76 (77.79*)	235.33 (74.50*)	0,1,4,6,7,9,12,16	AA = NHW
(Morris et al., 2019)	AA (n = 173) NHW (n = 1082)	All levels of cognitive impairment	INNOTEST, Fujirebio (formerly Innogenetics)	717.19$^{\Delta}$ (37.98*)	707.54$^{\Delta}$ (19.05*)	0,6,12,15,16	AA = NHW
(Kumar et al., 2020)	AA (n = 30) NHW (n = 50)	Normal cognition with a biological parent with AD	INNOTEST, Fujirebio (formerly Innogenetics)	722.0 (164.2)	703.7 (197.3)	NA	AA = NHW
(Hajjar et al., 2022)	AA (n = 300) NHW (n = 317)	Normal cognition and MCI	INNO-BIA AlzBio3/ multiplex platform (xMAP; Luminex Corp)	278.71 (99.26)	260.46 (95.91)	0,1,4,6,9,15,19	AA = NHW
			Lumipulse G1200, Fujirebio	740.70 (370.23)	634.98 (262.92)	0,1,4,6,9,15,19	AA = NHW
(Xiong et al., 2022)	AA (n = 37) NHW (n = 330)	Normal cognition	Lumipulse G1200, Fujirebio	810.95 (414.37)	855.85 (331.25)	NA	AA = NHW
(Windon et al., 2022)	AA (n = 47) HLA (n = 43) NHW (n = 141)	All levels of cognitive impairment	Elecsys (Roche Diagnostics)	933.1 (649.5–1590.8)	926.7 (677.7–1697.8)	0,1,6,19	AA = NHW
			Elecsys (Roche Diagnostics)	852.7 (787.1–1213.0)	951.6 (651.1–1530.5)	0,1,6,19	HLA = NHW
(Schindler et al., 2021)	AA (n = 99) NHW (n = 868)	All levels of cognitive impairment	Elecsys (Roche Diagnostics)	1096.63 (1.75)	1118.79 (1.70)	0,6,10,15,16	AA = NHW
(Bonomi et al., 2024)	AA (n = 156) NHW (n = 1193)	All levels of cognition	Lumipulse G1200, Fujirebio	650$^{\Delta}$ (26*)	690$^{\Delta}$ (14*)	0,1,2,6,15	AA = NHW
(Xiong et al., 2024)	AA (n = 80) NHW (n = 806)	Cognitively unimpaired and impaired	Immunoprecipitation–mass spectrometry assay (C2N Diagnostics)	840 ± 117$^{\Delta}$	915 ± 116$^{\Delta}$	0,2,4,6,9,10,12,15	AA < NHW
Plasma							
(Schindler et al., 2022)	AA (n = 76) NHW (n = 76)	All levels of cognitive impairment	Immunoprecipitation–mass spectrometry assay (C2N Diagnostics)	41.9 (39.3–49.6)	40.9 (37.8–46.3)	0,1,15	AA > NHW
(Hajjar et al., 2022)	AA (n = 300) NHW (n = 317)	Normal cognition and MCI	Lumipulse G1200, Fujirebio	10.35 (3.43)	9.12 (3.47)	0,1,4,6,9,15,19	AA > NHW
(J. R. Hall et al., 2022)	NHW (n = 86) HLA¶ (n = 146) AA (n = 74)	NC	Simoa (Quanterix, MA, USA)	11.86 (3.34)	12.24(3.12)	0	MA < NHW
				8.87 (3.03)	12.24(3.12)	0	AA < NHW
		MCI		12.24 (3.35)	12.74 (3.16)	0	HLA = NHW
				9.79 (3.49)	12.74 (3.16)	0	AA < NHW
		Dementia		11.28 (3.40)	11.92 (3.10)	0	HLA = NHW
				10.13 (3.49)	11.92 (3.10)	0	AA = NHW
(O'Bryant, Zhang, et al., 2022)	HLA¶ (n = 688) NHW (n = 617)	Normal cognition, MCI, AD	Simoa/HD−1 (Quanterix, MA, USA)	11.87 (3.51)	12.18 (3.10)	NA	HLA = NHW
(Xiong et al., 2024)	AA (n = 214) NHW (n = 1113)	Cognitively unimpaired and impaired	Immunoprecipitation–mass spectrometry assay (C2N Diagnostics)	26.25 ± 2.40$^{\Delta}$	26.41 ± 2.36$^{\Delta}$	0,2,4,6,9,10,12,15	AA = NHW

Δ adjusted means
¶ Mexican American

study with a smaller sample size for NHW (n = 208) did not find such differences in participants with hypertension, diabetes, and dyslipidemia (Martínez-Dubarbie et al., 2024). Martínez-Dubarbie et al. found significant inverse relationships between plasma Aβ42 level and estimated glomerular filtration rate (eGFR) and high-density lipoprotein cholesterol. For CSF, a study including a significant proportion of AA participants (23.3 %) found positive relationships between CSF Aβ42 and eGFG, and that the impact of eGFR was more robust in individuals with cognitive impairment (Hajjar, Neal, Yang, and Lah, 2024). For MCI or dementia in NHW, myocardial infarction were both associated with higher plasma Aβ42 levels whereas the presence of an *APOE* ε4 allele was associated with lower levels (Syrjanen et al., 2022).

4.3. *Aβ40*

4.3.1. *CSF*

For AA across all levels of cognitive function, one study found no differences in Aβ40 (Schindler et al., 2022) while the other two studies that we are aware of found AA had significantly lower levels of Aβ40 after controlling for covariates, including age, sex, *APOE* ε4, and cognitive status (Howell et al., 2017; Xiong et al., 2024). However, the finding became non-significant after adding hypertension, DM and total WMH as covariates in the statistical model.

4.3.2. *Plasma*

Lower levels of plasma Aβ40 have been found in AA as compared to NHW for those with normal cognition or MCI (Hajjar et al., 2022; Xiong et al., 2024) and when analyzed separately (J. R. Hall et al., 2022). However, other studies found no differences between AA and NHW in participants regardless of cognitive status (Schindler et al., 2022) and in a cohort that only included individuals with dementia (J. R. Hall et al., 2022) (Table 7). For HLA, a lower level of plasma Aβ40 was found as compared to NHW for those with normal cognition, as well as when all groups were combined (normal cognition, MCI, dementia) (J. R. Hall et al., 2022). However, when those with MCI or dementia were analyzed separately with no covariates included, HLA had similar levels of plasma

Table 7
Studies examining racial and ethnic differences in Aβ40 in normal cognition, MCI, and AD.

