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Metabolic Risk Factors as Differential Predictors of Profiles of Neurocognitive Impairment Among Older HIV+ and HIV- Adults: An Observational Study

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Metabolic Risk Factors as Differential Predictors of Profiles of Neurocognitive Impairment Among Older HIV+ and HIV- Adults --Manuscript Draft--

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Abstract:	<p>Objective: Neurocognitive (NC) performance among older persons, including those living with HIV (PLWH), exhibits significant heterogeneity, suggesting subpopulations with differing profiles of NC impairment (NCI). Metabolic factors are associated with NCI, but their relationships to profiles of NCI are unknown.</p> <p>Methods: Participants (144 PLWH, 102 HIV-uninfected) aged 50+ years completed a standard neuropsychological battery assessing seven cognitive domains. Latent class analysis (LCA) was used to identify NCI profiles, which were examined against the Montreal Cognitive Assessment (MoCA). Multinomial regression was used to identify metabolic factors associated with classification.</p> <p>Results: LCA identified three subgroups of NCI regardless of HIV status: Class 1 Multidomain NCI (high probability of impairment across multiple cognitive domains), Class 2 Learning & Recall NCI (high probability of impairment in learning and recall), and Class 3 NC Unimpaired (low probability of NCI across all domains). PLWH were more likely to be classified as Class 1 Multidomain NCI ($p < 0.05$). Relative to those in Class 3 NC Unimpaired, individuals in Class 1 Multidomain NCI and Class 2 Learning</p>

	<p>& Recall NCI had lower MoCA scores ($p < 0.05$). Among PLWH, those with dyslipidemia, central obesity, or hypertension had greater odds of classification in Class 1Multidomain NCI than in Class 3NC Unimpaired ($p < 0.05$). Regardless of HIV status, those with diabetes were more likely to be in Class 1Multidomain NCI. Conclusions: Similar profiles of impairment among PLWH and HIV-uninfected individuals suggests common mechanistic pathways to NCI. Metabolic risk factors confer heightened risk of multidomain NCI in HIV infection. Interventions to reduce metabolic risk factors may improve NC outcomes among PLWH.</p>	
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Willem J. Kop, Ph.D.
Editor-in-Chief
Psychosomatic Medicine

06/22/18

Dear Dr. Kop,

Please find our enclosed manuscript, titled “Metabolic Risk Factors as Differential Predictors of Profiles of Neurocognitive Impairment Among Older HIV+ and HIV- Adults”, which we would like to submit for publication as an original article in *Psychosomatic Medicine*. In this study, latent class analysis was used to identify profiles of neurocognitive impairment (NCI) among older persons living with HIV (PLWH) and HIV-uninfected adults. Furthermore, metabolic risk factors were examined as predictors of these profiles of NCI. We identified three patterns of NCI and PLWH were more likely to be classified as having extensive global NCI. Additionally, among PLWH, those with metabolic risk factors (dyslipidemia, central obesity, and hypertension) had greater odds of classification in this class characterized by extensive NCI. Lastly, regardless of HIV status, individuals with diabetes were also more likely to have extensive NCI.

This study is novel as little research has examined profiles and predictors of NCI among older adults, with comparisons by HIV-serostatus. Our work has implications for understanding factors associated with variability in cognition among older adults in the context of HIV infection and in the presence of cardio-metabolic conditions. We believe our findings are relevant to the discourse on cognitive change in older adulthood and that this work is of interest to the readers of *Psychosomatic Medicine*.

We confirm that this manuscript has not been published elsewhere and is not under consideration at any other journal. Additionally, all authors reviewed, approved this manuscript, and agree with submission to *Psychosomatic Medicine*. This study was funded with support from the NIH/NIMH. All study participants provided written informed consent and the study was approved by the University of California, San Diego’s institutional review board.

Sincerely,
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Metabolic Risk Factors as Differential Predictors of Profiles of Neurocognitive Impairment
Among Older HIV+ and HIV- Adults

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Running title: Metabolic Risk and Neurocognitive Impairment

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ABSTRACT

Objective: Neurocognitive (NC) performance among older persons, including those living with HIV (PLWH), exhibits significant heterogeneity, suggesting subpopulations with differing profiles of NC impairment (NCI). Metabolic factors are associated with NCI, but their relationships to profiles of NCI are unknown.

Methods: Participants (144 PLWH, 102 HIV-uninfected) aged 50+ years completed a standard neuropsychological battery assessing seven cognitive domains. Latent class analysis (LCA) was used to identify NCI profiles, which were examined against the Montreal Cognitive Assessment (MoCA). Multinomial regression was used to identify metabolic factors associated with classification.

Results: LCA identified three subgroups of NCI regardless of HIV status: Class 1_{Multidomain NCI} (high probability of impairment across multiple cognitive domains), Class 2_{Learning & Recall NCI} (high probability of impairment in learning and recall), and Class 3_{NC Unimpaired} (low probability of NCI across all domains). PLWH were more likely to be classified as Class 1_{Multidomain NCI} ($p < 0.05$). Relative to those in Class 3_{NC Unimpaired}, individuals in Class 1_{Multidomain NCI} and Class 2_{Learning & Recall NCI} had lower MoCA scores ($ps < 0.05$). Among PLWH, those with dyslipidemia, central obesity, or hypertension had greater odds of classification in Class 1_{Multidomain NCI} than in Class 3_{NC Unimpaired} ($ps < 0.05$). Regardless of HIV status, those with diabetes were more likely to be in Class 1_{Multidomain NCI}.

