Metabolic Syndrome and Neurocognitive Deficits in HIV Infection

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Background: The adverse consequences of HIV and related comorbidities on the central nervous system remain prevalent in the era of combination antiretroviral therapy. Metabolic syndrome (MetS) is a common comorbidity in HIV and has been linked to increased neurocognitive impairment in the general population. We investigated the association between MetS and neurocognition among persons living with HIV (PLHIV).

Methods: Participants included 109 PLHIV and 92 HIV-uninfected adults (HIV−) from the Multi-dimensional Successful Aging cohort study at the University of California San Diego (age: M = 50.8, SD = 8.0). Participants completed neuromedical, psychiatric, and neurocognitive assessments. Based on a comprehensive neurocognitive battery, we examined global neurocognitive deficits (based on the entire battery) and neurocognitive deficits in 7 domains (verbal fluency, learning, recall, executive function, working memory, speed of information processing, and fine motor skills). MetS was determined via the standard criteria by the National Cholesterol Education Program's Adult Treatment Panel-III. Covariates examined included demographics and psychiatric comorbidities (and HIV disease characteristics among PLHIV).

Results: MetS had an independent significant effect on global neurocognitive deficits among PLHIV (P = 0.03) but not among their HIV− counterparts (P = 0.93). Among PLHIV, MetS was most strongly associated with the neurocognitive domains of learning, fine motor skills, and executive function. Diabetes and elevated triglycerides were the MetS components most strongly linked with increased global neurocognitive deficits in PLHIV.

Conclusions: The present findings underscore the need for early identification of PLHIV at risk for MetS and the implementation of preventive and treatment approaches to lessen the development of MetS and neurocognitive impairment among PLHIV.

Key Words: central nervous system, HIV, AIDS, comorbidity, diabetes mellitus, triglycerides, abdominal obesity, hypertension, cholesterol

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INTRODUCTION

Despite dramatic reductions in HIV-related morbidity and mortality in the era of combination antiretroviral therapy (ART), the adverse consequences of HIV and related comorbidities on the central nervous system remain prevalent, with approximately 40% of persons living with HIV (PLHIV) showing neurocognitive impairment (NCI).[1,2] Whereas these impairments are most typically mild to moderate in severity, they are important predictors of everyday functioning, such as management of medication regimen and driving.[3]

Metabolic syndrome (MetS) is also commonly present in PLHIV,[4] and it is an important predictor of neurocognitive change in the general population.[5–7] MetS is a collection of metabolic risk factors,[8] including abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance/glucose intolerance, a proinflammatory state (characterized by elevated C-reactive protein), and a prothrombotic state (characterized by raised levels of plasminogen activator inhibitor-1 and fibrinogen).[9] Various criteria have been used to determine the presence of MetS. Based on the criteria by the National Cholesterol Education Program's Adult Treatment Panel III report (NCEP ATP III),[9] the overall prevalence of MetS among adults in the United States is estimated to be close to 35%,[10] with advanced age associated with increased prevalence[10,11] and some indication that HIV disease might confer an increased risk for MetS.[12–14]

MetS has been consistently associated with NCI and decline in the general population.[5–7] Specifically, it has been linked to worse executive functioning,[15–18] memory,[16,19] recall,[20] processing speed,[18] and overall intellectual functioning.[20] When the components of MetS are examined individually among HIV-uninfected persons (HIV−), hyperglycemia and hypertension tend to exhibit the strongest associations with NCI.[21,22] Among PLHIV, some of the components of MetS (ie, diabetes and central obesity) have been linked to HIV-associated NCI.[23–26] A small number of cross-sectional studies have found a significant link between diabetes and