Study	Study cohort	Clinical diagnosis	Assay /platform	Unadjusted mean pg/mL group 1 (SD/SE*/range)	Unadjusted mean pg/mL group 2 (SD/SE*/range)	Covariates	Main findings (after adjusted) (Group 1 vs Group 2)
CSF							
(Schindler et al., 2022)	AA (n = 76) NHW (n = 76)	All levels of cognitive impairment	Lumipulse G1200, Fujirebio	9490 (7150–11,600)	10,100 (8880–12,300)	0,1,15	AA = NHW
(Howell et al., 2017)	AA (n = 65) NHW (n = 70)	Normal cognition, MCI, AD	INNO-BIA AlzBio3 immunoassay (Fujirebio, PA, USA)/Luminex 200 platform	7.89 (2.92)	9.29 (3.32)	0,1,10,15,19	AA < NHW (significance did not survive after adding hypertension, DM and total WMH as covariates)
(Bonomi et al., 2024)	AA (n = 156) NHW (n = 1193)	All levels of cognition	Lumipulse G1200, Fujirebio	9600$^{\Delta}$ (280*)	10800$^{\Delta}$ (150*)	0,1,2,6,15	AA < NHW
(Xiong et al., 2024)	AA (n = 80) NHW (n = 806)	Cognitively unimpaired and impaired	Immunoprecipitation–mass spectrometry assay (C2N Diagnostics)	5552 ± 1277$^{\Delta}$	7284 ± 1272$^{\Delta}$	0,2,4,6,9,10,12,15	AA < NHW
Plasma							
(Schindler et al., 2022)	AA (n = 76) NHW (n = 76)	all levels of cognitive impairment	Immunoprecipitation–mass spectrometry assay (C2N Diagnostics)	409 (380–470)	425 (390–482)	0,1,15	AA = NHW
(Hajjar et al., 2022)	AA (n = 300) NHW (n = 317)	Normal cognition and MCI	INNO-BIA AlzBio3/ multiplex platform (xMAP; Luminex Corp)	160.68 (50.74)	186.79 (59.75)	0,1,6,4,9,15,19	AA < NHW
(J. R. Hall et al., 2022)	NHW (n = 86)	NC	Simoa (Quanterix, MA, USA)	237.73 (66.41)	266.01 (62.66)	0	HLA < NHW
	HLA¶ (n = 146)			163.38 (41.83)	266.01 (62.66)	0	AA < NHW
	AA (n = 74)	MCI		244.73 (66.47)	278.42 (63.38)	0	HLA = NHW
				168.55 (43.92)	278.42 (63.38)	0	AA < NHW
		Dementia		245.04 (67.46)	262.64 (62.11)	0	HLA = NHW
				174.79 (49.56)	262.64 (62.11)	0	AA = NHW
(O'Bryant, Zhang, et al., 2022)	HLA¶ (n = 688) NHW (n = 617)	Normal cognition, MCI, AD	Simoa /HD−1 (Quanterix, MA, USA)	241.98 (70.37)	267.18 (64.73)	NA	HLA < NHW
(Xiong et al., 2024)	AA (n = 214) NHW (n = 1113)	Cognitively unimpaired and impaired	Immunoprecipitation–mass spectrometry assay (C2N Diagnostics)	177.8± 22.7$^{\Delta}$	199.5 ± 22.4$^{\Delta}$	0,2,4,6,9,10,12,15	AA < NHW

¶ Mexican American
Δ adjusted means

Aβ40 as NHW (S. E. O'Bryant, Zhang, et al., 2022). Overall, it appears that cognitive diagnosis plays an important role in Aβ40 levels between AA, HLA, and NHW.

4.4. Other modifying factors

For cognitively unimpaired NHW individuals, hypertension, diabetes, atrial fibrillation, chemotherapy, CKD comorbid conditions, and BMI ≥ 40 were associated with higher plasma Aβ40 levels (Martínez-Dubarbie et al., 2024; Syrjanen et al., 2022). Furthermore, an inverse relationship between Aβ40 and estimated glomerular filtration rate, aspartate aminotransferase and high-density lipoprotein cholesterol was reported (Syrjanen et al., 2022). For MCI and dementia, comorbid conditions such as cardiovascular disease and pulmonary disease, hypertension, atrial fibrillation, myocardial infarction, and CKD were associated with higher Aβ40 levels (Syrjanen et al., 2022).

4.5. Aβ42/Aβ40

4.5.1. CSF

One study including only individuals with normal cognition found no difference between AA and NHW (Xiong et al., 2022) while other studies including those with cognitive impairment found significantly higher levels of Aβ42/Aβ40 in AA compared to NHW after controlling for age, sex, *APOE* ε4, and cognitive status (Hajjar et al., 2022; Schindler et al., 2022; Xiong et al., 2024) (Table 8). To our knowledge, only one study has investigated racial differences in longitudinal changes of CSF Aβ42/Aβ40, and found that AA had a slower decline as compared to NHW over a 4–6 year duration, but the finding did not survive adjustment for age, sex, *APOE* ε4, family history, education, BMI, and socioeconomic status (Xiong et al., 2022).

4.5.2. Plasma

Studies have consistently shown higher levels of plasma Aβ42/40 in AA as compared to NHW with normal cognition (J. R. Hall et al., 2022) and (or) MCI (Hajjar et al., 2022; J. R. Hall et al., 2022; Xiong et al., 2024), and dementia (J. R. Hall et al., 2022; Schindler et al., 2022) when a range of covariates were included (Table 8). No difference between AA and NHW was found when controlling for only age and sex (Ramanan et al., 2023). Additionally, a longitudinal study showed that AA and NHW had similar rates of decrease in plasma Aβ42/40 over the course of 5–7 years, controlling for baseline amyloid status, age, sex, *APOE* ε4 carrier status, education, cognitive status, BMI, hypertension, and diabetes (Xiong et al., 2024). For HLA, higher levels of plasma Aβ42/40 were found in HLA compared to NHW in those with normal cognition, whereas no differences were found in those with MCI or dementia after controlling for age and sex (J. R. Hall et al., 2022).

