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RESEARCH ARTICLE

Empirically derived psychosocial-behavioral phenotypes in Black/African American and Hispanic/Latino older adults enrolled in HABS-HD: Associations with AD biomarkers and cognitive outcomes

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Abstract

INTRODUCTION: Identification of psychosocial-behavioral phenotypes to understand within-group heterogeneity in risk and resiliency to Alzheimer's disease (AD) within Black/African American and Hispanic/Latino older adults is essential for the implementation of precision health approaches.

METHODS: A cluster analysis was performed on baseline measures of socioeconomic resources (annual income, social support, occupational complexity) and psychiatric distress (chronic stress, depression, anxiety) for 1220 racially/ethnically minoritized adults enrolled in the Health and Aging Brain Study-Health Disparities (HABS-HD). Analyses of covariance adjusting for sociodemographic factors examined phenotype differences in cognition and plasma AD biomarkers.

RESULTS: The cluster analysis identified (1) Low Resource/High Distress ($n = 256$); (2) High Resource/Low Distress ($n = 485$); and (3) Low Resource/Low Distress ($n = 479$) phenotypes. The Low Resource/High Distress phenotype displayed poorer cognition and higher plasma neurofilament light chain; differences between the High Resource/Low Distress and Low Resource/Low Distress phenotypes were minimal.

DISCUSSION: The identification of psychosocial-behavioral phenotypes within racially/ethnically minoritized older adults is crucial to the development of targeted AD prevention and intervention efforts.

KEYWORDS
Alzheimer's disease, psychosocial-behavioral phenotypes, racial disparities, social determinants of health

1 | BACKGROUND

As we continue to make important strides toward increasing the representation of Black/African American (henceforth Black) and Hispanic/Latino (henceforth Latino) community members in Alzheimer's disease (AD) research studies, it is essential that we move beyond racial/ethnic group comparison studies to non-Latino White (NLW) older adults and focus on characterizing heterogeneity in risk and resilience to AD within communities of color.[1,2] Although Black and Latino older adults are disproportionately affected by AD, they are severely underrepresented in AD research and clinical trial initiatives,[3] and our understanding of varied biological manifestations of the disease in these communities of color is limited.[4–6] The National Institute on Aging (NIA) health disparities research framework highlights that AD is shaped by exposure to an array of risk and resiliency factors that fall within discrete domains of influence (sociocultural, behavioral, environmental, and biological).[7] Racially/ethnically minoritized adults are more likely to be exposed to risk factors within each of these domains of influence and are less likely to be exposed to positive factors that may ultimately enhance cognitive or neural reserve.[8–11] This increased exposure to domain-specific risk factors is tied to systems of power and oppression that have created barriers intentionally designed to deprive racially/ethnically minoritized communities of resources and opportunity.[10,12,13] Most studies characterizing AD disparities have focused on examining associations between pathologic aging outcomes and factors within a single domain of influence. For example, lower levels of neighborhood economic resources and higher levels of chronic stress have been independently linked to an increased risk for dementia.[14–18] However, there may also be unique interactions between risk factors within these domains that ultimately accelerate cognitive aging trajectories for certain community members.[8,19]

Precision health initiatives may help to identify groups of individuals with varying degrees of susceptibility to AD and assist with targeted prevention and intervention efforts that reduce population-level racial/ethnic disparities. Data-driven approaches employing machine learning, latent class, or cluster analytic techniques have identified distinct biological and cognitive subgroups of patients with mild cognitive impairment (MCI) that have been shown progress to AD at different rates and display varied patterns of neurodegeneration.[20–25] While these investigations have supported theories that tailored AD pharmacotherapy interventions may be more effective in certain biological and cognitive subgroups, this research has largely taken place in racially homogeneous samples of NLW older adults and has generally not included the modeling other critical factors of influence. Since racial/ethnic disparities in AD are the consequence of social and structural inequities, there is a need to look beyond biological and genetic factors into other multidomain factors.[26–28]

Several recent research investigations started the practice of employing data-driven psychosocial-behavioral phenotyping methods that incorporate multidomain data pertaining to health behaviors, social determinants of health, environmental resources, and psychological functioning.[29–33] These studies have revealed that (1) unique psychosocial phenotypes and combinations of modifiable risk fac-

RESEARCH IN CONTEXT

1. **Systematic review**: The identification of distinct psychosocial-behavioral phenotypes may help clarify important targeted prevention and intervention that reduce racial/ethnic disparities in Alzheimer's disease.

2. **Interpretation**: Our study identified three distinct psychosocial-behavioral phenotypes (Low Resource/High Distress, High Resource/Low Distress [*n* = 485], and Low Resource/Low Distress) within Black and Latino older adults enrolled in Health and Aging Brain Study-Health Disparities (HABS-HD) that displayed varied cognitive and biomarker outcomes.

3. **Future directions**: AD risk may be elevated in individuals that belong to the Low Resource/High Distress, but individuals in the Low Resource/Low Distress phenotype appeared to be resilient and displayed similar outcomes to those in the High Resource/Low Distress phenotype. Future work should continue to explore the underlying mechanisms of resiliency that could be leveraged for health equity-based prevention initiatives and examine longitudinal cognitive and biomarker trajectories of these phenotypes.

tors can be identified in several samples of older adults and (2) risk for poor cognitive outcomes differ as a function of these identified phenotypes.[29–33] For example, in a large sample of community-dwelling Southeast Asians a latent profile analysis of psychiatric symptom, quality of life, social support, and life satisfaction inventories revealed three psychosocial phenotypes (Positive, Negative, and Neutral); while these groups did not differ in cognitive outcomes, individuals with MCI in the sample were more likely to have lower levels of education and perceived social support and report more severe depressive symptoms.[29] Similarly, in a large sample of Latino older adults, a principal component analysis on several acculturation and socioenvironmental variables revealed three composites (acculturation, socioenvironmental, and familism) that displayed varied associations with cognition.[30] Results revealed the acculturation composite was positively associated with baseline cognition (global, perceptual speed, and episodic memory), whereas the socioenvironmental was negatively associated with baseline cognition (global, perceptual speed, episodic memory, working memory) and faster longitudinal cognitive decline (visuospatial ability). Interestingly, no associations between the familism composite with level and rate of cognitive decline were observed. Although cognitive outcomes were not explored, data from the psychosocial assessment within the Health and Retirement Study was recently used to identify empirically derived adversity profiles among Black, Latino, and NLW middle-aged and older adults.[34] Results illustrate that across the racial/ethnic groups, individuals with low adversity profiles displayed better mental health

outcomes, although the frequency of these adversity profiles was found to differ as a function of nativity and racial/ethnic group status.[35] Taken together, these studies suggest that there is incredible heterogeneity in psychosocial and behavioral factors and that collective considerations of these factors may yield insight into varied cognitive outcomes of adults.