Conclusions: Similar profiles of impairment among PLWH and HIV-uninfected individuals suggests common mechanistic pathways to NCI. Metabolic risk factors confer heightened risk of multidomain NCI in HIV infection. Interventions to reduce metabolic risk factors may improve NC outcomes among PLWH.

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(250 words)

Keywords: HIV, neurocognitive impairment, metabolic syndrome, latent class analysis

HIV= human immunodeficiency virus, NC= neurocognitive, NCI= neurocognitive impairment,

PLWH= people living with HIV, MetS= metabolic syndrome, MoCA= Montreal Cognitive

Assessment, LCA= latent class analysis

INTRODUCTION

Despite the advent of combination antiretroviral therapy (cART), neurocognitive impairment (NCI) remains common among people living with HIV (PLWH). NCI among PLWH, also termed HIV-associated neurocognitive disorder (HAND), continues to be observed in up to half of PLWH in the cART era (1, 2). The neurocognitive profile of HAND reflects considerable interindividual variability, with a wide range of performance in terms of severity and patterns of domain-specific cognitive dysfunction (3). Although impairments in learning and executive functioning tend to be most prevalent in the cART era, many PLWH are also impaired in delayed recall, motor functioning, speed of information processing, and verbal fluency domains (2). Thus, NCI among PLWH exhibits significant heterogeneity, and this variability in cognitive performance suggests that subpopulations of PLWH may differ in risk factors and mechanisms contributing to NCI.

NCI among PLWH may be mediated by a variety of neuropathological processes including chronic inflammation, incomplete HIV suppression in the central nervous system, neurotoxicity of antiretroviral drugs, and legacy effects following severe immunosuppression (i.e., nadir CD4 levels < 200) (4-7). Additionally, with significant reductions in morbidity and mortality on cART, PLWH have improved longevity and are now experiencing age-related declines in cognition that are associated with neurodegenerative (such as Alzheimer's and Parkinson's) and cerebrovascular diseases (8-10).

Multiple studies implicate metabolic syndrome (MetS), a constellation of related conditions (i.e., central obesity, hyperglycemia, dyslipidemia, and hypertension), with worse neurocognitive performance in PLWH, similar to the effects of MetS in the general population (10-13). However, older PLWH are at greater risk for developing metabolic conditions,

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compared to age- and sex-matched controls (14-16). Thus, MetS may promote neuronal injury and could account for the higher risk of neurocognitive deficits among older PLWH (17). This notion of MetS-associated neurocognitive vulnerability among PLWH is supported by studies that have demonstrated that components of MetS heighten the risk for HAND and correlate with imaging markers of neurochemical abnormalities and neuroinflammation among older PLWH (11, 12, 18-20).

Given variability in neurocognitive performance among PLWH and older adults, as well as individual differences in the presence of comorbidities that may impact neurocognitive performance, identifying neurocognitive profiles and their predictors is an important area of research. One approach that has been used to identify subgroups of individuals with similar patterns of neurocognitive performance is latent class analysis (LCA). LCA is an analytic method allowing the characterization of categorical unobserved (latent) variables from analyses of the structure of relationships among several observed variables. LCA has been utilized to uncover latent classes associated with Alzheimer's and Parkinson's diseases (21-23). Although metabolic factors have been associated with NCI among PLWH and HIV-uninfected individuals, the relationship of metabolic risk factors to profiles of NCI and their differential contributions to NCI by HIV serostatus have not been examined. Thus, this project aimed to 1) determine profiles of NCI among PLWH and HIV-uninfected older adults using LCA and 2) compare the effect of HIV-infection on the relationship between metabolic syndrome risk factors and profiles of NCI. We hypothesized that LCA would identify subgroups of PLWH and HIV-uninfected individuals that differ in profiles of NCI and that metabolic risk factors would have greater negative effects on cognition among PLWH. Specifically, we hypothesized that among PLWH, metabolic risk

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factors would be associated with higher odds of classification in subgroups characterized by more extensive NCI.

METHODS

Participants

Data from 266 participants were selected from two HNRP-based studies of HIV and aging (*Successfully Aging Seniors with HIV* and *Multi-Dimensional Successful Aging Among HIV-Infected Adults*) at the University of California, San Diego. To enroll in these studies, participants had to be English-speaking and possessing the capacity to provide informed consent; an additional inclusion criterion for our analyses was age 50 years or older. Candidates were excluded if they had a history of conditions that might confound analyses, such as head injury with loss of consciousness for longer than 30 minutes, neurological disease with neurological or neuropsychiatric sequelae (e.g., stroke and seizure disorders), psychotic disorder, non-HIV degenerative brain diseases (e.g., diagnosis of dementia due to a condition other than HIV), or a severe learning disability (e.g., Wide Range Achievement Test Reading score <70).