4.6. Other modifying factors

For cognitively unimpaired NHW individuals, hypertension, previous cancer diagnosis, CKD, and comorbid conditions were associated with a higher Aβ42/40 ratio (Syrjanen et al., 2022) while a lower Aβ42/40 ratio was associated with the presence of an *APOE* ε4 allele and those with cerebrovascular disease and heart diseases (i.e. ischemic heart disease, atrial fibrillation, heart failure) (Valletta et al., 2024). For MCI or dementia in NHW, dyslipidemia was associated with a higher Aβ42/40 ratio while smoking, chemotherapy, and the presence of an

Table 8
Studies examining racial and ethnic differences in Aβ42/Aβ40 in normal cognition, MCI, and dementia.

Study	Study cohort	Clinical diagnosis	Assay /platform	Unadjusted mean pg/mL group 1 (SD/SE*/range)	Unadjusted mean pg/mL group 2 (SD/SE*/range)	Covariates	Main findings (after adjusted) (Group 1 vs Group 2)
CSF							
(Schindler et al., 2022)	AA (n = 76) NHW (n = 76)	All levels of cognitive impairment	Lumipulse G1200, Fujirebio	0.0874 (0.0681–0.0935)	0.0719 (0.0477–0.0870)	0,1,15	AA > NHW
(Hajjar et al., 2022)	AA (n = 300) NHW (n = 317)	Normal cognition and MCI	Lumipulse G1200, Fujirebio	0.08 (0.03)	0.06 (0.02)	0,1,6,4,9,15,19	AA > NHW
(Xiong et al., 2022)	AA (n = 37) NHW (n = 330)	Normal cognition	Lumipulse G1200, Fujirebio	0.084 (0.02)	0.079 (0.02)	NA	AA = NHW
(Bonomi et al., 2024)	AA (n = 155) NHW (n = 1192)	All levels of cognition	Lumipulse G1200, Fujirebio	0.0697$^{\Delta}$ (0.0015*)	0.0647$^{\Delta}$ (0.0008*)	0,1,2,6,15	AA > NHW
(Xiong et al., 2024)	AA (n = 80) NHW (n = 806)	Cognitively unimpaired and impaired	Immunoprecipitation–mass spectrometry assay (C2N Diagnostics)	0.1122 ± 0.0068$^{\Delta}$	0.1069 ±0.0068$^{\Delta}$	0,2,4,6,9,10,12,15	AA > NHW
Plasma							
(Schindler et al., 2022)	AA (n = 76) NHW (n = 76)	All levels of cognitive impairment	Immunoprecipitation–mass spectrometry assay (C2N Diagnostics)	0.1047 (0.0990–0.1101)	0.0963 (0.0904–0.1028)	0,1,15	AA > NHW
(Hajjar et al., 2022)	AA (n = 300) NHW (n = 317)	Normal cognition and MCI	INNO-BIA AlzBio3/ multiplex platform (xMAP; Luminex Corp)	0.07 (0.02)	0.05 (0.02)	0,1,6,4,9,15,19	AA > NHW
(J. R. Hall et al., 2022)	NHW (n = 86) HLA¶ (n = 146) AA (n = 74)	NC MCI Dementia 	Simoa (Quanterix, MA, USA)	0.051 (0.022) 0.065 (0.029) 0.051 (0.017) 0.058 (0.019) 0.049 (0.018) 0.058 (0.028)	0.047 (0.013) 0.047 (0.013) 0.047 (0.011) 0.047 (0.011) 0.046 (0.011) 0.046 (0.011)	0 0 0 0 0 0	HLA > NHW AA > NHW HLA = NHW AA > NHW HLA = NHW AA > NHW
(Ramanan et al., 2023)	AA (n = 267) NHW (n = 268)	Normal cognition, MCI, and dementia	Simoa/HD-X analyzer (Quanterix, MA)	0.06 (0.01)	0.06 (0.02)	0	AA = NHW
(Mohs et al., 2024)	AA (n = 112) HLA (n = 115) NHW (n = 755)	Cognitive normal, MCI, mild AD	Immunoprecipitation–mass spectrometry assay (C2N Diagnostics)	0.10 (0.0104) 0.099 (0.0110)	0.096 (0.0094) 0.096 (0.0094)	0,1,6	AA > NHW HLA > NHW
(Xiong et al., 2024)	AA (n = 324) NHW (n = 1547)	Cognitively unimpaired and impaired	Immunoprecipitation–mass spectrometry assay (C2N Diagnostics)	0.107 ±0.012§ 0.100 ±0.012§§	0.102 ± 0.011 0.096 ± 0.011	0,2,4,6,9,10,12,15	AA > NHW

¶ Mexican American
$^{\Delta}$Adjusted least-squared mean
§ Cognitively unimpaired;
§§ Cognitively impaired

APOE ε4 allele were associated with a lower Aβ42/40 ratio (Syrjanen et al., 2022). One Chinese study reported that for those with normal cognition and cognitive impairment, lower education and ischemic heart disease was associated with a lower Aβ42/40 ratio while cerebrovascular disease was associated with a higher Aβ42/40 ratio, an opposite direction from that in NHW (Pan et al., 2023).

4.7. Total tau, p-tau181

4.7.1. CSF

Seven out of nine studies found significantly lower levels of CSF total tau and CSF p-tau181 in AA compared to NHW with normal cognition but with a biological parent with AD (Kumar et al., 2020), normal cognition and MCI (Garrett et al., 2019; Hajjar et al., 2022) and in those across all levels of cognitive status (Howell et al., 2017; Morris et al., 2019; Schindler et al., 2021, 2022) with a wide range of covariates included in their models, except for (Kumar et al., 2020) (Table 9, Table 10). The remaining two studies found no difference between AA and NHW in CSF total tau and CSF p-tau181 levels in those with normal cognition (Xiong et al., 2022) and in participants regardless of cognitive status (Windon et al., 2022). Taken together, AA appear to have lower CSF total tau and CSF p-tau 181 compared to NHW. In contrast, one study found no differences in CSF total tau and CSF p-tau 181 between HLA and NHW after controlling for age, sex, education, MMSE, CDR-SB, and CSF Aβ42 level (Windon et al., 2022).

