Alzheimer's & Dementia: The Journal of the Alzheimer's Association

Empirically Derived Psychosocial Phenotypes in Black/African American and Hispanic/Latino Older Adults Enrolled in HABS-HD: Associations with AD Biomarkers and Cognitive Outcomes

--Manuscript Draft--

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Abstract:	Introduction: Identification of psychosocial 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 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 HABS-HD. ANCOVAs 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 phenotypes within racially/ethnically minoritized older adults is crucial for the development of targeted AD prevention efforts.

Cover Letter

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Professor of Neurology
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Alzheimer's & Dementia: The Journal of the Alzheimer's Association

September 21, 2023

Dear Dr. Wilcox:

We are pleased to submit the revised manuscript entitled ***"*Empirically Derived Psychosocial Phenotypes in Black and Latino Older Adults Enrolled in HABS-HD: Associations with AD Biomarkers and Cognitive Outcomes"** for consideration for publication in your esteemed *Alzheimer's and Dementia*.

The current study capitalized on **1,220 Black and Latino older adults enrolled in the Healthy Aging Brain-Health Disparities Study** and (1) cluster-analyzed individual measures of socioeconomic resources and psychiatric functioning to identify distinct psychosocial phenotypes and (2) explored whether these identified psychosocial phenotypes differed on AD biomarker and cognitive outcomes. We identified 3 distinct psychosocial phenotypes that appeared to have varying levels of risk and resiliency to AD. The Low Resource/High Distress group appeared vulnerable in that they performed more poorly on cognitive outcomes and had higher levels of plasma NfL relative to the Low Resource/Low Distress and High Resource/Low Distress phenotypes. However, the Low Resource/Low Distress appeared resiliency in that they displayed comparable for better outcomes relative to High Resource/Low Distress phenotypes. We believe that social support is an important protective mechanism that may promote resiliency among the Low Resource/Low Distress group. **This study helps highlight that there is incredible within-group heterogeneity in the lived experiences of minoritized older adults that can be modeled, and that the identification of psychosocial phenotypes is crucial to the development of targeted prevention and intervention efforts rooted in health equity.**

In general, the feedback from the reviewers was positive with recognition that the study was "exciting" and "timely". There were some requests for clarification of important study details and conceptualizations of the findings. These included an expanded literature review, acknowledgement of social and structural inequities that may differ across Black and Latino older adults, clarification of the cognitive composites, and some additional context to the findings. One reviewer also asked for a missing data analysis, which has been completed and we have added a helpful schematic (Supplemental Figure 1). We believe this constructive feedback has strengthened the scholarship of the manuscript. Responses to their feedback are attached and all changes within the manuscript are underlined.

On behalf of myself and all of my coauthors, I attest that all authors have contributed to the work and agree with the presented findings and that the work is based on original research that has not been previously published or submitted for concurrent consideration of publication elsewhere. As senior author, I take full responsibility for the

data, the analyses and interpretation, and the conduct of the research. As stated in the Compliance section of the submitted manuscript, the appropriate Institutional Review Boards approved this study, and all participants provided written informed consent prior to assessments. The treatment of human participants during the course of this study was in full accordance with the Helsinki Declaration of 1975.

Respectfully,

Alexandra L. Clark

REVISIONS (Clark et al.)
Psychosocial Phenotypes in Black & Latino Adults

CC: dwilcock@iu.edu

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MS Number: ADJ-D-23-00937
Title: Empirically Derived Psychosocial Phenotypes in Black and Latino Older Adults Enrolled in HABS-HD: Associations with AD Biomarkers and Cognitive Outcomes

Dear Dr. Clark,

The reviewers have now commented on your paper. The reviewers have recommended substantive revisions be made. We would be willing to consider a revised manuscript if you can fully respond to the reviewers' comments. It is the policy of the Journal to allow one opportunity to make substantive revisions.

Please carefully consider the referee reports (appended below), along with any additional editorial comments (if included). The reviewers' and editors' comments must be addressed before your revision is reconsidered.

If you decide to revise the work, please submit a list--as a "Response to Reviewers" file--of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. The revised manuscript will be due on Oct 06, 2023.

PLEASE NOTE:

It is expected that authors state in the "Response to Reviewers" the page and paragraph number for each specific change made. DO NOT simply reply to the reviewers: a response to a reviewer comment merits a change in the manuscript. If no change was made, authors must explicitly state "We did not make the change requested because…".

To submit a revision, please go to https://www.editorialmanager.com/adj/ and login as an Author.
Your username is: alexleighclark
If you need to retrieve password details please click the 'Send Login Details' link.

On your Main Menu page is a folder entitled "Submissions Needing Revision". You will find your submission record there. Along with addressing all reviewer and/or editor comments, please be sure to provide the following items:

1. New cover letter
2. Point by point response to comments with "comments" followed by "response" and some reference (page and line number) of where the corrections appear
3. Marked-up manuscript (highlighted) - this should be uploaded under the 'Marked Revision' file designation
4. Clean manuscript - this should be uploaded under the 'Manuscript' file designation. *Please note that, if accepted, this file will be the one typeset and published.

5. A single PDF file including completed ICMJE disclosure of interest forms from each co-author. The PDF should be uploaded as the "ICMJE Disclosures Forms" item type. If the manuscript is accepted for publication, a link to this combined file will be included with the published article.
6. Abstract, in the format outlined in our Guide for Authors.
7. Research in Context, as described in our Guide for Authors
8. References must follow AMA style, and be serially numbered. Please note that no web addresses should appear unless cited as references.
9. Figures must be uploaded as individual files in TIFF, EPS, JPG, or PDF format, of at least 300 DPI.

Please feel free to contact the editorial office at ADJEdOffice@jjeditorial.com with any questions.

Yours sincerely,

Donna M. Wilcock, Ph.D.
Editor-in-Chief
Alzheimer's & Dementia: The Journal of the Alzheimer's Association

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Reviewers' comments:

REVISIONS (Clark et al.)
Psychosocial Phenotypes in Black & Latino Adults

RESPONSES TO REVIEWER 1

R1, Comment 1: This work presents an exciting analysis of psychosocial phenotypes to identify unique subgroups of Black and Latino participants and differences in subgroup cognitive functioning and biomarker status. Importantly, the authors highlight the fact that racial and ethnic disparities in AD are due to social and structural inequities as justification for their methodological approach. Additional discussion regarding the social and structural inequities in relation to ADRD as well as a more detailed discussion around race is warranted to further substantiate this argument. Additional detail in methods is also warranted. Below are additional suggestions to improve the work.

Response 1: We thank the reviewer for their time and thoughtful suggestions. We have done our best to address comments and believe the quality of the overall manuscript is improved because of their constructive feedback. We agree with the reviewer that additional context to the social and structural inequities in relation to ADRD and race are needed. Please note that within the manuscript introduction and discussion, you will now find important content that has been added to the as a result of these suggestions, most of which are also detailed in the responses below.

R1, Comment 2: Abstract contains "NfL" but it is not clear to the read what this means b/c has not been defined.

Response 2: We have changed this to neurofilament light chain in the abstract.

R1, Comment 3: Abstract: "Minoritized adults" is vague and nondescriptive. Minoritized in what way?

Response 3: We have changed this to throughout the manuscript and now state "racially/ethnically minoritized" adults throughout.

R1, Comment 4: Statement: However, minoritized older adults are exposed to multiple risk factors within each of these domains and that there may be unique interactions between factors that accelerated cognitive aging trajectories for certain members within these communities [8,9]. "And that there" should be removed.

Response 4: We have edited this sentence accordingly.

R1, Comment 5: While there is justification for the exclusion of racial and ethnic minorities in the present study due to lack of representation in AD research and existing AD disparities, there is little explanation for why inequity differs across race and ethnicity. The authors speak to racial and ethnic minorities as if everyone is the same (minoritized populations). Because the authors are including two specific subpopulations (Black and Latino individuals), there should be more focus on distinct social and structural factors that may impact their experience and confer risk for ADRD.

Response 5: We have added the following content to the introduction to highlight variables of consideration in existing research studies that utilized psychosocial behavioral phenotyping methods in Black and Latino samples.

Pages 3-4, Lines 99-110:

"Similarly, in a large sample of Latino older adults, a principal component analysis on a 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 were 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."

Further, we have added content to the discussion to highlight that social and structural inequities may differ across these ethnoracial groups and to provide additional context to observations within the present study.

Page 8, lines 270-284:

"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 a 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, there were more nuanced patterns to our findings that 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 Black adults has significantly lower symptoms of stress, worry, and depression, but higher levels of income, social support, and occupational complexity when 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 (e.g., anti-Black, or anti-immigrant sentiments, language barriers) and have distinct lived experiences (e.g., acculturation, John Henryism). Indeed, as noted by Lamar and colleagues (2021) cultural-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]."

R1, Comment 6: While cluster analysis is considered exploratory in nature and there is no way to definitively know what subgroups will be identified, were there any specific hypotheses in regard to anticipated subgroup differences in cognitive and plasma AD biomarkers? The authors reference a paper with an MCI sample that identified distinct biological and cognitive subgroups and this may also inform hypotheses. Please include what you might anticipate seeing across subgroups in regards to meaningful differences in cognition and AD biomarkers.

Response 6: Building upon the studies now featured within the introduction, we have added the following hypotheses to the end of the introduction which now reads:

Page 4, lines 123-125"

"We hypothesized that the exploratory cluster analysis would identify groups in which high resources/low distress would buffer against poorer cognitive outcomes, and group with low resources/high distress that would display poorer cognitive and worse AD plasma biomarker outcomes."

R1, Comment 7: 2.3. Study Participants: I recognize that this may be a limitation of how data were collected, but how is Black and Latino differentiated in this sample? For instance, are there Black/Afro Latinos included? If so, what group do they fall into? Race and ethnicity are separate constructs, and it is not clear how this was treated in the methods section.

