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Racial differences in health and cognition as a function of HIV among older adults

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ABSTRACT

Objective: The present study investigated the contribution of health risk factors (using the Charlson Comorbidity Index [CCI]) on cognitive outcomes in a sample of 380 HIV-positive (HIV+; $n = 221$) and HIV-seronegative (HIV–; $n = 159$) African American and European American adults aged 50+. **Methods:** Participants were recruited from HIV clinics and community advertisements. HIV status was confirmed by serological testing. Self-report and chart history review was used to gather information about medical sss-comorbidities. The Charlson Comorbidity Index (CCI) was used to create a comorbidity score. Participants were administered a brief cognitive test battery. **Results:** As expected, health risks were greater among those with HIV. There was a HIV × Race interaction on CCI scores, such that in the HIV + group, European Americans had significantly higher CCI scores ($M = 3.74$; $SD = 2.1$) than African American HIV + participants ($M = 2.70$; $SD = 1.9$). However, in the HIV − group, African Americans had significantly higher CCI scores ($M = 2.20$; $SD = 1.1$) than HIV − European American participants ($M = 1.80$; $SD = 1.2$). Also, consistent with hypotheses, across the entire sample CCI score was significantly associated with global cognition ($\beta = -.24$, $p = .02$). **Conclusions:** Study results underscore the importance of considering HIV serostatus in studies examining racial disparities in health, and how multiple medical risks relate to cognitive outcomes. Neuropsychologists evaluating patients living with HIV should consider how the presence of multiple medical comorbidities may contribute to the course of cognitive decline as people age.

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Introduction

Incident medical conditions increase with age and impact a number of functional outcomes, including cognition (Clouston et al., 2013; Colon-Emeric et al., 2013; Mather, 2010; Murman, 2015). Further, there is an increased risk of medical comorbidities among persons with compromised immune systems (e.g. Human Immunodeficiency Virus (HIV)-infection). For example, approximately 70% of individuals with HIV also have comorbid medical conditions, which is 1.12 times greater than in non-HIV infected populations (Schouten et al., 2014). In a study of over 36,000 HIV-infected patients, hypertension, hyperlipidemia and endocrine disease emerged as the most common comorbid conditions (Gallant et al., 2017). Notably, these medical conditions place individuals at risk for cerebrovascular disease. Several studies have found higher rates of medical comorbidities associated with vascular compromise, such as cardiovascular disease (CVD), insulin resistance and dyslipidemia among HIV+individuals relative to uninfected individuals (Demir et al., 2018), and vascular risks such as high total cholesterol, diabetes, myocardial infarction, and congestive heart failure are associated with neuropsychological impairments in HIV-positive individuals (Becker et al., 2009; Foley et al., 2010; Wright et al., 2010).

Racial disparities

African Americans are disproportionately affected by both HIV and medical comorbidities associated with cognitive compromise. Despite comprising only 12% of the U.S. population, 42% of HIV+individuals are African American/Black (Centers for Disease Control & Prevention, 2019b). African Americans living with HIV also have lower levels of healthcare and viral suppression as compared to other racial groups, and are more likely to take concurrent hypertension or hypoglycemic medications as compared to European Americans (Crepaz et al., 2018). A similar disparity has been found in the general population, such that African American men and women have the highest number of medical comorbidities, particularly vascular risks as compared to other racial groups (Peters et al., 2019). This is of concern considering that the rates of dementia (e.g. Alzheimer's Disease) are more prevalent among African-Americans than among whites—with estimates ranging from 14% to almost 100% higher (Alzheimer's Association, 2020). Risk factors for Alzheimer's disease in African Americans may be related to vascular conditions (Barnes and Bennett, 2014).

African Americans over the age of 45 have a higher incidence of hypertension, diabetes mellitus, and dyslipidemia as compared to their European American counterparts (Howard et al., 2017). These racial disparities are evidence for both the age of onset and prevalence of comorbidities, where African Americans develop risk factors earlier in life as compared to European Americans (Bell et al., 2018; Carnethon et al., 2017). In a longitudinal study of HIV-uninfected (HIV−) adults, African American adults consistently manifested higher level of disability after social factors were controlled (Fuller-Thomson et al., 2009). On the other hand, incident morbidity, but not baseline health indicators, accounted for the disability gap between African American and European Americans, indicating that African Americans are at greater risk for developing medical comorbidities than European Americans. This disparity

may become more pronounced in the context of HIV-infection, particularly among older adults.

Owing to advances in HIV pharmacotherapy, the HIV + population is living longer, and the lifespan is now similar to adults without HIV (Marcus et al., 2016; Wing, 2016). Further, the number of HIV adults over the age of 50 has increased to represent nearly half of the people in the United States living with HIV (Centers for Disease Control & Prevention, 2019a). Given that the HIV + population is aging, mild to moderate levels of cognitive impairment remain prevalent in 30–50% of HIV + adults and are of increasing concern, despite adequate virologic control (Heaton et al., 2010). There have been a number of studies to suggest that these impairments worsen with advanced age (Cohen et al., 2015; Glisky, 2007; Hardy & Vance, 2009).

Medical comorbidities may contribute to the persistence of neurocognitive impairment among individuals living with HIV. In fact, it has been argued that the presence of medical comorbidities that impact CNS functioning may inflate rates of HIV associated neurocognitive disorder (HAND) (Gisslen et al., 2011). Nevertheless, studies have reported HAND among individuals living with HIV with minimal-to-moderate comorbidity burden (Heaton et al., 2010; Saloner et al., 2019). Older adults with HIV may not only be particularly vulnerable to HAND, but also to the acquisition of age-related comorbidities.