Characterizing psychosocial-behavioral phenotypes within racially/ethnically minoritized older adults may help with targeted public health prevention efforts, as the identification of socially patterned and multidomain upstream drivers of health disparities, before they become biologically embedded, is ultimately needed to improve health equity and reduce risk for AD in late life. This study sought to extend psychosocial-behavioral phenotyping methods into a large community-based study of Black and Latino middle-aged and older adults (age range 37 to 87) and add to the existing literature by enhancing our understanding of whether the identified psychosocial-behavioral phenotypes differed on plasma AD biomarkers in an effort to clarify the link between lived experiences and the biology of AD risk within the ethnoracially diverse community members. We (1) conducted a cluster analysis on measures of economic/social resources and psychiatric distress to identify distinct psychosocial-behavioral phenotypes and (2) compared cross-sectional cognitive and plasma AD biomarker outcomes of these phenotypes. Importantly, we leveraged key concepts from precision health and the NIA Health Disparities Research Framework that call for multidomain investigations and include measures of risk and resiliency in our modeling to ensure the characterization of prevention points rooted in the lived experiences of racially/ethnically minoritized older adults.[7,8] Our goal was to better understand important elements of within-group heterogeneity that shape or protect against pathologic aging outcomes of racially/ethnically diverse older adults. We hypothesized that the exploratory cluster analysis would identify groups in which high resources/low distress would buffer against poorer cognitive outcomes and groups with low resources/high distress that would display poorer cognitive and worse AD plasma biomarker outcomes.

2 | METHODS

2.1 | Data availability

This study leveraged data from Health and Aging Brain Study-Health Disparities (HABS-HD),[36] a large-scale research study centered on understanding key drivers of racial/ethnic disparities in AD. HABS-HD data are publicly available to qualified researchers upon request and were previously described in detail.[36] Participants in the study complete comprehensive neuropsychological testing, medical clinical labs, brain magnetic resonance imaging (MRI) scans, positron emission tomography (PET) scans (amyloid and tau), questionnaires, and functional exams. Participants enrolled in the HABS-HD study could complete the entire protocol in Spanish or English in accordance with their preferred language. Written informed consent was obtained for all study participants, and HABS-HD was approved by the Uni-

versity of North Texas Health Science Center Institutional Review Board.

2.2 | Inclusion/exclusion criteria

Inclusion criteria for the HABS-HD study were as follows: community-dwelling adults ages 30 and older; self-reported race or ethnicity of Black/African American, Latino, and NLW; fluency in English or Spanish; willingness to provide blood samples; willingness to provide an informant to answer questions regarding daily functioning; and eligible to undergo brain MRI and PET scans. Exclusion criteria included type 1 diabetes, current cancer diagnosis, severe mental illness or an active medical condition that could impact cognition (eg, end stage renal disease), traumatic brain injury with a loss of consciousness within the past 12 months, and current alcohol or substance abuse consistent with Diagnostic And Statistical Manual Of Mental Disorders, Fifth Edition (DSM-V) diagnostic criteria.[37]

2.3 | Study participants

Baseline data for 1479 participants were available for use and downloaded on December 1, 2022. This study included 1220 participants (810 Latino and 410 Black adults) that were without dementia at their baseline study visit that also had available psychosocial and psychiatric questionnaire data of interest. Self-described racial and ethnic groupings were used to categorize participants. Of note, one participant's race and ethnicity were self-reported as Black and Latino, respectively (the participant was also bilingual in English and Spanish), and this was coded as Latino in the present study.

2.4 | Objective cognition, subjective cognitive concerns, and cognitive diagnoses

Cognitive composites were created using sample-based z-scores from the entire HABS-HD sample. Raw scores from each test were converted to z-scores that were adjusted for age (stratified by ≤ 65 or ≥ 66), education (stratified by 0 to 7, 8 to 12, and ≥ 13 years) and primary language (English vs Spanish). These demographically adjusted sample-based z-scores were then used to create a z-score composite of memory and executive functioning. The adjusted z-scores from the immediate and delayed recall trials from the Wechsler Memory Scale, 3rd Edition (WMS-III), Logical Memory, and the Spanish-English Verbal Learning Test were averaged to create a memory composite.[38,39] The adjusted z-scores for the WMS-III Digit Span total score, Trail Making Test Parts A & B total time, and the Letter fluency (FAS) total scores were averaged to create an executive functioning composite.[39,40] Subjective memory concerns were assessed with the 14-item Subjective Memory Complaints Questionnaire.[41]

Cognitively unimpaired (CU) and mild cognitive impairment (MCI) status was based on consensus diagnoses by expert study clinicians.

The Mini-Mental Status Examination (MMSE) total score was used to characterize general cognition. Participants were determined to be CU if they had a Clinical Dementia Rating (CDR) sum of boxes score of 0, neuropsychological test scores considered broadly within normal limits (demographically adjusted cognitive z-scores > −1.5), and no self- or informant-reported complaints of cognitive change. Participants were determined to meet MCI criteria if they had a CDR sum of boxes score of 0.5 to 2, one or more demographically adjusted cognitive z-scores ≤ 1.5, and endorsed self- or informant-reported complaints of cognitive change.