Response 7: Data pertaining to self-described race and ethnicity are collected separately within the study. We have added some additional language to provide more context and clarity in the methods section, which states:

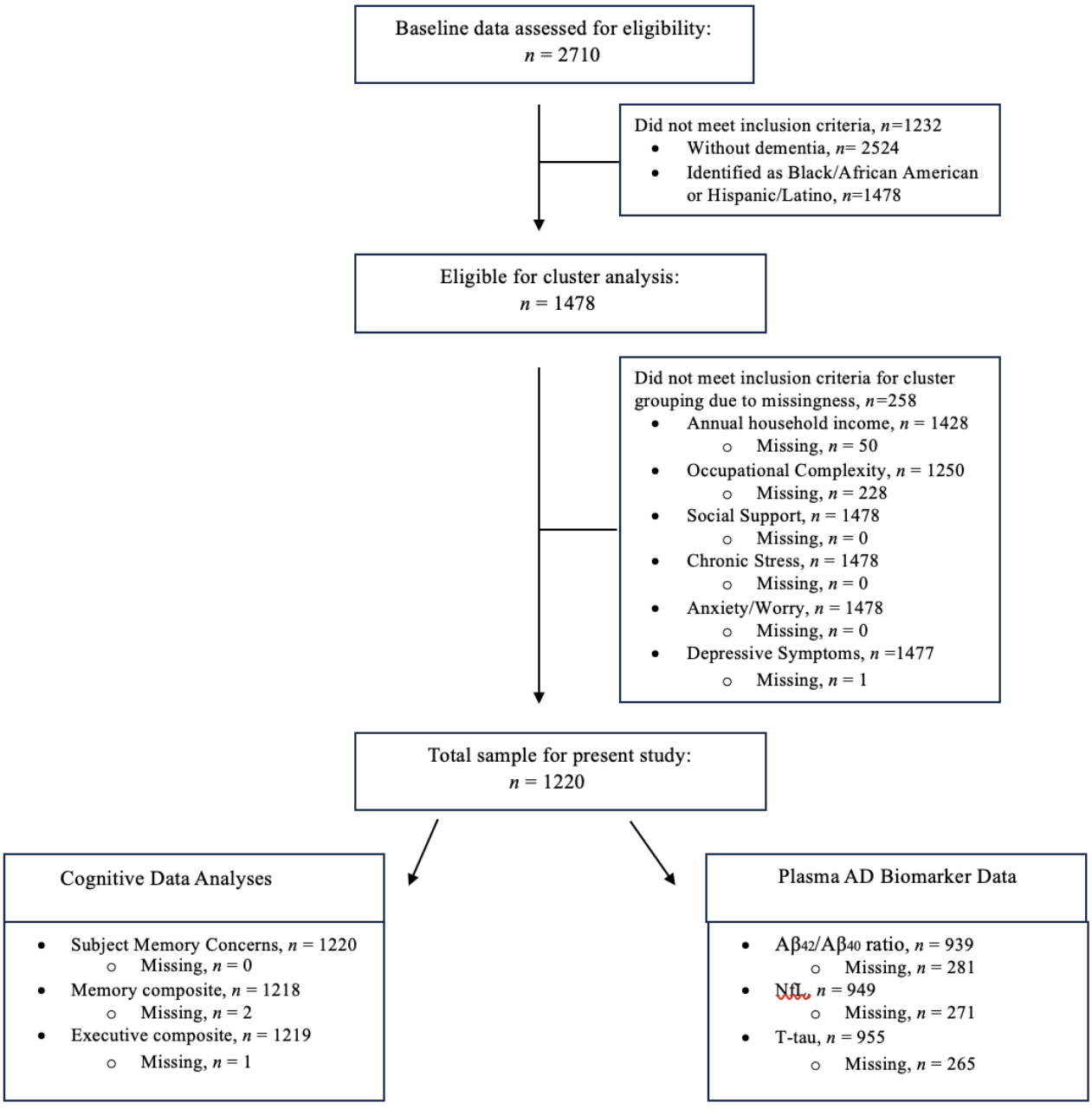
Page 5, Lines 145-147:

"Self-described racial and ethnic groupings were used to categorize participants. Of note, there was one participant that self-reported their race as Black and ethnicity as Latino (were also bilingual for English and Spanish) that was coded as Latino within this study. "

R1, Comment 8: Were there any differences (besides dementia diagnosis) between those who completed psychosocial and psychiatric questionnaires and those who did not?

Response 8: We have now included a schematic as supplemental Table 1 to help the reader immediately grasp who was included in the sample and what data may have been missing.

Supplemental Figure 1. Participant eligibility and enrollment in present study.



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Below we have also compiled a table comparing those that were included (n = 1120) vs. excluded (n = 258) from the study and a visual from our missing data analysis for all variables included in the study.

Variable	Included *n*= 1220	Excluded *n*= 258	Omnibus test result		
			Test statistic	*P*-value	*Effect Size (V or d)*
Age, M(SD)	63.33 (7.69)	60.68 (7.45)	t= -5.05	0.09	-0.35
Female, *n* (%)	779 (63.85)	214 (82.95)	x2 = 35.22	<0.001	0.15
Race/Ethnicity					
Latino, *n* (%)	810 (66.39)	204 (79.07)	x2= 15.89	<0.001	0.10
Black, *n* (%)	410 (33.60)	54 (20.93)			
Years of education, M(SD)	11.91 (4.58)	9.59 (4.62)	t= -7.38	0.14	-0.51
Spanish speaking, *n* (%)	496 (40.66)	172 (66.66)	x2= 58.17	<0.001	0.20
MCI, *n* (%)	287 (23.52)	59 (22.87)	x2 = 0.05	0.82	0.01
APOE e4 carrier, *n* (%)	108 (8.85)	26 (10.08)	x2= 0.07	0.79	0.01
Cardiometabolic Burden, M(SD)	2.44 (1.30)	2.69 (1.37)	t= 2.81	0.15	0.19
Psychosocial Resources/ Psychiatric Functioning					
Annual Household Income, M(SD)	51,167.56 (49,437.28)	48,886.49 (137619.53)	t= -0.44	<0.001	-0.03
Occupational Complexity Total Score, M(SD)	6.90 (4.03)	7.57 (4.71)	t= 0.89	0.19	0.17
Social Support Total Score, M(SD)	40.69 (6.23)	39.39 (6.54)	t= -3.02	0.25	-0.21
Chronic Stress Total Score, M(SD)	7.53 (6.67)	7.26 (7.26)	t= -0.60	0.33	-0.04
Anxiety/Worry Total Score, M(SD)	39.05 (14.42)	38.61 (14.55)	t= -0.45	0.99	-0.03
Depressive Symptoms Total Score, M(SD)	5.81 (5.62)	7.50 (6.41)	t= 4.28	0.001	0.29

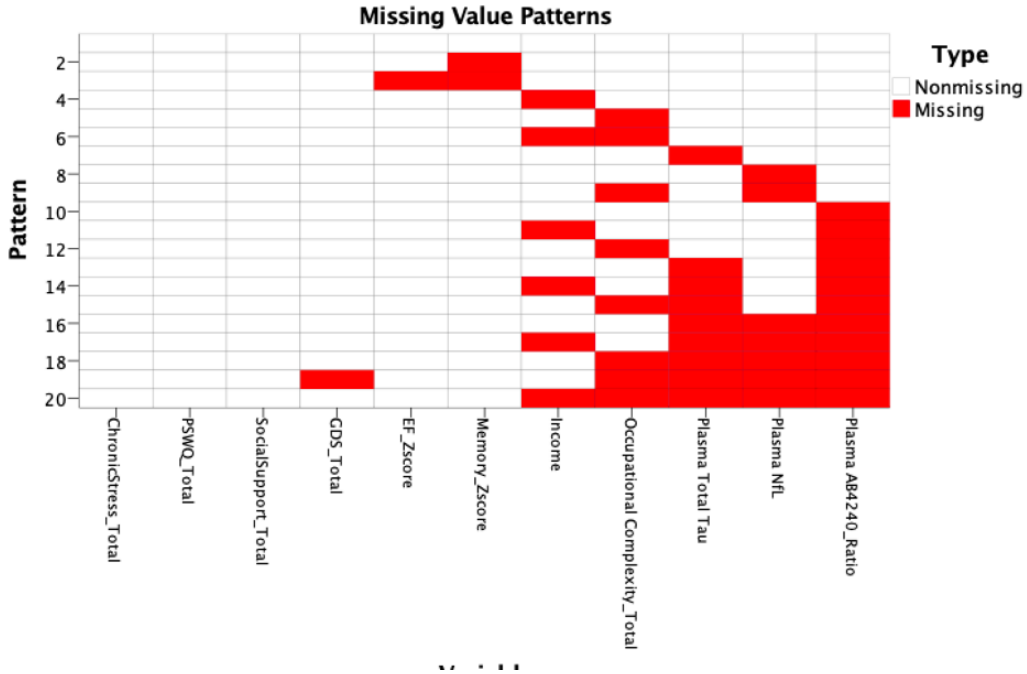
Note. M = Mean; SD = Standard deviation; MCI = mild cognitive impairment, APOE = Apolipoprotein; MMSE= Mini-Mental Status Examination.

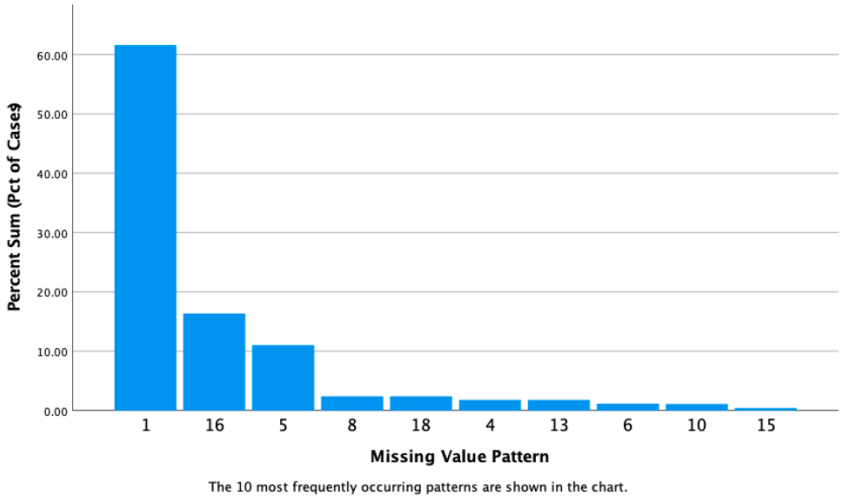
Variable Summary[a,b]

	Missing				
	N	Percent	Valid N	Mean	Std. Deviation
AB4240_Ratio	331	22.4%	1147	.0504	.01346
Plasma NfL	319	21.6%	1159	-.1091	.59668
Plamsa T Tau	315	21.3%	1163	.0163	.91039
Occupational Complexity	228	15.4%	1250	.0000000	1.00000000

a. Maximum number of variables shown: 25

b. Minimum percentage of missing values for variable to be included: 10.0%





The 10 most frequently occurring patterns are shown in the chart.

Everyone was required to have all psychiatric symptom and resource variables to be included in the cluster analysis. It seems that annual income and occupational complexity data were factors that led to

exclusion from the initial cluster analysis, and that a subset of individuals were missing plasma biomarker data due to the batched nature and processing of this data. This was confirmed by the missing data analysis charts above; as you can see, the majority of missing data was pattern 1(no missing data); followed by pattern 16 which was due missing biomarker data; and the next most common pattern 5 was due to missing income data only. Instances of multiple missing data were less frequent as indicated by the histogram of patterns 8-15.

