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Patterns of Factors in the National Institute on Aging Health Disparities Research Framework Domains and Mild Cognitive Impairment Risk

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Introduction: Alzheimer's disease and related dementias are public health and social care challenges. This study used the National Institute on Aging Health Disparities Research Framework to organize potential cognitive impairment risk factors. It aimed to examine patterns of environmental, sociocultural, behavioral, and biological factors and identify key components that predict mild cognitive impairment risk.

Methods: This study comprised 2,812 participants from the Mayo Clinic Study of Aging who were cognitively unimpaired at baseline (aged ≥50 years, mean age [SD]=68.9 [9.7] years, 50.4% female). Analyses utilized a 2-stage approach using factor and principal component analyses to group factors from multiple National Institute on Aging Health Disparities Research Framework domains and identify components that predict cognitive impairment risk. Using a cohort study design, the resulting composite scores were considered as covariates for incident mild cognitive impairment analysis using Cox proportional hazards models.

Results: Three principal components explained 40.30% of the variance and were differentially associated with mild cognitive impairment risk. One component (Principal Component 2), which included factors from all 4 domains of the National Institute on Aging Health Disparities Research Framework (including social, group, and playing game activities [sociocultural domain]; exercise and physical activity [behavioral domain]; education/occupation [environmental domain]; and absence of cardiometabolic risk factors/health self-rating [biological domain]), was associated with lower mild cognitive impairment risk (hazard ratio=0.80, 95% CI=0.73, 0.89). The other 2 principal components, also including factors from multiple framework domains, were associated with increased mild cognitive impairment risk.

Conclusions: Derived principal components included factors from multiple framework domains, supporting the multietiology pathways leading to cognitive impairment. These principal components were differentially associated with mild cognitive impairment risk. Identifying key factors

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from multiple National Institute on Aging Health Disparities Research Framework domains associated with cognitive impairment risk has implications for effectively targeting interventions at multiple levels (e.g., medical, societal, policy) to avert or delay cognitive impairment risk.

INTRODUCTION

Alzheimer's disease and related dementias (ADRDs) are public health and social care challenges[1,2] with devastating consequences for the patient and a tremendous impact on the family, community, healthcare services, and economies.[2,3] ADRDs are a major cause of disability, dependency, institutionalization, and mortality, with a global cost reaching 1.3 trillion U.S. dollars worldwide in 2019, without also forgetting the stigma and social isolation an ADRD diagnosis or lack of awareness and understanding might bring or the denial of basic rights and freedoms accessible to others.[2,4,5]

Multiple factors throughout a lifetime influence ADRD risk, whereas the biological processes are initiated decades before evident clinical symptoms.[4] The Lancet Commission 2024 report summarized knowledge on the modifiable ADRD risk factors that could account for 45% of ADRD cases, highlighting the tremendous potential for preventing or delaying the disease and the additional knowledge on risk factors needed to acquire.[6]

The National Institute on Aging Health Disparities Research Framework (referred to as NIA-HD framework in the remaining parts of this paper)[7] delineates 4 domains or levels of analysis related to health disparities in aging research; environmental, sociocultural, behavioral, and biological factors work together to influence aging and disease over the lifetime.

Longitudinal studies of cognitive aging, such as the Mayo Clinic Study of Aging (MCSA),[8] have a wealth of data and provide a unique opportunity to examine ADRD risk factors in all NIA-HD framework domains, as very few studies have done for other frameworks.[9] The study used the NIA-HD framework to organize potential ADRD risk factors and aimed to examine patterns of environmental, sociocultural, behavioral, and biological factors in cognitively unimpaired (CU) at baseline MCSA participants and identify key components that predict mild cognitive impairment (MCI) risk. MCI is a critical prodromal stage in the ADRD trajectory because the person might seek help for changes in their cognitive function, although autonomous in everyday activities,[10] and is also targeted by clinical trials because it offers opportunities to intervene early in the cognitive decline trajectory and possibly alter the disease course before ample damage in the central nervous system occurs.

METHODS

Study Population

The MCSA study design and methodology were published previously in detail.[8] Briefly, MCSA is a population-based study of cognitive aging; participants were recruited using an age- and sex-stratified random sample of community-dwelling Olmsted County (MN) residents without dementia, not terminally ill, or in hospice care using the Rochester Epidemiology Project resources.[11] This study included a cohort of 2,812 CU community-dwelling participants (aged ≥50 years) with complete NIA-HD framework variable data at the MCSA baseline visit; baseline visits occurred between April 5, 2006, and March 9, 2022 (inclusive), and data were reviewed for incident MCI through March 30, 2023. The total study mean (SD) follow-up time for incident MCI, including the medical record review follow-up, was 6.7 (3.7) years.

The IRBs of the Mayo Clinic and the Olmsted Medical Center approved the study protocol, and all participants provided written informed consent before participation. In the case of participants with cognitive impairment sufficient to interfere with capacity, assent was obtained from a legally authorized representative.