worse neurocognitive performance in PLHIV, even after adjusting for significant covariates.[24–26] A cross-sectional study on 130 PLHIV from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort found that central obesity was a significant predictor of NCI in a multivariable analysis that accounted for the impact of body mass index (BMI), triglyceride levels, self-reported diabetes, and a diagnosis of AIDS.[23] In this multivariable model, self-reported diabetes was also marginally associated with NCI but with a large odds ratio. These results indicate that at least certain components of MetS are associated with increased risk for NCI in HIV infection. It should be noted that in both of the aforementioned studies, components of MetS, as opposed to MetS as a cluster of symptoms, were analyzed for their association with neurocognitive functioning among PLHIV. No published studies to date have investigated the impact of MetS as a whole on neurocognition in HIV, which might be greater than the sum of its components' individual effects. Whether the cluster of abnormalities that comprise MetS affects HIV-associated NCI is unknown. Furthermore, although the mechanisms underlying the link between MetS and neurocognitive deficits are likely varied, at least some of these mechanisms, such as lower blood–brain barrier integrity and systemic inflammation,[21,27,28] might result in a larger impact of MetS on neurocognitive functioning among PLHIV compared with HIV− persons. This has not been explored in previous studies, however, which have not included an HIV− comparison group.[23–26]

The overall goal of our study was to examine the association between MetS (as a cluster of abnormalities[9]) and neurocognitive deficits in the context of HIV infection. Our first aim was to investigate the link between MetS and neurocognitive deficits among groups of persons with and without HIV and to assess the potentially modifying role of HIV infection on this association. We hypothesized that the association between MetS and neurocognitive deficits would be stronger among persons with HIV than among those without HIV. Our second aim was to further examine the association between MetS and neurocognitive deficits among PLHIV while accounting for the effects of other factors related to HIV-associated NCI, such as HIV disease characteristics. We hypothesized that even after accounting for these covariates, MetS would be associated with increased concurrent risk for neurocognitive deficits among PLHIV. We were also interested in exploring whether certain components of the MetS might be more strongly associated than others with neurocognitive deficits in PLHIV.

METHODS

Participants

Two hundred one adults (109 PLHIV and 92 HIV−) from the Multi-dimensional Successful Aging study at the University of California San Diego participated in the current study. PLHIV were recruited from a variety of sources that serve adults with HIV in the San Diego area, including community clinics and health care providers. HIV-uninfected participants were recruited from our existing participant pool (ie, participants who were enrolled in previous studies at our research center and who agreed to be contacted for future studies) via flyers posted throughout the community (ie, colleges, coffee shops, gyms) and via presentations by study staff at community organizations. Further details on this study have been published previously.[29,30] Briefly, the inclusion criteria were being between the ages of 35 and 65 years, English-speaking, and capable of providing informed consent. We attempted to recruit an equivalent number of persons in each of three 10-year age cohorts (35–45, 46–54, and 56–65). Exclusionary criteria were a history of non-HIV neurologic disorder (eg, head injury with loss of consciousness greater than 30 minutes or neurologic complications, seizure disorder, stroke with neurologic or neuropsychiatric consequences), current psychotic disorder, and a history of a severe learning disability [eg, Wide Range Achievement-Fourth Edition (WRAT-4)[31] score of <70]. Participants who had positive urine toxicology or Breathalyzer test on the day of testing were rescheduled. Additional inclusion criteria for the present analyses were having data available on neurocognition and MetS. Only data from baseline visits were included, which took place between May 2013 and January 2016. All participants successfully completed an assessment of capacity to consent[32] to participate in clinical research and subsequently provided written informed consent.

Materials and Procedures

Study procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Neuromedical Evaluation

HIV serostatus was determined using enzyme-linked immunoabsorbent assays and confirmatory Western blot analyses in all participants. Metabolic risk factors [ie, elevated triglycerides, reduced high-density lipoprotein (HDL-C), elevated waist circumference, diabetes mellitus, and elevated blood pressure] were determined via laboratory assessments (phlebotomy and anthropomorphic) and current medication use (via self-report and/or record review). These assessments were performed by a clinician or a trained staff under clinical supervision. Per NCEP ATP III criteria, measurements for any of these conditions at or above specific thresholds or current treatment for these conditions was considered as meeting criteria for the relevant metabolic risk factor.[8,33] These thresholds were[8]: (1) waist circumference > 102 cm in men and >88 cm in women, (2) triglycerides ≥ 150 mg/dL, (3) HLD-C < 40 mg/dL in men and <50 mg/dL in women, (4) blood pressure ≥ 130/85 mm Hg, and (5) fasting glucose ≥ 100 mg/dL. MetS was defined as the presence of 3 or more metabolic risk factors. BMI was also calculated using measurements of participants' height and weight.