4.7.2. Plasma

Lower levels of plasma total tau have been reported in AA with normal cognition, MCI, and dementia after adjusting for age and sex (J. R. Hall et al., 2022) whereas for HLA, higher or similar levels of plasma total tau were found as compared to NHW (J. R. Hall et al., 2022; S. E. O'Bryant, Zhang, et al., 2022) (Table 9). In addition, a significant interaction between ethnicity and plasma total tau was found with higher odds of dementia in NHW compared to HLA. However, the findings were no longer significant in a subset sample matched on age, sex, *APOE* ε4 status, education, and site (Gonzales et al., 2021).

For plasma p-tau 181, studies have shown no difference (Ramanan et al., 2023; Schindler et al., 2022; Windon et al., 2022) or significantly lower levels of plasma p-tau 181 in AA compared to NHW after controlling for a range of covariates including age, sex, *APOE* ε4, cognitive status, and education (Hajjar et al., 2022) (Table 10). For HLA, no differences in plasma p-tau 181 were found when compared to NHW regardless of cognitive status (Asken et al., 2024; Windon et al., 2022).

4.7.3. Other modifying factors

For cognitively unimpaired NHW, higher levels of plasma total tau have been associated with hypertension, diabetes, a history of stroke, myocardial infarction, atrial fibrillation, CKD, comorbid conditions, and higher BMI (de Crom, Ghanbari, Voortman, and Ikram, 2024; Martínez-Dubarbie et al., 2024; Merten et al., 2023; Syrjanen et al., 2022). A similar pattern was found in a cognitively unimpaired Chinese cohort such that increasing plasma total tau was associated with cerebrovascular disease, CKD, and higher BMI (Pan et al., 2023). For MCI or

Table 9
Studies examining racial and ethnic differences in total tau in normal cognition, MCI, and dementia.

Study	Study cohort	Clinical diagnosis	Assay /platform	Unadjusted mean pg/mL group 1 (SD/SE*/range)	Unadjusted mean pg/mL group 2 (SD/SE*/range)	Covariates	Main findings (after adjusted) (Group 1 vs Group 2)
CSF							
(Schindler et al., 2022)	AA (n = 76) NHW (n = 76)	All levels of cognitive impairment	Lumipulse G1200, Fujirebio	212 (165–287)	290 (217–482)	0,1,15	AA < NHW
(Howell et al., 2017)	AA (n = 65) NHW (n = 70)	Normal cognition, MCI, AD	INNO-BIA AlzBio3 immunoassay (Fujirebio, PA, USA)/Luminex 200 platform	47.0 (31.1)	71.5 (47.8)	0,1,10,15,19	AA < NHW
(Garrett et al., 2019)	AA (n = 152) NHW (n = 110)	Normal cognition and MCI	INNO-BIA AlzBio3/ multiplex platform (xMAP; Luminex Corp)	48.00 (29.51)	69.80 (45.52)	0,1,4,6,7,9,12,16	AA < NHW
(Morris et al., 2019)	AA (n = 173) NHW (n = 1082)	All levels of cognitive impairment	INNOTEST, Fujirebio (formerly Innogenetics)	293.65 (34.61)	443.28 (18.20)	0,6,12,15,16	AA < NHW
(Kumar et al., 2020)	AA (n = 30) NHW (n = 50)	Normal cognition with a biological parent with AD	INNOTEST, Fujirebio (formerly Innogenetics)	199.0◆ (166.0 – 244.0)	297.0◆ (228.0 – 423.0)	NA	AA < NHW
(Hajjar et al., 2022)	AA (n = 300) NHW (n = 317)	Normal cognition and MCI	INNO-BIA AlzBio3/ multiplex platform (xMAP; Luminex Corp)	42.61 (20.24)	60.67 (31.49)	0,1,4,6,9,15,19	AA < NHW
			Lumipulse G1200, Fujirebio	267.21 (143.52)	454.55 (269.61)	0,1,4,6,9,15,19	AA < NHW
(Xiong et al., 2022)	AA (n = 37) NHW (n = 330)	Normal cognition	Lumipulse G1200, Fujirebio	249.24 (142.62)	305.79 (222.88)	NA	AA = NHW
(Windon et al., 2022)	AA (n=47) HLA (n =43) NHW (n = 141)	All levels of cognitive impairment	Elecsys (Roche Diagnostics)	214.6 (152.4–290.7)	251.9 (194.5–351.4)	0,1,6,19	AA = NHW
			Elecsys (Roche Diagnostics)	216.5 (147.1–270.5)	257.2 (197.2–360.9)	0,1,6,19	HLA = NHW
(Schindler et al., 2021)	AA (n = 99) NHW (n = 868)	All levels of cognitive impairment	Elecsys (Roche Diagnostics)	167.34 (1.48)	230.44 (1.54)	0,6,10,15,16	AA < NHW
(Bonomi et al., 2024)	AA (n = 154) NHW (n = 1191)	All levels of cognition	Lumipulse G1200, Fujirebio	364$^{\Delta}$ (23*)	450$^{\Delta}$ (12*)	0,1,2,6,15	AA < NHW
Plasma							
(J. R. Hall et al., 2022)	NHW (n = 86)	NC	Simoa (Quanterix, MA, USA)	2.56 (1.07)	2.31(1.07)	0	HLA > NHW
	HLA¶ (n = 146)			1.71 (0.64)	2.31(1.07)	0	AA < NHW
	AA (n = 74)	MCI		2.66 (1.08)	2.62 (1.07)	0	HLA = NHW
				1.67 (1.27)	2.62 (1.07)	0	AA < NHW
		Dementia		2.76 (0.71)	2.63 (1.05)	0	HLA = NHW
				2.03 (0.74)	2.63 (1.05)	0	AA < NHW
(O'Bryant, Zhang, et al., 2022)	HLA¶ (n = 688) NHW (n = 617)	Normal cognition, MCI, AD	Simoa/HD−1 (Quanterix, MA, USA)	2.60 (1.08)	2.39 (1.13)	NA	HLA > NHW
(Gonzales et al., 2021)	HLA (n = 321) NHW (n = 321)	Normal cognition, MCI, dementia	Neurology 4-Plex A Kit/ HD−1 analyzer (Quanterix, MA, USA)	0.3 (0.1–0.4‡)	0.3 (0.1–0.5‡)	Matched cohort on 0,6,15	HLA = NHW

◆ Reported values are median
¶ Mexican American
‡ Quartile 1–Quartile 3
$^{\Delta}$ Adjusted least-squared mean

dementia, atrial fibrillation and CKD were associated with higher total tau levels (Syrjanen et al., 2022).