Participants underwent comprehensive risk factors and cognitive evaluation at baseline and every 15 months. At each MCSA visit, a study coordinator collected sociodemographic factors and asked questions on memory and daily function, and the participants also completed the Beck Depression Inventory-II (BDI-II)[12] and Beck Anxiety Inventory (BAI).[13] A physician reviewed the participant's medical history, administered the Short Test of Mental Status,[14] and performed a neurologic examination. A psychometrist administered 9 neuropsychological tests to assess cognitive performance in 4 domains: memory, language, attention/executive, and visuospatial.[8]

The final diagnosis (CU, MCI, or dementia) was adjudicated by consensus between the study coordinator, the physician, and a neuropsychologist after reviewing each

Table 1. Cognitively Unimpaired Participants' Characteristics (Aged ≥50 Years) at MCSA Baseline

Characteristics	*n* (%) N=2,812
Age, years, mean (SD)	68.9 (9.7)
Sex, female	1,416 (50.4%)
Environmental	
Education, years, mean (SD)	14.9 (2.5)
Education—occupation score, mean (SD)	12.7 (2.5)
English as the first language	2,688 (95.6%)
Residence type, house versus all other	2,201 (78.3%)
Self-reported multivitamin intake	1,332 (47.4%)
Contact with healthcare system in the last 1 year	2,757 (98.0%)
Retired	1,744 (62.0%)
Area Deprivation Index (ATLAS)[a]	
State rank, decile, mean (SD)	4.6 (2.6)
National rank, percentile, mean (SD)	40.3 (17.5)
Primary RUCA code	
1	2,326 (82.7%)
2	455 (16.2%)
All others	31 (1.1%)
Sociocultural	
Play games, more than once per month, past 1 year[b]	2,000 (71.1%)
Social activities, more than once per month, past 1 year[b]	2,283 (81.2%)
Group activities, more than once per month, past 1 year[b]	1,054 (37.5%)
Behavioral	
Beck Anxiety Inventory, mean (SD)	2.5 (4.0)
Beck Depression Inventory-II, mean (SD)	4.4 (4.7)
Ever smoked, yes	1,257 (44.7%)
Past year, all activity score, mean (SD)[c]	7.2 (3.7)
Biological	
Health rating, excellent/very good[d]	1,789 (60.6%)
Good	820 (29.2%)
Fair/poor	203 (7.2%)
Diabetes mellitus	471 (16.7%)
Hypertension	1,672 (59.5%)
Dyslipidemia	2,140 (76.1%)
Congestive heart failure	156 (5.5%)
Atrial fibrillation	273 (9.7%)
Coronary artery disease	631 (22.5)
Stroke	69 (2.5%)
Charlson index without dementia, mean (SD)	2.7 (2.9)
Obesity (BMI ≥30)	1,061 (37.7%)
Hearing difficulties (informant reported)[e]	507 (18.0%)
Visual difficulties (informant reported)[e]	163 (5.8%)
Walking/balance difficulties (informant reported)[e]	326 (11.6%)
Apolipoprotein E ε4 carrier	780 (27.7%)

Note: Data are presented as *n* (%) unless otherwise specified. Multivitamin use is self-reported (≥3 times per week vs <3 times per week). RUCA, at present residence: 1 for metropolitan area core (primary flow within UA), 2 for metropolitan area high commuting (primary flow of 30% or more to a UA), and 3 for all others.

[a]Neighborhood Atlas (2019, version 3.1; https://www.neighborhoodatlas.medicine.wisc.edu/).

[b]Versus once a month or never: social activities include, for example, going to the theater, movies, concerts, going out with friends, travel; group activities include, for example, bible study, book club, stock club, other organized discussion groups; and play games include, for example, playing cards, crossword puzzles, other puzzles, bridge, checkers, other board games. During the past 1 year: presented in this table as binary for brevity but used as 6 categories in further analysis (i.e., once a month or never, 2–3 times per month, 1–2 times per week, 3–4 times per week, 5–6 times per week, and every day).

[c]Including both physical activity and exercise in the past year.

[d]Presented in this table as 3 categories for brevity but used as 5 categories in further analysis (i.e., excellent, very good, good, fair, and poor).

[e]Significant difficulties interfere with daily activities.

MCSA, Mayo Clinic Study of Aging; RUCA, Rural-Urban Commuting Area; UA, urbanized area.

participant's information. Evaluators were blind to any previous cognitive diagnosis. Participants who performed in the normal range and did not meet the criteria for MCI[10] or dementia[15] were classified as CU. Follow-up visits were performed at 15-month intervals using the same clinical protocol for evaluation and diagnosis as at baseline. An extensive medical record review occurs every 5 years for participants when they reach the age of 70 years and who are lost to follow-up to ascertain cognitive impairment diagnosis.

Measures

The authors used the multidimensional NIA-HD research framework[7] to categorize variables collected by MCSA into the 4 domains of the framework: environmental, sociocultural, behavioral, and biological (Tables 1 and 2). The Appendix Methods (available online) include additional details on the measures used.