(1) With regard to the exclusion of individuals from the cluster analysis, it appears excluded individuals were on average: younger, less educated, had greater vascular risk, and were more likely to be Black and Spanish speaking. However, the effect sizes of these group differences were primarily small (Cohen's d or Cramer's V ≤.3), with the expectation of education which was d = .5. While we adjust for many of these factors (age, education, vascular burden) in our analyses for people that were included in the study, we now acknowledge this as an important limitation in the discussion.

(2) While mostly everyone included in the cluster analysis had cognitive data, there was some missing data for the plasma AD biomarkers. We have updated tables, included a supplemental figure, and made modifications to the discussion to acknowledge that this could be a factor of influence in the observed findings.

New content added to the discussion includes:

Page 9, lines 325-327:

"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 may have differed with the inclusion of these individuals."

Page 9, lines 327-331

"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 may have changed is these individuals had available data and were included. Similarly, plasma biomarker data was missing for around 20% of the sample given constraints surrounding the batched processing of this data and replication of observed patterns with these individuals are included in future."

R1, Comment 9: 2.4 Cognitive Diagnoses, Objective Cognition, and Subjective Cognitive Concerns: More detail is needed for how bilingual participants completed in neuropsychological testing; were they tested in their preferred language? Were z-scores created using all participants, including white participants? How was race and ethnicity considered when creating composite?

Were the raw test scores standardized, and those standardized scores used to create a composite z-score? Additional detail is needed.

Response 9: We have clarified these important details about language of testing and neuropsychological test data within the text as detailed below:

Page 4, lines 132-133:

- "Participants enrolled in the HABS-HD study could complete the entire protocol in Spanish or English in accordance with their preferred language."

Page 5, lines 149-156:

- "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 0-7, 8-12, 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 [22,23]. The adjusted z-scores WMS-III Digit Span total score, Trail Making Test Parts A & B total time, and the Letter (FAS) fluency total scores were averaged to create an executive functioning composite [23,24]. Subjective memory concerns were assessed with the 14-item Subjective Memory Complaints Questionnaire [25].

Importantly, these demographically adjusted cognitive z-scores are used widely across HABS-HD, so in order to be consistent and allow for comparisons to be made with other HABS papers, we create composites from these scores. However, we also include race/ethnicity as a covariate in our analyses with cognitive outcomes.

R1, Comment 10: 2.5 Psychosocial Resources and Psychiatric Functioning: Please include what instruments were used to evaluate chronic stress, worry, and depressive symptoms.

Response 10: We have made this edit and now include the measure descriptions on page 5, lines 164-168.

R1, Comment 11: 2.6. Plasma AD Biomarkers, Genetic Risk, and Vascular Burden: More detail is needed re: cardiometabolic vascular burden variable. Is it a simple summation across the three components (circumference, blood pressure, triglycerides) or was there some form of transformation that occurred?

Response 11: We have clarified content and this sentence on page 5, lines 174-177 now reads:

"Elevated waist-circumference (W-C; 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 0-5.

R1, Comment 12: 2.7. Statistical Analyses: Was there any missing data? If so, a missing data analysis should be completed.

Response 12: Please see the details of Response 8 above and supplemental Table 1.

R1, Comment 13: Typo on line 10 of the "Custers difference on cognition and AD plasma" should be "differed".

Response 13: Thank you, as we have corrected this typo in the text.

R1, Comment 14: If you are interested in speaking to racial and ethnic disparities, what is the justification for including race as a covariate?

Response 14: In our cluster analysis that was conducted across the whole sample, it is worthwhile to note that proportion of Black adults that were classified in Cluster 2 was higher than those observed in Cluster 1 and 3. In an effort to ensure that differences between the clusters on cognitive and biomarker outcomes weren't attributable to racial/ethnic representation differences across the clusters, this was included as a covariate. We do believe this is an important factor to acknowledge and have added some additional content in the discussion that speaks to important differences in psychosocial resources across the racial/ethnic groups that need to be considered. Please see response #5 above for these details.

R1, Comment 15: 2.8. Discussion: Statement "Of the three psychosocial phenotypes we identified, the Low Resource/High Distress group may be especially vulnerable for future cognitive decline" is perhaps an overstatement given you did not examine cognitive aging trajectories across multiple timepoints and looked at one timepoint.

Response 15: We agree with the reviewer's point and have removed this sentence.

R1, Comment 16: Please include discussion of ideas around why subgroup differences existed for executive functioning and not memory. Discussion should also include why subjective but not objective memory differences were observed.

Response 16: We agree this is important to highlight and have added the following details in the discussion on page 8, lines 285-295:

"Although the Low Resource/High Distress phenotype was a smaller subset of the larger sample, they 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 phenotype. 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]. Given 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."

R1, Comment 17: Additional limitations/future study may include considering how socioeconomic resources and psychiatric symptoms vary across the lifecourse and how this may also influence cognition.

Response 17: We agree with the reviewer and have added the following sentence to the manuscript to highlight this point on page 10, lines 337-339:

"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 on AD risk in late life."

RESPONSES TO REVIEWER 2

R2, Comment 1: Reviewer #2: Thank you for asking me to review this manuscript entitled 'Empirically Derived Psychosocial Phenotypes in Black and Latino Older Adults Enrolled in HABS-HD: Associations with AD Biomarkers and Cognitive Outcomes' For Alzheimer's and Dementia: The Journal of the Alzheimer's Association (ADJ-D-23-00937). In it, authors present their findings investigating psychosocial-behavioral phenotypes and their relationship to other socioeconomic, cognitive, and brain health-related outcomes in a well-established cohort study of minoritized participants. This work is timely as studies focused on minoritized cohorts that take a more holistic approach are needed. Several concerns hampered enthusiasm as outlined below.

Response 1: We thank the reviewer for their time and thoughtful suggestions. We have done our best to address comments and believe the quality of the overall manuscript is improved because of their constructive feedback.

R2, Comment 2: Throughout the Introduction and Discussion sections relevant references were not present that would have provided additional examples of similar work conducted in this area. For example, the Introduction highlighted results far afield from cognitive and brain aging to demonstrate the importance of investigating 'psychosocial-behavioral phenotyping methods that incorporate multi-domain data pertaining to health behaviors, social determinants of health, environmental resources, and psychological functioning'.

Additionally, the Discussion states that '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'. These statements (and associated text) are made despite the fact that examples of such psychosocial-behavioral phenotyping work exist in the cognitive and brain aging literature, and within minoritized populations more specifically (several are listed below). Such omissions might lead a novice reader to believe that work in this area has never been done before, which is not exactly the case.

While individual factors considered and/or statistical modelling techniques may differ (which the authors may wish to highlight so as to distinguish their work), and populations may not include the 3rd or 4th decade of life (a particular strength of this study unfortunately not highlighted in this submission), the conceptualization and aim of omitted studies are relevant and should be incorporated.

a. The Current and Retrospective Cognitive Reserve (2CR) survey and its relationship with cognitive and mood measures.Borella E, Ghisletta P, Carbone E, Aichele S.Eur J Ageing. 2023 Jun 14;20(1):23. doi: 10.1007/s10433-023-00766-x.PMID: 37314565 Free PMC article.
b. Psychosocial profiles within community-dwelling older adults with Mild Cognitive Impairment: A prevalence and latent profile analysis study. Siew SKH, Yu J, Kua EH, Mahendran R.Asian J Psychiatr. 2023 Apr;82:103503. doi: 10.1016/j.ajp.2023.103503. Epub 2023 Feb 3.PMID: 36791608 Free article.
c. Machine Learning for Prediction of Cognitive Health in Adults Using Sociodemographic, Neighbourhood Environmental, and Lifestyle Factors. Poudel GR, Barnett A, Akram M, Martino

E, Knibbs LD, Anstey KJ, Shaw JE, Cerin E.Int J Environ Res Public Health. 2022 Sep 2;19(17):10977. doi: 10.3390/ijerph191710977.PMID: 36078704 Free PMC article.
d. Acculturation in Context: The Relationship Between Acculturation and Socioenvironmental Factors With Level of and Change in Cognition in Older Latinos. Lamar M, Barnes LL, Leurgans SE, Fleischman DA, Farfel JM, Bennett DA, Marquez DX.J Gerontol B Psychol Sci Soc Sci. 2021 Mar 14;76(4):e129-e139. doi: 10.1093/geronb/gbaa156.PMID: 32918471 Free PMC article.

Response 2: We are appreciative of the reviewer's feedback and have added important literature and context to our findings in both the introduction and discussion. We also have further highlighted important strengths noted by the reviewer.

Please see the content we incorporated in the introduction and discussion below:

Page 3 & 4, lines 91-110:

- "Several recent research investigations have begun to employ data-driven psychosocial-behavioral phenotyping methods that incorporate multi-domain 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 factors 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 South East 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 a 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 were 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."

Page 8, lines 260-269:

- "While limited, there have been several recent efforts 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 multiple socioeconomic, contextual, and behavioral factors on cognitive outcomes [31,32]. One recent study employed machining learning methods within an large cohort study of Australian adults (N = 4141, age range 34-97) and identified that the collective influence of a number of sociodemographic (e.g., age, income, education) and lifestyle (e.g., sedentary behavior, exercise) factors were predictive of cognitive classes [32]. Notably, the authors in this particular study did not observe any associations between environmental factors (e.g., 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."

Page 8, lines 270-284:

- "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 a 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, there were more nuanced patterns to our findings that 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 Black adults has significantly lower symptoms of stress, worry, and depression, but higher levels of income, social support, and occupational complexity when 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 (e.g., anti-Black, or anti-immigrant sentiments, language barriers) and have distinct lived experiences (e.g., acculturation, John Henryism). Indeed, as noted by Lamar and colleagues (2021) cultural-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]."

Page 10, lines 341-345:

- Importantly, these analyses were done within a large sample size and racial/ethnic diverse adults that included individuals in mid-to-late life (age range 37-87), whereas most studies exploring psychosocial behavioral phenotyping methods within these groups have largely taken place in adults above the age of 50. Furthermore, cluster analysis was conducted both across and within these racial/ethnic groups to ensure these phenotypes were not specific to one group.

R2, Comment 3: While the HABS-HD study is well known, not all readers will be as familiar with the particulars of the methods section as the authors. As such, it may be helpful to provide more details regarding things like how current alcohol or substance abuse was defined, what criteria

were used to confirm that 'neuropsychological test scores [were] considered broadly within normal limits', and how APOE ε2/ε4 positivity was handled. More information is needed surrounding the key psychosocial resources and psychiatric functioning measures that are key to this manuscript as well as what was considered 'theoretically meaningful' when determining the final k=3 solution for the primary phenotyping analytics.