Higher levels of plasma p-tau 181 in those without cognitive impairment have been associated with age, the presence of the *APOE* ε4 allele, comorbid conditions, diabetes, CKD, hypertension and elevated amyloid PET (SUVR > 1.48) (Martínez-Dubarbie et al., 2024; Mielke et al., 2022; Valletta et al., 2024) while higher BMI, dyslipidemia, and being a current/former smoker were associated with lower levels of plasma p-tau 181 after adjusting for age and sex (Mielke et al., 2022; Valletta et al., 2024).

While no association between plasma p-tau 181 and eGFR was reported (Martínez-Dubarbie et al., 2024), a significant inverse relationship was found in participants with varying cognitive status after adjusting for age, sex, and Aβ status in NHW participants (Sarto et al., 2023) and participants including NHW and AA (Hajjar et al., 2024). For MCI or dementia, age, CKD, stroke, myocardial infarction, and elevated amyloid PET were associated with higher levels of plasma p-tau 181 in NHW (Mielke et al., 2022; Ramanan et al., 2023; Syrjanen et al., 2022) and in a Chinese cohort (Pan et al., 2023).

4.8. Neurofilament light chain (NfL)

4.8.1. CSF

For AA, studies have found either no difference (Howell et al., 2017; Schindler et al., 2022) or lower levels of CSF NfL (Garrett et al., 2019; Hajjar et al., 2022) in those with all levels of cognitive impairments as compared to NHW after controlling for age, sex, *APOE* ε4, and cognitive status (Table 11).

4.8.2. Plasma

For AA, studies have found either no difference (Ramanan et al., 2023; Schindler et al., 2022; Windon et al., 2022) or lower level of plasma NfL (Hajjar et al., 2022) compared to NHW in participants with normal cognition or with all levels of cognitive impairments (Table 11). Similar findings were observed for the HLA cohorts such that no difference (J. R. Hall et al., 2022; O'Bryant et al., 2022; Windon et al., 2022) or lower levels of plasma NfL (J. R. Hall et al., 2022; S. E. O'Bryant, Zhang, et al., 2022) were found in HLA compared to NHW.

Table 10
Studies examining racial and ethnic differences in p-tau 181 in normal cognition, MCI, and dementia.

Study	Study cohort	Clinical diagnosis	Assay /platform	Unadjusted mean pg/mL group 1 (SD/SE*/range)	Unadjusted mean pg/mL group 2 (SD/SE*/range)	Covariates	Main findings (after adjusted) (Group 1 vs Group 2)
CSF							
(Schindler et al., 2022)	AA (n = 76) NHW (n = 76)	All levels of cognitive impairment	Lumipulse G1200, Fujirebio	31 (24.6–41.1)	38.0 (30.4–55.7)	0,1,15	AA < NHW
(Howell et al., 2017)	AA (n = 65) NHW (n = 70)	Normal cognition, MCI, AD	INNO-BIA AlzBio3 immunoassay (Fujirebio, PA, USA)/Luminex 200 platform	17.9 (9.3)	25.6 (12.6)	0,1,10,15,19	AA < NHW
(Garrett et al., 2019)	AA (n = 152) NHW (n = 110)	Normal cognition and MCI	INNO-BIA AlzBio3/ multiplex platform (xMAP; Luminex Corp)	13.25 (6.37)	20.31 (14.82)	0,1,4,6,7,9,12,16	AA < NHW
(Morris et al., 2019)	AA (n = 173) NHW (n = 1082)	All levels of cognitive impairment	INNOTEST, Fujirebio (formerly Innogenetics)	53.18 (4.91)	70.73 (2.46)	0,6,12,15,16	AA < NHW
(Kumar et al., 2020)	AA (n = 30) NHW (n = 50)	Nnormal cognition with a biological parent with AD	INNOTEST, Fujirebio (formerly Innogenetics)	37.0◆ (34.0 – 42.0)	48.0◆ (37.0 – 64.0)	NA	AA < NHW
(Hajjar et al., 2022)	AA (n = 300) NHW (n = 317)	Normal cognition and MCI	INNO-BIA AlzBio3/ multiplex platform (xMAP; Luminex Corp)	14.05 (6.86)	18.46 (10.40)	0,1,4,6,9,15,19	AA < NHW
			Lumipulse G1200, Fujirebio	37.67 (21.77)	64.81 (44.15)	0,1,4,6,9,15,19	AA < NHW
(Xiong et al., 2022)	AA (n = 37) NHW (n = 330)	Normal cognition	Lumipulse G1200, Fujirebio	31.44 (15.62)	39.05 (23.24)	NA	AA = NHW
(Windon et al., 2022)	AA (n=47) HLA (n =43) NHW (n = 141)	All levels of cognitive impairment	Elecsys (Roche Diagnostics)	19.6 (14.4–27.3)	22.7 (17.0–33.3)	0,1,6,19	AA = NHW
			Elecsys (Roche Diagnostics)	19.4 (13.6–27.9)	24.7 (17.5–33.4)	0,1,6,19	HLA = NHW
(Schindler et al., 2021)	AA (n = 99) NHW (n = 868)	All levels of cognitive impairment	Elecsys (Roche Diagnostics)	15.33 (1.48)	20.91 (1.62)	0,6,10,15,16	AA < NHW
(Bonomi et al., 2024)	AA (n = 154) NHW (n = 1190)	All levels of cognition	Lumipulse G1200, Fujirebio	50.7Δ (3.1*)	61.4Δ (1.7*)	0,1,2,6,15	AA < NHW
Plasma							
(Schindler et al., 2022)	AA (n = 76) NHW (n = 76)	All levels of cognitive impairment)	Simoa (single molecule array)/HD−1 (Quanterix, MA, USA)	12.3 (10.2–16.2)	14.2 (10.6–19.3)	0,1,15	AA = NHW
(Hajjar et al., 2022)	AA (n = 300) NHW (n = 317)	Normal cognition and MCI	Simoa Platform Version 2 Advantage Kit (Quanterix, MA, USA)	17.99 (7.54)	21.78 (9.59)	0,1,4,6,9,15,19	AA < NHW
(Windon et al., 2022)	AA (n=47) HLA (n =43) NHW (n = 141)	All levels of cognitive impairment	Simoa (Quanterix, MA, USA)	14.5 (9.4–22.9)	15.5 (10.1–22.8)	0,1,6,19	AA = NHW
			Simoa (Quanterix, MA, USA)	18.0 (11.3–25.0)	15.7 (10.9–23.4)	0,1,6,19	HLA = NHW
(Ramanan et al., 2023)	AA (n = 267) NHW (n = 268)	Normal cognition, MCI, and dementia	Simoa/HD-X analyzer (Quanterix, MA, USA)	3.31 (2.14)	3.22 (1.95)	0	AA = NHW
Asken et al. (2024)	HLA (n = 135) NHW (n = 106=5)	Normal cognition and MCI	Simoa/SRX analyzer (Quanterix, MA, USA)	-	-	0	HLA = NHW
(Mohs et al., 2024)	AA (n = 112) HLA (n = 115) NHW (n = 755)	Cognitive normal, MCI, mild AD	Simoa (Quanterix, MA, USA)	15.41 (8.13) 17.60 (11.00)	20.13 (14.04) 20.13 (14.04)	0,1,6	AA < NHW HLA = NHW