Statistical Analysis

Participants' characteristics were summarized using descriptive statistics (mean, SD, count, percentage) and compared between groups using the chi-square test for categorical data and *t*-tests for continuous measures. The analysis utilized a 2-stage approach. In Stage 1, the authors used factor analysis to determine the appropriate loadings for the variables relating to the 4 domains of the NIA-HD framework. In Stage 2, the significant factors and their corresponding loadings from all domains were considered collectively as a secondary principal components analysis (PCA) of the entire framework. The resulting composite scores were considered as covariates for incident MCI and dementia analysis using Cox proportional hazards (PHs) models. Three participants were missing incident MCI/dementia outcomes and were not included in the analysis. The authors considered age (as the time scale) in all PH analyses and adjusted in models for sex. In addition, the authors examined effect modification by sex using

interaction terms (i.e., composite score × sex) in separate PH models for each composite score, but the interaction terms were not statistically significant ($p>0.05$), and further analysis was not pursued. Although the study had information on self-reported race and ethnicity, they were included only in descriptive analyses because most participants were White and non-Hispanic or Latino.

For both steps (factor and PCA), the PCA method was used utilizing initial communalities estimates of one. A scree test determined the number of factors retained in conjunction with Kaiser's Measure of Sampling

Table 2. Participants' Characteristics at MCSA Baseline by Incident MCI

	Incident MCI			
Characteristics	**No (*n*=2,404)**	**Yes (*n*=405)**	**Total (N=2,809)[a]**	***p*-value**
Age, years, mean (SD)	67.8 (9.5)	75.4 (7.5)	68.9 (9.7)	**<0.001**
Sex, female	1,210 (50.3%)	204 (50.4%)	1,414 (50.3%)	0.99
Environmental				
Education, years, mean (SD)	15.0 (2.5)	14.1 (2.5)	14.9 (2.5)	**<0.001**
Education—occupation score, mean (SD)	12.8 (2.4)	11.9 (2.5)	12.7 (2.5)	**<0.001**
English as the first language	2,292 (95.3%)	393 (97.0%)	2,685 (95.6%)	0.12
Residence type, house versus all other	1,402 (58.3%)	339 (83.7%)	1,741 (62.0%)	**<0.001**
Self-reported multivitamin intake	1,109 (46.1%)	221 (54.6%)	1,330 (47.3%)	**0.002**
Retired	1,402 (58.3%)	339 (83.7%)	1,741 (62.0%)	**<0.001**
Contact with healthcare system last year	2,353 (97.9%)	401 (99.0%)	2,754 (98.0%)	0.13
Area Deprivation Index (ATLAS)[b]				
State rank, decile, mean (SD)	4.5 (2.6)	5.1 (2.7)	4.6 (2.6)	**<0.001**
National rank, percentile, mean (SD)	39.9 (17.3)	43.1 (18.0)	40.3 (17.5)	**<0.001**
Primary RUCA code				0.52
1	1,980 (82.4%)	343 (84.7%)	2,323 (82.7%)	
2	397 (16.5%)	58 (14.3%)	455 (16.2%)	
All others	27 (1.1%)	4 (1.0%)	31 (1.1%)	
Sociocultural				
Play games, more than once per month[c]	677 (28.2%)	135 (33.3%)	812 (28.9%)	**0.034**
Social activities, more than once per month[c]	428 (17.8%)	100 (24.7%)	528 (18.8%)	**0.001**
Group activities, more than once per month[c]	1,501 (62.4%)	255 (63.0%)	1,756 (62.5%)	0.84
Behavioral				
Beck Anxiety Inventory, mean (SD)	2.5 (4.0)	3.2 (4.2)	2.5 (4.0)	**0.045**
Beck Depression Inventory-II, mean (SD)	4.2 (4.7)	5.0 (5.0)	4.4 (4.7)	**0.0013**
Ever smoked, yes	1,073 (44.6%)	183 (45.2%)	1,256 (44.7%)	0.84
Past year, all activity score, mean (SD)[d]	6.5 (4.6)	6.0 (4.7)	6.5 (4.6)	**0.026**
Biological				
Health rating, excellent/very good[e]	1,571 (65.3%)	217 (53.6%)	1,788 (63.7%)	**<0.001**
Good	672 (28.0%)	147 (36.3%)	819 (29.2%)	
Fair/poor	161 (6.7%)	41 (10.1%)	202 (7.2%)	
Diabetes mellitus	376 (15.6%)	95 (23.5%)	471 (16.8%)	**<0.001**
Hypertension	1,370 (57.0%)	299 (73.8%)	1,669 (59.4%)	**<0.001**
Dyslipidemia	1,804 (75.0%)	333 (82.2%)	2,137 (76.1%)	**0.002**
Congestive heart failure	116 (4.8%)	39 (9.6%)	155 (5.5%)	**<0.001**
Atrial fibrillation	222 (9.2%)	50 (12.3%)	272 (9.7%)	0.050
Coronary artery disease	489 (20.3%)	141 (34.8%)	630 (22.4%)	**<0.001**
Stroke	52 (2.2%)	16 (4.0%)	68 (2.4%)	**0.030**
Charlson index (without dementia), mean (SD)	2.6 (2.8)	3.6 (3.0)	2.7 (2.9)	**<0.001**
Obesity (BMI ≥30)	921 (38.3%)	139 (34.3%)	1,060 (37.7%)	0.13
Hearing difficulties[f]	405 (16.8%)	101 (24.9%)	506 (18.0%)	**<0.001**
Visual difficulties[f]	135 (5.6%)	27 (6.7%)	162 (5.8%)	0.40