Among PLHIV, a number of disease and treatment characteristics were collected, including self-reported

estimated duration of HIV infection, use of ART and other medications, lowest measured (nadir) CD4 T-cell count, and historical AIDS diagnosis. Current CD4 cell count and HIV RNA plasma levels were measured at a Clinical Laboratory Improvement Amendments-certified medical center laboratory using reverse transcriptase–polymerase chain reaction with a lower limit of quantitation at 50 viral copies per milliliter. HIV viral load was considered undetectable if values were below the lower limit of quantitation. Following established criteria, the Veteran's Aging Cohort Study Index (a composite measure of disease status and risk for all-cause mortality) was also calculated.[34,35]

Neurocognitive Evaluation

Participants completed a comprehensive neurocognitive test battery, which assessed neurocognitive domains in 7 ability areas: verbal fluency, abstraction/executive functioning, speed of information processing, verbal and visual learning, delayed recall, attention/working memory, and complex motor skills.[36] This battery was designed in agreement with the international consensus conference recommendations.[37] Following previously established and published procedures, domain deficit scores (DDSs) in each of the 7 domains, ranging from 0 (*no impairment*) to 5 (*severe impairment*), were computed from T-scores that were demographically corrected for the effects of age, education, sex, and race.[38,39] These DDSs were then averaged to obtain a summary measure of global NCI [Global Deficit Score (GDS)]. Participants also completed the WRAT-4[31] Reading Test, an estimate of the premorbid cognitive functioning/quality of education.

Psychiatric Evaluation

The presence/absence of current and lifetime major depressive disorder and substance use disorders (ie, of alcohol, tobacco, methamphetamine, cocaine, and 7 other illicit substances) was evaluated using the Composite International Diagnostic Interview[40,41] (CIDI v.2.1), which follows the diagnostic criteria based on the *Diagnostic and Statistical Manual of Mental Disorders—Version IV*.[42]

Statistical Analyses

HIV serostatus group differences on demographic factors, neurocognitive deficits, MetS (and its components), and psychiatric comorbidities were assessed via independent sample t tests (or nonparametric equivalent) and χ^2 tests. To examine whether HIV status modified the association between MetS and neurocognitive deficits, we ran a multivariable linear regression model on GDS with terms for HIV, MetS, their interaction, and significant covariates. Covariates considered included estimated premorbid neurocognitive function (WRAT-4 Reading Scaled Score [SS]) and psychiatric characteristics. Demographic characteristics were not considered as covariates given that GDS scores adjust for age, sex, education, and race. Covariates that differed by HIV status and were associated with GDS (at $P < 0.10$), based on independent sample t tests (or nonparametric equivalent) and χ^2 tests, were considered candidate covariates and included in the multivariable model.

Next, we investigated whether MetS was associated with GDS among PLHIV after considering the impact of significant covariates. To do so, we first examined the univariable association of WRAT-4 Reading SS and psychiatric and HIV disease characteristics to GDS among PLHIV via a series of Pearson product moment correlation coefficients and independent sample t tests. Variables associated with GDS at $P > 0.10$ were entered, along with MetS, as predictors in a multivariable model on GDS within the PLHIV group. To investigate the association between MetS and specific neurocognitive domains, we first ran separate independent sample t tests on each of the domains by MetS group (yes/no) among PLHIV. For domains significantly associated with MetS, we conducted separate multivariable linear regression models adjusting for significant covariates identified in the analyses described earlier. We followed a similar approach in our investigation of the association between specific components of the MetS and GDS.