In a prior study, our group developed and then cross-validated a weighting algorithm based on multiple comorbid risk factors (i.e. stimulant use, vascular disease, hepatitis C, HIV disease severity) to predict cognitive functioning among 366 HIV + adults. We found that among older adults (≥50 years old), the risk severity index was differentially predictive of learning/memory and verbal fluency, whereas among younger adults it was linked to working memory and executive function (Patel et al., 2013). However, a critical limitation of that study was the lack of an HIV-seronegative control group. As such, we were unable to determine if the relationship between medical comorbidities and cognition was specific to individuals with HIV-infection. Further, the role of race was not investigated.

Therefore, it is important to understand if racial disparities exist in medical comorbidities that increase risk for adverse cognitive outcomes in the context of HIV-infection. Identifying particularly vulnerable subgroups within the aging HIV population may help to prevent dementia outcomes.

Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) is a 20-factor, weighed index used to predict 10-year survival in patients with multiple medical comorbidities (e.g. vascular, pulmonary, and autoimmune diseases, etc.; Charlson et al., 1987; Fischer et al., 2006; Radovanovic et al., 2014). Lohse and colleagues (2011) adapted the CCI to determine if survival from time of HIV diagnosis in HIV-infected persons differed from that in age- and sex-matched HIV-uninfected persons with similar CCI scores. Among HIV-infected persons with CCI scores of 0, 1, or 2 at the time of HIV diagnosis, survival was significantly reduced as compared to the HIV-uninfected group, suggesting that the impact of preexisting conditions may be worsened in HIV infection. Another study found associations between CCI and poorer physical health-related quality of life

(HRQoL) in HIV-infected individuals, which was more pronounced with advancing age (Rodriguez-Penney et al., 2013).

The CCI has been utilized in research focused on elucidating racial and ethnic medical disparities (Duru et al., 2011; Elsharydah et al., 2018; Singh & Ramachandran, 2016). This literature is quite limited, however, as most studies have either conducted work in racially homogenous samples (Radovanovic et al., 2014) or did not explicitly examine racial differences (Culley et al., 2016; Dreyer & Viljoen, 2019). Therefore, racial differences in CCI and its impact on cognitive outcomes remain unknown.

Present study

The present study investigated the contribution of a range of health risk factors (as measured by the CCI) on cognitive outcomes among a representative sample of African American and European American adults aged 50+, of which 58% were HIV-positive. We hypothesized that: (a) HIV + participants would have a higher CCI score than HIV − participants, with HIV + African Americans demonstrating the highest CCI score relative to other racial and HIV-status groups; and (b) CCI would be associated with cognitive outcomes, and would partially explain cognitive performance differences between HIV + African Americans and European Americans.

Method

Participants

Participants were recruited from HIV clinics and from the local community using advertisements and word of mouth. Three hundred and eighty participants (HIV+ = 221; HIV− = 159) out of 394 participants were eligible for the study. HIV-status was confirmed using serologic testing (i.e. Western Blot confirmed by ELISA). Questionnaires and screeners about medical, neurological and psychiatric history were used to screen for potential confounds. Briefly, participants were screened for neurological, psychiatric, illicit drug use, and medical confounds using the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, (First, et al., 2002), Mini-Mental Status Exam (Folstein et al., 1975)—using an eligibility score of ≥26, urine toxicology test, and questionnaires about neurological and medical history. Participants were not eligible for testing study hypotheses if they reported past (12 months) dependence on stimulants ($n = 5$), opiates or hallucinogens, current or past diagnosis of psychotic-spectrum disorder ($n = 3$), recent use of stimulants, opiates, or hallucinogens ($n = 1$), head injury with loss of consciousness (>30 minutes) ($n = 5$), or HIV-associated CNS opportunistic infections (e.g. CNS lymphoma). We included participants who endorsed current abuse of alcohol ($n = 9$) and marijuana ($n = 18$), past abuse or dependence on alcohol ($n = 215$) and marijuana ($n = 135$), as well as past abuse of opiates ($n = 27$) and hallucinogens ($n = 13$). We also included participants who met criteria for either current ($n = 24$) or past major depression disorder ($n = 97$). All procedures were reviewed and approved by the University of California, Los Angeles (UCLA) and the University of Southern California Institutional Review Boards and participants signed informed consent forms before participation.

Demographics

Demographic data, including age, education, racial/ethnic identity, and sex, were obtained through self-report. Substance use data was collected through The Drug Use History Questionnaire created by the UCLA Center for Advancing Longitudinal Drug Abuse Research. Socioeconomic status (SES) was measured using the Hollingshead Four-Factor Index of Social Status (Hollingshead, 1975). The Hollingshead Index of Social Status (i.e. a weighted average of years of education, current or longest held occupation, and total household income of the participant)was used to assess current personal SES. Years of education were based upon self-report from the participant and occupation was coded using the Hollingshead Index (Hollingshead, 1975). For married participants, the spouse's education and occupation were also used to compute the score. The Hollingshead Index is a reliable and valid measure of social status (Cirino et al., 2002), and it has been used in a racially diverse sample of HIV adults (Arentoft et al., 2015). Hollingshead scores range from 0 to4, with higher scores representing higher levels of SES.

Medical comorbidities

Medical comorbidities were determined by both self-report (40% of sample) and chart review (60% of sample). Participants with available chart data were compared to participants who self-reported medical status on variables of HIV status, age, sex, education, SES, CCI, and global cognitive function. There were no significant group differences (all p's $> .50$). A modified version of the CCI (Charlson et al., 1987)was used to create a comorbidity score. The index assigns weighted scores for diseases based upon the relative risk for each individual disease, with weighted scores ranging from 0 to 6 (Charlson et al., 1987). Scores of 0 are assigned when there is absence of the disease. Additional points are added depending upon a patient's decade age group category (<50 years, 0 points; 50–59 years, 1 point; 60–69 years, 2 points; 70–79 years, 3 points; ≥80 years, 4 points). Summing the weighted disease scores and additional age decade points yields the CCI score (Lohse et al., 2011). In the original CCI index, a score of 1 is assigned to the following diseases: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and uncomplicated diabetes. Scores of 2 are assigned to the following diseases: hemiplegia, moderate-to-severe renal disease, diabetes with end-organ damage, any localized tumor, leukemia, and lymphoma. A score of 3 is assigned to moderate-to-severe liver disease. A score of 6 is assigned to metastatic solid tumors and AIDS. For HIV group comparisons on CCI, we did not include HIV/AIDS due to study focus. However, a subgroup analysis performed within the HIV + group included AIDS (defined as CD4 < 200 mm^3 or AIDS defining illness) as a risk factor. We did not include frank dementia or metastatic solid tumors as this was a study exclusion factor. In the original CCI, the maximum comorbidity score that a patient could receive is between 37 and 41 with the addition of age decade. In our modified version, the maximum comorbidity score (including age decade) that a patient could receive is 28. The full sample had a range of scores from 0–10. Without including AIDS (represented in 3.6%

