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Original Article

Association of neighborhood disadvantage with Alzheimer's disease pathology and the stability of blood-based biomarker performance☆

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ABSTRACT

Background: Neighborhood-level factors, measured by the Area Deprivation Index (ADI), are linked to comorbidities of Alzheimer's disease and related dementias (ADRD). However, their direct association with AD neuropathology is unclear. The accessibility of blood-based biomarkers (BBMs) like p-tau217 and Aβ42/40 offers a scalable way to investigate these relationships.
Objectives: To examine the relationship between ADI and levels of key BBMs (p-tau217/Aβ42, p-tau217, and Aβ42/40). We also aimed to assess whether the performance of these BBMs in predicting amyloid PET positivity is consistent across different levels of neighborhood disadvantage.
Design: A cross-sectional analysis using data from an observational cohort study of the Alzheimer's Disease Neuroimaging Initiative (ADNI).
Setting: Multicenter observational cohort conducted at 55 sites across the United States.
Participants: The study included 755 ADNI participants with ADI and amyloid PET data. A sub-cohort of 438 participants also had BBM data available.
Measurements: National ADI scores were used to stratify participants into least, intermediately, and most disadvantaged groups. Amyloid PET positivity was determined using Centiloid values. Plasma levels of p-tau217, Aβ42, and Aβ40 were measured using Fujirebio assays.
Results: ADI groups differed by sex, ethnoracial background, and MMSE scores. The intermediately disadvantaged group had 1.55 times higher odds of being amyloid PET positive compared to the least disadvantaged group. While this group also showed higher levels of plasma p-tau217/Aβ42 and p-tau217, these differences were no longer significant after accounting for the higher prevalence of amyloid positivity. Critically, the predictive accuracy of all three BBMs for amyloid PET status did not differ across the ADI groups. The p-tau217/Aβ42 ratio performed best, yielding the fewest indeterminate cases in a two-cut-point classification model.
Conclusions: The diagnostic performance of plasma AD biomarkers is robust and is not compromised by neighborhood-level disadvantage. These findings support the generalizability and equitable clinical utility of biomarkers like p-tau217/Aβ42 for AD diagnosis across diverse socioeconomic settings.

☆ Alzheimer's Disease Neuroimaging Initiative (ADNI): Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at:http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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1. Introduction

An individual's life circumstances, including a spectrum of environmental and background factors, are increasingly recognized as contributors to the risk and progression of Alzheimer's Disease (AD) and related dementias (ADRDs) [1–4]. One such factor is neighborhood socioeconomic status, which can be quantified by metrics like the Area Deprivation Index (ADI) [4–7]. ADI has been previously associated with dementia risk [5,8,9]. More importantly, the neighborhood-level characteristics quantified by ADI have been linked to an increased prevalence of health conditions, such as cardiovascular diseases, chronic stress, kidney disease, obesity, and diabetes [3,4,7,10–15], all of which are either well-established risk-factors for ADRD or comorbid conditions with ADRD due to shared biological pathways such as inflammation [16–19].

While the link between neighborhood characteristics and AD-related risk factors and comorbidities is established, the direct relationship between these factors and core AD brain pathology is less clear. Previous post-mortem and neuroimaging studies have produced conflicting findings. Some reports suggest an association between neighborhood-level factors and AD neuropathological changes [3,18,20–22], while others have found that while these factors correlate with lower cognitive performance, they do not correlate with dementia-related neuropathologic changes [23]. A comprehensive understanding of the relationship between these environmental factors and the presence of AD pathology remains elusive.

Resolving these conflicting findings is crucial, and the recent clinical availability of anti-amyloid treatments has transformed the diagnostic landscape for AD, creating a pressing need for biomarker confirmation of amyloid pathology. While positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) biomarker analysis are established reference standards, their costs and the specialized infrastructure required can limit their use in large-scale population studies needed to clarify these complex relationships. Blood-based biomarkers (BBMs) represent a more scalable and accessible approach that can be implemented in a wider range of settings. This shift has the potential to allow more individuals to receive a timely and accurate diagnosis and facilitate research across a broader spectrum of the population.

For BBMs to be broadly applicable, their performance must be consistent and reliable when compared to the amyloid PET reference standard across a full spectrum of populations. Key BBMs, particularly β-amyloid (Aβ42/40) and phosphorylated tau at position 217 (p-tau217), have proven to be robust indicators of AD pathology [24–28]. More recently, p-tau217/Aβ42 has also been found to correlate closely with measures of AD pathology [29–31]. Importantly, the Lumipulse p-tau217/Aβ42 plasma ratio from Fujirebio has been cleared by the FDA [32], which will allow it to be more widely used in aiding the diagnosis of AD in clinics nationwide.

Acceptable performance of blood biomarker tests of AD amyloid pathology requires not only strong accuracy for classifying amyloid status but also high confidence. A critical question remains whether the diagnostic performance of these BBMs is impacted by health conditions that have been linked to neighborhood-level factors [33–38].

This study aims to address this knowledge gap by leveraging data from the most recent phase of the Alzheimer's Disease Neuroimaging Initiative cohort (ADNI-4), which was designed to increase the generalizability of findings through recruitment efforts in different communities nationwide. In this cross-sectional study, we examine the relationship between neighborhood-level characteristics, as measured by ADI, and the prevalence of AD amyloid pathology as well as the performance of plasma AD biomarkers in detecting AD amyloid pathology positivity. We specifically assess whether the classification accuracy and confidence of plasma p-tau217/Aβ42, p-tau217, and Aβ42/40, relative to amyloid PET, are consistent across different ADI levels. By clarifying these relationships, this work will contribute to our understanding of the utility of BBMs and support their broad and effective application.

2. Methods

2.1. Subjects

This cross-sectional study utilizes data from ADNI-4, a longitudinal, multisite observational study of cognitively unimpaired (CU) individuals, individuals with mild cognitive impairment (MCI), and individuals clinically diagnosed with dementia due to AD. ADNI-4 classifies normal cognition, MCI, and dementia according to guidelines previously detailed in Petersen et al [39].