(*continued on next page*)

Table 2. Participants' Characteristics at MCSA Baseline by Incident MCI (*continued*)

Characteristics	Incident MCI			
	No (*n*=2,404)	Yes (*n*=405)	Total (N=2,809)[a]	*p*-value
Walking/balance difficulties[f]	256 (10.6%)	70 (17.3%)	326 (11.6%)	**<0.001**
Apolipoprotein E ε4 carrier	623 (25.9%)	155 (38.3%)	778 (27.7%)	**<0.001**

Note: Boldface indicates statistical significance ($p<0.05$).
Data are presented as *n* (%) unless otherwise specified; chi-square test was used for categorical data, and 2-sample *t*-tests were used for continuous data. Multivitamin use is self-reported (≥3 times per week vs <3 times per week). RUCA, at present residence: 1 for metropolitan area core (primary flow within an urbanized area (UA) and 2 for metropolitan area high commuting (primary flow of 30% or more to a UA).
[a]Three participants did not have available incident MCI status (thus, *n*=2,812−3=2,809); 88 participants included had 0 follow-up for incident MCI in the no MCI column.
[b]Neighborhood Atlas (2019, version 3.1; https://www.neighborhoodatlas.medicine.wisc.edu/).
[c]Versus once a month or never: social activities include, for example, going to the theater, movies, concerts, going out with friends, travel; group activities include, for example, bible study, book club, stock club, and other organized discussion groups; and play games include, for example, playing cards, crossword puzzles, other puzzles, bridge, checkers, and other board games. During the past 1 year: presented in this table as binary for brevity but used as 6 categories in further analysis (i.e., once a month or never, 2−3 times per month, 1−2 times per week, 3−4 times per week, 5−6 times per week, and every day).
[d]Including both physical activity and exercise in the past year.
[e]Presented in this table as 3 categories for brevity but used as 5 categories in further analysis (i.e., excellent, very good, good, fair, and poor).
[f]Significant difficulties interfere with daily activities (informant reported).
MCI, mild cognitive impairment; MCSA, Mayo Clinic Study of Aging; RUCA, Rural-Urban Commuting Area; UA, urbanized area.

Adequacy for sampling adequacy, keeping parsimony in mind. These results were compared in a sensitivity analysis with a decision rule of keeping all factors with an eigenvalue >1. A varimax rotation was applied to ease the interpretability of the factors, and variables with rotated factor loadings of 0.4 or higher (absolute value) were considered when interpreting results.

The resulting composite scores were considered as covariates for incident MCI analysis using Cox PHs models. The onset of incident MCI was assigned at the midpoint between the visit at which the MCI diagnosis was made and the prior visit. Participants who progressed to dementia without an MCI diagnosis (*n*=8) at an MCSA visit were considered to have gone through an undetected MCI phase and were included as incident MCI cases again at the midpoint between the visit at which the dementia diagnosis was made and the prior visit.[16] Duration of follow-up was computed from the diagnosis of CU (MCSA baseline) to first onset of MCI or date of last follow-up for those censored without having an event.

The authors employed 2 sensitivity analyses on the basis of prior MCSA work to further minimize associations driven by cognition.[16] In the first, the authors adjusted all final models by the baseline global cognitive z-score, recognizing that even among the CU participants, the level of cognitive function potentially has a large effect on the outcome. In the second sensitivity analysis, having in mind[16] that there are individuals who are considered CU but score lower than peers and, therefore, are at higher cognitive decline risk, as others have reported, the authors excluded participants with the lowest cognitive performance (−1.5 SD or lower in the global cognitive z-score; *n*=293) at baseline and performed factor analysis and PCA to assess whether the patterns of factors and/or associations with MCI changed. Findings of the second sensitivity analysis are presented in the Appendix, and the same variables, as in the main analysis, were considered. All analyses were considered statistically significant at a $p<0.05$ and were performed using the SAS statistical software, Version 9.4 (SAS Institute, Cary, NC).

RESULTS

The participants' characteristics are presented in Table 1. The participants' mean age (SD) was 68.9 (9.7) years, with 14.9 (2.5) mean (SD) years of education, and 50.4% were female. Most participants were retired (62%), were urban dwellers (with primary RUCA Codes 1 and 2), and would participate in social activities more than once per month (81.2%) (social activities, for example going to the theater, movies, concerts, going out with friends, traveling). Almost 97.7% of participants were White, and 99.1% were non-Hispanic or Latino participants. Eighteen percent of participants had hearing difficulties, 5.8% had visual, and 11.6% had significant walking and balance difficulties that interfered with daily activities, as reported by an informant; 7.2% of participants rated their health as fair or poor.