of the total HIV + sample), the distribution of scores for the total sample was as follows: CCI = 0: 4%, CCI = 1: 28%, CCI = 2: 25%, CCI = 3: 17%; CCI = 4: 11%, CCI = 5: 6%, CCI = 6: 5%, CCI = 7–10: 4%. The inclusion of AIDS resulted in the following distribution of scores for the total sample CCI = 0: 4%, CCI = 1: 28%, CCI = 2: 24%, CCI = 3: 16%, CCI = 4:10%, CCI = 5: 6%, CCI = 6: 5%, CCI = 7–12: 7%.

Neurocognitive functioning

Participants were administered a brief cognitive test battery used in prior studies (Mahmood et al., 2018; Thames et al., 2017). Premorbid intelligence was estimated using the Wide Range Achievement Test-4th edition (WRAT-4; Wilkinson & Robertson, 2006). Cognitive tests were classified into the domains of *verbal fluency* (Controlled Oral Word Association Test—FAS and Animals; Benton, Hamsher, & Sivan, Benton et al., 1994), *executive functioning* (Trail Making Test—Part B; Reitan, 1958; Letter-Number Sequencing subtest from the Wechsler Adult Intelligence Scale-4th edition; Wechsler, 2008; Stroop Test Interference condition; Golden & Freshwater, 1978), *information processing speed* (Trail Making Test—Part A; Reitan, 1958; Stroop Test Color Naming and Word Reading conditions; Golden & Freshwater, 1978; Symbol and Symbol Search subtests from the Wechsler Adult Intelligence Scale-4th edition; Wechsler, 2008), *learning* (Brief Visual Memory Test-Revised Immediate subtest; Benedict, 1997; Hopkins Verbal Learning Test-Revised Immediate subtest; Brandt & Benedict, 2001), *memory* (Brief Visual Memory Test-Revised Delay subtest; Hopkins Verbal Learning Test-Revised Delayed subtest), and *motor speed* (Grooved Pegboard Test, dominant and non-dominant hands; Reitan, 1958). All raw scores were converted to age-corrected T scores. Global cognition was a composite score of individual tests that were converted to age-corrected T scores.

Immune status

For HIV + participants, venipuncture was performed by study phlebotomist. Approximately ~20 mL of blood was collected to test for CD4 count and HIV RNA viral load. Samples were then centrifuged and stored in a −80-degree freezer. Frozen samples were sent to Quest Diagnostics for analyses. Self-reported nadir (lowest ever) CD4, highest ever viral load, and duration since HIV diagnosis (years) were also collected.

Functional impairment

A subset of our participants ($n = 180$) were administered the Barkley Functional Impairment Scale (BFIS; Barkley, 2011) is a 15-item scale used to measure psychosocial impairment in 15 specified domains: home life; work; social interactions; relationships with friends; chores and household tasks; community activities; educational activities; romantic relationships; sexual activities; management of finances; driving; organizing daily responsibilities; parenting; maintaining health (e.g. exercise, nutrition); and daily care (e.g. dressing, bathing). Participants rate their perceived difficulty in performing these domain-related tasks on a 10-point Likert scale that ranges from 0 (*Not at all*)

to 9 (*Severe*) or 999 (*Not Applicable*). Items were averaged (i.e. Total score/Number of items answered) to produce a mean impairment score with higher mean scores indicative of higher functional impairment across the 15 domains. The BFIS has demonstrated high validity and test-retest reliability (Barkley, 2011). In our sample, the BFIS demonstrated high internal consistency (Cronbach's alpha = .97). Functional impairment scores were used to classify HIV-associated Neurocognitive Disorder (HAND) among our HIV + participants. We used a cutoff of 1 standard deviation above the sample mean to classify individuals with functional impairment. In order for participants to meet criteria for Asymptomatic Neurocognitive Impairment (ANI), at least two cognitive domains must have demonstrated T scores ≤39, with a "normal" functional classification (according to the BFIS). Participants who were classified as having Mild Neurocognitive Disorder had at least two cognitive domains with T scores ≤39, and were classified as having functional impairment.

Statistical analyses

Univariate analysis of variance (ANOVA), Chi-square, Spearman's bivariate correlations, and linear regression were conducted to examine potential confounds as well as to test study hypotheses. Shapiro-Wilk W-test showed that CCI was not normally distributed ($p < 0.02$), so Spearman's rho (ρ) was used when we assessed correlations between CCI and other covariates. Point-biserial correlations (denoted as r_{pb}) were used to examine the association between CCI and HAND as well as the association between substance use variables, past major depressive disorder and CCI. In the linear regression models where CCI was the outcome, regression residuals were assessed for deviations from normality and no major deviations were detected. To reduce the number of comparisons, we used global cognition as our primary outcome variable. Ancillary analyses were performed on cognitive domains using a False Discovery Rate alpha correction of $p \leq .035$. Linear regressions were used to test main and interactive associations of HIV and race on outcomes of CCI and global cognition.

Results

Demographic and clinical comparisons

Table 1 provides demographic and clinical comparisons.