2.2. Area deprivation index (ADI)

Neighborhood characteristics was quantified using the Area Deprivation Index (ADI) and calculated from Census block group data [7,40]. ADI was developed by the Health Resources and Services Administration and data are available for download at the University of Wisconsin School of Medicine and Public Health's Neighborhood Atlas website (www.neighborhoodatlas.medicine.wisc.edu). The indicators of the neighborhood characteristics encompass domains including education (e.g., percentage of population without a high school degree), income (e.g., median household income), employment (e.g., percentage of unemployed individuals), and housing quality (e.g., percentage of housing units lacking complete plumbing). The ADI provides two normative rankings: a state decile rank (ranging from 1 to 10, with 10 indicating the highest level of disadvantage within the state) and a national percentile rank (ranging from 1 to 100, with 100 indicating the highest level of disadvantage nationwide). Broader adverse exposome factors like neighborhood disadvantage tend to be more influenced by national factors, which leads to some states having higher levels of disadvantage overall than others. Therefore, in this analysis we used national ADI as this metric is harmonized across the USA.

2.3. Blood based biomarkers

Blood based biomarkers (BBB) were assayed from plasma samples as described previously [41]. This study included p-tau217, Aβ42, and Aβ40 levels measured using immunoassay reagents provided by Fujirebio, on the Lumipulse G1200 platform (Plasma β-Amyloid 1–42 RUO IVD, Plasma β-Amyloid 1–40 RUO IVD and Plasma p-tau217 RUO IVD). The analyses focused on plasma measures of p-tau217/Aβ42, Aβ42/40, Aβ42, Aβ40 and p-tau217.

2.4. Neuroimaging amyloid biomarkers

^{18}F-florebetaben (FBB) amyloid PET image acquisition was performed 90–110 min after injection of 300 MBq of FBB, while ^{18}F-florbetapir (FBP) amyloid PET image acquisition was performed 50–70 min after injection of 370 MBq of FBP. For both tracers, individuals were scanned for 20 min (4 × 5-minute frames). After acquisition, images were processed with an MRI-based PET processing pipeline detailed in Landau et al [42]. Tracer-specific amyloid positivity thresholds of 1.11 and 1.08 SUVR were enforced for FBP and FBB, respectively [42]. SUVR values were converted to Centiloid as described in Royse et al [43].

2.5. Statistical analyses

Demographic data included in the analyses were age (in years), self-reported highest educational attainment (by degree), self-reported sex (male, female), self-reported ethnoracial background (Non-Hispanic White [NHW], Non-Hispanic Black [NHB], Hispanic/Latin American [HLA], Asian, and other), and ADI (national). Clinical data included in the analyses were clinical diagnosis (CU, MCI, Dementia), Mini Mental State Exam (MMSE), and Clinical Dementia Rating - Sum of Boxes (CDR-

SB). Measures of comorbid health conditions included estimated glomerular filtration rate (eGFR), body mass index (BMI) calculated as weight (lb)/[height (in)]^2 × 703, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, fasting blood glucose levels, and hypertension status defined as normal, stage 1 hypertension, stage 2 hypertension, or hypotensive.

The overall sample was stratified by ADI groups (G1–3) according to the division described in Powell et al [3], where national ADI scores < 20 represent the least disadvantaged (G1), national ADI scores > 20 and <40 are intermediately disadvantaged (G2), and national ADI scores > 40 are considered most disadvantaged (G3). Means and standard deviation for continuous variables and counted frequencies for categorical variables were calculated, comparing across ADI groups using analyses of variance (ANOVA) and chi-squared ($\chi 2$) tests, respectively.

In the analyses, the following variables were considered as covariates for the adjusted models: Age and sex were considered as established AD-related risk factors [44]. Age was also considered due to its known effect on overall BBM concentrations [38]. *APOE* ε4 carrier status was included as a major genetic risk factor for AD [45]. BMI was included as a potential modulator of plasma AD biomarkers, specifically due to evidence that it may affect blood volume and lead to dilution of BBM levels [46,47]. eGFR was included to account for the potential role of kidney function in the efficient clearance of proteins and waste products, which could influence circulating BBM concentrations [38]. Educational attainment as a fundamental component of ADI measure itself was not included as a covariate.

To assess potential differences in the prevalence of amyloid PET positivity between ADI groups, we used three logistic regression models (R1: unadjusted, R2: adjusted for sex, and R3: adjusted for sex and ethnoracial background). Estimates are presented as odds ratios (OR) and 95 % confidence intervals (95 % CI). Other AD-associated risk factors such as age and *APOE* ε4 carrier status were not included as covariates because they did not differ significantly by group.

Differences in the levels of BBMs (p-tau217/Aβ42, Aβ42/40, Aβ42, Aβ40, and p-tau217) were assessed between ADI groups using Wilcoxon rank-sum tests. We conducted these tests across three different models: unadjusted model (B1), model adjusted for sex (B2), and model adjusted for sex and BMI (B3). Per Rudolph et al [48], the time between amyloid PET and BBM collection was not included as a covariate. We excluded age, *APOE* ε4 carrier status, and eGFR levels as covariates because they did not differ significantly between groups. P-values from each model were corrected for five BBM comparisons using the Benjamini-Hochberg method, which controls the False Discovery Rate (FDR).

To evaluate the association between amyloid PET Centiloid levels and BBM levels (p-tau217/Aβ42, Aβ42/40, and p-tau217), we first conducted correlation analyses within each ADI group separately. We performed Pearson correlations for unadjusted values (P1), as well as partial correlations adjusting for age and sex (P2), and age, sex, BMI, and eGFR (P3). To compare correlations between ADI groups, we used the Fisher's z test. P-values for this analysis were corrected for three comparisons (G1 vs G2, G1 vs G3, G2 vs G3) using the Benjamini-Hochberg method.

To assess the predictive performance of BBMs (i.e., p-tau217/Aβ42, Aβ42/40, and p-tau217) for amyloid PET positivity, we used the cutpointR library in R to determine optimal thresholds. We employed a two cut-point method where one threshold was set to achieve a minimum of 90 % sensitivity, and the other was set to achieve a minimum of 90 % specificity. Cases falling between these two cut-points were classified as 'indeterminate,' as they could not be reliably classified with the predefined high sensitivity or specificity [41]. Each classification performance metric (accuracy, sensitivity, specificity, and percentage of indeterminate cases), as well as cut-point values, were calculated using 10-fold cross-validation runs. Confidence intervals were calculated through bootstrapping. We compared the distribution of metrics from the ten cross-validation runs for each ADI group against the other ADI groups and against the metrics from the whole cohort, using Wilcoxon signed-rank tests, with p-values adjusted for three comparisons, one for each BBM in this analysis.