◆ Reported values are median
Δ Adjusted least-squared mean
- group mean was calculated based on clinical diagnosis - normal controls, amnestic MCI or dementia, non-amnestic MCI or dementia, cognitively impaired but not MCI

4.8.3. Other modifying factors

For cognitively unimpaired NHW, a history of stroke, atrial fibrillation, history of cancer, CKD, comorbid conditions, smoke exposure/current smoker, and diabetes were associated with higher levels of plasma NfL (Merten et al., 2023; Ramanan et al., 2023; Syrjanen et al., 2022; Zhu, Zhu, Lin, Yu, and Cao, 2024). In addition, more pronounced higher NfL levels were found in participants who had higher systematic inflammation indicated by increased interleukin-6 levels in those with CKD, anemia, and cerebrovascular disease (Valletta et al., 2024). On the contrary, higher BMI and dyslipidemia were associated with lower levels of plasma NfL (de Crom et al., 2024; Merten et al., 2023; Ramanan et al., 2023; Syrjanen et al., 2022). For MCI and dementia, CKD, myocardial infarction, and BMI < 18 were associated with higher plasma NfL levels (Ramanan et al., 2023; Syrjanen et al., 2022). For HLA, a study found that higher Framingham Risk Scores were associated with higher levels of plasma NfL in Mexican American but not in NHW individuals after controlling for age, sex, education, *APOE* ε4, physical activity, alcohol use, renal function, and depression (Jiang, O'Bryant, Johnson, Rissman, and Yaffe, 2023). For studies including subjects with all cognitive levels, the findings are mixed. A prior stroke was associated with higher levels of NfL in AA and NHW combined (Ramanan et al., 2023), while a Spanish study found no associations between NfL and cardiovascular disease, myocardial infarction, diabetes, hypertension, smoking, BMI, or Charlson Comorbidity Index. Only age, blood volume and eGFR were associated with NfL levels, with a positive relationship with age and negative relationships with blood volume and eGFR (Sarto et al., 2023). In a cohort with a history of type 2 diabetes and a history of cardiovascular disease, older age, nonwhite race (primarily AA), higher systolic blood pressure, glomerular filtration rate < 60, and higher hemoglobin A1C were associated with increased NfL (Korley et al., 2019).

4.8.4. Glial fibrillary acidic protein (GFAP)

Lower GFAP levels were observed in HLA as compared to NHW participants across the whole sample and when the sample was stratified by diagnosis (cognitive unimpaired, MCI, and dementia) (Table 12)

Table 11
Studies examining racial and ethnic differences in NfL in normal cognition, MCI, and dementia.

