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Anthropometric measures and cognition in middle-aged HIV-infected and uninfected women. The Women's Interagency HIV Study

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Abstract

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Conflict of Interest: All authors, Deborah R. Gustafson, MS, PhD; Michelle M. Mielke, PhD; Phyllis C. Tien, MD; Victor Valcour, MD; Mardge Cohen, MD; Kathryn Anastos, MD; Chenglong Liu, MD, PhD; Leigh Pearce, PhD; Elizabeth T. Golub, PhD; Howard Minkoff, MD; and Howard A. Crystal, MD, have nothing to declare.

Objective—To explore the relationship of body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) with cognition in women with (HIV+) and without HIV (HIV-) infection.

Design/Methods—1690 participants (1196 HIV+, 494 HIV-) in the Women's Interagency HIV Study (WIHS) with data available on anthropometric measures comprise the analytical sample. Cross-sectional analyses using linear regression models estimated the relationship between anthropometric variables and Trails A, Trails B, Stroop interference time, Stroop word recall, Stroop color naming and reading, and Symbol Digit Modalities Test (SDMT) with consideration for age, HIV infection status, Wide Range Achievement Test score, CD4 count, insulin resistance, drug use, and race/ethnicity.

Results—Among HIV+ women, BMI < 18.5 kg/m² was associated with poorer cognitive performance evidenced by longer Trails A and Trails B and shorter SDMT completion times. An obese BMI (30 kg/m² or higher) was related to better performance on Trails B and worse performance on the Stroop Interference test. Among HIV- women, an obese BMI was related to worse performance on the Stroop – Color naming test. Few and inconsistent associations were observed between WC, WHR and cognition.

Conclusion—Among women at mid-life with chronic (at least 10 years) HIV infection, common anthropometric measures, primarily BMI, were differentially related to cognitive test performance by cognitive domain. Higher levels of BMI were associated with better cognitive function. In this era of antiretroviral therapies, restoration of health evidenced as higher BMI due to effective antiretroviral therapies, may improve cognitive function in middle-aged HIV infected women.

Keywords

Cognition; HIV; Women; Overweight; Obesity; Middle-Aged

Introduction

Human Immunodeficiency Virus (HIV) infection is one of the most prevalent infectious diseases worldwide. Since survival of those with HIV infection is extended because of adherence to antiretroviral therapies, HIV infection will become a chronic infection of aging.

According to the CDC, in 2010 there were an estimated 47,500 people newly infected with HIV in the United States. Of these, 15% (N=7125) were aged 45-55 years and 5% (n=2375) were aged 55 years and older.(Prevention, 2012a) Add to this, prevalent infections in 2009, when there were 381,000 prevalent HIV infections among those aged 45-54 years, and almost 200,000 prevalent HIV infections among those aged 55 years and older.(Prevention, 2012b) This totals almost 600,000 HIV infected adults age 45 years or older in the U.S., which is an underestimate. Thus, these data, illustrate the potential burden of HIV associated cognitive disorders due to the high proportion of HIV/AIDS survivors over age 45 years.

In many countries, the advent of antiretroviral therapy (ART) has been accompanied by an increase in BMI due to normalization of health that also mirrors trends in the general population. However, WIHS women are overweight and obese on average, and overweight and obesity are leading causes of disability and death in the United States and around the world and have been linked to cognitive impairments. Obesity is associated with hypertension, dyslipidemias, Type 2 diabetes mellitus, and cardiovascular disease, and these metabolic complications may be more prevalent in HIV.(2006; Sobieszczyk *et al*, 2008) These factors also increase risk for age-related, late onset cognitive impairments (CI) and eventually clinical Alzheimer's disease (AD) and vascular dementias.(Gustafson and Skoog, 2009) Given the aging HIV-infected population, it is important to understand how HIV-

infection influences aging, as well as accompanying morbidities such as obesity and outcomes such as cognitive impairments and dementia.