The predictive performance of BBMs for amyloid PET positivity was assessed using three models: unadjusted model (M1) for which BBM values were used to derive the thresholds; model adjusted for age, sex, and *APOE* ε4 carrier status (M2); and one adjusted for age, sex, *APOE* ε4 carrier status, eGFR, and BMI (M3). For the adjusted models (M2 and M3), predicted probabilities (ranging from 0–1) were used as the continuous predictors when deriving the thresholds.

As a sub-analysis, we repeated the correlation analyses and predictive performance within a sub-cohort of individuals with MCI or dementia. The purpose of this was to replicate our findings from the main cohort in a population where these BBMs are considered clinically relevant.

All analyses were conducted with statistical software in R.

3. Results

3.1. Cohort characteristics

As of September 12, 2025, 928 individuals in ADNI-4 had National ADI scores available. Of these, 755 underwent an amyloid PET scan and 640 had relevant demographic and clinical data (age, sex, education, clinical diagnosis, *APOE* ε4 carrier status). Out of 640, 438 participants had BBM levels of Aβ42, Aβ40, and p-tau217 within 14 months of their amyloid PET scan (average time interval of 1.35 months), as well as relevant medical comorbidity data such as eGFR (within one year of plasma collection) and BMI (within two years of plasma collection).

National ADI percentiles for the amyloid PET cohort ($n = 755$) were widely distributed, ranging from 1 to 99, with a median of 31 (Fig. 1a). The distribution was skewed, with only 51 cases (6.8 %) from the top 20 % most disadvantaged neighborhoods. When participants were categorized into groups based on National ADI percentiles, the grouping was as follows: G1 (least disadvantaged) comprised 273 participants (36.2 %) with ADI percentiles ranging from 1 to 20; G2 (intermediately disadvantaged) included 201 participants (26.6 %) with ADI percentiles ranging from 21 to 40; and G3 (most disadvantaged) consisted of 281 participants (37.2 %) with ADI percentiles ranging from 41 to 100. The distribution of individuals in each ADI group across the USA is shown in Supplementary Figure S1.

3.2. Demographic and clinical differences across ADI groups

Demographic and clinical characteristics of participants within ADI groups for the plasma cohort (primary focus of the study) are presented in Table 1, with characteristics for the amyloid PET cohort listed in Supplementary Table S1. A significantly higher proportion of male participants was observed in the most disadvantaged group (G3) compared to the intermediately disadvantaged group (G2; chi-square=5.40, $p = 0.02$). Additionally, the ethnoracial background (NHW, NHB, HLA, and Asian) differed significantly across all pairwise comparisons of the ADI groups (G1 vs G2: chi-square=28.0, $p < 0.001$, G1 vs G3: chi-square=31.44, $p < 0.001$, G2 vs G3: chi-square=20.99, $p < 0.001$; Fig. 1b). Individuals in G1 had significantly higher MMSE scores compared to G2 ($t = 2.51$, $p = 0.013$). Average BMI in G3 was significantly higher than in G1 ($t = 3.69$, $p < 0.001$) and G2 ($t = 2.66$, $p = 0.008$). Notably, ADI groups did not differ in proportion of clinical diagnosis groups.

3.3. ADI groups and amyloid PET status

Within the amyloid PET cohort, the odds of being amyloid PET positive were significantly higher in the intermediately disadvantaged group (OR: 1.55, CI: [1.04, 2.31], $p = 0.033$; Supplementary Table S3, Supplementary Figure S3) compared to the least disadvantaged group, even after accounting for difference in sex distribution (OR: 1.54, CI:

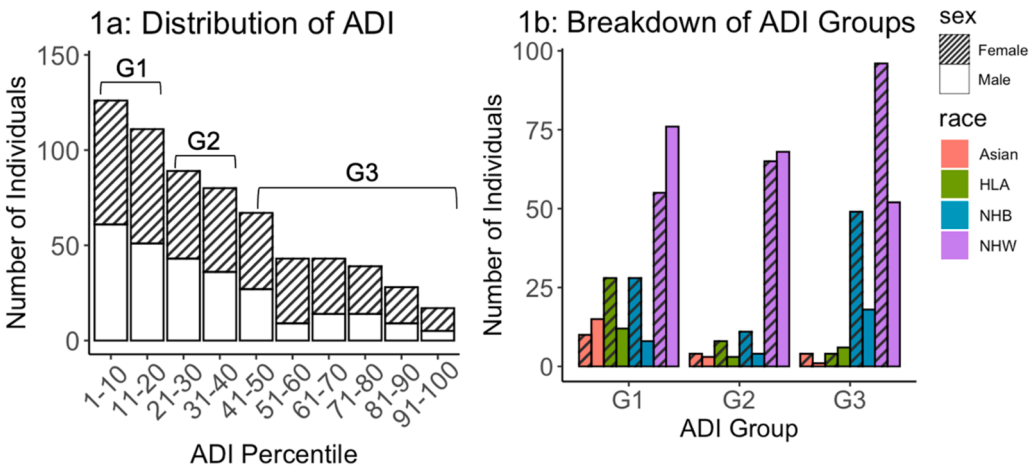

Fig. 1. a) Distribution of neighborhood disadvantage by National ADI in the study cohort. Bars are divided by sex (striped = female), G1= least disadvantaged (National ADI ≤ 20), G2 = intermediately disadvantaged (20 < National ADI ≤ 40), G3 = most disadvantaged (National ADI > 40); b) Breakdown of each ADI group by self-reported ethnoracial background (NHW, NHB, HLA, and Asian) and sex.

Table 1
Demographic and clinical characteristics of sub-cohort with plasma data. Continuous variables were compared with linear regression while categorical variables were compared through chi-square analysis.