HIV status group comparisons

There were no significant differences between HIV status groups with respect to age, education, WRAT-4 reading score, SES, depressive symptoms, sex, and race ($ps > 0.10$). There were significant HIV group differences in past alcohol dependence, χ^2 (1, 379) = 6.31, $p < .01$,ω = .15, past opiate abuse, χ^2 (1, 379) = 4.32, $p < .04$, ω = .13, and past hallucinogen abuse, χ^2 (1, 379) = 4.96, $p < .04$, ω = .13, and current alcohol use (i.e. number of days in past 4 weeks), $U = 1044.50$, $N = 380$, $p = .006$, with HIV + participants reporting greater use/abuse/dependence. There were no significant HIV group differences in current alcohol abuse, current marijuana use (i.e. number of days in

Table 1. Demographic variables mean, standard deviation and percentage.

	HIV+ ($n = 221$)		HIV− ($n = 159$)			
Variable	African American ($n = 116$) (a)	European American ($n = 105$) (b)	African American ($n = 82$) (c)	**European American ($n = 77$) (d)**	p-value	Effect size
Age	56.41 (5.39)	57.98 (7.15)	58.15 (6.06)	58.15 (6.30)	*Not Significant (NS) $p = .34$	**$\eta^2 = .002$
Education	13.05 (1.77)	14.52 (2.41)	13.35 (2.21)	14.53 (2.27)	a,c < b,d $p < .0001$	$\eta^2 = .08$
‡Wide Range Achievement Test (WRAT)-4 standard score	98.08 (16.2)	109.37 (14.29)	95.15 (15.89)	110.29 (14.27)	a,c < b,d $p < .0001$	$\eta^2 = .18$
Sex %male	76%	88%	61%	70%	a,b > c,d $p = .023$	$\eta^2 = .03$
Hollingshead Index (Socioeconomic Status)	38.64 (12.13)	44.78 (11.95)	37.62 (12.50)	45.40 (11.28)	a,c < b,d $p < .0001$	$\eta^2 = .09$
Cluster of Differentiation 4 (CD4) recent count	582.56 (315.24)	583.20 (288.83)	–	–	NS $p = .98$	$\eta^2 = .000$
Nadir CD4	240.27 (239.55)	213.89 (190.06)	–	–	NS $p = .38$	$\eta^2 = .004$
(%)Undetectable Viral Load (< 20 copies/ML)	73%	80%	–	–	NS $p = .26$	$\eta^2 = .005$
Duration of known HIV infection	15.0 (7.90)	18.15 (9.17)	–	–	$p = .007$	$\eta^2 = .06$
Past Alcohol Abuse (met Structured Clinical Interview for DSM (SCID) criteria)	39%	31%	29%	30%	a,b = c,d: $p = .88$ b,d: $p = .92$ a,c: $p = .21$	a,b = c,d: $^{T}\omega = .03$ b,d: $\omega = .01$ a,c: $\omega = .10$
Past Alcohol Dependence (met SCID criteria)	36%	23%	15%	18%	a,b > c,d: $p = .01$ a > b: $p = .005$ c,d: $p = .57$	a,b > c,d: $\omega = .16$ a > b:$\omega = .22$ c,d: $\omega = .05$
Current Alcohol Abuse (met SCID criteria)	1%	3%	2%	6%	a,b = c,d: $p = .55$ b,d: $p = .57$ a,c: $p = .65$	a,b = c,d: $\omega = .03$ b,d: $\omega = .03$ a,c: $\omega = .05$
Current Alcohol Use (#days in past 4 weeks)	3.0 (5.4)	2.4 (5.2)	4.7 (6.5)	4.2 (8.3)	a,b < c,d = $p = .006$	$\eta^2 = .02$
Past Marijuana Abuse (met SCID criteria)	32%	25%	27%	18%	a,b = c,d: $p = .32$ a,c: $p = .48$ b,d: $p = .42$	a,b = c,d: $\omega = .06$ a,c:$\omega = .08$ b,d: $\omega = .05$

Past Marijuana Dependence (met SCID criteria)	13%	9%	6%	6%	a,b = c,d: p = .17 a,c: p = .20 b,d: p = .57	a,b = c,d: ω = .17 a,c:ω = .20 b,d: ω = .05
Current Marijuana Abuse (met SCID criteria)	2%	5%	8%	6%	a,b = c,d: p = .15 a,c: p = .09 b,d: p = .80	a,b = c,d: ω = .08 a,c:ω = .11 b,d: ω = .02
Current Marijuana Use (#days in past 4 weeks)	3.2 (8.3)	3.2 (8.0)	2.3 (5.2)	3.6 (8.0)	a,b = c,d: p = .53	a,b = c,d η^2 = .002
Past Hallucinogen Abuse (met SCID criteria)	8%	10%	2%	3%	a,b > c,d: p = .04 a,c: p = .14 b,d: p = .23	a,b > c,d: ω = .14 a,c:ω = .14 b,d: ω = .13
Past Opiate Abuse (met SCID criteria)	14%	12%	3%	9%	a,b > c,d: p = .04 a > c: p = .03 b,d: p = .59	a,b > c,d: ω = .13 a > c:ω = .17 b,d: ω = .05
Past Major Depression Disorder (met SCID criteria)	34%	39%	19%	17%	a,b > c,d: p = .01 a > c: p = .02 b > d: p = .01	a,b > c,d: ω = .18 a,c:ω = .16 b,d: ω = .21
Current Major Depression Disorder (met SCID criteria)	5%	13%	6%	2%	a,b = c,d: p = .17 a,c: p = .86 b,d: p = .03	a,b = c,d: ω = .07 a,c:ω = .01 b,d: ω = .18
[+]Beck Depression Inventory-II (BDI-II) score	9.47 (9.40)	10.40 (4.76)	6.72 (6.02)	4.76 (6.60)	ab > cd: p < .0001	η^2 = .05
‡‡Charlson Comorbidity Index (CCI) score	2.71 (1.91)	3.74 (2.13)	2.20 (1.10)	1.80 (1.2)	p = .002 b > a, c > d	η^2 = .03
Global cognitive T-score	44.07 (6.17)	44.18 (6.54)	44.05 (5.77)	46.65 (6.61)	NS p = .06	η^2 = .03
Executive Function T-score	48.26 (8.26)	46.25 (7.92)	48.75 (7.02)	49.58 (7.79)	NS p = .15	η^2 = .006
Memory T-score	35.12 (11.04)	41.88 (13.41)	35.14 (11.43)	44.95 (12.22)	a,c < b,d p < .0001	η^2 = .09
Learning T-score	34.19 (10.04)	40.11 (11.79)	34.77 (9.42)	42.73 (11.62)	a,c < b,d p < .008	η^2 = .09
Processing Speed T-score	44.63 (8.34)	44.21 (7.03)	45.33 (7.25)	47.12 (6.73)	a,b < c,d p = .03	η^2 = .01
Motor Function T-score	46.66 (9.04)	42.50 (9.48)	45.66 (9.80)	41.98 (11.94)	b,d < a,c p < .0001	η^2 = .04