Obesity is associated with age-related cognitive impairments and dementia in populations without HIV. Mid-life obesity, estimated using BMI, waist circumference (WC), or waist-to-hip ratio (WHR), measured decades before dementia onset has been linked to higher risk of AD.(Fitzpatrick *et al*, 2009; Gustafson *et al*, 2009a; Whitmer *et al*, 2007) However, associations of obesity with cognitive impairments in mid-life are unclear.(Gustafson *et al*, 2009a) It has been suggested that the aging HIV population may experience more than the anticipated burden of cognitive impairments since many HIV infected individuals have experienced metabolic and vascular consequences of early ART regimens and other medications, in addition to earlier, mid-life cognitive impairments due to the HIV infection. While use of ART has been suggested to decrease the incidence and prevalence of AIDS- or HIV-associated dementias,(Berger and Brew, 2005; Bhaskaran *et al*, 2008; González-Scarano and Martín'García, 2005; Moroni and Antinoria, 2003; Saktor, 2002) the frequency of cognitive impairments has not changed(Heaton *et al*, 2011). The impact of HIV, multi-morbidities and ART on late life sporadic dementias and AD (incident after age 65 years) remains to be understood. Some studies suggest that the prevalence of cognitive impairments, ranging from 15 to 50%, will worsen as the HIV population ages, thus putting them at risk for AD.(Cohen and Gongvatana, 2010; Heaton *et al*, 2010; McArthur and Brew, 2010)

In the present study, we determined whether anthropometric indices are differentially associated with cognitive performance in women who are HIV+ or HIV- from the Women's Interagency HIV Study (WIHS).(Bacon *et al*, 2005; Barkan *et al*, 1998) Demographic, cardiovascular, and HIV-related factors were considered as confounders.

Methods

The WIHS(Bacon *et al*, 2005) is an ongoing prospective study of HIV in women. The WIHS began in 1994 and enrolled 3766 women across six sites in San Francisco, Los Angeles, Chicago, Washington, DC, Brooklyn and the Bronx (New York). WIHS initially recruited 2054 HIV infected (HIV+) and 569 HIV uninfected (who in WIHS, are their 'at risk' counterparts, HIV-) women in 1994-95, and an additional 737 HIV-infected and 406-HIV uninfected women in 2001-2002. Participants are evaluated every six months with an extensive interview that includes history of interval illnesses and interval substance abuse, current medications and medication adherence, physical exam, and blood and gynecological specimen collection.

Demographic measures

All demographic measures were self-reported. Race(Bacon *et al*, 2005; Barkan *et al*, 1998) was self-reported as white, Hispanic, African-American, or 'other' (self-reported as Native American/Alaskan, Asian/Pacific Islander or other) for all participants. Participants are also asked to report their current smoking status, and use of marijuana, 'crack', cocaine, and heroin.

Clinical measures

Anthropometric measures were conducted according to NHANES III protocol and included body weight (pounds), body height (inches), waist and hip circumferences (cm), and BMI (kg/m^2).(Justman *et al*, 2008) Anthropometric measurements were conducted with participants wearing only undergarments. Those who conduct the measurements are recertified every two years. Body weight was recorded to the nearest 1.0 pound, and body

height was measured to the nearest 1.0 inch. After conversion of body weight and height to metric units, body mass index (BMI) was calculated as kilograms per meter squared (kg/m^2). Categories of BMI used to denote total body adiposity were $\geq 25 \text{ kg}/\text{m}^2$ for overweight and obesity, and $\geq 30 \text{ kg}/\text{m}^2$ for obesity.(1989) Waist and hip circumferences were measured to the nearest 0.5 cm. WHR was calculated as the ratio of waist to hip circumference. Central obesity was defined as $\text{WHR} > 0.80$ or $\text{WC} \geq 88 \text{ cm}$.(Croft *et al*, 1995)

Eight hour fasted blood samples were collected and total cholesterol levels were determined as previously described.(Crystal *et al*, 2011) Systolic (SBP) and diastolic blood pressures (DBP) were recorded using a standardized protocol.(Mansoor *et al*, 2009) Hypertension was defined as either average measured systolic BP $>140 \text{ mm Hg}$, or diastolic BP $>90 \text{ mm Hg}$, or a self-reported hypertension with use of antihypertensive medications. Previous myocardial infarction (MI) and diabetes mellitus (DM) were self-reported.(Bacon *et al*, 2005; Barkan *et al*, 1998)