2.5 | Psychosocial resources and psychiatric functioning

With regard to psychosocial resources, participants completed a background question that collected annual household income and occupational history data; local study staff (N.O.) used industry classification data to complete occupational complexity ratings for each subject.[42–44] The Interpersonal Support and Evaluation List was used to characterize perceived social support.[45] With regard to psychiatric functioning, worry was assessed using the Penn State Worry Questionnaire,[46] the Geriatric Depression Scale (GDS) characterized depressive symptoms[47], and the Chronic Burden Scale assessed chronic stress.[36,48]

2.6 | Plasma AD biomarkers, genetic risk, and vascular burden

Plasma amyloid beta 40 ($A\beta_{40}$)/42 ($A\beta_{42}$) ratio, neurofilament light chain (NfL), and total tau (t-tau) were assessed using the ultra-sensitive Simoa technology platform (Quanterix.com). Higher plasma NfL and t-tau but lower plasma $A\beta42/A\beta40$ are associated with poor clinical and cognitive outcomes.[49–51] APOE $\varepsilon4$ positivity was determined by the possession of at least one $\varepsilon4$ allele (i.e., $\varepsilon2/\varepsilon4$; $\varepsilon3/\varepsilon4$; $\varepsilon4/\varepsilon4$ carriers were coded as positive). Assay preparation was completed using a custom automatic StarPlus system from Hamilton Robotics.[36] Elevated waist circumference (WC; women > 35, men > 40 inches), blood pressure (systolic > 129 or diastolic > 84 mm Hg), triglycerides (> 149 mg/dL), glucose (> 100 mg/dL), and low levels of high-density lipoprotein (HDL; < 50 mg/dL in women, < 40 mg/dL in men), consistent with the clinical criteria for metabolic syndrome,[52] were summed into a cardiometabolic vascular burden variable that ranged from 0 to 5.

2.7 | Statistical analyses

All analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 26 and R version 3.5.0 (https://cran.r-project.org/). Data were screened to ensure basic assumptions were met. Independent and dependent variables of interest were z-scored, and values that physiologically implausible values or determined to be outliers per Grubb's test were excluded from analyses. Sample sizes differed slightly for biomarker data given these data are released in biannual batches, and some subjects may not have had available data at the time. See Supplemental Figure 1 for a visual schematic of data included in the study.

Psychosocial resource and psychiatric functioning variables were converted to standardized z-scores, and hierarchical cluster analysis using Ward's methods was performed on these scores.[53] The cluster analysis was performed in an iterative fashion with k set to 2, 3, and 4 in order to yield a predetermined set of groupings that were maximally different from each other. A discriminant function analysis then tested whether each psychosocial resource and psychiatric functioning variable could predict the k = 2, 3, and 4 group membership. The stability of the cluster solution was also examined using leave-one-out cross-validation in an effort to reduce the potential bias of utilizing the same participants to develop the classification matrix and compute the discriminant function.[54] The k = 3 solution was considered to be statistically and theoretically meaningful relative to the other iterations; this determination was based on visual inspection on each cluster solution and the classification statistics for the discriminant functional analysis, as the cluster solution with the greatest leave-one-out cross-validation statistics that also resulted in the classification of each participant was chosen.

Analyses of variance (ANOVAs) were used to determine whether the cluster groups differed on continuous demographic and clinical variables. Chi-squared analyses examined group differences on categorical demographic and clinical variables. Analyses of covariance (ANCOVAs) were used to determine whether the clusters differed on cognition and AD plasma biomarkers. Covariates included age, sex, education, race, and vascular risk burden.

3 | RESULTS

3.1 | Cluster-derived psychosocial-behavioral phenotypes

The cluster analysis resulted in 3-group solution that included a (1) *Low Resource/High Distress* group (n = 256), (2) *High Resource/Low Distress* group (n = 485), and *Low Resource/Low Distress* group (n = 479). A discriminate function analysis using the standardized psychosocial resource and psychiatric functioning variables to predict cluster group membership correctly classified 83.3% of the participants. Cross-validation of the solution using the leave-one-out method correctly classified 82.7% of the participants (Figure 1). The cluster analysis was repeated within the Latino and Black participant groups separately to ensure the general pattern of clusters was similar.

Within the Latino participant group, the 3-group solution included a (1) *Low Resource/High Distress* group (n = 170), (2) *High Resource/Low Distress* group (n = 344), and a *Low Resource/Low Distress* group (n = 296). A discriminate function analysis using the standardized psychosocial resource and psychiatric functioning variables to predict
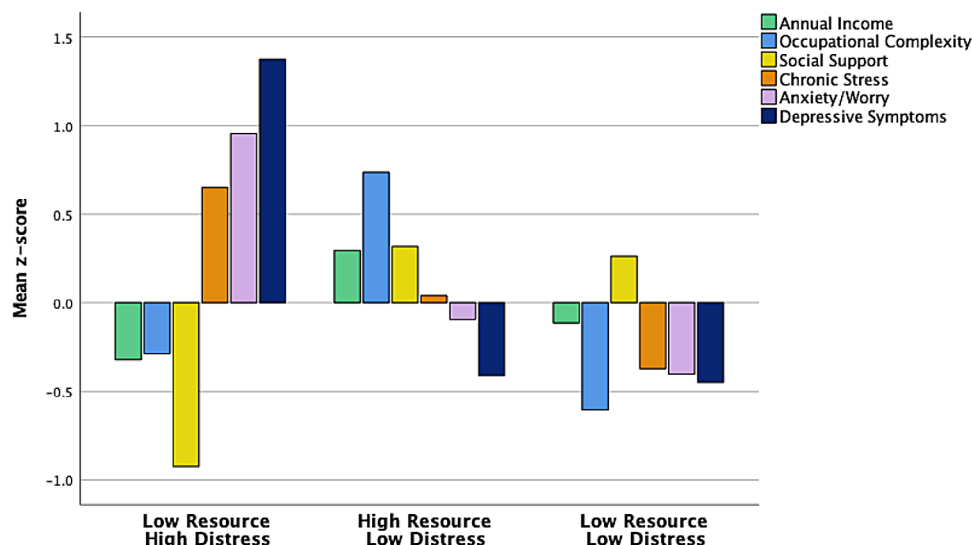
FIGURE 1 Psychosocial-behavioral phenotypes of all racially/ethnically minoritized HABS-HD older adults. Top: bar graph of mean resource and psychiatric factors across identified clusters. Bottom: violin plot showing distribution across mean resource and psychiatric factors across identified clusters.

cluster group membership correctly classified 91.0% of the participants. Cross-validation of the solution using the leave-one-out method correctly classified 90.6% of the participants (Figure 2).