(*Continued*)

Table 1. (*Continued*)

Variable	HIV+ ($n = 221$)		HIV− ($n = 159$)		p-value	Effect size
	African American ($n = 116$) (a)	European American ($n = 105$) (b)	African American ($n = 82$) (c)	European American ($n = 77$) (d)		
	African American ($n = 105$)	**European American ($n = 75$)**				
[++]HIV associated Neurocognitive Disorder (HAND)Classification (Asymptomatic Neurocognitive Impairment [ANI])	14%	8%	–	–	NS $p = .08$	$\omega = .11$
HAND Classification (Mild Neurocognitive Disorder [MND])	23%	14%	–	–	a > b: $p = 0.02$	$\omega = .16$
No HAND Diagnosis	20%	21%	–	–	NS $p = .92$	$\omega = .01$

[*]NS = Not significant ($p > .05$).
[**]η^2 = partial eta.
[τ]ω—Phi statistic from Chi-Square comparisons.
[ǂ]WRAT-4 = Wide Range Achievement Test-4th edition.
[ǂǂ]CCI = Charlson Comorbidity Index.
[+]BDI = Beck Depression Inventory.
[++]HAND = HIV-Associated Neurocognitive Disorder; ANI = Asymptomatic Neurocognitive Impairment, MND = Mild Neurocognitive Disorder.

past 4 weeks), current marijuana abuse, past marijuana abuse, or past marijuana dependence (all *p*'s > .15). There were significant HIV group differences in past major depressive disorder (MDD), χ^2 (1, 379) = 7.39, $p < .01$, ω = .18, with a greater proportion of HIV + participants endorsing past MDD.

Race group comparisons

There were no significant differences between race groups in terms of age, HIV status, depressive symptoms, or sex (*p*s > 0.10). There were significant race group differences in past dependence on alcohol, but only within the HIV + group, χ^2 (1, 379) = 11.94, $p < .005$,ω = .22 with African Americans reporting greater past dependence on alcohol than European Americans. Significant group differences in education were found, with European American participants reported significantly more years of education, F(1, 379)= 33.88, $p < .0001$, partial η^2 = .08, and demonstrated higher WRAT-4 scores, F (1, 379) = 70.22, $p < .0001$, partial η^2 = .24, and SES, F (1, 379) = 19.75, $p < .0001$, partial η^2 = .15 than African American participants.

Examination of HIV-specific variables revealed that HIV + European Americans had a longer duration of known HIV infection than HIV + African Americans, F(1, 220) = 7.43, p = .007, partial η^2 = .10. There were no race group differences in current CD4 count, nadir CD4 count, highest ever viral load, or proportion of participants with a detectable viral load (*p*s > 0.20). A subset of our HIV + participants had functional impairment data available (n = 105). Therefore, the rates of HAND were examined within the HIV + group. African Americans were more likely to meet HIV-associated Neurocognitive Disorder (HAND) criteria for Mild Neurocognitive Disorder (MND) based upon established criteria (Antinori et al., 2007), χ^2 (1, 179) = 5.98, $p < .02$, ω = .16. There were no significant associations between HAND classification and age, education, or sex (all *p*s > .30). HAND was significantly associated with nadir CD4, r_{pb} = −.12, p = .04, but weakly associated with other HIV variables (*p*s < .40).

CCI and demographic variables

There were significant sex differences in CCI score, F (1, 377) = 6.50, p = .011, partial η^2= .02, such that males had a higher CCI score (M = 2.83; SD = 2.00) than females (M = 2.26; SD = 1.41). There was a significant association between CCI score and education, ρ(379) = .136, p = .008 and SES ρ(379) = −.235, $p < .0001$. There were no statistically significant relationships between CCI and detectable viral load, current CD4 count, nadir CD4 count, or highest ever viral load (*p*'s > .20).

Past opiate abuse was significantly correlated with CCI score, r_{pb} = .22, $p < .0001$ and motor functioning, r_{pb} = −.15, p = .02, such that past opiate abuse was associated with increased CCI score and lower motor functioning. No other substance use/abuse/dependence variables (as assessed by the SCID or the UCLA Drug Use History Questionnaire) were significantly associated with outcomes of CCI or cognition (all *p*'s > .30). Past major depressive disorder was not associated with CCI or cognitive outcome variables r_{pb} = .043, p = .44.

Duration of known HIV infection was significantly associated with CCI score, ρ (220) = .227, p = .001. This overall association was driven by medical conditions of cancer, ρ(220) = .15, p = .03, hepatitis A, ρ (220) = .14, p = .04, and hepatitis B, ρ(220) = .239, p = .001, all of which were higher in the HIV+European American group (see Table 2). HAND classification was also significantly associated with CCI score, r_{pb} = .13, p = .04.