	Least Disadvantaged (G1)	Intermediately Disadvantaged (G2)	Most Disadvantaged (G3)	P-value
N	167	116	155	–
Age (years), mean (SD)	74.0 (9.05)	74.4 (8.04)	72.8 (8.32)	0.267
Sex (Female)	73 (43.7 %)	56 (48.3 %)	52 (33.5 %)	0.037
Ethnoracial Background				
NHW	84 (50.3 %)	94 (81.0 %)	96 (61.9 %)	<0.001
NHB	29 (17.4 %)	9 (7.8 %)	47 (30.3 %)	
HLA	34 (20.4 %)	9 (7.8 %)	7 (4.5 %)	
Asian	20 (12.0 %)	4 (3.4 %)	5 (3.2 %)	
Diagnosis				
CU	109 (65.3 %)	63 (54.3 %)	100 (64.5 %)	0.137
MCI	9 (5.4 %)	15 (12.9 %)	14 (9.0 %)	
Dementia	49 (29.3 %)	38 (32.8 %)	41 (26.5 %)	
Educational attainment (College or more)	134 (80.2 %)	86 (74.1 %)	108 (69.7 %)	0.09
Amyloid PET positive	58 (34.7 %)	55 (47.4 %)	63 (40.6 %)	0.1
APOE e4 carriers	63 (37.7 %)	43 (37.1 %)	62 (40.0 %)	0.866
MMSE, mean (SD)	28.3 (2.57)	27.5 (3.04)	27.9 (2.44)	0.024
CDR-SB, mean (SD)	0.656 (1.39)	1.04 (1.76)	0.823 (1.45)	0.114
eGFR, mean (SD)	71.2 (19.6)	69.5 (19.5)	70.0 (20.9)	0.748
Fasting glucose, mean (SD)	99.3 (20.7)	96.7 (17.1)	97.2 (14.8)	0.393
Body Mass Index, mean (SD)	26.6 (5.01)	27.1 (5.46)	29.1 (7.05)	<0.001
High Density Lipoprotein, mean (SD)	60.9 (16.1)	63.3 (18.5)	62.6 (17.4)	0.493
Missing	1 (0.6 %)	1 (0.9 %)	0 (0 %)	
Low Density Lipoprotein, mean (SD)	99.9 (35.1)	100 (30.4)	97.2 (34.0)	0.692
Missing	1 (0.6 %)	1 (0.9 %)	0 (0 %)	
Triglycerides, mean (SD)	104 (55.2)	99.9 (43.0)	106 (57.1)	0.605
Hypertension				
Normal	8 (4.8 %)	7 (6.0 %)	7 (4.5 %)	0.063
Stage 1 Hypertension	60 (35.9 %)	30 (25.9 %)	59 (38.1 %)	
Stage 2 Hypertension	54 (32.3 %)	37 (31.9 %)	31 (20.0 %)	
Hypotension	45 (26.9 %)	42 (36.2 %)	58 (37.4 %)	
Plasma to PET interval (months), mean (SD)	1.40 (2.77)	1.10 (2.25)	1.49 (3.02)	0.49
p-tau217/Aβ42, mean (SD)	0.008 (0.008)	0.013 (0.014)	0.010 (0.012)	<0.001
p-tau-217 (pg/mL), mean (SD)	0.196 (0.181)	0.324 (0.313)	0.246 (0.266)	<0.001
Aβ42/40, mean (SD)	0.084 (0.013)	0.084 (0.013)	0.083 (0.013)	0.582
Aβ42 (pg/mL), mean (SD)	27.3 (6.77)	27.3 (5.75)	26.1 (5.34)	0.158
Aβ40 (pg/mL), mean (SD)	326 (81.6)	327 (61.7)	318 (64.1)	0.51

Missing: number of individuals for whom data was not collected in category; Abbreviations: NHW=Non-Hispanic White, NHB=Non-Hispanic Black, HLA= Hispanic or Latino/a, CU= cognitively unimpaired, MCI=mild cognitive impairment, MMSE = Mini Mental State Exame, CDR-SB= Clinical Dementia Rating Sum of Boxes, eGFR= estimated glomerular filtration rate.

[1.03, 2.31], $p = 0.034$). However, this difference was no longer significant with the addition of ethnoracial background as a covariate (OR: 1.25, CI:[0.83, 1.90], $p = 0.29$).

3.4. ADI groups and BBMs

3.4.1. p-tau217/ Aβ42 levels

The p-tau217/Aβ42 ratio was significantly elevated in the intermediately disadvantaged group compared to the least disadvantaged group, irrespective of adjustment for sex and BMI (B1: unadjusted; B2: adjusted for sex; B3: adjusted for sex and BMI), with an effect size ranging from 0.2 to 0.21 (p-FDR < 0.003; Fig. 2, Supplementary Table S3). A significant difference between the most disadvantaged and intermediately disadvantage groups (G3 > G2) was observed only after adjusting for sex and BMI (B3), showing an effect size of 0.18 (p-FDR = 0.005; Fig. 2, Supplementary Table S3).

However, in a post-hoc analysis (B4) further accounting the higher rates of amyloid PET positivity rates in the intermediately disadvantaged group, the observed group differences in the p-tau217/Aβ42 levels across the ADI groups were no longer statistically significant.

3.4.2. p-tau217 levels

Similar to the findings for the plasma p-tau217/Aβ42 ratio, levels of plasma p-tau217 alone were significantly higher in the intermediately disadvantaged group compared to the least disadvantaged group across all three models (B1: unadjusted; B2: adjusted for sex; B3: adjusted for sex and BMI). The effect sizes ranged from 0.21 to 0.23 (p-FDR < 0.002; Fig. 2, Supplementary Table S3). The most disadvantaged group also showed significantly elevated p-tau217 levels compared to G1, but only in the fully adjusted model (B3) (effect size: 0.15, p-FDR = 0.024). Interestingly, the unadjusted model (B1) indicated that the p-tau217 levels in G3 were significantly higher than those in G2 (effect size: 0.17, p-FDR = 0.03). However, this specific difference between G3 and G2 disappeared upon adjustment for sex and BMI (B2 and B3).