Response 3: We have now added important genetic risk information into the text: "APOE ε4 positivity was determined by the possession of at least one ε4 allele (ε2/ε4; ε3/ε4; ε4/ε4 carriers)."

> Importantly, positivity status includes ε2/ε4 carriers given established research illustrating they are at increased risk for AD relative to ε3/ε3 carriers (see Oveisgharan S, Buchman AS, Yu L, et al. *APOE* ε2ε4 genotype, incident AD and MCI, cognitive decline, and AD pathology in older adults. *Neurology*. 2018;90(24):e2127–e2134. doi:10.1212/WNL.0000000000005677)

- Additional detail about cognitive composites and diagnostic criteria were also added on page 5, lines 149-162:

  "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 0-7, 8-12, 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 [22,23]. The adjusted z-scores WMS-III Digit Span total score, Trail Making Test Parts A & B total time, and the Letter (FAS) fluency total scores were averaged to create an executive functioning composite [23,24]. Subjective memory concerns were assessed with the 14-item Subjective Memory Complaints Questionnaire [25].

  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 = 0; neuropsychological test scores considered broadly within normal limits (demographically adjusted cognitive z-score > -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 = 0.5-2; one or more demographically adjusted cognitive z-score ≤ 1.5; and endorsed self- or informant-reported complaints of cognitive change."

- We also now described that DSM-V diagnostic criteria was used for alcohol use and describe the measures used to characterize psychosocial resources and psychiatric functioning within the sample.

- We also included the following information about why the 3-cluster solution was selected and how this determination was made on page 6, lines 186-193:

"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 [36]. 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 potential bias of utilizing the same participants to develop the classification matrix and compute the discriminant function [37]. 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 was chosen."

R2, Comment 4: Although the authors discussed the fact that the stratified cluster analyses were relatively similar for the Latino and Black participant groups, Figure 2 did suggest some critical divergence. This combined with the more robust nature of the discriminant function analyses and cross-validation studies when these phenotypes were tested within ethno-racial groups and the differences in lived experiences between these ethno-racial groups more generally, did leave significant questions about the rationale for combining the Latino and Black participant groups. What did results look like when these groups were considered separately?

Response 4: The findings were generally the same when broken down by each group. Given the consistency in the presented phenotypes and patterns, and in an effort to reduce multiple comparisons, we only present the biomarker and cognitive outcomes across the whole sample. However, the reviewer highlighted that some important context to patterns across the groups that are noteworthy, and we have further elaborated on these within the discussion:

Page 8, lines 270-284:

"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 a 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, there were more nuanced patterns to our findings that 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 Black adults has significantly lower symptoms of stress, worry, and depression, but higher levels of income, social support, and occupational complexity when 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 (e.g., anti-Black or anti-immigrant sentiments, language barriers) and have distinct lived experiences (e.g., acculturation, John Henryism). Indeed, as noted by Lamar and colleagues (2021) cultural-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]."

R2, Comment 5: While the paragraph on page 8 discussing the two resilient groups was very thoughtful and true to the results, the Discussion contained other interpretations that would only be possible with longitudinal study or - as written - did not seem supported by the results as presented. For example, discussions of cognitive decline seem premature (page 7). Additionally, to say that the phenotypes may have varying degrees of susceptibility to AD (page 6) seemingly ignores the fact that they did not differ on memory performance, tau, or MCI status; all hallmarks of susceptibility to AD. It would seem that either more evidence should be provided to support the authors' claim here or the claim should be reworded given these null results.

Response 5: We have further edited the discussion and removed language regarding susceptibility on page 6 and further discuss the null objective memory and AB42/40 and t-tau findings.

R2, Comment 6: The Box plots were a very nice addition; however, they did - at times - highlight what may be outliers in the data that may have driven some of the results reported. Did the authors strategically assess for outliers and/or consider their influence in their work? This seemed particularly relevant to NfL.

Response 6: We did screen for outliers and have noted this in the methods section, on pages 5-6, lines 180-183:

"Data were screened to ensure basic assumptions were met. Independent and dependent variables of interest were z-scored; physiologically implausible values or values determined to be outliers per Grubb's test were excluded from analyses."

You will also find that there is a supplemental Table 1 that breaks down inclusion/exclusion criteria and details about missing or excluded data are included in figure table legends as well.

R2, Comment 7: How highly correlated are the education, income, and occupational complexity variables? Are these proxies for each other? or are they truly providing complementary information? Depending, the latter two variables may help address educational quality…these nuances were not addressed in the manuscript and, if supported by correlations, could add valuable information to the text.

Response 7: We have provided a correlation table for review below. The correlations for the psychosocial resource variables ranged from .09 to .31, whereas correlations between the psychiatric symptom inventories ranges from .35 to .49. Therefore, we believe each variable is providing complementary information and have also added some context about this in the discussion. (maybe add as a strength?)

Further, when you examine the cluster figures, you can see that the relationship between income, occupation, and social support behave differently across each cluster; for example, (1) in review of the Low Resource/High Resource cluster and High Resource clusters you can see income and occupation

complexity are grouped together, but the magnitude of these differ across clusters; (2) social support is not a perfect mirror of the resources across the clusters, and (3) chronic stress also behaves different in each cluster.

We view this type of phenotyping as helpful, especially over a data reduction technique and have added this following sentence to the discussion:

Page 10, lines 341-347:

"Importantly, these analyses were conducted within a large sample (N ~ 1400) of racial/ethnically diverse adults that included individuals in mid-to-late life (age range 37-87), 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."

Correlations

		Social Support	Occupational Complexity	Annual Income
Social Support	Pearson Correlation	1	.099**	.250**
	Sig. (2-tailed)		<.001	<.001
	N	1220	1220	1220
Occupational Complexity	Pearson Correlation	.099**	1	.310**
	Sig. (2-tailed)	<.001		<.001
	N	1220	1220	1220
Annual Income	Pearson Correlation	.250**	.310**	1
	Sig. (2-tailed)	<.001	<.001	
	N	1220	1220	1220

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

		Chronic Stress	Anxiety/Worry (PSQW)	Depressive Symptoms (GDS)
Chronic Stress	Pearson Correlation	1	.356**	.380**
	Sig. (2-tailed)		<.001	<.001
	N	1220	1220	1220
Anxiety/Worry (PSQW)	Pearson Correlation	.356**	1	.499**
	Sig. (2-tailed)	<.001		<.001
	N	1220	1220	1220
Depressive Symptoms (GDS)	Pearson Correlation	.380**	.499**	1
	Sig. (2-tailed)	<.001	<.001	
	N	1220	1220	1220

**. Correlation is significant at the 0.01 level (2-tailed).

R2, Comment 8:

1. Additional limitations should be mentioned including

a. the use of one cognitive test to determine MCI; alternatively, the authors may wish to state how many of those with MCI were diagnosed on the basis of only 1 cognitive test. This would, perhaps, alleviate this weakness if that number was small/limited;
b. cognitive composites adjusted for education (in years presumably) despite the fact that it is well known that quality of education varies widely within and between ethno-racial groups;
c. NfL is a non-specific marker of disease.

Response 8: We have added the following related points to the limitations section.

Page 9-10, lines 318-339:

"While MCI was diagnosed in a consensus meeting by trained study staff and consisted 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], though much more research in representative samples of racially/ethnically is needed to confirm the utility of these criteria which have largely been applied in homogenous 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 may have changed if these individuals had available data and were included. Similarly, plasma biomarker data was missing for around 20% of the sample given constraints surrounding the batched processing of this data and replication of observed patterns with these individuals are included in future. Plasma AD markers are population feasible biomarkers that 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 marker is 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 on AD risk in late life."

R2, Comment 9: the authors may wish to consider changing their nomenclature from the 'Black' group to the Black participant group as some readers may take offense to using this term as a noun. Also, were all Black participants non-Latino ethnically speaking?

Response 9: We appreciate the reviewer pointing this important correction out to us and have used the qualifiers "older adults" or "participants" throughout the manuscript now. We have also added some information in the race/ethnic groupings in the methods section as well.

Page 5, Lines 145-147:

"Self-described racial and ethnic groupings were used to categorize participants. Of note, there was one participant that self-reported their race as Black and ethnicity as Latino (were also bilingual for English and Spanish) that was coded as Latino within this study. "

R2, Comment 10: 3. Table 1 appears to have mis-named Cluster 2 as High Distress Low Distress.

Response 10: Thank you for pointing this error out, which has now been corrected.

Empirically Derived Psychosocial 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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*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, & 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

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ABSTRACT

INTRODUCTION: Identification of psychosocial 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 HABS-HD. ANCOVAs 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 phenotypes within racially/ethnically minoritized older adults is crucial to the development of targeted AD prevention and intervention efforts.

Word Count: 150

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 Whites (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 of 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 homogenous samples of NLW older adults and has generally not included the modeling other critical factors of influence. Given racial/ethnic disparities in AD are the consequence of social and structural inequities, there is need to look beyond biological and genetic factors into other multi-domain factors [26–28].

Several recent research investigations have begun to employ data-driven psychosocial-behavioral phenotyping methods that incorporate multi-domain 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 factors 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 South East 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 a 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 were 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 multi-domain upstream drivers of health disparities, before they become biologically embedded, are ultimately needed to improve health equity and reduce risk for AD in late life. The present study seeks to extend psychosocial behavioral phenotyping methods into a large community-based study of Black and Latino middle aged and older adults (age range 37-87), and add to the existing literature by enhancing our understanding of whether identified psychosocial behavioral phenotypes differ 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 leverage key concepts from precision health and the NIA Health Disparities Research Framework that call for multi-domain 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. Building upon We hypothesized that the exploratory cluster analysis would identify an “at-risk” and “resilient” group, and that the “at-risk” group would display poorer cognitive and worse AD plasma biomarker outcomes.

METHODS

2.1 Data Availability

The present study leveraged data from HABS-HD [36], a large-scale research study centered on understanding key drivers of racial/ethnic disparities in AD. HABS-HD data is publicly available to qualified researchers upon request and has been previously described in detail [36]. Participants in the study complete comprehensive neuropsychological testing, medical clinical labs, brain magnetic resonance imaging (MRI) scans, 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 UNTHSC Institutional Review Board.

2.2 Inclusion/Exclusion Criteria

Inclusion criteria for the HABS-HD study were as follows: community-dwelling adults ages 30 and above; self-reported race or ethnicity of Black/African American, Latino, and NLW; fluency in English or Spanish; willingness to provide blood samples; willing to provide an informant to answer questions regarding daily functioning; and eligible to undergo brain magnetic resonance imaging (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 (e.g., 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 DSM-V diagnostic criteria [37]).