RESULTS

Characteristics of the Study Cohort by HIV Status

Table 1 summarizes the characteristics of the study cohort by HIV serostatus. Although there were no significant group differences in age, PLHIV had less formal education and were more likely to be male and identified as racial/ethnic minorities than the HIV− group. PLHIV exhibited increased neurocognitive deficits and had a higher prevalence of MetS, particularly elevated triglycerides, reduced HDL cholesterol, and diabetes, but did not significantly differ in BMI compared with the HIV− group. PLHIV had increased rates of current and lifetime major depressive disorder and also lifetime substance use disorder when compared with the HIV− group. Most PLHIV had AIDS, were on ART, and were HIV suppressed (Table 1).

Association Between MetS and Neurocognitive Function in the Overall Cohort

Univariable analyses aimed at selecting significant covariates showed that among the variables that were different by HIV status at $P < 0.10$ (Table 1), only WRAT-4 Reading SS was significantly associated with GDS ($P < 0.01$). A multivariable model in the overall sample on GDS, with HIV status, MetS, and their interaction as predictors, and adjusting for WRAT-4 Reading SS, found a borderline significant HIV by MetS interaction ($P = 0.07$). The F-test for the overall regression model was statistically significant: $F(4, 197) = 6.17$, $P < 0.001$, *Adjusted* $R^2 = 0.10$. Follow-up multivariable linear regression analyses of GDS (stratified by HIV status) with MetS and WRAT-4 Reading SS as predictors found that MetS was significantly associated with GDS among PLHIV (*Estimate* = 0.22, SE = 0.10, $P = 0.03$) but not in the HIV− group (*Estimate* = −0.01,

TABLE 1. Descriptive Characteristics of the Study Cohort by HIV Status

Factor	HIV+ (n = 109)	HIV− (n = 92)	*P**
Demographics			
Age, M (SD)	50.5 (8.5)	51.1 (7.7)	0.61
Education, M (SD)	13.9 (2.4)	15.1 (2.3)	<0.001
Sex, % male	83.5	69.6	0.02
Race/ethnicity, %			0.02
Non-Hispanic White	53.2	69.6	
Non-Hispanic Black	19.3	14.1	
Hispanic	19.3	15.2	
Other	8.3	1.1	
WRAT-4 Reading SS, M (SD)	102.5 (13.9)	106.9 (13.7)	0.02
Global deficit scores, M (SD)	0.53 (0.54)	0.35 (0.36)	0.006
MetS, %	39.5	20.7	0.004
Elevated waist circumference	40.4	51.1	0.13
Elevated triglycerides	43.1	18.5	<0.001
Reduced HDL-C	51.4	37.0	0.04
Elevated blood pressure	51.4	40.2	0.11
Diabetes mellitus	27.5	14.1	0.02
BMI, M (SD)	27.7 (5.4)	27.7 (6.9)	0.99
Psychiatric characteristics, %			
Current major depression	11.4	0.0	<0.001
LT major depression	53.8	20.0	<0.001
LT any substance use disorder	68.5	37.8	<0.001
HIV disease characteristics			
Estimated duration of infection (yr), median (IQR]	18.4 (9.0–25.1)	—	
Nadir CD4 (cells/mm^3), median (IQR)	176 (45–323)	—	
AIDS, %	59.6	—	
Current CD4, median (IQR)	629 (422–853)	—	
On ART, %	95.4	—	
Detectable plasma RNA†	7.4	—	
VACS index, median (IQR)	17 (7–24)	—	

*Based on independent sample *t* tests or χ^2 tests.
†Among those on ART (missing data in 9 participants).
LT, lifetime; VACS, Veterans Aging Cohort Study.

SE = 0.09, $P = 0.93$). Figure 1 shows the least squares means for the association between MetS and GDS based on these multivariable models.