HIV-related variables

Methods for determining HIV status, AIDS diagnosis, CD4 count, viral load, and duration of ART use were described previously.(Bacon *et al*, 2005; Barkan *et al*, 1998; Kaplan *et al*, 2008)

Cognitive tests

The cognitive tests were administered to all English-speaking WIHS participants during visits 21 to 24 (October 2004 to September 2006) as part of the WIHS core assessment; the Comalli-Kaplan Stroop was administered to a subgroup during visits 25-28, October 2006 to September 2008 (Table 1). These tests have been previously described.(Crystal *et al*, 2011) These tests were selected for a number of reasons. Most importantly, these tests overlap with those that had already been used for several years in the Men's AIDS cooperative study (MACS),(Miller *et al*, 1990) which is a "brother" study to the WIHS. In addition, these tests are sensitive to the domains most affected in HIV in the pre-ART era, are relatively short, can be administered reliably by trained personnel who are not neuropsychologists, are less sensitive to practice effects than many other cognitive tests, and cover a number of important cognitive domains shown to be affected early in late onset Alzheimer's disease, in addition to being sensitive to HIV-associated neurocognitive disorder (HAND). Among participants who completed testing on multiple visits, and therefore have more than one score, only the first score was used. Times greater than 240 seconds were coded as 240 seconds. Errors were recorded, but were not used to adjust interference times. For all cognitive tests, we used raw scores rather than normalized data.

Inclusion criteria

We include all data collected by visit 28, concluding in September 2008 on 1690 participants (494 uninfected and 1196 HIV-infected) with data available on both anthropometric and cognitive measures.

Statistical analysis

Anthropometric factors were considered as continuous and categorical variables according to commonly defined cutpoints (stated above). BMI, WHR and WC, were categorized into tertiles to assist in understanding nonlinear relationships between the anthropometric measures and cognitive test scores, and to practically apply the results to commonly used overweight and obese categories. Linear regression analyses were used to examine the association between the continuous or categorical anthropometric factors and cognitive test scores (time to completion) of Trails A, Trails B, Stroop Interference, Stroop Color Naming,

and Stroop Word Recall; or SDMT score. A longer time to completion (higher score) indicates worse cognitive performance for the first 6 tests; in contrast, a lower SDMT score denotes worse performance. Regression models were run separately for HIV+ and HIV-.

Several covariates were considered, including: age, race, highest educational level attained, Wide Range Achievement Test (WRAT) score, HIV status, ART, CD4 count, CD4 nadir, prevalent DM, SBP, DBP, use of anti-hypertensive medications, use of exogenous insulin, blood cholesterol level, current smoking status, and use of marijuana, 'crack', cocaine, and/or heroin. Potential covariates were included if significant in age-adjusted models at a level of $p < 0.05$. Given this significance level, final models included the following covariates: age, WRAT, race, exogenous insulin, and any recreational drug use. Other covariates evaluated, such as CD4 count or CD4 nadir, were not significant. In analyses of women who were HIV+, we also adjusted for HIV viral load. In analyses of both HIV+ and HIV- women we included and excluded drug users. STATA 12 was used for all statistical analyses. Results were considered statistically significant at $p < 0.05$.

Results

Both anthropometric factors and cognition were available for 1664 WIHS participants (1196 HIV+ and 494 HIV- women). Demographic, anthropometric, and health characteristics are presented in Table 2. Notably, based on average age, these women were not at risk for late-onset, aging-related cognitive impairments or dementias. HIV+ women were approximately 4 years older than HIV- women, however educational attainment, a key influencer of cognitive performance, did not differ between HIV+ and HIV-women. In addition, most (69%) women were overweight or obese ($> 25.0 \text{ kg/m}^2$) and the prevalence of central obesity was high. There was a very low percentage of women with BMI < 18.5 , in concordance with the low prevalence of AIDS among those who were HIV+. HIV+ women had lower average BMI and WC, and higher WHR, compared to HIV- women. Among published vascular risk factors for dementia, hypertension was also more prevalent in HIV+ women, however average total blood cholesterol levels and the prevalence of diabetes mellitus did not differ.