Measures

Neurocognitive Functioning

Participants completed a comprehensive neurocognitive test battery covering seven ability domains (verbal fluency, executive functioning, speed of information processing, verbal and visual learning, verbal and visual delayed recall/memory, working memory, and motor

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skills) (24). Following established procedures, Domain Deficit Scores (DDS) were computed from conversions of T-scores, demographically-corrected for the effects of age, education, sex and ethnicity (1, 25). Previous studies have shown a balance of sensitivity and specificity in identifying NCI using DDS cutoffs of > 0.5 (25); thus, participants were classified with NCI vs. no NCI in each of the seven domains using this DDS threshold. Additionally, deficit scores were averaged across all tests in the battery to create a Global Deficit Score (GDS) for each individual which was similarly dichotomized into ratings of impairment ($GDS \geq 0.5$) vs. no impairment ($GDS < 0.5$) (25, 26).

Metabolic Comorbidities

Metabolic risk factors (i.e., dyslipidemia (elevated triglycerides and/or low HDL), central obesity (i.e., large waist circumference), diabetes, and hypertension) were determined from a combination of self-report (e.g., history of diabetes and/or hypertension) and objective laboratory (i.e., phlebotomy and anthropomorphic) assessments. Metabolic risk factors examined were consistent with the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for metabolic risk (27, 28). The NCEP ATP III panel defines metabolic risk as 1) large waist circumference (> 102 cm [40 in] for men, 88 cm [35 in] for women), 2) elevated triglycerides (≥ 150 mg/dl) or prescription, 3) low HDL cholesterol (< 40 mg/dl in men, < 50 mg/dl in women) or prescription, 4) hypertension (> 130 mmHg systolic or > 85 mmHg diastolic) or prescription, and 5) elevated fasting glucose (≥ 100 mg/dl) or prescription. Thus, if participants reported receiving a prior medical diagnosis, reported prescription of drug treatment for a condition, or if they had laboratory measurements for any of the conditions at or above NCEP ATP III thresholds, they were considered positive for that metabolic risk factor. Finally, to obtain

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a diagnosis of MetS, indicators of MetS were summed into a composite variable, which ranged from 0 to 5, and an NCEP ATP III diagnosis of MetS applied if they had 3 or more of the factors.

Alternative Measure of Cognitive Functioning

In addition to completing the standard neuropsychological battery, participants were also assessed using the Montreal Cognitive Assessment (MoCA), a well-validated neurocognitive screener for clinical geriatric populations (29).

Potential Covariates

In addition to demographics, the following variables that have previously been associated with neurocognitive performance or MetS were considered as potential covariates affecting latent classification:

Premorbid Functioning

All participants completed the reading subtest of the Wide Range Achievement Test-IV (WRAT-IV-Reading) (30). Single-word reading tests, such as the WRAT-IV, are common performance-based tools for estimating premorbid verbal IQ and the WRAT-IV has shown strong test-retest reliability as a measure of premorbid functioning (31, 32)

Psychiatric, Behavioral, and Medical Conditions

The presence/absence of lifetime mood (e.g., major depressive disorder) and substance use disorders (e.g., alcohol use disorder) were evaluated with the Composite International

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Diagnostic Interview (CIDI v.2.1), using diagnostic criteria based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (33).

Hepatitis C and Tobacco Smoking

Hepatitis-C (HCV) infection was diagnosed by enzyme-linked immunosorbent assay and lifetime smoking was obtained by participant self-report of tobacco smoking.

HIV Disease and Treatment Characteristics.

For PLWH, disease and treatment characteristics were collected by participant self-report and laboratory assessment. In particular, PLWH provided information about their estimated duration of HIV infection, length on current and previous ART regimens, and nadir CD4+ T-cell counts. Blood was also collected and clinical assays (e.g., complete blood count) performed by a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory at the UCSD Medical Center. Current CD4+ T-cell count was measured by flow cytometry and HIV RNA levels in blood were measured by reverse transcriptase-polymerase chain reaction with a lower limit of quantitation (LLQ) at 50 viral copies/mL.

Data Analysis

LCA was used to estimate the number of classes that best-captured similar patterns of DDS across the seven domains of neurocognitive performance. To determine the number of categorical latent classes underlying the observed patterns, several models with increasing numbers of latent classes were estimated. The best-fitting model was selected based on four indices: the Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC), entropy,

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and the bootstrapped likelihood ratio test (BLRT). For each model with k number of classes, the best log-likelihood was replicated in order to avoid convergence at a local maximum.

Additionally, in log-likelihood ratio tests to examine model fit, the log-likelihood for the null model with $k-1$ classes was verified as being equal to the best log-likelihood value of the previously-tested model with one fewer class (34).

Once the optimum number of classes was identified, the final LCA model was adjusted for relevant covariates (i.e., any of the previously-described potential covariates that were correlated with latent classes at $p < 0.10$). Convergent validity of these covariate-adjusted classes was examined by comparisons of the means of scores on the MoCA across each of the identified latent classes using Wald χ^2 -tests; corrections for Type I errors in multiple comparisons were made using the Benjamini-Hochberg procedure (35). The extent to which HIV infection moderated the association between metabolic disease characteristics and group membership in the identified latent classes was determined using multinomial regression.