A post-hoc analysis was performed to account for the significantly higher rates of amyloid PET positivity observed in the intermediately disadvantaged group. When the models were further adjusted for differences in amyloid PET positivity status (B4), the observed group differences in the p-tau217 levels between G1 and G3 became non-significant, but the difference between G1 and G2 remained significant (effect size:0.18, p-FDR=0.015).

3.4.3. Amyloid-β (Aβ) levels

There were no significant differences in plasma Aβ40, Aβ42, or the Aβ42/Aβ40 ratio across any of the ADI groups in either the unadjusted (B1) or adjusted (B2 and B3) models, after correcting for multiple comparisons (Supplementary Table S3). However, prior to multiple comparison correction, the most disadvantaged group showed significantly lower Aβ42 levels compared to the intermediately disadvantaged group in the model adjusted for sex and BMI (B3) (effect size: −0.13, $p = 0.03$) (Supplementary Figure S3, Supplementary Table S3).

3.5. Correlations between amyloid PET Centiloid and BBM levels

The unadjusted analysis (P1) demonstrated a significant positive correlation between Centiloid values and both the plasma p-tau217/Aβ42 ratio ($r = 0.59$ to 0.74) and plasma p-tau217 levels ($r = 0.57$ to 0.71). Conversely, a significant negative correlation was found between Centiloid values and the plasma Aβ42/Aβ40 ratio (r=−0.49 to −0.43). Using the Fisher's z test, we found that the correlation between p-tau217/Aβ42 and Centiloid values was significantly stronger within the least disadvantaged group ($r = 0.74$) compared to both the intermediately disadvantaged group ($r = 0.59$; $z = 2.23$, p-FDR=0.039) and the most disadvantaged group ($r = 0.62$; $z = 2.00$, p-FDR=0.046; Fig. 3, Supplementary Tables S4-S5). This pattern of group differences was similarly observed in partial correlation models adjusted for sex only and for sex and BMI. Furthermore, in the fully adjusted partial correlation model (sex and BMI), the correlation between p-tau217 levels and Centiloid values was also significantly strongest in the least disadvantaged group compared to the intermediately disadvantaged group (partial $r = 0.73$ vs. 0.58; $z = 2.18$, p-FDR =0.045).

The sub-analysis including only MCI and dementia cases yielded results that generally mirrored those of the whole cohort, but with less variability across the ADI groups. Specifically, Centiloid values remained significantly positively correlated with the p-tau217/Aβ42 ratio ($r = 0.72$ to 0.75) and p-tau217 levels ($r = 0.69$ to 0.74), and significantly negatively correlated with the Aβ42/Aβ40 ratio (r=−0.48 to −0.35). Crucially, no significant differences in the strength of these within-group correlations were observed across the ADI groups in this sub-cohort (Supplementary Tables S6-S7, Supplementary Figure S4).

3.6. Predictive performance of BBMs for amyloid PET positivity

The predictive performance of BBMs for amyloid PET positivity was evaluated using unadjusted and adjusted models (Fig. 4, Supplementary Tables S8-S31). A two-cut-point approach was employed, optimized to achieve ≥ 90 % sensitivity and ≥ 90 % specificity in the overall cohort, resulting in three-tier classification (Negative, Indeterminate, Positive).

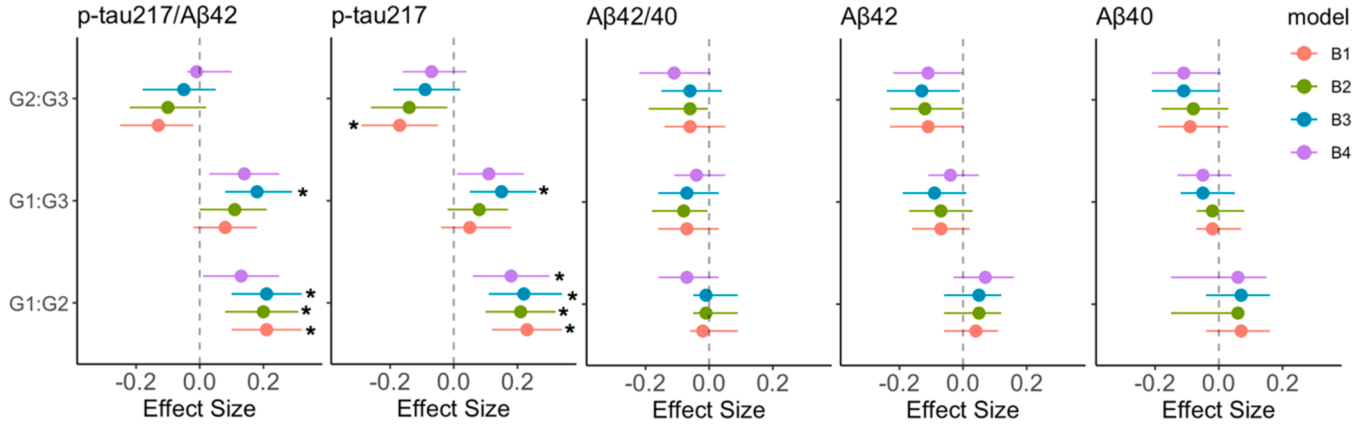

Fig. 2. BBM levels between ADI groups. Differences in BBM levels between each pair of ADI groups are represented by effect size of the comparison with a 95 % confidence interval. Positive effect size indicates that the second group had greater levels of the BBM compared to the first group. G1: least disadvantaged (ADI National ≤ 20), G2: intermediately disadvantaged (20 < ADI National ≤ 40), G3: most disadvantaged (ADI National > 40). B1: unadjusted model; B2: model adjusted for sex; B3: model adjusted for sex and BMI; B4: post-hoc analysis, model adjusted for sex, BMI, and amyloid status. Group differences that were statistically significant and survived multiple comparison correction are denoted with *.