HIV and race interactive associations on CCI

Linear regression was performed with CCI as the outcome variable and sex (coded as Male = 0, Female = 1), SES (continuous), HIV status (coded as HIV− = 0, HIV+ = 1), education (continuous), race (coded as European American = 0; African American = 1), Past opiate abuse (Yes = 1, No = 0) and the HIV × Race interaction as predictors. The overall model was significant, r^2 = .21, F = 10.23, p < .0001. Consistent with our hypothesis, beta weights revealed that HIV was significantly predictive of CCI score (β = .53, p < .001), with the HIV+group having significantly higher CCI scores than the HIV-control group. There was a HIV × Race interaction on CCI scores, (β = −.37, p < .001), such that in the HIV+group, European Americans had significantly higher CCI scores (M = 3.74; SD = 2.1) than African American HIV+participants (M = 2.70; SD = 1.9). However, in the HIV−group, African Americans had significantly higher CCI scores (M = 2.20; SD = 1.1) than HIV−European American participants (M = 1.80; SD = 1.2) (see Figure 1). Follow-up analysis were conducted within the HIV group using HIV-related covariates of nadir CD4, duration of known HIV-infection, and detectable viral load with CCI that included AIDS diagnosis as the outcome. The model was no longer significant after adjusting for covariates, F (4, 191) = 2.968, p = .09. Table 2 provides detailed information about medical risks by race for both HIV status groups.

CCI and cognitive function

With respect to cognition, significant associations were observed between CCI score and global cognition for the entire sample, ρ(379) = −.15, p = .02 (see Figure 2) as well domains of processing speed, ρ(379) = −.13, p = .01, and a non-significant trend in executive functioning, ρ(379) = −.098, p = .04. No other cognitive domains were significantly associated with CCI score (ps > .30).

Interactive associations between HIV, race, CCI on cognitive function

For the outcome of global cognitive performance, linear regression was conducted with covariates that differed between HIV and or race groups and were significantly associated with outcomes of CCI and/or cognition. These covariates included: WRAT-4 reading subtest standard score, education (years), sex, SES, and past opiate abuse. Predictors included: race, HIV status, CCI score, and interaction terms of HIV × CCI, HIV × race, race × CCI, and HIV × CCI × race as predictors. The overall model was

Table 2. Charlson Comorbidity Index medical factors by HIV status and race.

	HIV+ ($n = 221$)		HIV− ($n = 159$)			0
Variable	African American ($n = 116$) (a)	European American ($n = 105$) (b)	African American ($n = 82$) (c)	European American ($n = 77$) (d)	p-value*	**Effect size****
Cancer	10%	27%	2%	2%	b > a: p = .002 c,d: p = .98	b > a: ω = .23 c,d: ω = .002
Myocardial Infarction	2%	7%	0	0	a,b: p = .11 c,d: p = .98	a,b: ω = .08 c,d: ω = .002
Congestive Heart Failure	3%	3%	2%	0	a,b: p = .92 c,d: p = .32	a,b: ω = .006 c,d: ω = .08
Diabetes mellitus	11%	13%	11%	10%	a,b: p = .62 c,d: p = .89	a,b: ω = .03 c,d: ω = .01
Hypertension	40%	30%	30%	10%	a,b: p = .15 c > d: p = .01	a,b: ω = .10 c > d: ω = .19
Sleep Apnea	8%	8%	1%	2%	a,b: p = .95 c,d: p = .70	a,b: ω = .005 c,d: ω = .01
Chronic Obstructive Pulmonary Disease	9%	8%	2%	0	a,b: p = .83 c,d: p = .32	a,b: ω = .01 c,d: ω = .08
Emphysema	5%	2%	0	2%	a,b: p = .23 c,d: p = .15	a,b: ω = .08 c,d: ω = .11
Chronic Bronchitis	6%	10%	5%	2%	a,b: p = .30 c,d: p = .39	a,b: ω = .07 c,d: ω = .07
Kidney Failure	1%	4%	2%	2%	a,b: p = .20 c,d: p = .98	a,b: ω = .09 c,d: ω = .002
Hepatitis A	5%	13%	0	6%	a,b: p = .06 d > c: p = .01	a,b: ω = .13 d > c: ω = .28
Hepatitis B	9%	27%	2%	4%	b > a: p = .001 c,d: p = .46	b > a: ω = .24 c,d: ω = .06
Hepatitis C	20%	17%	5%	0	a,b: p = .55 c,d: p = .11	a,b: ω = .04 c,d: ω = .12

*p-values comparing columns a,b and c,d.
**Phi statistic reported for column a,b and c,d Chi-Square comparisons.

significant, r^2 = .33, $F = 11.56$, $p < .0001$. WRAT score was significantly associated with global cognition (β = .41, $t = 8.27$, $p < .0001$). As expected, CCI score was significantly associated with global cognition (β = −.31, $t = -2.181$, $p = .03$). No other variables were significantly associated with global cognition (p's > .10).

Linear regressions were conducted with the aforementioned predictors with individual cognitive domain as outcomes. WRAT-4 (β = .35, $t = 5.312$, $p < .0001$), SES (β = .14, $t = 1.947$, $p = .05$), CCI (β = −.31, $t = -2.042$, $p = .03$) were the only significant predictors in the model with processing speed as the outcome. With regard to processing speed, WRAT-4 (β = .39, $t = 6.535$, $p < .0001$), sex (β = .10, $t = 2.044$, $p = .042$), CCI (β = −.22, $t = -1.723$, $p = .04$) and the HIV × race interaction (β = −.30, $t = -2.128$, $p = .03$). Analysis of the HIV × race interaction revealed that African American HIV − controls demonstrated lower processing speed than HIV − European Americans ($p = .001$). The association between race and processing speed was not found in the HIV + group ($p > .30$). In the model with motor functioning as an outcome, WRAT-4 (β = .17, $t = 2.508$, $p < .01$), SES (β = .17, $t = 2.168$, $p = .03$), CCI (β = −.39, $t = -2.391$, $p = .01$), and past opiate abuse (β = .15, $t = 1.968$, $p < .04$) were significant predictors. No other variables were associated with outcome variables.