Within the Black participant group, the cluster analysis resulted in a 3-group solution that included a (1) *Low Resource/High Distress* group ($n = 162$), (2) *High Resource/Low Distress* group ($n = 63$), and (3) *Low Resource/Low Distress* group ($n = 185$). With regard to the Low Resource/Low Distress group, there was some variability in the overall levels of the resource and distress variables when compared to the larger sample, but these were still in the low/average range. A discriminate function analysis using the standardized psychosocial resource and psychiatric functioning variables to predict cluster group membership correctly classified 86.1% of the participants. Cross-validation of the solution using the leave-one-out method correctly classified 85.1% of the participants. Given the consistency and acceptable classification statistics of the racial/ethnic subgroup analyses, all subsequent analyses were conducted with the cross-sample 3-cluster solution (Figure 2).

3.2 | Demographic comparisons of cluster-derived psychosocial-behavioral phenotypes

Demographic and clinical characteristics by cluster group are shown in Table 1. ANOVAs revealed the cluster groups significantly differed on education ($F = 82.57$, $p < .001$, $\eta^2 = 0.12$), MMSE total score ($F = 37.44$, $p < .001$, $\eta^2 = 0.06$), and cardiovascular risk ($F = 5.19$, $p = .004$, $\eta^2 = 0.008$); there were no cluster group differences in age ($F = 0.53$, $p = .591$, $\eta^2 = 0.009$). There were significant cluster group differences in the proportion of Black older adults ($\chi^2 = 42.14$, $p < .001$, $V = 0.19$) and women ($\chi^2 = 14.27$, $p < .001$, $V = 0.11$) across clusters; however, the groups did not significantly differ in the proportion of APOE-e4 car-

riers ($\chi^2 = 2.02$, $p = .36$, $V = 0.06$) or individuals diagnosed with MCI ($\chi^2 = 4.21$, $p = .12$, $V = 0.06$).

3.3 | Cognitive comparisons of cluster-derived psychosocial-behavioral phenotypes

ANCOVAs adjusted for age, sex, education, vascular risk, and race/ethnicity revealed that the cluster groups significantly differed on the executive functions composite ($F = 15.43$, $p < .001$, partial $\eta^2 = 0.025$). Pairwise comparisons revealed that the Low Resource/High Distress group performed significantly worse than the High Resource/Low Distress and Low Resource/Low Distress groups ($ps < 0.001$). There were no significant differences between the High Resource/Low Distress and Low Resource/Low Distress groups ($p = .91$). There were no significant group differences on the memory composite ($F = 1.68$, $p = .19$, partial $\eta^2 = 0.003$). However, the groups significantly differed on subjective memory concerns ($F = 143.14$, $p < .001$, partial $\eta^2 = 0.19$). Pairwise comparisons revealed that the Low Resource/High Distress group had significantly greater memory concerns relative to the High Resource/Low Distress and Low Resource/Low Distress groups ($ps < 0.001$). Additionally, the High Resource/Low Distress group had significantly greater memory concerns relative to the Low Resource/Low Distress group ($p = .012$) (Figure 3).

3.4 | AD plasma biomarker comparisons of cluster-derived psychosocial-behavioral phenotypes

ANCOVAs adjusted for age, sex, education, vascular risk, and race/ethnicity revealed the groups differed significantly on plasma
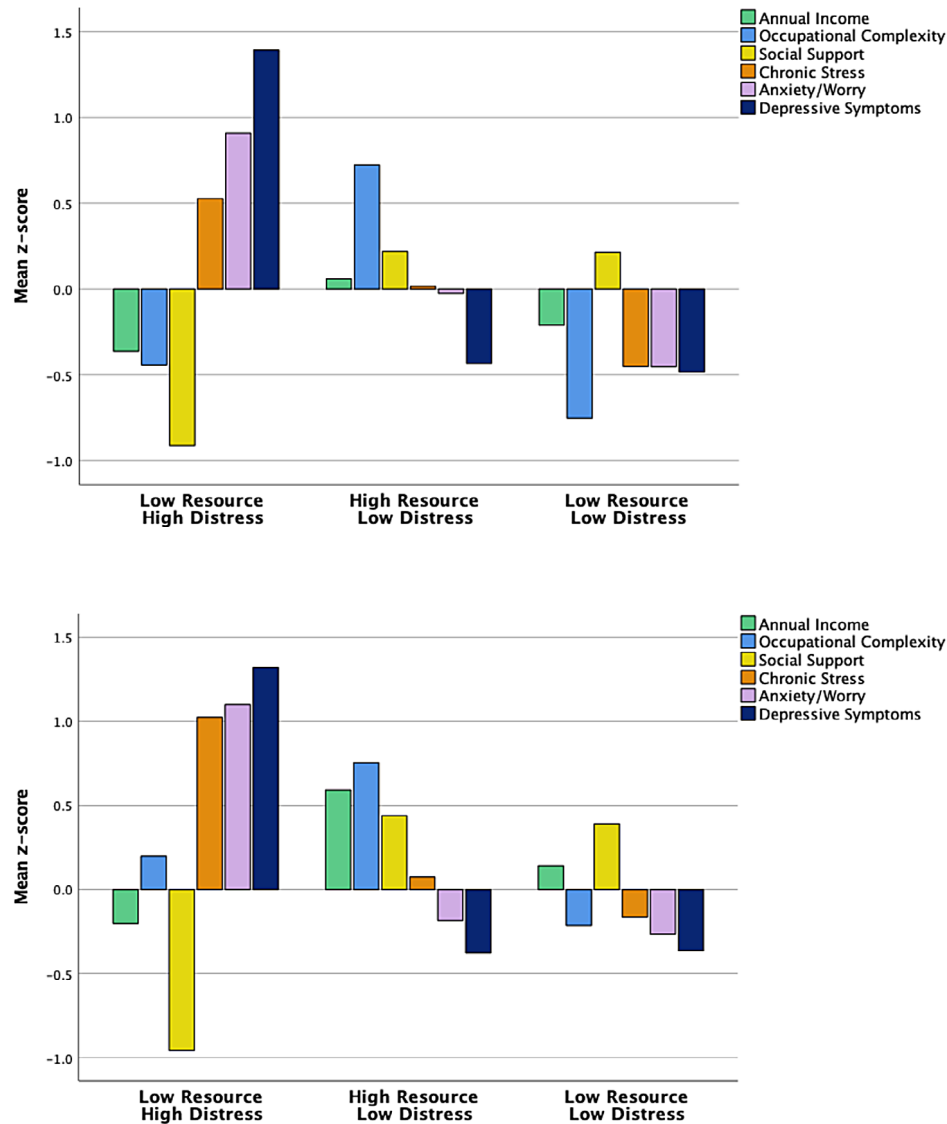
FIGURE 2 Psychosocial-behavioral phenotypes of Latino and Black older adults only. Top: bar graph of mean resource and psychiatric factors across identified clusters in Latino older adults. Bottom: bar graph of mean resource and psychiatric factors across identified clusters in Black older adults.