2.3 Study Participants

Baseline data for 1479 participants were available for use and downloaded on 12/1/22. The present 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, there was one bilingual (English and Spanish) participant that self-reported their race as Black and ethnicity as Latino that was coded as Latino within 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 0-7, 8-12, 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 WMS-III Digit Span total score, Trail Making Test Parts A & B total time, and the Letter (FAS) fluency 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 = 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 = 0.5-2; one or more demographically adjusted cognitive z-score ≤ 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 Aβ42/Aβ40 is associated with poor clinical and cognitive outcomes [49–51]. APOE ε4 positivity was determined by the possession of at least one ε4 allele (ε2/ε4; ε3/ε4; ε4/ε4 carriers were coded as positive). Assay preparation was completed using a custom automatic StarPlus system from Hamilton Robotics [36]. Elevated waist-circumference (W-C; 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 0-5.

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 considered

excluded from analyses. Sample sizes slightly differed for biomarker data given this data is 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 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 (i.e., with no unclassified individuals) 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.

2. RESULTS

3.1 Cluster-Derived Psychosocial 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 a *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. See 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 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. See Figure 2.

Within the Black participant group, the cluster analysis resulted in 3-group solution included a 1) *Low Resource/High Distress* group (n = 162); 2) *High Resource/Low Distress* group (n= 63); and a *Low Resource/Low Distress* group (n = 185). With regard to the Low Resource/Low Distress, 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. See Figure 2.

3.2 Demographic Comparisons of Cluster-Derived Psychosocial Phenotypes

Demographic and clinical characteristics by cluster group are shown in Table 1. ANOVAs revealed the cluster groups significantly differed on education ($F = 82.57$, $p < .001$, $eta^2 = .12$), MMSE total score ($F = 37.44$, $p < .001$, $eta^2 = .06$), and cardiovascular risk ($F = 5.19$, $p = .004$, $eta^2 = .008$); there were no cluster group differences in age ($F = 0.53$, $p = .591$, $eta^2 = .009$). There were significant cluster group differences in the proportion of Black older adults ($\chi^2 = 42.14$, $p < .001$, $V = .19$) and women ($\chi^2 = 14.27$, $p < .001$, $V = .11$) across clusters; however, the groups did not significantly differ in the proportion of APOE-e4 carriers ($\chi^2 = 2.02$, $p = .36$, $V = .06$) or individuals diagnosed with MCI ($\chi^2 = 4.21$, $p = .12$, $V = .06$).

3.3 Cognitive Comparisons of Cluster-Derived Psychosocial Phenotypes

ANCOVAs adjusting for age, sex, education, vascular risk, and race/ethnicity revealed the cluster groups significantly differed on the executive functions composite ($F = 15.43$, $p < .001$, partial $eta^2 = .025$). 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 <.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 on the memory composite ($F = 1.68$, $p = .19$, partial $eta^2 = .003$). However, the groups significantly differed on the subjective memory concerns ($F = 143.14$, $p < .001$, partial $eta^2 = .19$). Pairwise comparisons revealed the Low Resource/High Distress endorsed significantly greater memory concerns relative to the High Resource/Low Distress and Low Resource/Low Distress groups (ps <.001). Additionally, the High Resource/Low Distress endorsed significantly greater memory concerns relative to the Low Resource/Low Distress group ($p = .012$). See Figure 3.

3.4 AD Plasma Biomarker Comparisons of Cluster-Derived Psychosocial Phenotypes

ANCOVAs adjusting for age, sex, education, vascular risk, and race/ethnicity revealed the groups significantly differed on plasma NfL ($F = 7.47$, $p < .001$, partial $eta^2 = .016$). Pairwise comparisons revealed the Low Resource/High Distress ($p = .003$) and High Resource/Low Distress ($p < .001$) groups had significantly higher levels of plasma NfL relative to 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 ($p = .91$). See Figure 4. Finally, no significant group differences in plasma total tau ($F = 2.07$, $p = .13$, partial $eta^2 = .004$) or AB42/40 levels ($F = 0.05$, $p = .95$, partial $eta^2 < .001$) were observed.

3. DISCUSSION

In this study we employed a data-driven approach to identify distinct psychosocial phenotypes in an effort to better understand risk and resiliency to AD in Black and Latino older adults. Our analyses revealed three distinct phenotypes that included a 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 worse 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.

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 been 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 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 NHW and Latino older adults and the biological factors underlying neurodegeneration these within each racial/ethnic group differ across the MCI and AD phase [59]. While limited, there have been several recent efforts 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 multiple socioeconomic, contextual, and behavioral factors on cognitive outcomes [31,32]. One recent study employed machining learning methods within an large cohort study of Australian adults (N = 4141, age range 34-97) and identified that the collective influence of a number of sociodemographic (e.g., age, income, education) and lifestyle (e.g., sedentary behavior, exercise) factors were predictive of cognitive classes [32]. Notably, the authors in this particular study did not observe any associations between environmental factors (e.g., 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 a 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, there were more nuanced patterns to our findings that 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 Black adults has significantly lower symptoms of stress, worry, and depression, but higher levels of income, social support, and occupational complexity when 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 (e.g., anti-Black, or anti-immigrant sentiments, language barriers) and have distinct lived experiences (e.g., acculturation, John Henryism). Indeed, as noted by Lamar and colleagues (2021) cultural-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, they 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 phenotype. 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]. Given 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 has 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 marker is non-specific marker of neurodegeneration and other pathologic processes may be at play [76]. Thus, it is possible the observed cognitive outcomes and elevated levels of NfL observed are indicative of neurodegenerative process that is fundamentally tied to the underlying lived experiences of this psychosocial phenotype, including the increased anxiety, depressive symptoms, and stress all in the context of lack of social support or other financial resources to help manage cognitive difficulties. 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 presently available in the HABS-HD study, has been shown to be a more reliable correlate amyloid PET 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 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 multi-domain 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 consisted 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], though much more research in representative samples of racially/ethnically is needed to confirm the utility of these criteria which have largely been applied in homogenous 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 may varied with the inclusion of these individuals. Similarly, plasma biomarker data was missing for around 20% of the sample given constraints surrounding the batched processing of this data and replication of observed patterns with these individuals are included in future.

Plasma AD markers are population feasible biomarkers that 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 marker is 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 on AD risk in late life.

There are several notable strengths of the study which include the data-driven approach and novel psychosocial characterization of distinct phenotypes. Importantly, these analyses were conducted within a large sample (N ~ 1400) of racial/ethnically diverse adults that included individuals in mid-to-late life (age range 37-87), 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 socio-biological pathways (i.e., 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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Figure 1 Legend. Psychosocial phenotypes of all racially/ethnically minoritized HABS-HD older adults. Top part of the figure is a bar graph of mean resource and psychiatric factors across the identified clusters. Bottom part of the figure is a violin plot showing the distribution across mean resource and psychiatric factors across the identified clusters.

Figure 2 Legend. Psychosocial phenotypes of Latino and Black older adults only. Top part of the figure is a bar graph of mean resource and psychiatric factors across the identified clusters in Latino older adults. Bottom part of the figure is a bar graph of mean resource and psychiatric factors across the identified clusters in Black older adults.

Figure 3 Legend. Psychosocial phenotypes and subjective/objective cognition. Top part of the figure is a boxplot of subjective memory concerns across the clusters. Bottom part of the figure is a boxplot of performance on the executive functioning composite across the clusters.

Figure 4 Legend. Boxplot of neurofilament light chain across the psychosocial phenotypes.

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

Empirically Derived Psychosocial Phenotypes in Black/African American and Hispanic/Latino Adults Enrolled in HABS-HD: Associations with AD Biomarkers and Cognitive Outcomes

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ABSTRACT

INTRODUCTION: Identification of psychosocial 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 HABS-HD. ANCOVAs 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 phenotypes within racially/ethnically minoritized older adults is crucial to the development of targeted AD prevention and intervention efforts.

Word Count: 150

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 Whites (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 of 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 homogenous samples of NLW older adults and has generally not included the modeling other critical factors of influence. Given racial/ethnic disparities in AD are the consequence of social and structural inequities, there is need to look beyond biological and genetic factors into other multi-domain factors [26–28].

Several recent research investigations have begun to employ data-driven psychosocial-behavioral phenotyping methods that incorporate multi-domain 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 factors 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 South East 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 a 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 were 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 multi-domain upstream drivers of health disparities, before they become biologically embedded, are ultimately needed to improve health equity and reduce risk for AD in late life. The present study seeks to extend psychosocial behavioral phenotyping methods into a large community-based study of Black and Latino middle aged and older adults (age range 37-87), and add to the existing literature by enhancing our understanding of whether identified psychosocial behavioral phenotypes differ 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 leverage key concepts from precision health and the NIA Health Disparities Research Framework that call for multi-domain 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. Building upon We hypothesized that the exploratory cluster analysis would identify groups in which high resources/low distress would buffer against poorer cognitive outcomes, and group with low resources/high distress that would display poorer cognitive and worse AD plasma biomarker outcomes.

METHODS

2.1 Data Availability

The present study leveraged data from HABS-HD [36], a large-scale research study centered on understanding key drivers of racial/ethnic disparities in AD. HABS-HD data is publicly available to qualified researchers upon request and has been previously described in detail [36]. Participants in the study complete comprehensive neuropsychological testing, medical clinical labs, brain magnetic resonance imaging (MRI) scans, 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 UNTHSC Institutional Review Board.

2.2 Inclusion/Exclusion Criteria

Inclusion criteria for the HABS-HD study were as follows: community-dwelling adults ages 30 and above; self-reported race or ethnicity of Black/African American, Latino, and NLW; fluency in English or Spanish; willingness to provide blood samples; willing to provide an informant to answer questions regarding daily functioning; and eligible to undergo brain magnetic resonance imaging (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 (e.g., 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 DSM-V diagnostic criteria [37]).

2.3 Study Participants

Baseline data for 1479 participants were available for use and downloaded on 12/1/22. The present 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, there was one participant that self-reported their race as Black and ethnicity as Latino (were also bilingual in English and Spanish) that was coded as Latino within 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 0-7, 8-12, 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 WMS-III Digit Span total score, Trail Making Test Parts A & B total time, and the Letter (FAS) fluency 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 = 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 = 0.5-2; one or more demographically adjusted cognitive z-score ≤ 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 Aβ42/Aβ40 is associated with poor clinical and cognitive outcomes [49–51]. APOE ε4 positivity was determined by the possession of at least one ε4 allele (ε2/ε4; ε3/ε4; ε4/ε4 carriers were coded as positive). Assay preparation was completed using a custom automatic StarPlus system from Hamilton Robotics [36]. Elevated waist-circumference (W-C; 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 0-5.