Association Between MetS and Neurocognitive Function in PLHIV

Among PLHIV, univariable analyses to identify significant covariates showed that nadir CD4 ($P = 0.03$) and WRAT-4 Reading SS ($P < 0.001$) were significantly associated with GDS. A multivariable model on GDS with nadir CD4, WRAT-4 Reading SS, and MetS as predictors showed that MetS continued to be significantly associated with GDS ($P < 0.05$), after consideration of the effect of WRAT-4 Reading SS ($P < 0.01$), and nadir CD4 ($P = 0.08$). The F-test for the model was significant: $F(3,104) = 5.93$, $P < 0.001$, *Adjusted* $R^2 = 0.12$. Similar separate models among

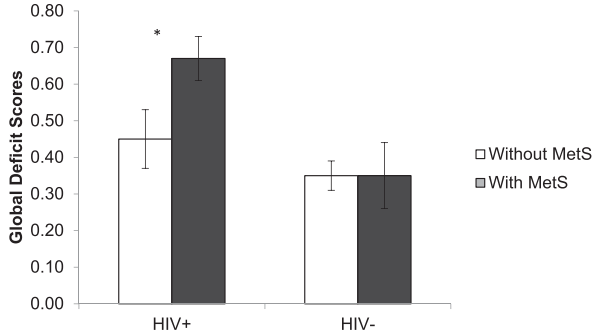

FIGURE 1. Least mean squares (SE) based on the results from separate multivariable linear regression models on GDS by HIV status group investigating the association of MetS with GDS, after accounting for WRAT-4 Reading SS. *$P < 0.05$.

PLHIV on ART (n = 104) and among PLHIV on ART with undetectable plasma viral loads (n = 88) yielded comparable findings.

Next, we ran a series of independent sample *t* tests investigating the association between MetS and neurocognitive DDSs. Compared with PLHIV without MetS, PLHIV with MetS had lower scores in the domains of learning ($P = 0.04$) and fine motor skills ($P = 0.04$) and had borderline lower scores in executive functioning ($P = 0.09$). No other group differences were significant (P's > 0.11). Figure 2 shows Cohen's *d* effect sizes on the association of MetS with each of the neurocognitive domains among PLHIV. Multivariable analyses on neurocognitive DDSs (adjusting for nadir CD4 and WRAT-4 Reading) showed that MetS remained significantly associated with worse fine motor skills (*Estimate* = 0.14, SE = 0.07, $P < 0.05$) and borderline associated with learning (*Estimate* = 0.18, SE = 0.09, $P = 0.07$) but not with executive function (*Estimate* = 0.12, SE = 0.08, $P = 0.12$) or other neurocognitive domains (verbal fluency: *Estimate* = 0.05, SE = 0.06, $P = 0.44$; speed of information processing: *Estimate* = 0.08, SE = 0.06, $P = 0.19$; recall: *Estimate* = 0.11, SE = 0.11, $P = 0.32$; working memory: *Estimate* = 0.11, SE = 0.08, $P = 0.16$).

A series of independent sample *t* tests, assessing differences by each component of the MetS on GDS within PLHIV, showed that elevated triglycerides ($P = 0.04$, Cohen's $d = 0.53$) and diabetes ($P = 0.02$, Cohen's $d = 0.52$) were significantly associated with worse neurocognitive performance, whereas other components of MetS were not (P's >0.10; Fig. 3). Of note, the Cohen's d effect size for the association of MetS (as a whole) and GDS (without adjustment for other covariates) was comparable with that of triglycerides and diabetes (0.53). Prior findings among PLHIV showed that central obesity was associated with neurocognitive function after considering the effect of overall BMI.[23] Thus, we performed a multivariable model on GDS with elevated waist circumference and BMI as predictor variables, and found that waist circumference remained nonsignificant as a predictor of GDS ($P = 0.50$). A similar model with waist circumference as a continuous variable showed comparable findings. Separate multivariable models on GDS with elevated triglycerides and diabetes as predictors

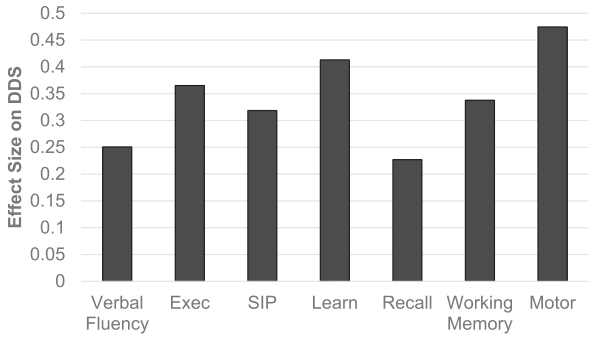

FIGURE 2. Cohen's *d* effect sizes on the association between MetS and neurocognitive DDSs among PLHIV. Exec, executive functioning; SIP, the speed of information processing; learn, verbal and visual learning; recall, delayed recall; motor, fine motor skills.