NfL (F = 7.47, p < .001, partial η^2 = 0.016). Pairwise comparisons revealed that the Low Resource/High Distress (p = .003) and High Resource/Low Distress (p < .001) groups had significantly higher levels of plasma NfL relative to the Low Resource/Low Distress group. However, there was no significant differences in plasma NfL levels between the Low Resource/High Distress and High Resource/Low Distress groups (p = .91) (Figure 4). Finally, no significant group differences in plasma total tau (F = 2.07, p = .13, partial η^2 = 0.004) or AB42/40 levels (F = 0.05, p = .95, partial η^2 < 0.001) were observed.

4 | DISCUSSION

In this study we employed a data-driven approach to identify distinct psychosocial phenotypes in an effort to better understand risk of and resiliency to AD in Black and Latino older adults. Our analyses revealed three distinct phenotypes: Low Resource/High Distress, High Resource/Low Distress, and a Low Resource/Low Distress. The Low Resource/High Distress phenotype made up the smallest proportion of the sample but represented a vulnerable group that displayed the worst cognitive outcomes and had the highest levels of plasma NfL relative to the other phenotypes. Interestingly, analyses also revealed a resilient Low Resource/Low Distress phenotype that did not differ from the High Resource/Low Distress phenotype on several biomarker or objective cognitive outcomes. Results from this study revealed that cluster analysis techniques can be used to explain within-group heterogeneity in the lived experiences of minoritized adults and that these distinct psychosocial phenotypes may have varying degrees of susceptibility to AD and poor cognitive outcomes.

TABLE 1 Sociodemographic characteristics of psychosocial-behavioral phenotypes.

Variable	Cluster 1: Low Resource/High Distress n = 256	Cluster 2: High Resource/Low Distress n = 485	Cluster 3: Low Resource/Low Distress n = 479	Omnibus test result Test statistic	P value	Effect size (V or η^2)	Pairwise comparisons φ1-2	φ1-3	φ2-3
Age, M (SD)	63.72 (8.02)	63.11 (7.88)	63.34 (7.30)	F = 0.53	.60	0.001	-	-	-
Female, n (%)	180 (70.31)	323 (66.60)	276 (57.62)	χ^2 = 14.27	<.001	0.11	0.30	<0.001	0.004
Race/ethnicity									
Latino, n (%)	193 (75.40)	270 (55.67)	347 (72.44)	χ^2 = 42.14	<.001	0.19	<0.001	0.39	<0.001
Black, n (%)	63 (24.61)	215 (44.33)	132 (27.56)						
Years of education, M (SD)	9.94 (4.52)	13.79 (3.97)	11.06 (4.51)	F = 82.57	<.001	0.12	<0.001	<0.001	<0.001
Spanish speaking, n (%)	132 (51.56)	131 (27.01)	233 (48.64)	χ^2 = 62.72	<.001	0.23	<0.001	0.45	<0.001
MCI, n (%)	72 (28.13)	104 (21.44)	111 (23.17)	χ^2 = 4.21	.12	0.06	-	-	-
APOE e4 carrier, n (%)	23 (14.84)	41 (20.20)	44 (16.36)	χ^2 = 2.02	.36	0.06	-	-	-
Cardiometabolic burden, M (SD)	2.66 (1.31)	2.33 (1.29)	2.43 (1.29)	F = 5.19	.004	0.008	0.001	0.03	0.23
Psychosocial Resources/Psychiatric Functioning									
Annual household income, M (SD)	28,259.93 (23,712.43)	71,513.55 (63,123.41)	42,809.62 (33,574.07)	F = 85.91	<.001	0.12	<0.001	<0.001	<0.001
Occupational complexity total score, M (SD)	5.76 (4.30)	9.90 (2.64)	4.47 (2.96)	F = 372.15	<.001	0.38	<0.001	<0.001	<0.001
Social support total score, M (SD)	34.65 (6.28)	42.47 (5.17)	42.13 (5.10)	F = 203.73	<.001	0.25	<0.001	<0.001	0.33
Chronic stress total score, M (SD)	11.89 (7.58)	7.77 (6.55)	4.97 (4.74)	F = 105.76	<.001	0.15	<0.001	<0.001	<0.001

(Continues)

TABLE 1 (Continued)

	M (SD)	M (SD)	M (SD)	F	p	p	p	p	p
Psychosocial Resources/Psychiatric Functioning									
Anxiety/worry total score, M (SD)	52.77 (13.23)	37.61 (13.79)	33.18 (10.32)	F = 212.87	<.001	0.26	<0.001	<0.001	<0.001
Depressive symptoms total score, M (SD)	14.08 (5.50)	3.73 (3.16)	3.49 (2.82)	F = 825.50	<.001	0.58	<0.001	<0.001	0.32
Cognition									
MMSE total score, M (SD)	26.31 (3.30)	27.91 (2.01)	26.92 (2.56)	F = 37.44	<.001	0.06	<0.001	0.002	<0.001
SMC (z-score), M (SD)[a]	0.89 (1.10)	−0.19 (0.83)	−0.29 (0.81)	F = 143.14	<.001	0.19	<0.001	<0.001	0.012
Memory composite (z-score), M (SD)[a]	−0.02 (0.76)	0.14 (0.74)	0.13 (1.91)	F = 1.68	.19	0.003	–	–	–
Executive composite (z-score), M (SD)[a]	−0.40 (0.84)	0.05 (0.74)	−0.05 (0.82)	F = 15.43	<.001	0.025	<0.001	<0.001	0.91
Plasma AD Biomarkers									
Aβ42/Aβ40 ratio (z-score), M (SD)[a]	−0.07 (0.79)	0.04 (1.25)	−0.004 (0.82)	F = 0.05	.95	<0.001	–	–	–
NfL pg/ml (z-score), M (SD)[a]	−0.04 (0.55)	−0.12 (0.54)	−0.19 (0.42)	F = 7.47	<.001	0.016	0.91	0.003	<0.001
Total tau pg/ml (z-score), M (SD)[a]	0.14 (0.89)	−0.06 (0.82)	−0.08 (0.80)	F = 2.07	.13	0.004	–	–	–

[a] Denotes estimated marginal means reported from ANCOVA models adjusted for age, sex, education, cardiometabolic burden, and race/ethnicity.