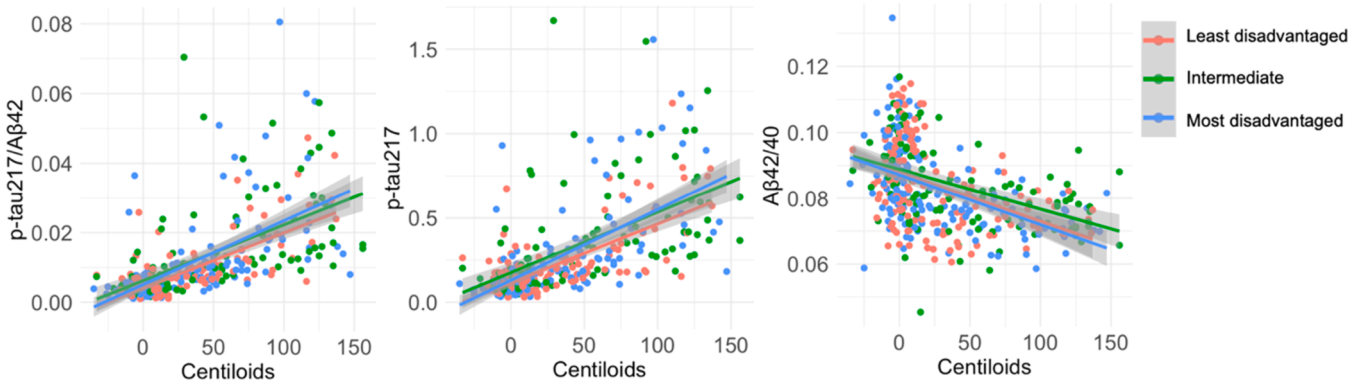

Fig. 3. Correlations between amyloid PET Centiloid levels and BBMs. Data shown is unadjusted for covariates.

Specifically in the unadjusted models, cut-points for p-tau217/Aβ42 were estimated as 0.006 and 0.008. This ratio showed high accuracy in the whole cohort (89 %) and across ADI groups (G1: 91 %, G2: 87 %, G3: 89 %), with a low percentage of indeterminate cases (8.5 % overall; G1: 12 %, G2: 6 %, G3: 6.5 %). Cut-points for p-tau217 levels were set at 0.13 and 0.21. Its overall accuracy was 88 % (G1: 87 %, G2: 86 %, G3: 89 %), but it had a higher percentage of indeterminate cases (22.4 % overall; G1: 26.8 %, G2: 20.7 %, G3: 18.6 %). Cut-points for the Aβ42/40 ratio were 0.073 and 0.085. Aβ42/40 achieved an accuracy of 84 % in the whole cohort (G1: 85 %, G2: 85 %, G3: 84 %), but a considerably higher percentage of indeterminate cases (36.2 % overall; G1: 32.8 %, G2: 38 %, G3: 38.6 %) (Supplementary Table S8).

The analysis was repeated with a model adjusted for age, sex, and *APOE* ε4 carrier status (M2). This adjustment resulted in new two-cut-point probability thresholds: p-tau217/Aβ42: 0.28 and 0.41; p-tau217: 0.25 and 0.50; and Aβ42/40: 0.28 and 0.66. The performance of these adjusted models was similar to the unadjusted ones. For the whole cohort, the accuracy for p-tau217/Aβ42 and p-tau217 was 89 %, while Aβ42/40 had an accuracy of 85 %. The percentage of indeterminate cases remained lowest for p-tau217/Aβ42 (9.1 % overall) and highest for Aβ42/40 (28.6 % overall; Supplementary Table S12). When examining performance by ADI group: p-tau217/Aβ42 had an accuracy of 90 % in G1, 85 % in G2, and 92 % in G3, with indeterminate cases ranging from 9.0 % to 12.4 %. P-tau217 had an accuracy of 88 % in G1, 86 % in G2, and 88 % in G3, with indeterminate cases ranging from 10.0 % to 19.7 %. Aβ42/40 had an accuracy of 83 % in G1, 84 % in G2, and 88 % in G3, with indeterminate cases ranging from 25.3 % to 32.2 % (Supplementary Table S12).

The last model adjusting for age, sex, *APOE* ε4 carrier status, eGFR, and BMI (M3) resulted in the following two-cut-point probability thresholds: p-tau217/Aβ42: 0.28 and 0.41; p-tau217: 0.26 and 0.47; and Aβ42/40: 0.29 and 0.66. For the whole cohort, the accuracy for p-tau217/Aβ42 was 89 %, p-tau217 was 89 %, while Aβ42/40 had an accuracy of 85 %. The percentage of indeterminate cases remained lowest for p-tau217/Aβ42 (10.0 % overall) and highest for Aβ42/40 (26.3 % overall) (Supplementary Table S16). When examining performance by ADI group: p-tau217/Aβ42 had an accuracy of 91 % in G1, 85 % in G2, and 91 % in G3, with indeterminate cases ranging from 6.7 % to 11.8 %. P-tau217 had an accuracy of 90 % in G1, 86 % in G2, and 89 % in G3, with indeterminate cases ranging from 11.1 % to 16.7 %. Aβ42/40 had an accuracy of 83 % in G1, 83 % in G2, and 88 % in G3, with indeterminate cases ranging from 24.1 % to 29.6 % (Supplementary Table S16).

3.6.1. *Comparisons between ADI groups*

The unadjusted and adjusted models showed no significant differences in accuracy, sensitivity, specificity, or the percentage of indeterminate cases when comparing the ADI groups to each other or to the overall cohort (Supplementary Tables S9-S10, S13–14, S17–18).

3.6.2. *Comparisons between biomarkers*

Across both unadjusted (M1) and adjusted models (M2 and M3), there were no significant differences in the core predictive metrics—accuracy, sensitivity, or specificity—when comparing the three plasma biomarkers (p-tau217/Aβ42, *p*−tau217, and Aβ42/Aβ40) (Fig. 4a, Supplementary Tables S11, S15, S19).

In contrast, significant differences were found in the percentage of indeterminate cases. The p-tau217/Aβ42 ratio consistently generated the fewest indeterminate cases across the entire cohort in all models (M1–M3) (Supplementary Table S13). In the unadjusted model (M1), the p-tau217/Aβ42ratio also had significantly fewer indeterminate cases than both *p*−tau217 and Aβ42/Aβ40 within every ADI group (Supplementary Table S11).

However, in Model 2 (M2) and Model 3 (M3) (the adjusted models), the difference in the percentage of indeterminate cases between p-tau217/Aβ42 and p-tau217 was no longer statistically significant within the intermediately and most disadvantaged groups (Supplementary Tables S15, S19).