As previously mentioned, participants needed to have complete data for the factor and PCA analysis. Participants with complete data included in the analyses (*n*=2,665) were younger (aged 68.9 [9.7] vs 75.7 [9.1] years), were a little higher on average years of education (14.9 [2.5] vs 14.3 [2.8]), were more likely to be retired,

had lower average BAI and BDI-II scores, had lower state and national Area Deprivation Index (ADI) ranking, were more likely to live in a house (versus townhome, apartment, etc.), had higher frequency of apolipoprotein E ε4 genotype and obesity at baseline, had lower Charlson comorbidity index, had lower number of cardiometabolic conditions, and were less likely to have incident MCI in the follow-up than those MCSA participants not having complete data and not included.

Four hundred and five participants in the study population developed MCI during the follow-up. Participants with incident MCI were older at baseline, had fewer years of education on average, had higher BDI-II and BAI total scores, and were less likely in general to participate in social activities than CU participants who did not develop MCI (more than once per month) (Table 2). Participants with incident MCI were more likely to be retired at baseline, had a higher frequency of multivitamin use, had hearing and walking/balance difficulties, and had higher state and national ADI ranking on average.

Factor analysis for the environmental domain revealed 3 significant factors that explained 52.5% of the variability in the data (Appendix Table 1 available online). Additional details are presented in Appendix Results (available online). Factor analysis for the sociocultural domain resulted in a single significant factor (SC1), including social activities, group activities, and playing games within the last year. This factor explained 40.4% of the variability in the data and included all eigenvalues >1. Factor analysis for the behavioral domain revealed 4 significant factors (BF1−4) that accounted for 36.1% of the variability in the data. Factor analysis for the biological domain loaded onto 2 factors (BLF1−2), accounting for 28.8% of the variability in the data.

PCA was conducted on all significant/selected factors from the factor analysis of each framework domain. The collection of 10 factors (Appendix Table 1 available online) can be reduced to 3 principal components (PCs) (PC1, PC2, and PC3), accounting for 40.3% of the total variation represented in these data (Table 3). The 3 PCs included PC1 (environment factor 3 [retired status/residence type/multivitamin use], biological factor 2 [heart diseases, Charlson index, walking/balance difficulties], and behavioral factor 3 [BDI-II questions, mainly from the somatic dimension]), PC2 (behavioral factor 4 [physical activity/exercise component], sociocultural factor [social, group, play game activities], environmental factor 2 [education/occupation], and biological factor 1 [absence of cardiometabolic risk factors/health self-rating]), and PC3 (environment factor 1 [national and state ADI ranking] and behavioral factor 1 [mainly BDI-II questions, mostly in the cognitive dimension]). A sensitivity analysis that included all factors with eigenvalues >1 revealed 5 significant factors accounting for 60.8% of the variation in the data.

Some differences were seen in factor analysis when participants with lower cognitive performance at baseline were excluded (participants characteristic are presented in Appendix Table 2), but the factor loadings into the 4 NIA-HD domains remained relatively similar (Appendix Table 3 available online). The sociocultural and the environmental factors, which included the national and state ADI rankings, loaded onto more than 1 sensitivity analysis PC (sPC) with rotated factor loadings >0.4 (absolute value) (Appendix Table 4 available online) and thus were excluded from the interpretation, as generally done with factors having higher loadings on multiple components.

The resulting composite scores from the final PCA were considered as predictors for incident MCI analysis in separate models for each factor through Cox PHs models utilizing age as the timescale. One component (PC2), which included factors from all 4 domains of the NIA-HD research framework (i.e., including social, group, and playing game activities [i.e., sociocultural domain]; exercise and physical activity [i.e., behavioral domain]; education/occupation [i.e., environmental domain]; and absence of cardiometabolic risk factors/health self-rating [i.e., biological domain]), was associated with lower MCI risk (hazard ratio [HR]=0.80, 95% CI=0.73, 0.89, $p<0.001$) (Table 4). PC1 and PC3 were associated with increased MCI risk. Adjusting for sex did not change these estimates appreciably. Next, the authors included all 3 uncorrelated PCs in the same model (Table 4), and PC estimates were minimally attenuated.

When the models were adjusted for the MCSA baseline global cognitive z-score, PC1 was associated with an increased risk for MCI, whereas the associations of the other 2 PCs with MCI lost statistical significance (Table 4).