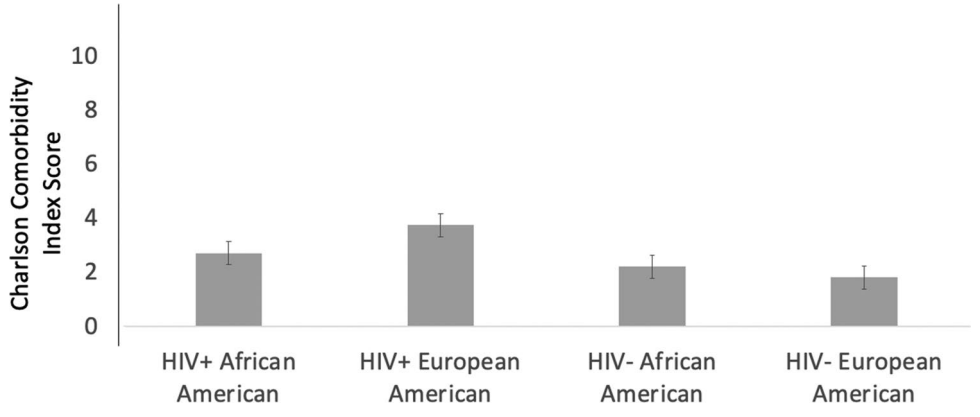

Figure 1. Charlson comorbidity score by HIV status and race group ($N = 380$). Bars represent mean Charlson Comorbidity Index score.

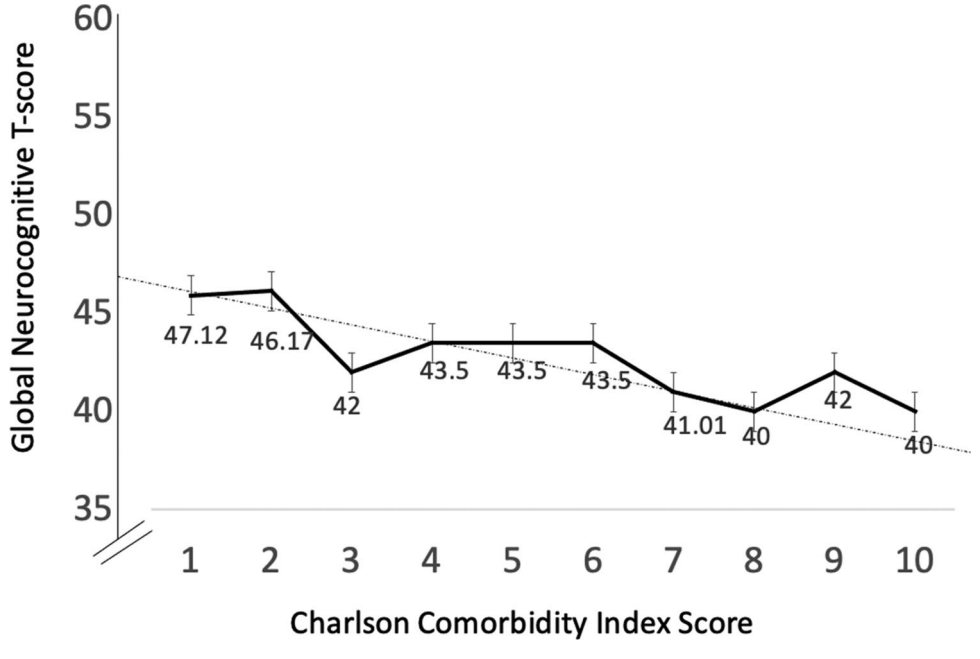

Figure 2. Charlson comorbidity score and mean-level global cognitive performance ($N = 380$). Regression line represented in the dashed line. Each data point represents mean level of global neurocognitive performance by Charlson comorbidity score.

Discussion

The present study examined how a variety of health risk factors are associated with cognitive outcomes among a representative sample of African American and European American HIV-positive (HIV+) and HIV-seronegative (HIV−) adults aged 50+. As hypothesized, we found that HIV + individuals have significantly greater multimorbidities as indexed by the CCI as compared to HIV − participants. This finding is consistent with

prior studies demonstrating increased medical comorbidities among individuals with HIV-infection. Contrary to expectations, HIV + European Americans had significantly higher CCI scores than HIV + African Americans. However, further analysis revealed that this difference was largely accounted for by longer duration of known HIV-infection than the HIV + African American group as well as differences in the type of medical risk factors in each racial group. Examining individual medical risk factors revealed that European American HIV + adults demonstrated conditions that have been associated with long-term HIV infection, including cancer, hepatitis A, and hepatitis B. Nevertheless, our HIV-seronegative control African Americans demonstrated higher CCI scores than HIV − European Americans, which is consistent with prior research on racial disparities in health outcomes (Fuller-Thomson et al., 2009; Howard et al., 2017). Further, examining racial group differences in medical risk factors among the HIV-seronegative group demonstrated that HIV − African Americans had higher rates of hypertension than HIV − European Americans. These findings are consistent with African Americans having higher rates of vascular risk factors that may place them at risk for cerebrovascular disease (Bell et al., 2018; Carnethon et al., 2017).

Our second hypothesis was partially supported in that multimorbidites (as indexed by CCI scores) were significantly associated with global cognition; however, the HIV x race interaction was not consistent with expectations. We found cognitive performance differences between African Americans and European Americans in the domain of processing speed in the HIV − group, but not in the HIV + group. Examination of our data reveals that HIV + African Americans and HIV − African Americans had similar CCI scores, whereas CCI scores differed between HIV + and HIV − European Americans. It is possible that the deleterious effects of HIV on health may be more apparent among European Americans because the traditional comparison group (i.e. HIV − European Americans) are less likely to experience the level of social inequities that are faced by African Americans (regardless of HIV status). In other words, the "HIV effect" as it pertains health or cognition may be obscured among African Americans due to a number of social factors that are beyond the scope of this study.