In all regressions and Wald tests, a “3-step” approach, in which class membership was assigned using observed DDS categorizations and relevant covariates prior to the inclusion in the model of outcome or predictors variables was used in order to prevent these auxiliary factors from altering the structure of latent classes and influencing final class membership (36, 37). All LCA analyses were conducted using Mplus version 7.4 using robust maximum likelihood estimation (MLR) that is robust to missing data and non-normal distributions of outcomes (38).

RESULTS

Prevalence of demographic and metabolic risk factors

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By the combined self-report and/or NCEP ATP III criteria, 162 (65.9%) participants had hypertension, 91 (37%) had central obesity, 173 (70.3%) had dyslipidemia, 42 (17.1%) had diabetes, and 93 (37.8%) had MetS. Of these, 46.3% of participants who were categorized as hypertensive reported prescription of antihypertensive medication, 69.0% of those categorized as having diabetes reported prescription of diabetes medication, and 48.6% of those with dyslipidemia were on lipid-lowering medication. With regards to demographics, participants were on average 57.96 years old ($SD= 6.10$ years), with 14.43 years of education ($SD= 2.55$ years), and were predominantly non-Hispanic white (72.4%) and male (79.3%). Further detailed descriptive statistics of the sample, including summaries of study variables are presented in Table 1.

Identification of Number of Latent Classes

Table 2 reports numbers of individuals assigned to latent classes and the indices of fit for LCA models that were tested separately among PLWH and HIV-uninfected participants. Through comparisons of indices of fit of LCA models with increasing number of classes, which ranged from 1 to 4, a 3-class model was found to best fit the observed DDS profiles in both the PLWH (BIC= 1057.50, Entropy= 0.91, and BLRT= 56.67, $p < 0.001$) and HIV-uninfected samples (BIC= 656.40, Entropy= 0.92, and BLRT= 20.84, $p < 0.001$). Panel A of Figure 1 depicts the DDS profiles of the 3 classes among PLWH while Panel B depicts the profiles among HIV-uninfected individuals. As can be observed from the pattern of DDS categories across domains, the three classes in both the PLWH and HIV-uninfected samples can generally be described as Class 1_{Multidomain NCI} (high probability of impairment across multiple domains),

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Class 2_{Learning & Recall NCI} (high probability of impairment in learning and recall), and Class 3_{NC Unimpaired} (having low probability of NCI across all domains).

A series of Wald chi-square tests (with adjustments for multiple comparisons) were carried out to examine differences in the estimated probabilities of impairment across all domains of cognitive performance within the three similar pairs of classes by HIV status. Comparing across all domains for Class 1_{Multidomain NCI}, the estimated probability of impairment in speed of information processing was found to be significantly greater among PLWH than among HIV-uninfected individuals (Wald $\chi^2(1) = 155.14$, adjusted $p < 0.001$). Among individuals classified as Class 2_{Learning & Recall NCI}, verbal learning and working memory were more likely to be impaired among PLWH (Wald $\chi^2(1) = 155.11$, $p < 0.001$ and Wald $\chi^2(1) = 164.72$, $p < 0.001$, respectively). Additionally, despite the overall low probabilities of impairment, among individuals in Class 3_{NC Unimpaired}, delayed recall was more likely to be impaired among PLWH (Wald $\chi^2(1) = 137.59$, $p < 0.001$).

As the number of latent classes and the overall pattern of impairment were similar for PLWH and HIV-uninfected individuals, both samples were combined and a new best-fitting LCA model that accounted for HIV (through the regression of class on HIV-serostatus) was estimated. Consistent with previous results, a 3-class model in the combined sample (with HIV serostatus as a covariate) was found to best describe the DDS categories across the seven neurocognitive domains (BIC = 1714.99, Entropy = 0.90, and BLRT = 83.78, $p < 0.001$).

Multivariable regression analyses identified other potential covariates for inclusion as variables affecting class formation. Because only WRAT-IV reading level was associated with class membership in the HIV-adjusted LCA ($p < 0.10$), WRAT-IV was subsequently included as a covariate affecting class formation. Table 3 reports fit indices of the series of LCAs on the

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combined sample for models that adjusted for HIV infection only and for the final 3-class LCA model that adjusted for HIV infection as well as WRAT-IV (BIC= 1714.08, Entropy= 0.92, and BLRT= 86.60, $p < 0.001$).

Panel C of Figure 1 depicts the profiles of NCI of the final model (HIV serostatus- and WRAT-IV-adjusted) estimated on the combined sample. The interpretation of latent classes remained that of an impaired class across multiple domains (Class 1_{Multidomain NCI}; $N_{Total} = 39$, $N_{PLWH} = 31$, $N_{HIV-uninfected} = 8$), an impaired class in learning and recall (Class 2_{Learning & Recall NCI}; $N_{Total} = 83$, $N_{PLWH} = 32$, $N_{HIV-uninfected} = 51$), and an NC unimpaired class (Class 3_{NC Unimpaired}; $N_{Total} = 124$, $N_{PLWH} = 62$, $N_{HIV-uninfected} = 62$). Examinations of the frequencies of global neurocognitive impairment ($GDS \geq 0.5$) across the three latent classes revealed that all participants in Class 1_{Multidomain NCI} and 60.2% of participants in Class 2_{Learning & Recall NCI} were also categorized as globally neuropsychologically-impaired. Despite low overall estimated probabilities of impairment among individuals in Class 3_{NC Unimpaired}, 5.6% of participants in Class 3_{NC Unimpaired} were also classified as impaired based on GDS.