M = mean; SD = standard deviation; MCI = mild cognitive impairment; APOE = apolipoprotein; MMSE = Mini-Mental Status Examination; SMC = subjective memory concerns; Aβ = amyloid beta; NfL = plasma neurofilament light chain; Tau = plasma total tau. Missing data: Of the 1220 participants, 593 (48.61%) had missing APOE genotyping. Of the 256 participants from the Low Resource/High Distress phenotype, 101 (39.45%) had missing APOE genotyping. Of the 485 participants from the High Resource/Low Distress phenotype, 282 (58.14%) had missing APOE genotyping. Of the 479 participants from the Low Distress group, 210 (43.84%) had missing APOE genotyping. Of the 256 participants from the Low Resource/High Distress phenotype, 64 (25%) had missing Aβ42/Aβ40 ratio data, 60 (23%) had missing plasma NfL data, and 60 (23%) had missing plasma total tau data. Of the 485 participants from the High Resource/Low Distress phenotype, 122 (25%) had missing Aβ42/Aβ40 ratio data, 118 (24%) had missing plasma NfL data, and 116 (24%) had missing plasma total tau data. Of the 479 participants from the Low Resource/Low Distress group, 95 (19%) had missing Aβ42/Aβ40 ratio data, 93 (19%) had missing plasma NfL data, and 89 (29%) had missing plasma total tau data.
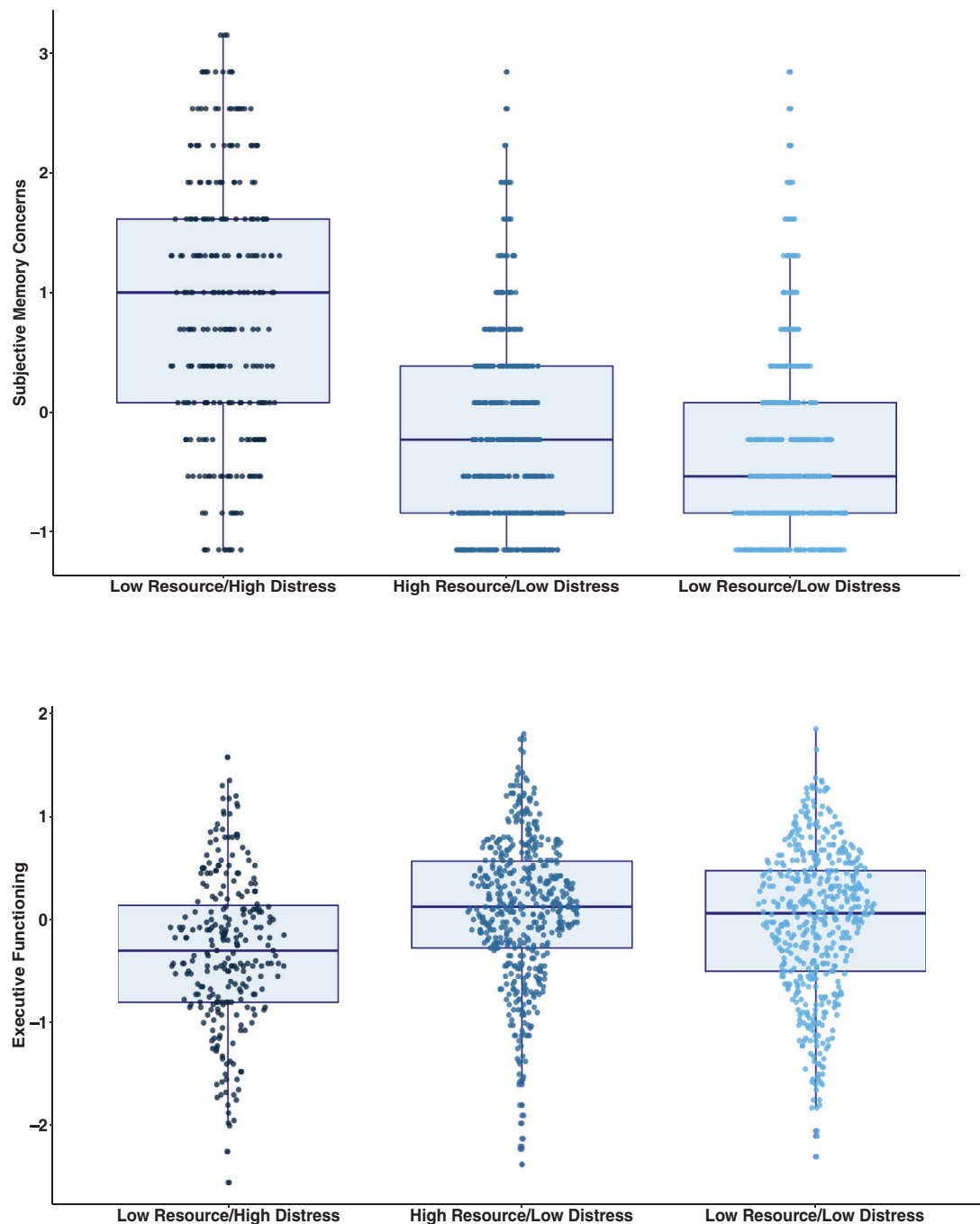
FIGURE 3 Psychosocial-behavioral phenotypes and subjective/objective cognition. Top: boxplot of subjective memory concerns across clusters. Bottom: boxplot of performance on executive functioning composite across clusters.