Multivariate linear regression analyses relating anthropometric measures to cognitive test scores showed divergent results by test and anthropometric measure. It is important to note that the covariates included in the final multivariate models are those that were significant in age-adjusted models. Variables associated with HIV disease and typically included in models of HIV, such as CD4 count, are not included in final models since they were not significantly associated in age-adjusted models.

Body mass index, BMI (Table 3)

Among women with HIV, compared to those with normal BMI ($18.5\text{--}25.0 \text{ kg/m}^2$), having a very low BMI ($< 18.5 \text{ kg/m}^2$) was associated with a longer time to completion (poorer performance) on Trails A and Trails B. Compared to a BMI in the healthy range ($20\text{--}24.9 \text{ kg/m}^2$), an obese BMI (30 kg/m^2 or higher), and an increasing continuous BMI were related to shorter Trails B completion time (better performance), and longer time to Stroop Interference test completion (worse performance), both executive function measures. A BMI $< 18.5 \text{ kg/m}^2$ was associated with lower SDMT score, a measure of psychomotor speed, and evidence of worse performance. Among HIV- women, an obese BMI was related to worse performance on the Stroop-Color naming test.

Waist circumference (Table 4)

Among women with HIV, a waist circumference of 88 cm or more was related to shorter completion time on Trails B (better performance); and a nonlinear relation with Trails A, such that the shortest time to completion (best performance) was observed among those in the middle category of waist circumference (80-87.9 cm). Among HIV- women, there were no associations between waist circumference and performance on any test after adjusting for potential confounders.

Waist-to-hip ratio, WHR (Table 5)

Among women with HIV, a higher WHR was associated with a better SDMT score. However, there were no other associations between WHR and cognitive performance in HIV+ or HIV- women.

Subanalyses

In subsequent analyses, ART use was evaluated as a potential confounder in multivariate models predicting cognitive test scores. Use versus no use of ART use was not found to influence the results. Over 80% of participants were on ART. Similarly, we excluded women who reported recent use of recreational drugs and the results were similar in all essential aspects.

Discussion

Among women at mid-life with HIV for at least 10 years, the association between common anthropometric measures (primarily BMI) and cognitive test performance differed depending on the cognitive domain being assessed. Perhaps these observations illustrate the severity and variable metabolic dysregulation in women with HIV.

Considering any anthropometric measure – BMI, WC, or WHR – in relation to cognition, we observed some patterns in women with HIV infection. There appears to be an association between higher BMI and better performance on the Trails B test, and the SDMT. At a significance level of $p < 0.10$, an obese phenotype based on BMI or WC, was associated with longer Stroop Interference time, yet higher SDMT score. Considering all observed associations, aside from Trails B and SDMT, being more overweight and obese was related to worse performance.

Similar to other reports in non-HIV samples that relate anthropometric measures to cognition, anthropometric measures of being overweight and obesity are related to worse cognitive performance. Executive function and speed of information processing are the cognitive domains most commonly associated with these measures.

The association between anthropometric measures and cognitive performance was more pronounced among HIV+ women than HIV- women. Among women in whom higher BMI and WC measures were related to better cognitive function, it may be indicative of a normalization of health due to HIV treatments and better medical and nutritional care and status, for which higher BMI and central obesity may be markers. Among HIV+ women with a BMI $< 18.5 \text{ kg/m}^2$, longer completion times on Trails A and B may be due to the detrimental influence of HIV-related illness, such as AIDS or cancer, on cognition, and/or lack of adherence to ART over time. Attempting to evaluate individuals with AIDS as a group was difficult due to a low number of participants; and adjustment for HIV disease markers was not informative.