and adjusting for nadir CD4 and WRAT-4 Reading showed that diabetes (*Estimate* = 0.28, SE = 0.11, $P = 0.02$) remained significantly associated with GDS, whereas elevated triglycerides was unrelated (*Estimate* = 0.12, SE = 0.10, $P = 0.23$).

DISCUSSION

The present cross-sectional study investigated whether MetS, a cluster of metabolic abnormalities, had a stronger impact on neurocognitive deficits among PLHIV than among HIV− persons. We found that (in a sample with average age of 50 years) MetS had an independent significant effect on global neurocognitive deficits among PLHIV but not among their HIV− counterparts. Among PLHIV, MetS was most strongly associated with the neurocognitive domains of learning, fine motor skills, and executive function. Also among PLHIV, diabetes and elevated triglycerides were the MetS components most strongly associated with increased global neurocognitive deficits.

The presence of a significant association between MetS and global neurocognitive deficits among PLHIV but not among HIV− persons indicates that HIV might worsen the impact of MetS on neurocognitive functioning. Although the mechanisms underlying the link between MetS and NCI are likely varied, at least some of these mechanisms, such as

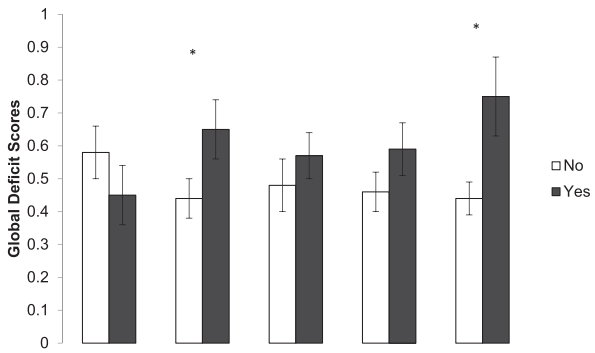

FIGURE 3. Results from independent sample *t* tests on GDS by each of the components of the MetS among PLHIV. HBP, high blood pressure; WC, waist circumference. $*P < 0.05$.

systemic inflammation and lower blood–brain barrier integrity,[27] may predispose PLHIV to a higher risk of neurocognitive deficits. The rate of MetS was much lower among HIV− persons than among PLHIV in the present study, which might have affected our ability to find a significant effect in the HIV− group. Yet, HIV serostatus groups were of comparable age, underscoring the importance of MetS in HIV-associated NCI and the potential for even larger effects in older samples.

Interestingly, among PLHIV, the association between MetS and GDS remained significant after considering the impact of significant covariates. This suggests that the link between MetS and worse neurocognition in this group is likely unexplained by other factors known to affect NCI in HIV, including HIV disease burden. It also highlights the importance of treating MetS in PLHIV to maintain or improve neurocognition.

Although the effect of MetS on individual neurocognitive domains was generally small to medium in this sample of middle- to older-aged PLHIV, MetS was most notably associated with worse learning, executive function, and fine motor skills (Fig. 2). We did not assess for peripheral neuropathy in the present study, which might have confounded the association between MetS and fine motor skills. Of note, our findings linking MetS to executive functioning and learning in PLHIV are consistent with previous work in HIV− individuals.[15–18] However, MetS has also been linked with other neurocognitive domains in the HIV− population (ie, recall,[20] processing speed[18]), which had very small effects in our sample of PLHIV. This suggests that MetS may differentially affect specific neurocognitive domains in the context of HIV infection.