When CU participants with the lowest at-baseline global cognitive z-scores (i.e., −1.5 SD or lower) were excluded, sensitivity analysis sPC1 (i.e., including physical activity/exercise [i.e., behavioral domain], education/occupation [i.e., environmental domain], absence of cardiometabolic risk factors/better health rating [i.e., biological domain]) was associated with lower MCI risk (HR=0.84, 95% CI=0.75, 0.94, $p=0.003$) (Appendix Table 5 available online), and sPC2 (including heart diseases, hearing and walking/balance difficulties [i.e., biological domain] and BDI-II questions, mainly from the somatic dimension [i.e., behavioral domain]) was associated with higher MCI risk (HR=1.28, 95% CI=1.14, 1.43,

Table 3. Principal Component Analysis Results

Factors	Components			Communality	Overall percentage variance explained
	PC1[a]	PC2[a]	PC3[a]		
Environment Factor 3 (retired status/residence type/multivitamin use)	**0.68763**	0.06762	−0.19014	0.52	40.3%
Biological Factor 2 (heart diseases, Charlson index, walking/balance difficulties)[b]	**0.64058**	0.07568	0.26954	0.49	
Behavioral Factor 3 (BDI-II questions, mainly from the somatic dimension)[c]	**0.55688**	-0.2887	0.14274	0.41	
Sociocultural factor (social, group, play game activities)[d]	0.27099	**0.60066**	−0.23516	0.49	
Behavioral Factor 4 (physical activity/exercise component)	0.01968	**0.59143**	−0.13575	0.37	
Environmental Factor 2 (education/occupation)	−0.07507	**0.5704**	0.13122	0.35	
Biological Factor 1 (cardiometabolic risk factors/ health self-rating)[e]	−0.35852	**0.56496**	0.08181	0.45	
Environment Factor 1 (national and state ADI ranking)	0.13795	0.02591	**0.72927**	0.55	
Behavioral Factor 1 (mainly BDI-II questions, mostly in the cognitive dimension)[f]	−0.21191	−0.01885	**0.55444**	0.35	
Behavioral Factor 2 (BAI component)[g]	0.10487	−0.04434	0.19371	0.05	

[a]Rotated factor loadings.
[b]Coronary artery disease (myocardial infarction, ischemic heart disease), congestive heart failure, atrial fibrillation, Charlson comorbidity index (without dementia), and walk/balance difficulties (informant reported).
[c]Tiredness or fatigue (BDI), concentration difficulty (BDI), loss of interest in sex (BDI), changes in sleeping patterns (BDI-II), and changes in appetite (BDI).
[d]Social activities: for example, going to the theater, movies, concerts, going out with friends, travel. Group activities: for example, bible study, book club, stock club, and other organized discussion groups. Play games: for example, playing cards, crossword puzzles, other puzzles, bridge, checkers, and other board games, past 1 year.
[e]Absence of diabetes mellitus, hypertension, dyslipidemia, obese BMI ≥30. Health self-rate: *Overall, would you say your health is*.
[f]Self-dislike (BDI-II), self-criticalness (BDI-II), worthlessness (BDI-II), pessimism (BDI-II), sadness (BDI-II), past failure (BDI-II), guilty feelings (BDI-II), indecisiveness (BDI-II), fear of the worst happening (BAI), loss of interest (BDI-II), irritability (BDI-II), punishment feelings (BDI-II), agitation (BDI-II), fear of losing control (BAI), and crying (BDI-II).
[g]Shaky (BAI), dizzy or lightheaded (BAI), feeling hot (BAI), heart pounding or racing (BAI), sweating not due to heat (BAI), face flushed (BAI), wobbliness in legs (BAI), hands trembling (BAI), terrified (BAI), faint (BAI), indigestion or discomfort in abdomen (BAI), unable to relax (BAI), scared (BAI), feelings of choking (BAI), and numbness or tingling (BAI).
ADI, Area Deprivation Index; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; PC, principal component. Boldface indicates the factors included in each component.

$p<0.001$). sPC3 (including retirement status, residence type, multivitamin use [i.e., environmental domain] and mainly BDI-II questions in the cognitive dimension [i.e., behavioral domain]) was not associated with MCI risk. sPC estimates changed minimally when included together in the same model.

DISCUSSION

The study evaluated the grouping of factors in the 4 NIA-HD research framework domains and examined their association with MCI risk. Derived PCs included factors from multiple framework domains, supporting the multietiology pathways leading to cognitive impairment. These PCs were differentially associated with MCI risk, with PC1 and PC3 associated with higher risk and PC2 associated with lower risk. Most factors included in the 3 PCs have been important determinants of late-life cognitive impairment.

In the main analysis, PC2 was associated with reduced MCI risk, including activities that benefit cognition, such as social activities, group activities, and playing games in the past year.[17,18] A recent meta-analysis suggested that good social connections were associated with slower cognitive decline, and the WHO suggests that social connections are an important determinant of brain health optimization.[19,20] In the same component, there was a factor that included education and the education/occupation score. Higher levels of education and higher education/occupation scores have been associated with higher cognitive performance and lower dementia risk.[17,21,22] In addition, consistent research supports the beneficial effect of physical activity on brain health throughout life, included in PC2.[23,24] Additional factors in PC2 included the absence of cardiometabolic risk factors and self-rated health; better cardiometabolic risk factors and better self-rated health are also known to be associated with better health (including cognitive)