While high mid-life BMI (Fitzpatrick *et al*, 2009; Kivipelto *et al*, 2005; Whitmer *et al*, 2005) and central obesity (measured as waist circumference or WHR) (Gustafson *et al*, 2009b; Whitmer *et al*, 2008) have been shown to increase risk for AD in non-HIV infected populations, cross-sectional relationships with cognition in mid-life are not clear. In addition, these simple anthropometric measures reflect different aspects of body composition, and are crude estimates of body adiposity at best. A high BMI is reasonably correlated with whole body amount of adipose tissue in healthy HIV-negative adults. (Shah and Braverman, 2012) A high waist circumference is a measure of central obesity. However, a high WHR may reflect both higher waist circumference and/or lower hip circumference. In HIV+ individuals who experience lipoatrophy of the hip region, a higher WHR may be more reflective of the lipoatrophy than the central obesity. Thus, these HIV-associated alterations in anthropometric measurements may increase the variability in the measure making it a less accurate measure when compared to an uninfected population. High BMI and WC during mid-life are also related to other vascular risk factors, such as DM, (Capeau *et al*, 2012) hypertension, and hyperlipidemia, which increase risk for cognitive impairments and dementia in non-HIV populations. Hypertension was more prevalent in HIV+ women in this sample compared to HIV- women. However, adjustment for hypertension and insulin resistance did not alter the association of anthropometric factors with cognition in multivariate models. In HIV+ individuals, mid-life relationships of vascular risk factors and cognition are also unclear. The relationship between mid-life risks and late-life cognitive impairment is not known, but will be investigated when this cohort of women enters later stages of life.

At least one other study has investigated the relationship of anthropometric variables on cognitive function in HIV. (McCutchan *et al*, 2012) Similar results for BMI in relation to cognitive impairment were reported among 130 participants in the CHARTER study, (McCutchan *et al*, 2012) in relation to cognitive impairment. Higher BMI was protective for cognitive impairment, after adjustment for WHR among HIV+ participants. Vascular factors associated with being overweight and obese have also been related adversely to cognitive function. For example, prior cardiovascular disease, hypertension, and hypercholesterolemia have been related to measures of motor speed in 292 participants from the SMART study. (Wright *et al*, 2010) Hypertension has also been reported to adversely influence cognition in WIHS. (Crystal *et al*, 2011)

The influence of ART on cognition and overall health in HIV is mixed depending on the severity cognitive outcome being assessed and age of the patient. Data suggest no difference in the proportion of individuals with HIV-associated cognitive disorder (HAND) in the pre-versus post-ART eras, (Heaton *et al*, 2011) however, the prevalence of AIDS dementias, the most severe form of impairment, has fallen precipitously concurrent with optimization of medication regimens and better care overall. As HIV infected populations survive to older ages, they may be at risk for more severe cognitive impairments. This would be a new phenomenon, but is speculative at this time. ART may have cardiovascular side effects, such as atherosclerosis, (Bozzette *et al*, 2003; Currier, 2007) DM, and hypertension, even in children. These cardiovascular factors have been related to AD in populations without HIV infection; and cardiovascular risk factors are associated with worse cognition in persons with HIV. (Becker *et al*, 2009; Wright *et al*, 2010) While, the positive influence of ART on cognition is clear; there are several studies that provide controversial data to suggest a concurrent negative influence. Some studies show that discontinuing ART is associated with improved performance on cognitive tests; (Mary-Krause *et al*, 2003), (Robertson *et al*, 2010) and it has been speculated that certain ART regimens are deleterious for cognition. (Andrieu *et al*, 2011) Alternatively, ART has shown a positive effect on health, eliminating HIV and improving health status. Even so, alterations in adipose tissue, adipose tissue distribution,

adipose tissue hormones, and/or lipid metabolism, may create an altered metabolic and hormonal milieu that may be undesirable for the brain.(Gustafson, 2010)

This is a large study of anthropometric measures and cognition in women with and without HIV-infection. Strengths include the large multi-ethnic participant sample, and a variety of anthropometric measures that are commonly used to estimate total and regional body fatness. The primary limitations include a limited battery of cognitive tests and cross-sectional analyses. Due to multiple comparisons, and relatively high p-values one must also consider risk for false discoveries. Only 3 p-values were < 0.005, all among HIV infected women. These included BMI < 18.5 kg/m² being associated with worse Trails A and worse SDMT performance, and waist > 88 cm associated with better Trails B performance. Our analyses were not adjusted for multiple comparisons. However, this is one of the first reports of a consistently reported risk factor for late-onset AD in relation to cognition in HIV. In summary, these data suggest the need for continued follow up of these women to determine mid-life and late-life effects of adipose tissue and adipose tissue alterations on cognition and dementia in HIV.