Among PLHIV, diabetes and increased triglycerides were the MetS components most strongly associated with increased global neurocognitive deficits, with medium effect sizes. Although only the association between a diagnosis of diabetes mellitus and GDS remained statistically significant when accounting for relevant covariates, the separate effect of both diabetes and triglycerides on GDS was comparable with that of the overall MetS as a cluster of metabolic abnormalities. Other individual components of MetS (ie, elevated waist circumference, reduced HDL-C, and elevated blood pressure) were not significantly associated with GDS. Our findings are consistent with previous studies that demonstrated significant associations between diabetes mellitus and worse cognitive performance in HIV[25,26] and indicate that this might be an important risk factor for HIV-associated NCI. Our results are also in-line with previous findings showing that other components of MetS, such as hypertension and HDL-C, might not be as important for neurocognition among PLHIV.[24] Contrary to our findings, a previous cross-sectional study showed that greater waist circumference increased the risk for NCI among PLHIV in the context of considering the impact of BMI and other variables.[23] Why these studies have disparate findings is unclear. Measurements of waist circumference and neurocognition followed similar procedures in both studies and thus are less likely to have played a notable role. Small demographic differences between participants in the 2 studies in mean age

(approximately 4 years) and education (approximately 1 year) also seem unlikely to explain the difference in results.[23] Future studies with larger and more diverse samples in terms of sex and race/ethnicity might help determine whether these factors modify the association of waist circumference and neurocognitive deficits in HIV.

Whereas investigating rates of MetS in HIV infection was not the focus of the present study, PLHIV in the current sample had nearly twice the rate of MetS than the HIV− comparison group. This increased prevalence of MetS in HIV is consistent with previous studies[14] and with findings linking worse HIV disease to MetS.[12,13] Higher HIV viral load has been linked to MetS,[12] possibly due to the increased inflammation and immune activation resulting from poorly controlled HIV infection. Alterations in lipid and glucose metabolism that result from undergoing various ART modalities, particularly protease inhibitors,[43–45] might also play a role in increasing the prevalence of MetS in HIV. Yet, findings linking ART use to HIV have been mixed.[4,12–14,44] Furthermore, a population-based study in the United States did not find an increased risk for MetS among PLHIV.[4] Importantly, this previous study[4] included PLHIV who were evaluated between 2000 and 2003 and had an average age of almost 10 years younger than participants in the present study. HIV disease has been transformed considerably since these earlier days of the US HIV epidemic, which might explain some of the disparate findings.

The present study has a number of limitations. First, the cross-sectional design prevents us from ascribing directionality to our findings. Longitudinal observational studies and intervention research will be needed to test potential causal relationships. Second, the relatively small sample sizes and the demographic characteristics of our cohort might have limited our power to detect associations. For example, despite previous findings showing a robust association between MetS and neurocognitive functioning,[5–7] we found that among HIV− participants, MetS was unrelated to global neurocognitive deficits. This null finding may have been a consequence of the young age of participants relative to those from previous studies, who tended to be at least 60 years old. As MetS is typically considered a condition of older age, too few of our HIV− participants may have developed MetS (only 21% compared with 39% of PLHIV). Furthermore, as expected, neurocognitive deficits were significantly higher among PLHIV than among HIV− individuals. These factors likely limited our ability to detect significant associations between MetS and neurocognitive performance in the HIV−group.[11] Due to a small number of women living with HIV and relatively low numbers of specific racial/ethnic minority participants in our study, we were unable to examine how these other potentially important demographic factors might affect the relationship between MetS and NCI. This seems particularly important in light of previously established differences on MetS by sex and race/ethnicity[11,46,47] and higher rates of NCI among Hispanics living with HIV.[48] Future studies should use a larger, more diverse sample to examine the effects of age, sex, and race/ethnicity.

Overall, the present findings underscore the importance of considering cardiometabolic disease as a potential risk factor for poor neurocognitive outcomes among PLHIV. Additional longitudinal studies will best determine whether there is a causal role of MetS on neurocognitive deficits. Intervention research, including investigations of whether treatment for components of the MetS might affect NCI, would help identify treatment approaches that might be best suited to lessen the development of MetS and its potential impact on NCI among PLHIV.

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