3.6.3. *Amyloid PET positivity prediction in MCI and dementia cases only*

The predictive performance of the BBMs for amyloid PET positivity within the MCI and dementia sub-cohort are reported in Supplementary Tables S20-S31. In each model (M1-M3), the p-tau217/Aβ42 ratio still consistently demonstrated the highest accuracy among the three biomarkers. Crucially, within this cognitively impaired sub-cohort, the percentage of indeterminate cases identified by each biomarker (p-tau217/Aβ42, p-tau217, and Aβ42/40) was no longer significantly different when comparing the whole group or when comparing across the ADI groups.

4. Discussion

In this study, we investigated the interplay between neighborhood disadvantage, as measured by the ADI, and the performance of AD BBMs in predicting amyloid PET positivity. The major findings were threefold: 1) While the initial analyses showed that plasma p-tau217/Aβ42 and p-tau217 levels were significantly elevated in the intermediately disadvantaged group, post-hoc analyses revealed these differences were driven by the higher prevalence of underlying amyloid pathology in this group. 2) Significant differences were found in the strength of correlation between amyloid PET Centiloid values and plasma p-tau217/Aβ42 and p-tau217 across ADI groups in the whole cohort. Specifically, the least disadvantaged group consistently showed the strongest correlations. However, this difference in correlations strength disappeared in the clinically relevant sub-cohort of individuals with MCI or dementia. 3) Most critically, the predictive performance of all three tested BBMs (p-tau217/Aβ42, p-tau217, and Aβ42/40) for classifying amyloid PET status was robust and did not differ across ADI groups, regardless of whether the models were unadjusted or adjusted for covariates. Among

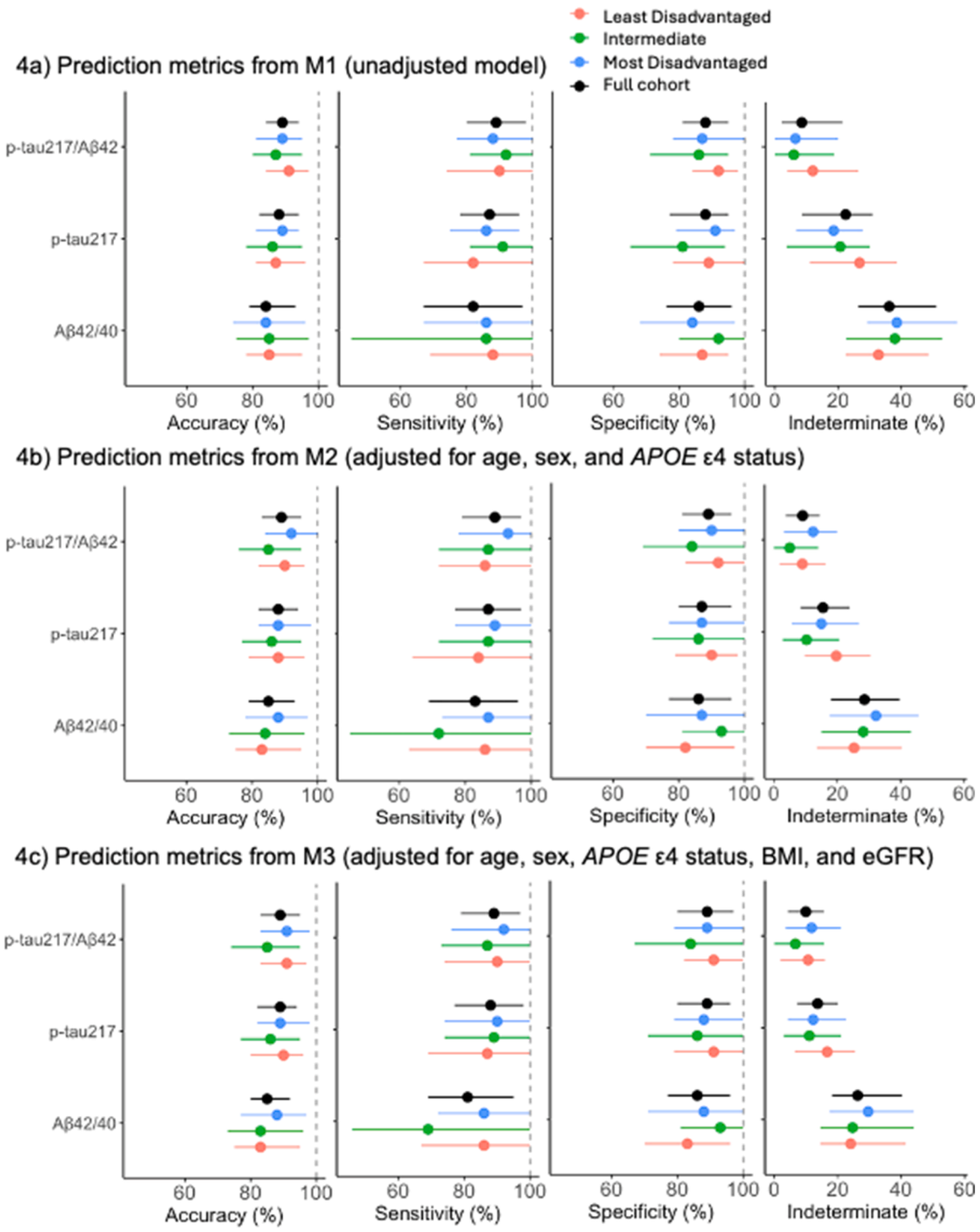

Fig. 4. The performance of BBMs in predicting amyloid PET positivity using (4a) unadjusted models (M1), 4b) models adjusted for age, sex, and APOE ε4 carrier status (M2), and 4c) models adjusted for age, sex, APOE ε4 carrier status, eGFR, and BMI (M3). The predictive performance for amyloid PET positivity was assessed using classification metrics: accuracy, sensitivity, and specificity. The percentage of cases where the biomarker result was inconclusive are reported as indeterminate percentage. These metrics are presented for the entire study cohort and then separately for each ADI group.

them, the p-tau217/Aβ42 ratio was the most effective classifier, consistently yielding the fewest indeterminate cases. Taken together, these findings support the generalizability of plasma biomarkers like p-tau217/Aβ42, suggesting they can be reliably used for AD diagnosis across populations with varying neighborhood characteristics.