Study	Study cohort	Clinical diagnosis	Assay /platform	Unadjusted mean pg/mL group 1 (SD/SE*/range)	Unadjusted mean pg/mL group 2 (SD/SE*/range)	Covariates	Main findings (after adjusted) (Group 1 vs Group 2)
CSF							
(Schindler et al., 2022)	AA (n = 76) NHW (n = 76)	All levels of cognitive impairment	NFlight® ELISA (Uman Diagnostics, Umeå, Sweden)	644 (493–868)	736 (542–973)	0,1,15	AA = NHW
(Howell et al., 2017)	AA (n = 65) NHW (n = 70)	Normal cognition, MCI, AD	NFlight® ELISA (Uman Diagnostics, Umeå, Sweden)	741.31 (1.86)	933.25 (1.55)	0,1,10,15,19	AA = NHW
(Hajjar et al., 2022)	AA (n = 300) NHW (n = 317)	Normal cognition and MCI	Simoa Platform Version 2 Advantage Kit (Quanterix Corp)	740.11 (342.20)	902.23 (374.76)	0,1,4,6,9,15,19	AA < NHW
(Schindler et al., 2021)	AA (n = 99) NHW (n = 868)	All levels of cognitive impairment	NFlight® ELISA (Uman Diagnostics, Umeå, Sweden)	1211.97 (1.62)	1587.63 (1.67)	0,6,10,15,16	AA < NHW
(Bonomi et al., 2024)	AA (n = 148) NHW (n = 1145)	All levels of cognition	ELISA kit (UMAN Diagnostics)	6.61$^{\Delta}$ (0.04*)	6.79$^{\Delta}$ (0.02*)	0,1,2,6,15	AA < NHW
Plasma							
(Schindler et al., 2022)	AA (n = 76) NHW (n = 76)	All levels of cognitive impairment	Simoa Nf-Light Assay kits /HD-X (Quanterix, MA, USA)	11.1 (7.6–15.5)	11.8 (8.9–16.7)	0,1,15	AA = NHW
(Hajjar et al., 2022)	AA (n = 300) NHW (n = 317)	Normal cognition and MCI	Simoa Platform Version 2 Advantage Kit (Quanterix, MA, USA)	11.19 (6.38)	13.41 (6.18)	0,1,4,6,9,15,19	AA < NHW
(Windon et al., 2022)	AA (n=47) HLA (n =43) NHW (n = 141)	All levels of cognitive impairment	Simoa (Quanterix, MA, USA)	29.3 (21.6–42.5)	35.5 (27.0–49.6)	0,1,6,19	AA = NHW
			Simoa (Quanterix, MA, USA)	36.7 (24.4–50.4)	35.6 (25.6–47.1)	0,1,6,19	HLA = NHW
(Gonzales et al., 2021)	HLA (n = 321) NHW (n = 321)	Normal cognition, MCI, dementia	Neurology 4-Plex A Kit/ HD−1 analyzer (Quanterix, MA, USA)	20 (14–30‡)	26 (18–37‡)	Matched cohort on 0,6,15	HLA < NHW
(O'Bryant et al., 2022)	HLA¶ (n = 890) NHW (n = 813)	All levels of cognitive impairment	Simoa/ HD−1 (Quanterix, MA, USA)	17.43 (11.97)	20.87 (11.29)	0,6	HLA = NHW
(O'Bryant, Zhang, et al., 2022)	HLA¶ (n = 688) NHW (n = 617)	Normal cognition, MCI, AD	Simoa/ HD−1 (Quanterix, MA, USA)	17.41 (12.87)	20.78 (13.94)	NA	HLA < NHW
(J. R. Hall et al., 2022)	NHW (n = 86)	NC	Simoa (Quanterix, MA, USA)	16.75 (12.97)	20.10 (12.69)	0	HLA < NHW
	HLA¶ (n = 146)			12.58 (10.45)	20.10 (12.69)	0	AA < NHW
	AA (n = 74)	MCI		18.36 (12.93)	25.84 (12.79)	0	HLA < NHW
				14.51 (10.35)	25.84 (12.79)	0	AA < NHW
		Dementia		26.11 (1.65)	25.98 (1.87)	0	HLA = NHW
				21.85 (2.41)	25.98 (1.87)	0	AA < NHW
(Ramanan et al., 2023)	AA (n = 267) NHW (n = 268)	Normal cognition, MCI, and dementia	Simoa/HD-X analyzer (Quanterix, MA, USA)	40.09 (28.08)	38.60 (26.93)	0	AA = NHW

◆ Reported values are median
¶ Mexican American
$^{\Delta}$Adjusted least-squared mean

Table 12
Studies examining racial and ethnic differences in GFAP in normal cognition, MCI, and dementia.

Study	Study cohort	Clinical diagnosis	Assay /platform	Unadjusted mean pg/mL group 1 (SD/SE*/range)	Unadjusted mean pg/mL group 2 (SD/SE*/range)	Covariates	Main findings (after adjusted) (Group 1 vs Group 2)
CSF							
(Gonzales et al., 2021)	HLA (n = 321) NHW (n = 321)	Normal cognition, MCI, dementia	Neurology 4-Plex A Kit/ HD−1 analyzer (Quanterix, MA, USA)	184 (131–309‡)	286 (175–424‡)	Matched cohort on 0,6,15	HLA < NHW
(Gonzales et al., 2023)	HLA¶ (n = 1156) NHW (n = 587)	Unimpaired cognition, MCI, and dementia	Neurology 4-Plex A Kit/ HD−1 analyzer (Quanterix, MA, USA)	154 (108–222‡)	345 (206–488‡)	NA	HLA < NHW

¶ Mexican American
‡ Quartile 1–Quartile 3

(Gonzales et al., 2021, 2023). However, differences in demographic characteristics between HLA and NHW from these two studies were reported, including BMI, blood pressure, and number of subjects with diabetes. No difference was found between AA and NHW in GFAP levels nor in the association between higher GFAP levels and the development of clinical AD after controlling for sex, gender, education, and the presence of the *APOE* ε4 allele. Specifically, higher GFAP levels at baseline have been associated with lower cognitive scores and increased rate of cognitive decline over an average of 10 years follow up, and this association did not differ between AA and NHW (Rajan et al., 2020).

4.8.5. Other modifying factors

For NHW, a higher number of co-occurring chronic diseases was associated with higher levels of GFAP, including cerebrovascular disease, heart diseases, CKD, and anemia (Valletta et al., 2024). For both NHW and HLA, older age, *APOE* ε4 carrier, and presence of cognitive impairment were positively associated with GFAP levels whereas BMI, diabetes, and tobacco were associated with lower GFAP levels across diagnostic groups (cognitively unimpaired, MCI, and dementia) (Gonzales et al., 2023).

5. Discussion

This narrative review summarizes studies that focus on racial and ethnic differences in imaging and biofluid biomarkers. Race and ethnicity used in the literature are self-identified social constructs rather than a fixed genetic characteristic. While race indicates racial and national origin, ethnicity, a broader category than race, identifies people based on similarities such as common ancestry, language, history, society, culture, or nationality (Ardila, 2020; Rosselli, Uribe, Ahne, and Shihadeh, 2022). Therefore, a high degree of variability in backgrounds and disease risks are inherently included when studying biomarkers across races and ethnicities. In this review, we found that for PET, *APOE* genotyping significantly affects amyloid SUVRs. For MRI, no evidence of racial and ethnic differences was indicated after controlling for cognitive status and cardiovascular risks (diabetes, hypertension, hyperlipidemia, BMI, smoking status). Furthermore, socioeconomic status, life-course factors, psychological factors, environmental factors, and family history of dementia are important factors modifying imaging biomarkers. For biofluid biomarkers, AA have consistently been shown to have higher levels of plasma Aβ42/Aβ40 and lower levels of CSF total tau and p-tau 181 compared to NHW. Comorbid medical conditions, such as CKD, myocardial infarction, stroke, hypertension, diabetes, hyperlipidemia, higher BMI can increase or attenuate AD biomarker levels.