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 considered

excluded from analyses. Sample sizes slightly differed for biomarker data given this data is 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 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.

2. RESULTS

3.1 Cluster-Derived Psychosocial 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 a *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. See 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 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. See Figure 2.

Within the Black participant group, the cluster analysis resulted in 3-group solution included a 1) *Low Resource/High Distress* group (n = 162); 2) *High Resource/Low Distress* group (n= 63); and a *Low Resource/Low Distress* group (n = 185). With regard to the Low Resource/Low Distress, 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. See Figure 2.

3.2 Demographic Comparisons of Cluster-Derived Psychosocial Phenotypes

Demographic and clinical characteristics by cluster group are shown in Table 1. ANOVAs revealed the cluster groups significantly differed on education ($F = 82.57$, $p < .001$, $eta^2 = .12$), MMSE total score ($F = 37.44$, $p < .001$, $eta^2 = .06$), and cardiovascular risk ($F = 5.19$, $p = .004$, $eta^2 = .008$); there were no cluster group differences in age ($F = 0.53$, $p = .591$, $eta^2 = .009$). There were significant cluster group differences in the proportion of Black older adults ($\chi^2 = 42.14$, $p < .001$, $V = .19$) and women ($\chi^2 = 14.27$, $p < .001$, $V = .11$) across clusters; however, the groups did not significantly differ in the proportion of APOE-e4 carriers ($\chi^2 = 2.02$, $p = .36$, $V = .06$) or individuals diagnosed with MCI ($\chi^2 = 4.21$, $p = .12$, $V = .06$).

3.3 Cognitive Comparisons of Cluster-Derived Psychosocial Phenotypes

ANCOVAs adjusting for age, sex, education, vascular risk, and race/ethnicity revealed the cluster groups significantly differed on the executive functions composite ($F = 15.43$, $p < .001$, partial $eta^2 = .025$). 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 <.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 on the memory composite ($F = 1.68$, $p = .19$, partial $eta^2 = .003$). However, the groups significantly differed on the subjective memory concerns ($F = 143.14$, $p < .001$, partial $eta^2 = .19$). Pairwise comparisons revealed the Low Resource/High Distress endorsed significantly greater memory concerns relative to the High Resource/Low Distress and Low Resource/Low Distress groups (ps <.001). Additionally, the High Resource/Low Distress endorsed significantly greater memory concerns relative to the Low Resource/Low Distress group ($p = .012$). See Figure 3.

3.4 AD Plasma Biomarker Comparisons of Cluster-Derived Psychosocial Phenotypes

ANCOVAs adjusting for age, sex, education, vascular risk, and race/ethnicity revealed the groups significantly differed on plasma NfL ($F = 7.47$, $p < .001$, partial $eta^2 = .016$). Pairwise comparisons revealed the Low Resource/High Distress ($p = .003$) and High Resource/Low Distress ($p < .001$) groups had significantly higher levels of plasma NfL relative to 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 ($p = .91$). See Figure 4. Finally, no significant group differences in plasma total tau ($F = 2.07$, $p = .13$, partial $eta^2 = .004$) or AB42/40 levels ($F = 0.05$, $p = .95$, partial $eta^2 < .001$) were observed.

3. DISCUSSION

In this study we employed a data-driven approach to identify distinct psychosocial phenotypes in an effort to better understand risk and resiliency to AD in Black and Latino older adults. Our analyses revealed three distinct phenotypes that included a 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 worse 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.

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 been 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 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 NHW and Latino older adults and the biological factors underlying neurodegeneration these within each racial/ethnic group differ across the MCI and AD phase [59]. While limited, there have been several recent efforts 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 multiple socioeconomic, contextual, and behavioral factors on cognitive outcomes [31,32]. One recent study employed machining learning methods within an large cohort study of Australian adults (N = 4141, age range 34-97) and identified that the collective influence of a number of sociodemographic (e.g., age, income, education) and lifestyle (e.g., sedentary behavior, exercise) factors were predictive of cognitive classes [32]. Notably, the authors in this particular study did not observe any associations between environmental factors (e.g., 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 a 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, there were more nuanced patterns to our findings that 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 Black adults has significantly lower symptoms of stress, worry, and depression, but higher levels of income, social support, and occupational complexity when 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 (e.g., anti-Black, or anti-immigrant sentiments, language barriers) and have distinct lived experiences (e.g., acculturation, John Henryism). Indeed, as noted by Lamar and colleagues (2021) cultural-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, they 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 phenotype. 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]. Given 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

298 embedded, negatively impact cognitive and neural reserve, and accelerate cognitive decline [7,9]. Furthermore, higher levels of
299 psychiatric symptomatology has been linked to neurodegeneration and accelerated cognitive decline in older adults [71–73]. While
300 NfL levels have been shown to increase across the preclinical to clinical phase of AD [74,75], this is marker is non-specific marker of
301 neurodegeneration and other pathologic processes may be at play [76]. Thus, it is possible the observed cognitive outcomes and
302 elevated levels of NfL observed are indicative of neurodegenerative process that is fundamentally tied to the underlying lived
303 experiences of this psychosocial phenotype, including the increased anxiety, depressive symptoms, and stress all in the context of lack
304 of social support or other financial resources to help manage cognitive difficulties. However, it is important to note that plasma AD
305 biomarkers also have varied degrees of prognostic utility, and that plasma phosphorylated tau, which was not presently available in the
306 HABS-HD study, has been shown to be a more reliable correlate amyloid PET metrics of AD pathology [77–79]. Future work
307 exploring the longitudinal cognitive, biomarker, and neuroimaging trajectories of this psychosocial phenotypes is also needed.
308 Our study also identified two resilient groups that had low levels of psychiatric distress in the presence of varied levels of
309 resources. While these two groups did not differ on objective neuropsychological measures and plasma markers of amyloid and tau,
310 there were some notable differences in subjective cognition and plasma AD markers. Interestingly, the identified Low Resource/Low
311 Distress group had fewer subjective memory concerns and lower levels of plasma NfL relative to the High Resource/Low Distress
312 group. While the economic and occupation resources were generally much lower in the Low Resource/Low Distress group, it is
313 important to recognize that the levels of social support was largely comparable to the observed levels in the High Resource/Low
314 Distress group. Results suggest that social support may be an important mechanism of resiliency within the Low Resource/Low
315 Distress group that warrants close attention and may ultimately buffer against the other low resources [80,81]. Given loneliness and
316 social isolation may accelerate cognitive decline [82], enhanced social support and interaction may represent an important modifiable
317 prevention and intervention factor within minoritized older adults.
318 Notable limitations of the study include the need to model multi-domain psychosocial factors that do not transcend multiple
319 socioecological levels of influence, and future studies that include geocoded variables may help provide more insight into other
320 important elements of these psychosocial phenotypes. This sample consisted largely of cognitively unimpaired individuals and base
321 rates of MCI were low; as such, studies examining whether these phenotypes emerge and display different biomarker and cognitive
322 trajectories is needed. While MCI was diagnosed in a consensus meeting by trained study staff and consisted with conventional
323 Petersen/Winblad criteria [83], other criteria have been shown to lead to a better balance of sensitivity and reliability in MCI [84–86],
324 though much more research in representative samples of racially/ethnically is needed to confirm the utility of these criteria which have
325 largely been applied in homogenous samples of largely educated White older adults. A subset of individuals (n = 258) that did not
326 have psychiatric or resource data of interest were excluded from the study, and sensitivity analyses revealed these individuals were
327 slightly younger, more likely to be Black or Spanish speaking, and less educated relative to those that were included. While we adjust
328 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
329 is important to acknowledge that observed cluster patterns and outcomes may have changed if these individuals had available data and
330 were included. Similarly, plasma biomarker data was missing for around 20% of the sample given constraints surrounding the batched
331 processing of this data and replication of observed patterns with these individuals are included in future. Plasma AD markers are
332 population feasible biomarkers that can be easily implemented in traditionally underserved populations, but neuroimaging markers of
333 amyloid, tau, or neurodegeneration may provide more insight into ongoing patterns of neural change across the groups. It is important
334 to note that while NfL levels have been shown to increase across the preclinical to clinical phase of AD [74,75], this is marker is non-
335 specific marker of neurodegeneration and other pathologic processes may be at play [76]. Given vascular health disparities, future
336 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 on AD risk in late life.

There are several notable strengths of the study which include the data-driven approach and novel psychosocial characterization of distinct phenotypes. Importantly, these analyses were conducted within a large sample (N ~ 1400) of racial/ethnically diverse adults that included individuals in mid-to-late life (age range 37-87), 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 socio-biological pathways (i.e., 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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Figure 1 Legend. Psychosocial phenotypes of all racially/ethnically minoritized HABS-HD older adults. Top part of the figure is a bar graph of mean resource and psychiatric factors across the identified clusters. Bottom part of the figure is a violin plot showing the distribution across mean resource and psychiatric factors across the identified clusters.

Figure 2 Legend. Psychosocial phenotypes of Latino and Black older adults only. Top part of the figure is a bar graph of mean resource and psychiatric factors across the identified clusters in Latino older adults. Bottom part of the figure is a bar graph of mean resource and psychiatric factors across the identified clusters in Black older adults.

Figure 3 Legend. Psychosocial phenotypes and subjective/objective cognition. Top part of the figure is a boxplot of subjective memory concerns across the clusters. Bottom part of the figure is a boxplot of performance on the executive functioning composite across the clusters.

Figure 4 Legend. Boxplot of neurofilament light chain across the psychosocial phenotypes.

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CONSENT STATEMENT: Informed consent was not necessary for this study.