A key finding was that the intermediately disadvantaged group exhibited both higher levels of p-tau217/Aβ42 and p-tau217 biomarkers and a significantly greater odds of being amyloid PET positive compared to the least disadvantaged group. Our post-hoc analysis strongly suggests that the elevated p-tau levels were a direct consequence of the higher amyloid burden in this group, aligning with the established biological cascade where amyloid pathology drives subsequent tau pathology. This raises the question of why the intermediately disadvantaged group had a higher prevalence of amyloidosis. One potential explanation lies in the unique demographic composition of our cohort, where this group had a significantly higher proportion of NHW

individuals compared to the other groups. While the literature is mixed, some studies report higher rates of amyloid PET positivity among NHW individuals compared to other ethnoracial groups, which could contribute to our observation. Other studies, however, have found no such differences [49–51,21,52]. Here, we found that including ethnoracial background as a covariate in the odds ratio analysis of amyloid PET positivity did in fact account for the significant difference in the intermediately disadvantaged group.

Interestingly, while the core amyloid biomarkers (Aβ42/40) and clinical diagnosis rates did not differ significantly across ADI groups, cognitive performance did, with the intermediately disadvantaged group showing lower MMSE scores. This divergence suggests that neighborhood disadvantage may influence cognitive health through pathways independent of, or additive to, core cerebral amyloid accumulation, highlighting that the observed cognitive deficits may be driven by factors contributing to all-cause dementia rather than being solely attributable to AD-specific amyloid pathology. Factors associated with neighborhood deprivation—such as chronic stress, barriers to quality education and healthcare, and higher prevalence of vascular risk factors—are known to diminish cognitive reserve and contribute to cognitive decline irrespective of AD neuropathology. This underscores the complex relationship between socioeconomic factors, brain health, and the clinical manifestation of dementia.

The significant difference in the correlation between p-tau217/Aβ42 and Centiloid between ADI groups initially points to the potential role that factors associated with neighborhood-level disadvantage may play in how well BBMs correspond with the gold-standard of amyloid PET. However, the sensitivity analysis with only cognitively impaired individuals revealed that there were no significant differences in correlations between BBMs and Centiloid between any ADI groups, suggesting that the difference in correlations within the whole cohort may have been driven by lower correlations within CU individuals, 74 % of whom are amyloid PET negative. Indeed, studies suggest that the correlation between BBMs and Centiloid may be lower in amyloid PET negative individuals [53]. This lack of significant differences in correlations between ADI groups in cognitively impaired individuals is encouraging from the standpoint of generalizability of BBMs, especially in clinical cohorts. Given the increased accessibility of BBMs compared to imaging biomarkers, BBMs are a viable option for collecting information in communities that may not have access to or adequate resources for neuroimaging.

From a clinical standpoint, our most significant finding is the consistent predictive performance of the BBMs across all ADI groups. The accuracy, sensitivity, and specificity for identifying amyloid PET positivity did not significantly differ by neighborhood disadvantage, even after adjusting for demographic and health-related covariates. This stability is critical, as it supports the equitable deployment of these tests in diverse community and clinical settings. The p-tau217/Aβ42 ratio, recently cleared by the FDA, distinguished itself by yielding the fewest indeterminate results, a key practical advantage that enhances diagnostic confidence and reduces the need for more invasive or expensive follow-up testing [29,30]. Given that disadvantaged communities often face barriers to accessing specialized neuroimaging facilities, the validation of a robust and accessible blood test that performs well irrespective of neighborhood characteristics is a vital step toward mitigating health disparities in AD diagnosis. The results from the sensitivity analysis in cognitively impaired individuals mirrored those found within the whole cohort. Confirming that these results remain significant within individuals who are already exhibiting signs of cognitive decline further supports the potential utility of biomarkers like p-tau217/Aβ42 in a clinical setting.

It is also important to consider that in our study cohort, ethnoracial and sex composition differed significantly, particularly in the most disadvantaged ADI group compared to the least disadvantaged and intermediately disadvantaged ADI groups. Individuals in the most disadvantaged ADI group also exhibited lower levels of educational attainment, as well as greater BMI. The higher BMI in this group represents a key health disparity that was accounted for in our adjusted models, and the stability of the biomarker associations across groups reinforces their utility in populations with varying comorbidity profiles. These findings highlight the disproportionate impact of socioeconomic status on specific demographic groups and suggest that individuals in more disadvantaged neighborhoods may face barriers that can subsequently influence health outcomes [4,6,7,23,40].

This study has several limitations. First, the sample size of participants with BBM data was relatively modest, and these findings require confirmation in larger, more diverse cohorts. Second, the cross-sectional design prevents us from drawing causal inferences about the temporal relationship between neighborhood disadvantage and AD pathology. Third, while we adjusted for key comorbidities like BMI and renal function, data on other relevant conditions (e.g., stroke, myocardial infarction[38,54]) and medications [55,56] that could influence BBM levels were not available for this analysis. Fourth, the ADNI cohort is, on average, more highly educated and less racially diverse than the general U.S. population, which may limit the generalizability of our findings. Finally, ADI is only applicable to the U.S., where disadvantages in general are fewer than in other countries such as Asia and Africa. Therefore, a replication of these findings in other geographies is warranted.

In conclusion, this study provides valuable evidence that while neighborhood-level disadvantage is linked to significant demographic and health disparities, the diagnostic performance of leading plasma AD biomarkers is not compromised. In particular, the p-tau217/Aβ42 ratio stands out as a robust and reliable tool for predicting brain amyloidosis across different socioeconomic landscapes. These findings bolster confidence in the clinical utility of BBMs and support their role in facilitating a more accessible and equitable approach to AD diagnosis. Future longitudinal research is essential to further delineate the impact of social determinants of health on the trajectory of AD and to ensure that diagnostic advancements benefit all segments of the population.

Declaration of Generative AI and AI-assisted technologies in the writing process

No Generative AI or AI-assisted technologies were used in the writing process of this manuscript.

ADNI collaborators

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Supplementary materials

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