Convergent validity of Latent Classes

Convergent validity of classification was examined by comparison of MoCA scores across the latent classes. Individuals in Class 3_{NC Unimpaired} had the highest MoCA scores (Mean= 26.32, $SE = 0.26$), followed by those in Class 2_{Learning & Recall NCI} (Mean= 24.18, $SE = 0.32$), and finally by individuals in Class 1_{Multidomain NCI} (Mean= 22.60, $SE = 0.80$). The omnibus χ^2 -test was statistically significant ($\chi^2(3) = 36.75$, $p < 0.001$) and, relative to those in Class 3_{NC Unimpaired}, individuals in Class 2_{Learning & Recall NCI} and in Class 1_{Multidomain NCI} had significantly lower scores on the MoCA ($\chi^2(1) = 25.27$, adjusted $p = 0.001$ and $\chi^2(1) = 18.63$, adjusted $p = 0.001$,

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respectively). MoCA scores between individuals in Class 1_{Multidomain NCI} and in Class 2_{Learning & Recall NCI} differed only with marginal significance, ($\chi^2(1)= 3.19$, adjusted $p= 0.074$).

Predictors of Classification

Table 4 reports results of the multinomial regression of latent classes on metabolic risk factors. In all analyses, the interaction between metabolic risk and HIV serostatus was included in order to examine the differential effects by HIV serostatus. When an interaction was not significant, that term was discarded in order to interpret the main effects. PLWH with central obesity ($OR= 2.80$, $p=.035$), dyslipidemia ($OR= 3.68$, $p=.029$), and hypertension ($OR= 3.79$, $p= 0.019$) had greater odds of classification in Class 1_{Multidomain NCI}, relative to Class 3_{NC Unimpaired}. PLWH with MetS had marginally greater odds of classification in Class 1_{Multidomain NCI}, relative to Class 3_{NC Unimpaired} ($OR= 5.80$, $p= 0.078$). Although the interaction of HIV serostatus and diabetes was not significant, diabetes was associated with greater odds of classification in Class 1_{Multidomain NCI}, relative to Class 3_{NC Unimpaired} ($OR= 2.86$, $p= 0.017$). No significant differences by HIV serostatus were observed in the likelihood of classification as Class 2_{Learning & Recall NCI} versus Class 3_{NC Unimpaired}. Furthermore, there were no significant predictors of classification in Class 2_{Learning & Recall NCI} among the metabolic risk factors.

Post-hoc analyses

Additional post-hoc analyses examining the effect of HIV disease characteristics on classification were carried out to further examine the HIV effects. No significant relationships in the regression of the latent classes on nadir CD4, current CD4 count, duration of HIV infection, detectability of HIV viral proteins above the LLQ of 50 copies/mL, or duration on ART were

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found. However, higher nadir CD4 was negatively associated with diagnosis of dyslipidemia ($\rho = -0.18, p = 0.035$) while longer duration on cART was associated with MetS ($\rho = 0.20, p = 0.019$) and diabetes ($\rho = 0.30, p < 0.001$),

DISCUSSION

Multiple studies examining NCI have observed an association between aging, metabolic risk factors, and HIV infection; however, relationships between specific profiles of NCI, metabolic risk factors, and HIV serostatus have not been explored. Thus, in a sample of older adults, we aimed to characterize profiles of NCI and to examine HIV serostatus as a moderator of the link between metabolic risk factors and profiles of impairment.

We utilized LCA, a person-centered statistical classification technique of examining heterogeneity to identify distinct neuropsychological profiles of NCI among PLWH and HIV-uninfected individuals. In our sample of older adults, approximately 8% of HIV-uninfected and 22% of PLWH were classified as having overall high rates of impairment across all neurocognitive domains (Class 1_{Multidomain NCI}), while 31% of HIV-uninfected and 35% of PLWH were classified as primarily impaired in learning and delayed recall (Class 2_{Learning & Recall NCI}). A sizeable proportion of individuals in both groups (~ 61% of HIV-uninfected individuals and 43% of PLWH) were classified as neurocognitively intact (Class 3_{NC Unimpaired}). Thus, PLWH were more heavily represented in the latent class characterized by appreciable NCI. The convergent validity of these classes was supported by findings of the degree of NCI within latent classes tracking with worsening neurocognitive performance on an independent measure of neurocognitive performance, the MoCA. In particular, individuals in Class 1_{Multidomain NCI} and Class 2_{Learning & Recall NCI} had average MoCA scores below the clinical cutoff of 26/30 that

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corresponds to a preliminary diagnosis of mild NCI (29). Furthermore, the average MoCA scores of individuals in Class 1_{Multidomain NCI} was lower than that of individuals in Class 2_{Learning & Recall NCI}, suggesting that the widespread pattern of NCI observed in Class 1_{Multidomain NCI} paralleled a greater degree of clinical impairment than in the other two classes.