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

Figure 1

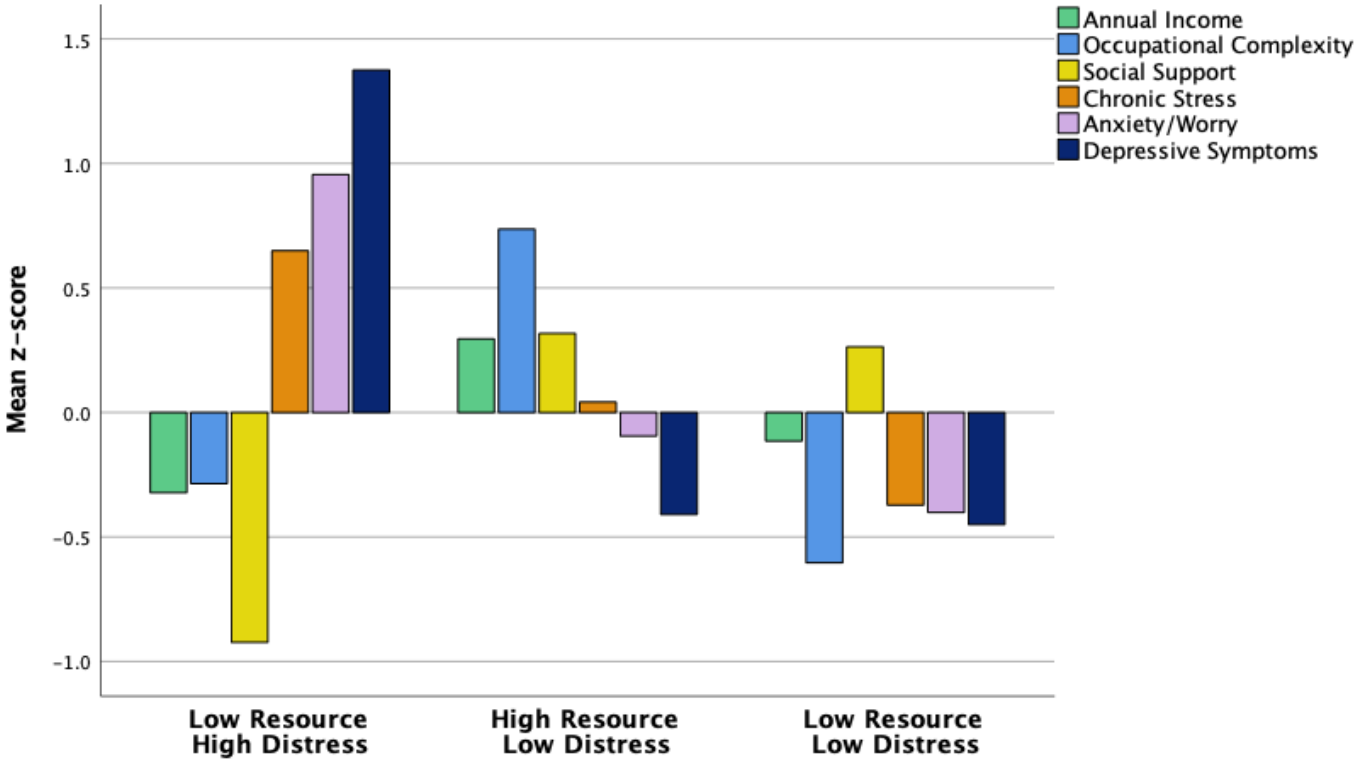
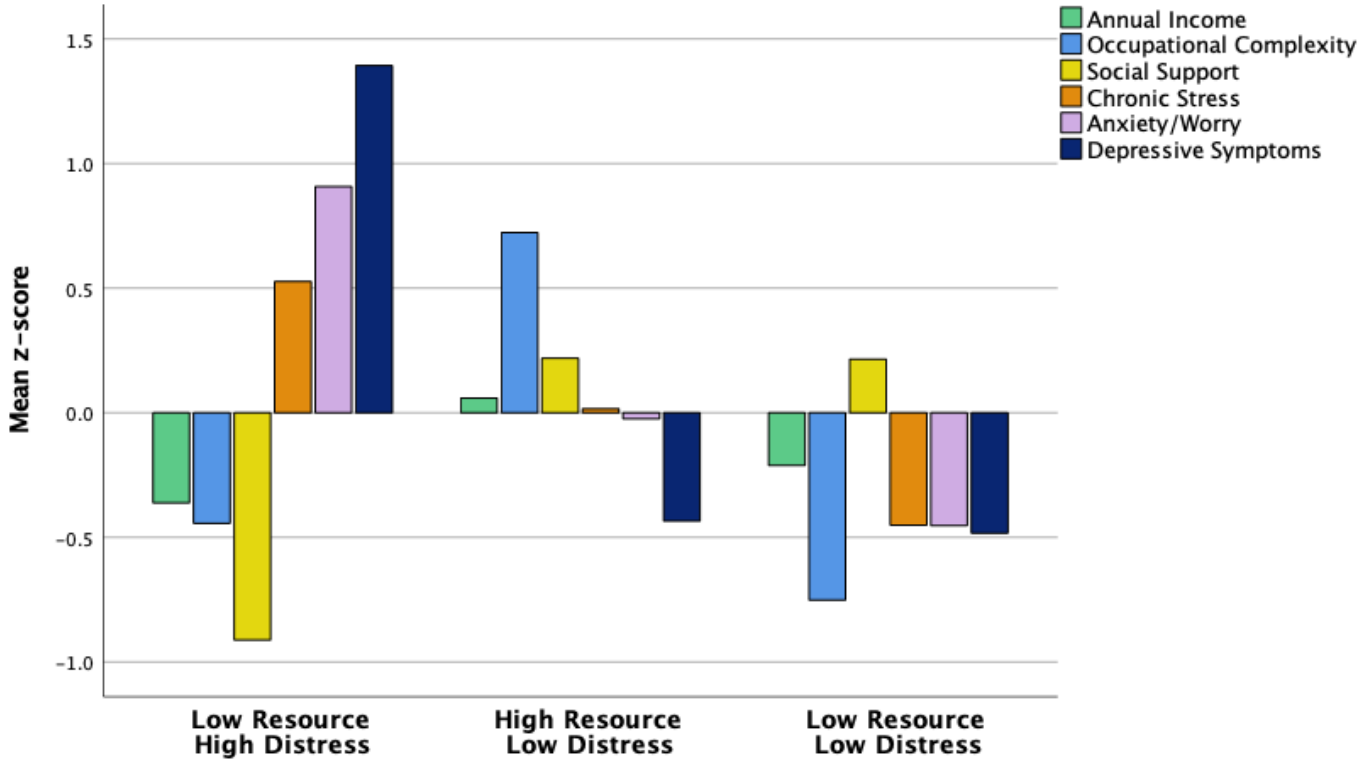

Annual Income
Occupational Complexity
Social Support
Chronic Stress
Anxiety/Worry
Depressive Symptoms
Mean z-score
1.5
1.0
0.5
0.0
-0.5
-1.0
Low Resource
High Distress
High Resource
Low Distress
Low Resource
Low Distress

Figure 2


Annual Income
Occupational Complexity
Social Support
Chronic Stress
Anxiety/Worry
Depressive Symptoms
Mean z-score
1.5
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-0.5
-1.0
Low Resource
High Distress
High Resource
Low Distress
Low Resource
Low Distress

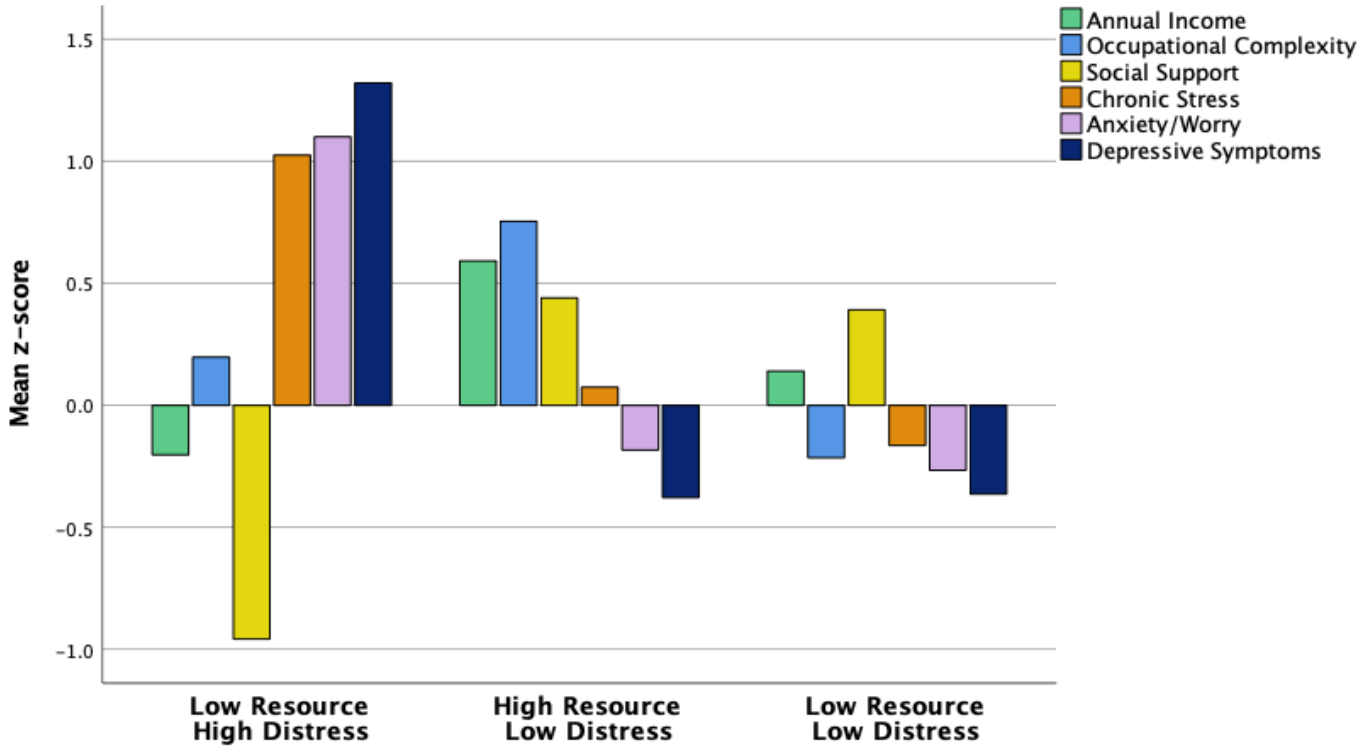

Annual Income
Occupational Complexity
Social Support
Chronic Stress
Anxiety/Worry
Depressive Symptoms
Mean z-score
1.5
1.0
0.5
0.0
-0.5
-1.0
Low Resource
High Distress
High Resource
Low Distress
Low Resource
Low Distress