Although comorbidities and AD risks change biomarker levels, more studies are needed to further examine their impact on prediction of amyloid status or diagnostic discrimination, and to what degree, across different racial and ethnic groups. For predicting amyloid status, in NHW individuals, Sarto et al. found minimal impact of medical comorbidities on the predictability of plasma p-tau181 for Aβ status defined by CSF or amyloid PET with varying degrees of cognitive impairments and etiology (Sarto et al., 2023). When comparing between HLA and NHW participants, Asken et al. showed similar prediction results when plasma p-tau 181, GFAP, and NfL were used individually to predict amyloid PET positivity when age, sex, and *APOE* ε4 carriers were included in the model (Asken et al., 2024). Schindler et al. found that being AA did not affect the ability of using plasma Aβ42/Aβ40 to predict amyloid PET positivity after including covariates such as sex, age, *APOE*, and cognitive status (Schindler et al., 2022). For diagnostic discrimination, Mielke et al. found that the cutoff of plasma p-tau181 significantly decreased for normal reference (cognitive unimpaired without elevated brain amyloid) with the exclusion of participants with CKD, stroke, and myocardial infarction in a primarily NHW cohort. For Mexican Americans, Gonzales et al. showed that although there were no ethnic differences in the accuracy of plasma GFAP in discriminating between dementia and cognitive unimpaired diagnoses, a lower cut-off value was observed for Mexican Americans relative to NHW with the inclusion of age, sex, BMI, tobacco use, and *APOE* ε4 carrier status. For discriminating between normal cognition and MCI in an AA cohort, Garrett et al. found that the direction of the cutoffs of CSF total tau and p-tau 181 flipped after accounting for demographic characteristics, educational level, family history of AD, BMI, and cognitive scores (before AA $<$ NHW; after: AA $>$ NHW) (Garrett et al., 2019). Taken together, it appears that biofluid biomarkers predict amyloid status and clinical diagnosis equally well across different races/ethnicities. However, the cut-offs are likely to change when considering AD risks and comorbidities. Indeed, the consideration of comorbidities are particularly important in racial and ethnic minority groups given that the prevalence and incidence of comorbidities often vary across races/ethnicities. (Mielke et al., 2022).

In addition to AD risks and comorbidities, genetics play a significant role in contributing to biomarker differences. Existing literature points to the variability in the frequency of AD-related genes across different races and ethnicities and that the same gene may operate differently, which may lead to racial and ethnic differences in AD biomarkers (Ali et al., 2023; Barnes and Bennett, 2015; Corbo and Scacchp, 1999; Maestre et al., 1995). For example, in Caribbean Hispanics, Hispanic Americans, and NHW, the frequency of the *APOE* ε4 allele was similar (21.8 %–25.4 %), but the prevalence of *APOE* ε4 was substantially higher in AAs (33.6 %) (Barnes and Bennett, 2015; Llibre-Guerra et al., 2023). However, compared to NHW, the association between AD and *APOE* ε4 was weaker in individuals with African ancestry (Maestre et al., 1995; Naslavsky et al., 2022; Reitz, Pericak-Vance, Foroud, and Mayeux, 2023). Caribbean Hispanic individuals, who are known to have a higher proportion of African ancestry, have shown blunted effects of *APOE* ε4 homozygosity or no increased AD risk among heterozygotes (Reitz et al., 2023). When assessing the link between *APOE* ε4 and brain amyloid, a significantly reduced positive association was found in an AA cohort (Royse et al., 2024), HLA cohort compared to NHW cohorts (Duara et al., 2019) and in an Asian cohort compared to NHW and AA cohorts from a large multi-ethnic genetic study (N = 13,409) (Ali et al., 2023). While *APOE* ε2 decreases the risk of late-onset AD and is associated with milder AD pathology in primarily NHW cohorts (Zonghua Li, Shue, Zhao, Shinohara, and Bu, 2020), studies have found that *APOE* ε2 was associated with increased risk of AD in AA (Maestre et al., 1995) and in HLA (Xiao, Pappas, Aksman, O'Bryant, and Toga, 2023) Together, these studies suggest a race/ethnic-specific *APOE* effect on AD risks and AD biomarkers.

There are several limitations of the prior studies. First, most of the studies have been of small selected cohorts, where selection bias may be at play. Population-based samples are needed to better evaluate biomarkers and assess risk profiles for racial and ethnic minority groups, especially in Asian cohorts (Ho et al., 2024). Second, lack of evidence from minorities on the effect of comorbidities on fluid biomarker levels. It is unclear whether the modifying effects of medical conditions and comorbidities are the same in AA, HLA and Asian Americans as those in NHW. Third, there is not yet substantial evidence comparing p-tau 217 levels across races/ethnicities, which has shown to be the most promising biomarker in early detection of amyloid and tau pathologies (Mohs et al., 2024). Forth, lack of studies examining the impact of psychosocial factors, environmental factors (Caunca et al., 2020; Glymour and Manly, 2008), and SDOH (Bailey, Feldman, and Bassett, 2021; K. S. Hall, Gao, Unverzagt, and Hendrie, 2000; Zuckerman et al., 2008) on imaging and fluid biomarkers, as they contribute to a higher risk of developing dementia in underrepresented groups.

6. Conclusions

This paper reviewed studies on racial and ethnic differences in neuroimaging and biofluid biomarkers in older adults across the spectrum of cognition. While there is no strong evidence of racial and ethnic differences in imaging biomarkers, factors such as *APOE* ε4 status, cognitive levels, cardiovascular risk, and socioeconomic status can lead to differences in imaging markers across races and ethnicities. Higher levels of plasma Aβ42/Aβ40, and lower levels of CSF total tau and CSF p-tau 181, were indicated in AA. The inclusion of AD risk and medical comorbidities, such as kidney function, BMI, hypertension, and diabetes are important factors to consider, especially when establishing cutoffs for different racial and ethnic groups. Future studies evaluating psychosocial factors, environmental factors, and SDOH in addition to medical comorbidities are needed to examine the effects of these factors on biomarkers in diverse racial and ethnic groups cross-sectionally and longitudinally, and the degree to which biomarkers are considered when clinical decisions are made.

Declaration of Competing Interest

The authors declare no competing financial interest.

Data Availability

No data was used for the research described in the article.

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