Previous studies have described the domain-specific patterns of NCI in PLWH as “spotty” and this study confirmed findings of variable patterns of NCI among PLWH (1). We found that three distinct patterns of NCI predominate among PLWH and that they are similar to profiles of NCI among HIV-uninfected individuals; thus, NCI phenotypes in HIV-infection may not be unique and may reflect shared or similar pathogenic mechanisms. Although the patterns of impairment and interpretations of classes were similar across PLWH and HIV-uninfected samples, some domains within similar pairs of classes appeared to be more vulnerable to impairment among PLWH. In particular, in Class 1_{Multidomain NCI}, impaired speed of information processing tended to be more prevalent among PLWH, while learning and working memory were more greatly affected in Class 2_{Learning & Recall NCI}, and delayed recall appeared more affected in Class 3_{NC Unimpaired}. This greater impairment among PLWH in speed of information processing, learning, recall, and working memory is consistent with preferential involvement of fronto-striatal brain regions (39).

Previous work has also used clustering approaches to identify profiles of neurocognitive performance among PLWH and HIV-uninfected individuals and identified varying numbers of classes (21, 40-44). Some of the differences in these studies may be a function of the clustering method (e.g., cluster analysis vs. LCA), sample size, the nature of indicators of neuropsychological performance, and populations at risk for NCI. Thus, the number of classes obtained in this study may differ from those previously identified in other studies. However,

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despite variability in the number of estimated classes underlying neurocognitive performance, clusters of NC performance similar to the three classes obtained in this study have previously been observed. Indeed, other studies have found evidence of classes of individuals with few deficits, classes with some exhibiting global NCI, and others with NCI that is primarily amnesic, suggesting the ubiquity of these patterns of NCI across different samples (21, 41-43).

When predictors of classification were examined, diabetes was found to be associated with multidomain NCI, regardless of HIV status. Additionally, PLWH classified as having widespread multidomain NCI were more likely to have hypertension, dyslipidemia, and central obesity. These findings, that HIV infection can amplify the detrimental effects of metabolic risk factors on cognition, are consistent with those of other studies that have similarly noted the potentiation of neurocognitive insults in the context of HIV infection (14, 17). Given this, there may be a need for interventions that focus on supporting the cardio-metabolic well-being of PLWH that may limit or reverse declines in cognition. Additionally, strategies to further promote neurocognitive well-being may need to be applied. A good example of this may be of the provision of “cognitive prescriptions” by medical professionals to their patients (i.e., advocating physical activity and engagement in cognitively-demanding activities, as well as promoting adequate nutrition and sleep) in order to maintain or improve cognitive health (45). Such encouragement of healthy behaviors would stand to benefit all individuals and PLWH in particular. Furthermore, given documented low rates of diagnosis of metabolic conditions and prescription of medications to manage them within the general population, facilitating increased access and engagement in medical care will also have significant implications for individual well-being and public health (46).

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Our study had several important limitations. First, following the inclusion of HIV serostatus as a covariate in our classification, only a small number of HIV-uninfected individuals were classified in Class 1_{Multidomain NCI}. Thus, comparisons of the effects of MetS components by HIV status are limited by the small numbers of HIV-uninfected participants in this class. Furthermore, a sizeable proportion of both PLWH and HIV-seronegative individuals were identified as significantly impaired in learning and recall and found to have measurable deficits on the MoCA. However, a limitation of this work is that our findings do not speak to the identification of predictors of learning and recall impairment. Future work should consider alternative sets of risk factors to identify vulnerabilities for this form of NCI.

Second, we examined the convergent validity of latent classification against the MoCA and found evidence to suggest that differences in the degree of severity of NCI implied by the three latent classes corresponded to differences in cognitive dysfunction captured by this standardized external measure. However, as the MoCA is a brief screener, it is less comprehensive and almost certainly less sensitive to HAND and other forms of NCI than the standard neuropsychological test battery that was utilized in LCA analyses. Given this, more comprehensive measures should be considered in future work to assess construct validity.

Furthermore, our analyses are cross-sectional; thus, we are unable to determine whether these latent classes have implications for the future course of neurocognitive health. Longitudinal studies are needed to examine if metabolic risk factors predict future cognitive impairment, including the development of dementia, and whether they may speak to the disentanglement of HAND from Alzheimer's among PLWH (47). Future studies should also examine the effects of sex and racial /ethnic differences on patterns of performance on neuropsychological tests among

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older individuals and combine these studies with neuroimaging and the assessment of biomarkers.

In summary, this study utilized LCA to model heterogeneity in the neurocognitive performance of older adults living with and without HIV infection and related profiles of NCI to metabolic risk factors. PLWH with metabolic risk factors were at increased risk of multi-domain NCI and early intervention to reduce these metabolic risk factors may improve the neurocognitive outcomes of PLWH. However, additional longitudinal observational studies, coupled with imaging and biomarkers, could help to inform and target interventional approaches.