Figure 3

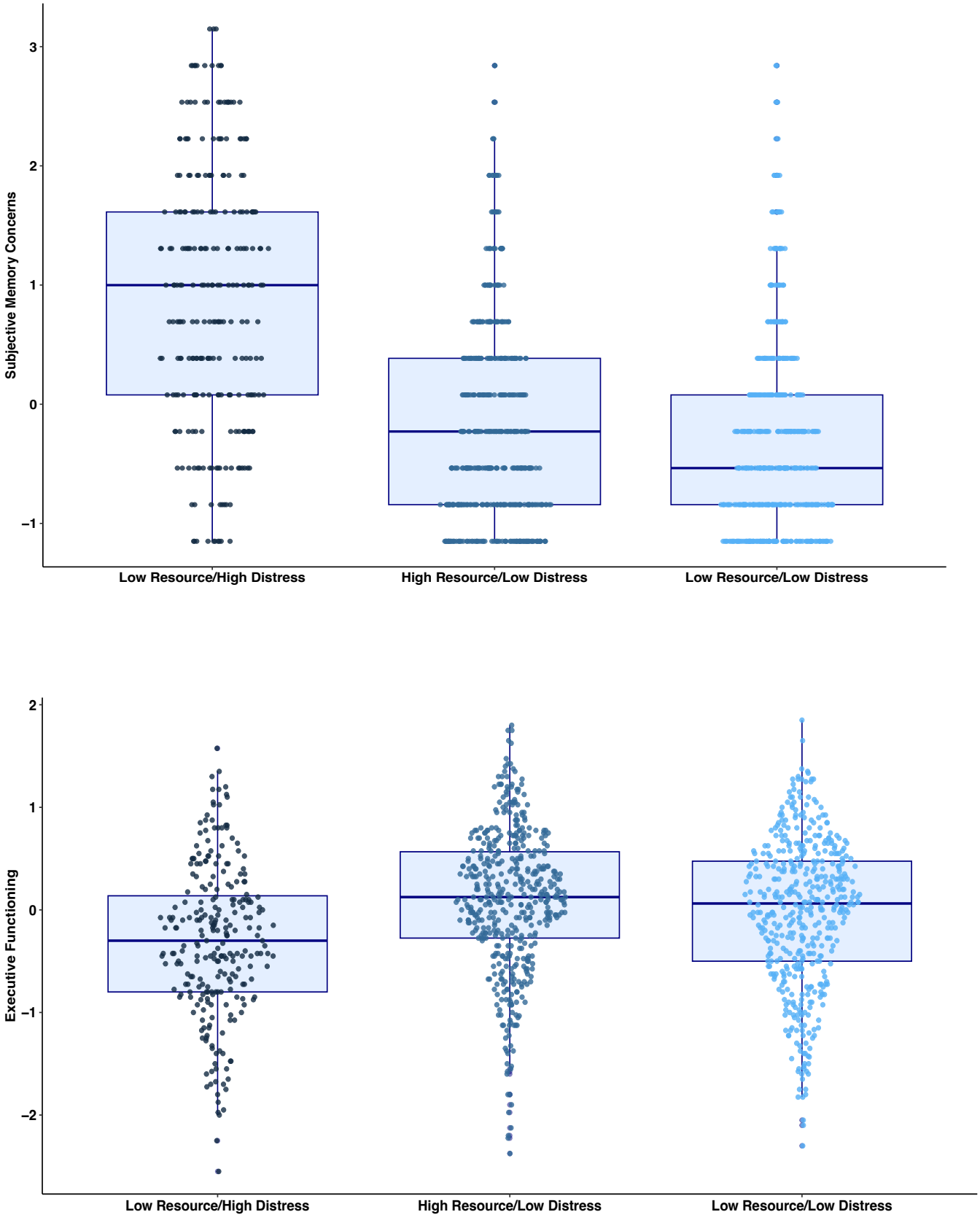
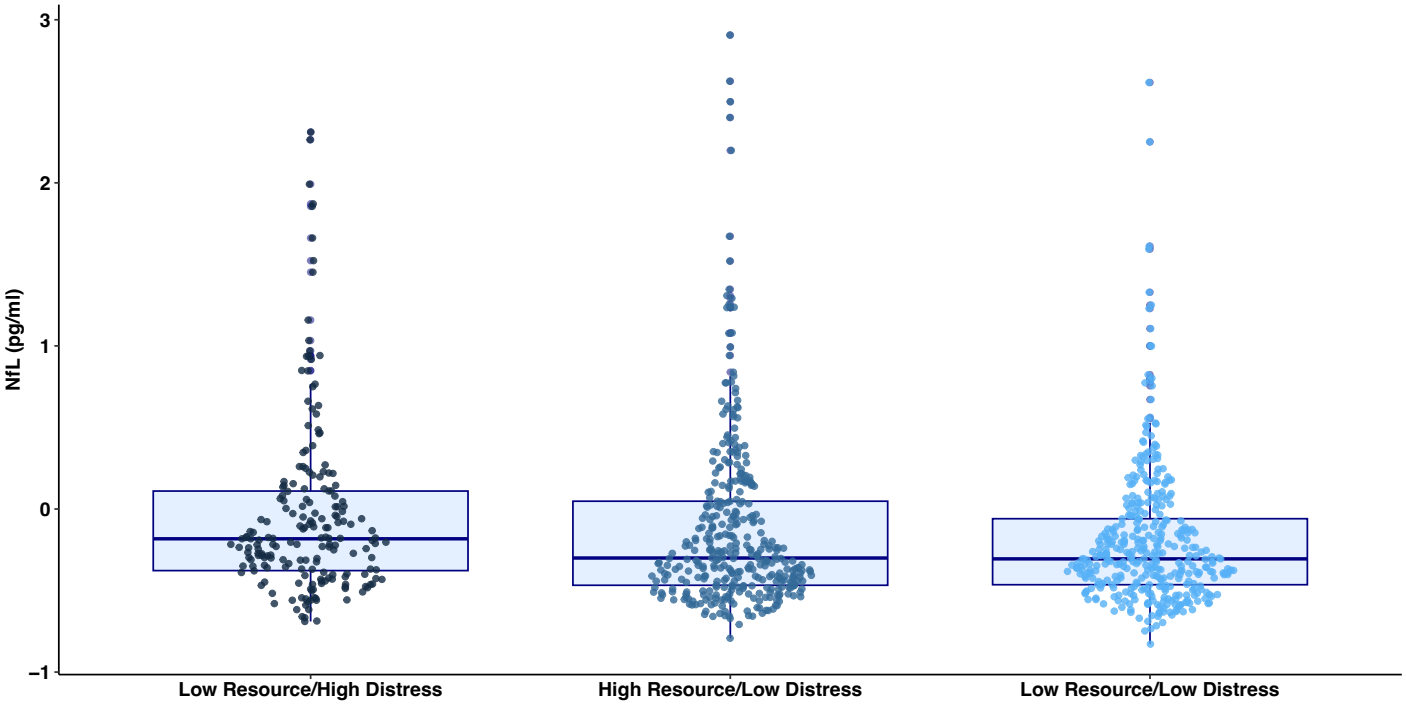

Subjective Memory Concerns
3
2
1
0
−1
Low Resource/High Distress
High Resource/Low Distress
Low Resource/Low Distress
Executive Functioning
2
1
0
−1
−2
Low Resource/High Distress
High Resource/Low Distress
Low Resource/Low Distress

Figure 4


NfL (pg/ml)
3
2
1
0
−1
Low Resource/High Distress
High Resource/Low Distress
Low Resource/Low Distress

Table

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			Pairwise comparisons		
				Test statistic	*P*-value	*Effect Size (V or eta²)*	φ1-2	φ1-3	φ2-3
Age, M(SD)	63.72 (8.02)	63.11 (7.88)	63.34 (7.30)	F= 0.53	0.60	0.001	-	-	-
Female, *n* (%)	180 (70.31)	323 (66.60)	276 (57.62)	x2= 14.27	<0.001	0.11	0.32	<0.001	0.004
Race/Ethnicity									
Latino, *n* (%)	193 (75.40)	270 (55.67)	347 (72.44)	x2= 42.14	<0.001	0.19	<0.001	0.41	<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	<0.001	0.12	<0.001	<0.001	<0.001
Spanish speaking, *n* (%)	132 (51.56)	131(27.01)	233 (48.64)	x2= 62.72	<0.001	0.23	<0.001	0.43	<0.001
MCI, *n* (%)	72 (28.13)	104 (21.44)	111 (23.17)	x2= 4.21	0.12	0.06	-	-	-
APOE e4 carrier, *n* (%)	23 (14.84)	41 (20.20)	44 (16.36)	x2= 2.02	0.36	0.06	-	-	-
Cardiometabolic Burden, M(SD)	2.66 (1.31)	2.33 (1.29)	2.43 (1.29)	F= 5.19	0.004	0.008	0.001	0.03	0.23
<u>Psychosocial Resources/ Psychiatric Functioning</u>									
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	<0.001	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	<0.001	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	<0.001	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	<0.001	0.15	<0.001	<0.001	<0.001
Anxiety/Worry Total Score, M(SD)	52.77 (13.23)	37.61 (13.79)	33.18 (10.32)	F= 212.87	<0.001	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	<0.001	0.58	<0.001	<0.001	0.32
<u>Cognition</u>									
MMSE Total Score, M(SD)	26.31 (3.30)	27.91 (2.01)	26.92 (2.56)	F= 37.44	<0.001	0.06	<0.001	0.002	<0.001
SMC (z-score), M(SD)[#]	0.89 (1.10)	-0.19 (0.83)	-0.29 (0.81)	F= 143.14	<0.001	0.19	<0.001	<0.001	0.012
Memory composite (z-score), M(SD)[#]	-0.02 (0.76)	0.14 (0.74)	0.13 (1.91)	F= 1.68	0.19	0.003	-	-	-
Executive composite (z-score), M(SD)[#]	-0.40 (0.84)	0.05 (0.74)	-0.05 (0.82)	F= 15.43	<0.001	0.025	<0.001	<0.001	0.91
<u>Plasma AD Biomarkers</u>									
$A\beta_{42}/A\beta_{40}$ ratio (z-score), M(SD)[#]	-0.07 (0.79)	0.04 (1.25)	-0.004 (0.82)	F= 0.05	0.95	<0.001	-	-	-
NfL pg/ml (z-score), M(SD)[#]	-0.04 (0.55)	-0.12 (0.54)	-0.19 (0.42)	F= 7.47	<0.001	0.016	0.91	0.003	<0.001
Total tau pg/ml (z-score), M(SD)[#]	0.14 (0.89)	-0.06 (0.82)	-0.08 (0.80)	F= 2.07	0.13	0.004	-	-	-

Note. [#]Denotes estimated marginal means reported from ANCOVA models that 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 concenrs; 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 Resource/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 $A\beta_{42}/A\beta_{40}$ 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 $A\beta_{42}/A\beta_{40}$ 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 $A\beta_{42}/A\beta_{40}$ ratio data, 93 (19%) had missing plasma NfL data, and 89 (29%) had missing plasma total tau data.

RESEARCH IN CONTEXT

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.

Interpretation: Our study identified 3 distinct psychosocial-behavioral phenotypes (Low Resource/High Distress; 2) High Resource/Low Distress (n=485); and 3) Low Resource/Low Distress) within Black and Latino older adults enrolled in HABS-HD that displayed varied cognitive and biomarker outcomes.

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.

Word Count: 130