Data-driven approaches to phenotyping have primarily included biological characterizations of individuals "at risk" for AD due to the advancement of high-throughput multi-omics methods.[55,56] This emphasis on biology has centered on (1) the development of therapeutic targets and enrichment of clinical trial recruitment efforts that may optimize outcomes and reduce costs and (2) the characterization of biological processes associated with racial/ethnic differences in AD risk. For example, the identification of amyloid-positive individuals that may be more likely to benefit from anti-amyloid agents prior to

the onset of cognitive impairment has been used to direct some clinical trial initiatives.[57,58] Furthermore, as illustrated by another recent HABS-HD investigation, there are distinct proteomic profiles of neurodegeneration in NHL and Latino older adults, and the biological factors underlying neurodegeneration within each racial/ethnic group differ across the MCI and AD phases.[59] While limited, several recent efforts have been made to engage in psychosocial and behavioral phenotyping methods within middle-aged and older adult samples, with specific efforts to take into account the *cumulative* influence of
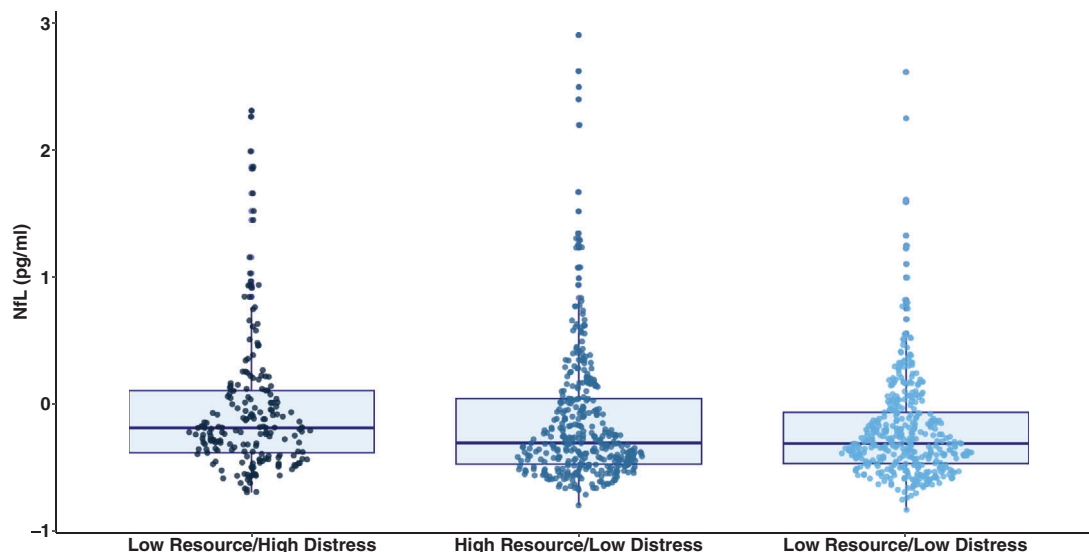
FIGURE 4 Boxplot of neurofilament light chain across psychosocial phenotypes.

multiple socioeconomic, contextual, and behavioral factors on cognitive outcomes.[31,32] One recent study employed machine learning methods within a large cohort study of Australian adults ($n = 4141$, age range 34 to 97) and identified that the collective influence of a number of sociodemographic (eg, age, income, education) and lifestyle (eg, sedentary behavior, exercise) factors were predictive of cognitive classes.[32] Notably, the authors in that study observed no associations between environmental factors (eg, population density, aerial distance to parkland) and cognition.[32] Collectively, our results suggest empirical psychosocial-behavioral phenotyping methods may allow for a more nuanced understanding of how AD risk is shaped and, ultimately, prove useful for the development of individualized interventions essential to promoting longevity and health equity within racially/ethnically minoritized older adults.

Although other studies have employed similar empirical methods,[29,30,34] a comparative strength of our study was that we performed our cluster analyses both across and within each racial/ethnic group. Results revealed the Low Resource/High Distress, High Resource/Low Distress, and Low Resource/Low Distress phenotypes emerged within each set of analyses and that classification statistics were high within each racial/ethnic group as well. However, more nuanced patterns to our findings warrant recognition, as Black adults were overrepresented in the High Resource/Low Distress phenotype relative to the other two phenotypes. Additionally, ancillary exploratory analyses revealed that within the High Resource/Low Distress phenotype, Black adults had significantly higher levels of income and social support relative to Latinos; within the Low Resource/Low Distress phenotype, Black adults had significantly lower symptoms of stress, worry, and depression but higher levels of income, social support, and occupational complexity compared to Latinos. In other words, while overall patterns of phenotypes are similar across the groups, measured levels of these variables may also differ within each group. It is also critical to recognize that there is also incredible variability in precisely which risk factors Black and Latino

community members are exposed to across the life course and that these racial/ethnic groups may face unique barriers (eg, anti-Black or anti-immigrant sentiments, language barriers) and have distinct lived experiences (eg, acculturation, John Henryism). Indeed, as noted by Lamar and colleagues (2021), culture-specific psychosocial-behavioral factors may differentially contribute to cognitive outcomes in Latino older adults, and there is a need to further delineate these within the context of AD research initiatives centered on communities of color.[4,5,60,61]

Although the Low Resource/High Distress phenotype was a smaller subset of the larger sample, the individuals in this group displayed poorer performance on the executive functioning composite and endorsed more severe subjective memory concerns relative to the Low Resource/ Low Distress and High Resource/Low Distress phenotypes. In contrast, there were no differences in performance on the memory composite across the phenotypes. The larger literature has highlighted that executive dysfunction is commonly observed within these ethnoracial groups, and elevated rates of vascular risk and psychiatric symptoms may represent mechanisms underlying this observation.[62–66] With regard to memory, the relationship between subjective concerns and objective performance is small,[67,68] and investigators have noted differences in the frequency and severity of subjective cognitive concerns between ethnoracial groups.[69,70] Since subjective memory concerns have been tightly linked with affective symptoms,[7] we suspect the notable differences in subjective, but not objective, memory performance may have been a function of psychiatric distress within the Low Resource/High Distress phenotype. Targeted management of psychiatric symptoms and enhanced access to socioeconomic or care-support resources may help mitigate poor future outcomes within this group.