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TABLE 1. Characteristics of Study Participants by HIV Serostatus

	PLWH (n = 144)	HIV-uninfected (n = 102)	p-value
Demographic Characteristics			
Age; mean (SD)	57.85 (6.17)	58.10 (6.03)	.76
Years of education; mean (SD)	14.36 (2.62)	14.53 (2.46)	.61
WRAT	103.08 (14.71)	106.35 (14.5)	.085
MoCA	24.66 (3.43)	25.67 (2.96)	.015
Male, n (%)	129 (89.6%)	66 (64.7%)	<.001
Race/Ethnicity			.54
Non-Hispanic white, n (%)	105 (72.9%)	73 (71.6%)	--
Black, n (%)	18 (12.5%)	17 (16.7%)	--
Hispanic, n (%)	12 (8.3%)	9 (8.8%)	--
Other, n (%)	9 (6.3%)	3 (2.9%)	--
Ever Smoked, n (%)	62 (43.1%)	27 (26.5%)	.004
Lifetime Substance Use Disorder, n (%)	72 (50.0%)	43 (42.2%)	.24
Lifetime Major Depression, n (%)	83 (57.6%)	25 (24.5%)	<.001
Hepatitis C virus-infected, n (%)	25 (17.4%)	8 (7.8%)	.024
Metabolic Conditions			
Diabetes, n (%)	31 (21.5%)	11 (10.8%)	.020
Hypertension, n (%)	98 (68.1%)	64 (62.7%)	.35
Dyslipidemia, n (%)	115 (79.9%)	58 (56.9%)	<.001
Central Obesity, n (%)	40 (27.8%)	51 (50.0%)	<.001
Metabolic Syndrome, n (%)	59 (40.1%)	34 (33.3%)	.22
HIV Disease Characteristics			
Undetectable viral load, n (%)	130 (90.3%)	-	-
Estimated duration of HIV (years), median [IQR]	19.2 [13.1, 25.8]	-	-
On cART, n (%)	138 (97.2%)	-	-
Months on current cART regimen, median [IQR]	37.6 [11.1, 72.3]	-	-
Months on any cART regimen, median [IQR]	141.3 [77.0, 207.5]	-	-
Nadir CD4+ T-cells, median [IQR]	145 [39, 300]	-	-
Current CD4+ T-cells, median [IQR]	602 [414, 785]	-	-

Note: IQR = interquartile range. Nadir CD4 count is the lowest of self-reported or laboratory-obtained value.

TABLE 2. Results of LCAs Among PLWH And HIV-uninfected Adults

Number of classes	Log-likelihood (# of free parameters)	AIC	BIC	Entropy	Number (%) per class	BLRT
PLWH						
1	-631.61 (7)	1277.22	1275.86	1.00	144 (100%)	N/A
2	-536.321 (15)	1102.65	1099.73	0.83	47 (32.6%) 97 (67.4%)	190.57, $p < 0.001$
3	-507.989 (23)	1061.98	1057.53	0.91	30 (20.8%) 52 (36.1%) 62 (43.1%)	56.67, $p < 0.001$
4	-500.37 (31)	1062.75	1056.72	0.92	5 (3.5%) 28 (19.4%) 50 (34.7%) 61 (42.4%)	15.23, $p = 0.29$
HIV-uninfected						
1	-364.22 (7)	742.43	738.69	1.00	120 (100%)	N/A
2	-321.76 (15)	673.16	665.51	0.83	37 (36.3%) 65 (63.7%)	84.91, $p < 0.001$
3	-311.34 (23)	668.67	656.40	0.92	15 (14.7%) 27 (26.5%) 60 (58.8%)	20.84, $p < 0.001$
4	-303.24 (31)	668.48	651.94	0.91	6 (5.8%) 9 (8.8%) 32 (32.4%) 55 (53.9%)	16.19, $p = 0.17$

Note: AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, LMR-LT = Lo Mendell Rubin Likelihood Ratio Test, BLRT = Bootstrapped Likelihood Ratio Test

TABLE 3. Results for LCAs in the Combined Sample (PLWH and HIV-uninfected Individuals), Adjusted for Relevant Covariates

	Log-likelihood (# of free parameters)	AIC	BIC	Entropy	Number (%) per class	BLRT
HIV-adjusted						
1	-1013.80 (7)	2041.59	2043.94	1.00	246 (100%)	N/A
2	-870.19 (16)	1772.39	1777.75	0.79	82 (33.3%) 164 (66.7%)	287.20, $p < 0.001$
3	-828.30 (25)	1706.61	1714.99	0.90	39 (15.9%) 74 (30.0%) 133 (54.1%)	83.78, $p < 0.001$
4	-823.26 (34)	1714.52	1725.93	0.87	31 (12.6%) 36 (14.6%) 53 (21.5%) 126 (51.2%)	10.09, $p > 0.99$
HIV- and WRAT-adjusted						
3	-825.51 (27)	1705.03	1714.08	0.92	39 (15.9%) 83 (33.7%) 124 (50.4%)	86.60, $p < .001$

Note: AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, LMR-LT = Lo Mendell Rubin Likelihood Ratio Test, BLRT = Bootstrapped Likelihood Ratio Test

TABLE 4. Regression Estimates Obtained From Multinomial Models Examining Predictors of Classification