Although we recognize that the overall effect size was relatively small, we found that for the entire sample each 1-point increase in participants' CCI score, there was an approximate 0.22–0.24-point decrease in global cognitive performance for both HIV + and HIV − adults. This is clinically relevant, as a data from this sample indicate that a CCI score of 2 or more (which was over half of our sample) could result in a half a standard deviation decrease in cognitive performance. Further, our results demonstrate that CCI is associated with HAND classification among individuals with HIV-infection. Our results also suggest that individuals with long durations of known HIV-infection are at particular risk for comorbid medical conditions. To our knowledge, this is the first study to examine the predictive utility of CCI on cognition among a large racially diverse group of HIV and HIV-infected older adults aged 50+.

There are study limitations that should be noted. First, the duration of medical comorbid conditions was unknown and the presence of certain conditions was based upon self-report and/or review of medical records. Therefore, length of chronic illnesses such as diabetes and cancer will be important to consider in future research examining the impact of chronic illness on cognitive health. Second, the range of CCI was rather truncated 0–10 (out of a possible 28), which implies that this was

a relatively healthy sample. Our results may have been different in a sample with greater health conditions. Third, we also recognize that comorbidity indices that are specific to HIV-seropositive individuals exist (e.g. Veterans Aging Cohort Study [VACS]), and associated with increased risk of morbidity and mortality (Brown et al., 2014; Justice et al., 2012). The VACS index uses variables of increased age, HIV-related variables (i.e. low CD4 count and high viral load), and markers of chronic comorbid conditions including renal dysfunction, anemia, liver fibrosis, and Hepatitis C co-infection. However, we were limited in our access to biological data (e.g. laboratory markers of renal dysfunction), and elected to use an index that could be equally applied to our HIV + and HIV-seronegative groups. Nevertheless, future studies should consider a combination of the CCI and VACS indices when examining HIV + populations.

We also note that because this is a cross-sectional study, interpretations about directionality cannot not be determined and it is unclear if CCI scores predict cognitive decline over time. It is also unclear if the presence of HIV-infection increased risk for the development of medical risk factors among African Americans and European Americans. In concern of conducting multiple comparisons, we chose not report analyses with regard to specific comorbidities. Nevertheless, further inspection of our data revealed that HIV-related factors such as nadir CD4 count was significantly associated with COPD, highest ever viral load was associated with sleep apnea, and duration of HIV infection was associated with hepatitis A, hepatitis B, and cancer. Future investigations should examine the incidence of specific comorbidities that may be associated with HIV-infection, aging, as well as the interaction between HIV and aging.

Individual profiles of medical risk factors vary throughout the life course, and single measures of exposure may not reflect the longitudinal variation and cumulative burden associated risks (Yaffe et al., 2014). Further, functional health disparities tend to be more prominent in mid-adulthood versus late-adulthood (Kim & Miech, 2009; Zahodne et al., 2016). Therefore, it is unclear if the present findings would generalize to adults aged 70+.

Finally, we did not include variables such as HIV-related stigma and racial discrimination, which may also contribute to racial group differences in comorbidities. Our group has previously found that Black-White differences observed in the expression of genes that promote the inflammatory response were largely accounted for by experiences with racial discrimination (Thames et al., 2019).

Although the present findings from this diverse sample may generalize to the population attending HIV clinics in the U.S., they may not generalize to patients taking long-term antiretroviral therapy that was started during early stages of infection and who have demonstrated good recovery (Nightingale et al., 2014).

Despite these limitations, we believe that there are several strengths to the study and these findings provide important contribution to the extant literature on racial disparities in health among older adults with and without HIV-infection. This study used a well-characterized HIV + and HIV − cohort aged 50+ to demonstrate relationships between race, multiple medical comorbidities, and cognition, which were found to interact with HIV status. Our findings underscore the importance of considering HIV serostatus in studies examining racial disparities in medical risk factors, and how

multiple medical risks relate to cognitive outcomes. Second, this study found that CCI score was associated with global cognitive outcomes, particularly in cognitive domains of processing speed and executive functioning, which are domains that often decline with age and cerebrovascular medical risks. Finally, this study demonstrates that the Charlson Comorbidity Index is useful for predicting individuals at risk for poor cognitive outcomes, and that scores of 2 or more were associated with a 0.5 standard deviation drop in cognitive performance. Capturing the prevalence and severity of comorbidities might explain some of the differences in the prevalence estimates of HAND in previous studies (Nightingale et al., 2014). These findings may also help to explain Black-White differences observed in neuropsychological outcomes that cannot be fully accounted for factors such as educational attainment and educational quality. Considering that African Americans receive suboptimal healthcare in comparison to Whites (Chin, Walters, Cook, & Huang, 2012), including cognitive screenings, it is important for neuropsychologists to consider how the presence of multiple medical comorbidities (i.e. HIV status + other health risks) may contribute to the course of cognitive decline as people age. In our study, we found that HIV + African Americans were more likely to meet MND criteria for HAND. This is important to highlight considering that our HIV + African American sample had a shorter duration of infection as well as a similar immune status to the HIV + European American sample. This suggests that other factors unrelated to HIV-specific factors may explain racial disparities in the incidence HAND.

Further, it is important for neuropsychologists who work with minoritized groups (e.g. HIV-positive, racial/ethnic minorities), to be aware of the many forms of which racism and discrimination permeate healthcare systems (e.g. physician referrals to specialized services) and economic structures (e.g. housing), all of which shown to be associated with poor cognitive outcomes (Knapp & Hall, 2018; Kolak et al., 2020). Future research should not only examine the utility of the CCI index in predicting cognitive outcomes over an extended period of time, but also the influence of psychosocial risk and resiliency factors.

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