Table 4. Association Between PCA Components and Incident MCI Risk

Parameters	*n*/events	HR[a]	95% CI	*p*-value
Outcome: Incident MCI				
Separate models built for each PC				
PC1 [1]	2,721[b]/405	1.29	1.16, 1.44	**<0.001**
PC2 [2]	2,721/405	0.80	0.73, 0.89	**<0.001**
PC3 [3]	2,721/405	1.19	1.08, 1.32	**<0.001**
PCs simultaneously included in 1 model				
PC1 [1]	2,721/405	1.31	1.174, 1.45	**<0.001**
PC2 [2]		0.78	0.71, 0.86	**<0.001**
PC3 [3]		1.17	1.05, 1.29	**0.003**
Sensitivity analysis				
(adjusted also for baseline global cognitive z-score)				
Separate models built for each PC				
PC1 [1]	2,595[c]/384	1.20	1.08, 1.35	**0.001**
PC2 [2]	2,595/384	1.01	0.91, 1.12	**0.852**
PC3 [3]	2,595/384	1.10	0.99, 1.24	0.069
PCs simultaneously included in 1 model				
PC1 [1]	2,595/384	1.20	1.07, 1.35	**0.001**
PC2 [2]		0.97	0.87, 1.07	0.525
PC3 [3]		1.08	0.97, 1.20	0.161

Note: Boldface indicates statistical significance ($p<0.05$).
PC1: Environment Factor 3 (residence/retired/multivitamin use) + Biological Factor 2 (heart disease, comorbidities, walking/balance difficulties) + Behavioral Factor 3 (BDI, mostly somatic dimension: tiredness or fatigue [BDI-II], concentration difficulty [BDI-II], loss of interest in sex [BDI-II], changes in sleeping pattern [BDI-II], and changes in appetite [BDI-II]). PC2: sociocultural component (social activities: e.g., going to the theater, movies, concerts, going out with friends, travel.; group activities: e.g., bible study, book club, stock club, and other organized discussion groups; and play games: e.g., playing cards, crossword puzzles, other puzzles, bridge, checkers, and other board games) + Behavioral Factor 4 (exercise component) + Environmental Factor 2 (education—occupation) + Biological Factor 1 (absence of diabetes mellitus, hypertension, dyslipidemia, obesity (BMI ≥30; overall health rating). PC3: Environmental Factor 1 (state and national ADI ranking + Behavioral Factor 1 [mainly BDI, primarily cognitive dimension: self-dislike [BDI-II], self-criticalness [BDI-II], worthlessness [BDI-II], pessimism [BDI-II], sadness [BDI-II], sadness [BDI-II], past failure [BDI-II], guilty feelings [BDI-II], indecisiveness [BDI-II], fear of the worst happening [BAI-II], loss of interest [BDI-II], irritability [BDI-II], punishment feelings [BDI-II], agitation [BDI-II], fear of losing control [BAI], and crying [BDI-II]).
[a]Cox proportional hazards models utilizing age as the timescale, adjusted for sex.
[b]Two participants did not have available incident MCI status, and 89 had 0 follow-up for MCI; thus, n=2,721.
[c]A total of 126 participants did not have available global cognitive z-score.
ADI, Area Deprivation Index; BDI, Beck Depression Inventory; HR, hazard ratio; MCI, mild cognitive impairment; PC, principal component; PCA, principal component analysis.

outcomes.[6,25–27] On the other hand, several of the factors included in PC1 and PC3 are known cognitive impairment risk factors, such as depression, coronary artery disease, atrial fibrillation, congestive heart failure, and neighborhood socioeconomic deprivation.[6,25,28,29]

It is important to note that all PCs in the overall population and most PCs in the sensitivity analysis included factors from more than 1 framework domain. The study included a wide range of factors in the 4 domains of the NIA-HD research framework that need to be considered in aging-related health disparities research.[7] The multilevel factors included in the framework extend from the macro level (e.g., environmental) to the micro level (the individual).[30] Such a multidimensional approach is critical. Health disparities interventions often ignore the physical and social environments; however, eliminating health disparities requires multilevel interventions simultaneously or in close succession.[31] The increasing aging population and the projected growth of ADRD cases will majorly affect health and social care, presenting a public health challenge unless mitigated by multilevel effective medical, social, and systems interventions[23] instead of only targeting individuals. Cognitive changes associated with beneficial neighborhood characteristics (e.g., enriched neighborhood resources) may appear smaller than changes related to individual health behaviors; however, implementing neighborhood changes might be easier than altering individual health behaviors in resource-deprived environments.[32] Lifestyles are not always freely chosen but could be molded fundamentally by people's economic and social environments.[33]