Outcome: Classification in Class 1 _{Multidomain NCI}					Outcome: Classification in Class 2 _{Learning & Recall NCI}				
Predictor	Estimate	SE	Odds Ratio	<i>p</i> - value	Predictor	Estimate	SE	Odds Ratio	<i>p</i> - value
Central Obesity	-0.45	0.41	0.64	0.27	Central Obesity	-1.12	0.68	0.33	0.10
Central Obesity*HIV Status	1.03	0.49	2.80	0.035	Central Obesity*HIV Status	1.21	0.81	3.34	0.14
WRAT	-0.04	0.02	0.97	0.093	WRAT	-0.01	0.02	0.99	0.55
HIV Status	1.41	0.51	4.11	0.005	HIV Status	0.42	0.32	1.53	0.18
Dyslipidemia	-0.79	0.67	0.46	0.24	Dyslipidemia	-0.64	0.42	0.53	0.12
Dyslipidemia*HIV Status	1.30	0.60	3.68	0.029	Dyslipidemia*HIV Status	0.56	0.39	3.02	0.15
WRAT	-0.04	0.02	0.97	0.093	WRAT	-0.01	0.02	0.99	0.55
HIV Status	1.41	0.51	4.11	0.005	HIV Status	0.42	0.32	1.53	0.18
Hypertension	-0.35	0.63	0.71	0.58	Hypertension	-0.09	0.39	0.91	0.81
Hypertension*HIV Status	1.33	0.57	3.79	0.019	Hypertension*HIV Status	0.38	0.38	1.46	0.32
WRAT	-0.04	0.02	0.97	0.093	WRAT	-0.01	0.02	0.99	0.55
HIV Status	1.41	0.51	4.11	0.005	HIV Status	0.42	0.32	1.53	0.18
Diabetes	0.16	0.87	1.17	0.86	Diabetes	-1.04	0.94	0.35	0.27
Diabetes*HIV Status	1.19	0.94	3.28	0.21	Diabetes*HIV Status	0.89	1.06	2.43	0.40
WRAT	-0.04	0.02	0.97	0.093	WRAT	-0.01	0.02	0.99	0.55
HIV Status	1.41	0.51	4.11	0.005	HIV Status	0.42	0.32	1.53	0.18
MetS	-1.08	0.96	0.34	0.26	MetS	-0.37	0.47	0.69	0.42
MetS*HIV Status	1.76	1.00	5.80	0.078	MetS*HIV Status	0.59	0.54	1.81	0.27
WRAT	-0.04	0.02	0.97	0.093	WRAT	-0.01	0.02	0.99	0.55
HIV Status	1.41	0.51	4.11	0.005	HIV Status	0.42	0.32	1.53	0.18

Note: Provided estimates are relative to classification in Class 3_{NC Normal}.

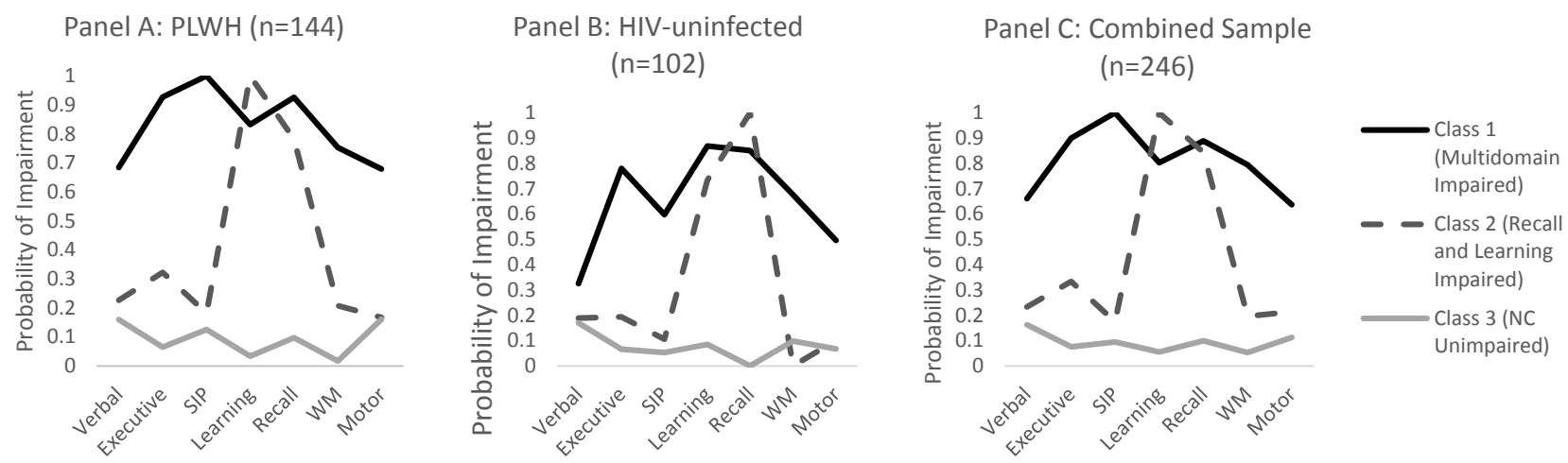


FIGURE 1. Panels depicting the 3-class LCAs of Cognitive Impairment Among PLWH, HIV-uninfected participants, and in a Combined Sample