The Low Resource/High Distress phenotype also displayed higher levels of plasma NfL, although there were no differences between any of the groups in plasma markers of amyloid or tau. Importantly, socially patterned inequities can become biologically embedded,

negatively impact cognitive and neural reserve, and accelerate cognitive decline.[7,9] Furthermore, higher levels of psychiatric symptomatology have been linked to neurodegeneration and accelerated cognitive decline in older adults.[71–73] While NfL levels have been shown to increase across the preclinical to clinical phase of AD,[74,75] this is a non-specific marker of neurodegeneration, and other pathologic processes may be at play.[76] Thus, it is possible that the observed cognitive outcomes and elevated levels of NfL observed are indicative of a neurodegenerative process that is fundamentally tied to the underlying lived experiences of this psychosocial phenotype, including the increased anxiety, depressive symptoms, and stress in the context of lack of social support or other financial resources to help manage cognitive challenges. However, it is important to note that plasma AD biomarkers also have varied degrees of prognostic utility and that plasma phosphorylated tau, which was not available in the HABS-HD study, has been shown to be a more reliably correlated with amyloid PET neuroimaging metrics of AD pathology.[77–79] Future work exploring the longitudinal cognitive, biomarker, and neuroimaging trajectories of this psychosocial phenotypes is also needed.

Our study also identified two resilient groups that had low levels of psychiatric distress in the presence of varied levels of resources. While these two groups did not differ on objective neuropsychological measures and plasma markers of amyloid and tau, there were some notable differences in subjective cognition and plasma AD markers. Interestingly, the identified Low Resource/Low Distress group had fewer subjective memory concerns and lower levels of plasma NfL relative to the High Resource/Low Distress group. While the economic and occupation resources were generally much lower in the Low Resource/Low Distress group, it is important to recognize that the levels of social support was largely comparable to the observed levels in the High Resource/Low Distress group. Results suggest that social support may be an important mechanism of resiliency within the Low Resource/Low Distress group that warrants close attention and may ultimately buffer against the other low resources.[80,81] Given that loneliness and social isolation may accelerate cognitive decline,[82] enhanced social support and interaction may represent an important modifiable prevention and intervention factor within minoritized older adults.

Notable limitations of the study include the need to model multidomain psychosocial factors that do not transcend multiple socioecological levels of influence, and future studies that include geocoded variables may help provide more insight into other important elements of these psychosocial phenotypes. This sample consisted largely of cognitively unimpaired individuals, and base rates of MCI were low; as such, studies examining whether these phenotypes emerge and display different biomarker and cognitive trajectories is needed. While MCI was diagnosed in a consensus meeting by trained study staff and was consist with conventional Petersen/Winblad criteria,[83] other criteria have been shown to lead to a better balance of sensitivity and reliability in MCI;[84–86] additional research in more racially/ethnically representative samples is ultimately needed to confirm the utility of these MCI criteria, especially given they have been primarily developed in homogeneous samples of largely educated White older adults. A subset of individuals (n = 258) that did not have psychiatric or resource data of interest were excluded from the study, and sensitivity analyses revealed these individuals were slightly younger, more likely to be Black or Spanish speaking, and less educated relative to those that were included. While we adjust for many of these factors in our analyses and HABS-HD allows for the completion of the study in a participant's preferred language, it is important to acknowledge that observed cluster patterns and outcomes might have changed if these individuals had had available data and had been included. Similarly, plasma biomarker data were missing for around 20% of the sample given constraints surrounding the batched processing of these data, and replication of observed patterns with these individuals will be included in the future. Plasma AD markers can be easily implemented in traditionally underserved populations, but neuroimaging markers of amyloid, tau, or neurodegeneration may provide more insight into ongoing patterns of neural change across the groups. It is important to note that while NfL levels have been shown to increase across the preclinical to clinical phase of AD,[74,75] this is a non-specific marker of neurodegeneration, and other pathologic processes may be at play.[76] Given vascular health disparities, future work may need to look beyond traditional plasma AD markers to assessing vascular, inflammatory, and metabolic biomarkers that may play an important role in accelerated aging trajectories across the sample. Finally, modeling longitudinal change or variation in socioeconomic resources and psychiatric functioning across the life course and its association with cognition may ultimately improve our understanding of modifiable risk factors in AD risk in late life.

There are several notable strengths of the study, including its data-driven approach and novel psychosocial characterization of distinct phenotypes. Importantly, these analyses were conducted within a large sample ($N \approx 1400$) of racially/ethnically diverse adults that included individuals in mid-to-late life (age range 37 to 87), whereas most studies exploring psychosocial-behavioral phenotyping methods within these groups have largely taken place in adults above the age of 50 or used data reduction techniques that do not allow for a more nuanced pattern of how variables are behaving within each cluster. Furthermore, cluster analysis was conducted both across and within these racial/ethnic groups to ensure these phenotypes were not specific to one group. Finally, our psychosocial-behavioral phenotyping provides insight into sociobiological pathways (ie, Low Resource/High Distress and neurodegeneration as indexed by NfL) that is important for identifying prevention and intervention points specific to minoritized older adults. In conclusion, distinct patterns of psychosocial variables can be identified within racially/ethnically minoritized older adults, and these clusters show varied cognitive and AD biomarker profiles. The identification of psychosocial phenotypes within large samples of racially/ethnically minoritized older adults is crucial to the development of targeted prevention and intervention efforts rooted in health equity.

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CONFLICTS OF INTEREST STATEMENTS

The authors have no conflicts of interest to report. Author conflict of interest disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

Data used in preparation of this article were obtained from the HABS-HD database (https://apps.unthsc.edu/itr/researchers). HABS-HD MPIs include Sid E. O'Bryant, Kristine Yaffe, Arthur Toga, Robert Rissman, and Leigh Johnson and the HABS-HD investigators Meredith Braskie, Kevin King, James R. Hall, Melissa Petersen, Raymond Parlmer, Robert Barber, Yonggang Shi, Fan Zhang, Rajesh Nandy, Roderick McColl, Monica Rivera Mindt, Amrita Cheema, Lisa Barnes, Mark Mapstone, Annie Cohen, Amy Kind, Ozioma Okonkwo, Raul Vintimilla, Zhengyang Zhou, Michael Donohue, Rema Raman, Matthew Borzage, Michelle Miekle, Beau Ances, Ganesh Babulal, Jorge Llibre-Guerra, Carl Hill, and Rocky Vig. The consent is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CONSENT STATEMENT

Informed consent was not necessary for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.