Study findings also make it possible to see which factors are the most influential in the respective components. Such findings could be important for prioritizing interventions at the individual and community levels. For example, the factors in PC3 suggest that Environmental Factor 1 (national and state ADI ranking) is the

more influential factor in this PC.[34,35] ADRD disproportionately affects those residing in socioeconomically disadvantaged neighborhoods,[28,29,35–37] even after controlling for individual-level SES.[38] ADI,[35] an estimate of neighborhood socioeconomic deprivation, integrates indicators of employment, poverty, education, and housing, which are social determinants of health (SDoH) measures. The WHO[39] broadly defined SDoH as "the non-medical factors that influence health outcomes, such as the conditions in which individuals are born in, work, play, age, as well as the wider set of forces and systems shaping the conditions of daily life." SDoH influence health disparities, accounting for up to 30%–55% of health outcomes, with lower socioeconomic conditions related to worse health.[39] A complex interplay between social, political, and physical environments and human behavior influences brain health, ADRD risk factors, and outcomes.[40] The continued assessment of non-pharmacological pathways[41] for cognitive impairment later in life could provide additional avenues for prevention and/or postponement of disease, especially given the currently limited treatment options. Estimates project that delaying Alzheimer's disease by 5 years would result in 41% lower prevalence and 40% lower cost of Alzheimer's disease in 2050.[42]

Research examining all domains of a framework is limited. In a recent study by Clay et al.,[9] using data from the ACTIVE trial, employed a single PCA to reproduce the SDoH domains in the *Healthy People 2030* framework; higher domain scores were cross-sectionally associated with better cognitive function and health-related quality of life. However, studies often examine single exposures and disparities, and research does not necessarily focus on the different NIA-HD framework domains to the same extent.[30]

Because some associations could be driven by cognition, the authors performed 2 sensitivity analyses. In the first sensitivity analysis, adjusting for cognitive performance at the MCSA baseline resulted in the attenuation of PC2 and PC3 associations with MCI risk, whereas the PC1 association with MCI was better preserved, suggesting that cognitive performance could be responsible for some of the variability related to health behaviors and characteristics. The second sensitivity analysis, excluding participants with the lowest cognitive performance at baseline, resulted in similar but not the same multilevel PCs. The sociocultural and environmental factors that included the national and state ADI rankings were not included in the derived PCs because each one of these factors loaded onto more than 1 PC with an absolute value >0.4; thus, they were excluded from the interpretation, as generally done with factors having higher loadings on multiple components. PCA is used to reduce dimensionality and simplify the data, but cross-loading items (such as the sociocultural factor and environmental factor 1) make interpretation more difficult. Another approach to dealing with such situations would be to drop these variables and rerun the analysis. However, because this was a sensitivity analysis, the authors did not pursue this option. Nevertheless, research suggests that people who live in poverty but are in more affluent neighborhoods could have better health outcomes than those living in poverty and most disadvantaged neighborhoods.[35]

Findings underscore the complexity of these associations and the need for further research beyond this study's aims and emphasize how multifactorial/multilevel cognitive impairment risk is and that a life course approach, with studies including more measures in earlier life epochs (e.g., childhood, early adulthood), would help to further clarify these factor patterns and associations. The study also provides the stimulus to identify and target high-risk individuals with multiple risk factors for cognitive impairment at multiple exposure levels (individual, neighborhood, etc.) for health promotion and preventive interventions. It should also be noted that there is considerable underdiagnosis of cognitive impairment in older adults (on average, only about 8% of the expected MCI cases were diagnosed on the basis of Medicare administrative data), especially in socioeconomically disadvantaged groups.[43,44] An estimated 13.8 million persons in the U.S. have MCI (due to any cause), which will continue to grow with the aging population[45]; thus, realistically, community interventions would target older individuals with diverse cognitive functioning, including persons with undiagnosed cognitive impairment.

The study has significant strengths. The MCSA is a well-characterized cohort with serial comprehensive cognitive evaluations for incident cognitive impairment. The evaluations followed the same protocol in all visits and were blind to any previous clinical diagnosis. The study used multiple measures in 4 framework domains gathered by MCSA and external sources, and the evaluators were blind to most of these measurements.

Limitations

The study should also be considered in light of its limitations that limit generalizability. The study included only participants with complete data (as required by the methodology used), and participants included in this study had differences in characteristics (e.g., better comorbidities profile) compared with those not included in the analysis; thus, additional investigations in populations with variable characteristics are necessary. Study participants were 97.7% White and 99.1% non-Hispanic

or Latino. Investigations in racially and ethnically diverse populations are warranted. Although the authors used their best judgment in choosing the variables and the domain they represent, this selection was limited by the available data. Self-selection bias (e.g., neighborhood, residency type) and reverse causation could have biased the observed associations because the authors assessed later life outcomes.[46] Studies that include more measures in earlier life are desired and would help to further clarify these associations with cognitive impairment.

CONCLUSIONS

Study findings suggest that 3 PCs, which included factors from multiple NIA-HD framework domains, support the multietiology pathways leading to cognitive impairment and that PCs were differentially associated with cognitive impairment risk. PC1 and PC3 were associated with increased MCI risk, and PC2 was associated with decreased MCI risk. Studying a wide range of factors in the NIA-HD research framework domains is crucial for capturing multifactorial contributors to cognitive impairment risk and providing the knowledge to support effective health promotion and preventive interventions at multiple levels (e.g., medical, societal, or policy) to avert or delay cognitive impairment risk.

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SUPPLEMENTARY MATERIALS

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