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Table 1

Cognitive tests administered in WIHS and corresponding cognitive domains measured.^{23,26}

Cognitive Domain	Test
Executive Function	Trails A, Trails B Stroop Interference ^{27,28}
Speed of Information Processing	Symbol Digit Modalities Test (SDMT) ^{* 29,30} Stroop Color Naming and Reading
Learning and Memory	Stroop Word Recall

* The SDMT score is the number of correct items in 90 seconds, all other test scores are times with lesser time indicating better performance.

Table 2

Demographic and health characteristics of Women's Interagency HIV Study (WIHS) participants with anthropometric measurements.

Characteristic	ALL		HIV+		HIV-		p-value
	N	mean (SD)/n(%)	N	mean (SD)/n(%)	N	mean (SD)/n(%)	
Age (years)	1690	41.3 (9.4)	1196	42.5 (8.9)	494	38.4 (10.1)	<0.0001
Race	1690		1196		494		0.187
White		347 (20.5%)		257 (21.5%)		90 (18.2%)	
African American (AA)		1078 (63.8%)		746 (62.4%)		332 (67.2%)	
Non-white, non-AA Hispanic		214 (12.7%)		159 (13.3%)		55 (11.1%)	
Other		51 (3.0%)		34 (2.8%)		17 (3.4%)	
Highest education	1685		1194		491		0.571
Grades 7-11		586 (34.8%)		428 (35.9%)		158 (32.2%)	
Completed High School		539 (32.0%)		377 (31.6%)		162 (33.0%)	
Some college		436 (25.9%)		305 (25.5%)		131 (26.7%)	
4-year degree		94 (5.6%)		62 (5.2%)		32 (6.5%)	
attend/completed graduate school		30 (1.8%)	1176	22 (1.8%) 463.7 (275.4)		8 (1.6%)	
CD4 count			1176	463.7 (275.4)			
Viral load			1187	20626.1 (107073.0)			
<i>Cognitive test scores</i>							
Trails A	1674	38.2 (16.5)	1183	39.2 (16.5)	491	36.0 (14.2)	<0.001
Trails B	1631	91.1 (49.6)	1147	93.2 (50.8)	484	86.0 (46.3)	0.007
Symbol Digit	1650	42.4 (12.5)	1163	41.3 (12.5)	487	45.0 (12.2)	<0.0001
Stroop - Color Name Time	972	71.6 (19.8)	658	73.1 (19.8)	314	68.4 (15.7)	<0.001
Stroop -- Word Read Time	974	55.1 (15.2)	661	56.1 (15.9)	313	52. (13.5)	0.002
Stroop -- Interference Time	957	129.4 (31.2)	647	131.8 (31.9)	310	124.5 (29.1)	<0.001
<i>Anthropometric Indices</i>							
BMI (kg/m ²)	1680	29.3 (7.8)	1188	28.6 (7.5)	492	30.9 (8.3)	<0.0001
<18.5				27 (3.1%)		5 (1.0%)	
18.5 – 24.9				380 (32.%)		120 (24.4%)	
25 - < 29.9				355 (29.9%)		129 (26.2%)	
30				426 (35.9%)		238 (48.4%)	<0.001
Waist measurement (cm)	1501	92.0 (16.3)	1054	91.3 (15.5)	447	93.7 (18.1)	0.01

Characteristic	ALL		HIV +		HIV -		p-value
	N	mean (SD)/n(%)	N	mean (SD)/n(%)	N	mean (SD)/n(%)	
< 80				261 (24.8%)		108 (24.2%)	
80-87.9				220 (20.9%)		83 (18.6%)	
88				573 (54.4%)		256 (57.3%)	0.509
WHR	1498	0.89 (0.08)	1053	0.90 (0.08)	445	0.86 (0.08)	<0.0001
< 0.85				309 (29.3%)		202 (45.4%)	
0.85 - <0.90				241 (22.9%)		92 (20.7%)	
0.90 - <0.95				243 (23.1%)		76 (17.1%)	
0.95				260 (24.7%)		75 (16.9%)	<0.001
Marijuana Use since last visit	1684	335 (19.9%)	1190	205 (17.2%)	494	130 (26.3%)	<0.001
Any indicator of hypertension *	1690	727 (43.0%)	1196	543 (45.4%)	494	184 (37.3%)	0.002
Diabetes mellitus	1463	102 (7.0%)	1040	74 (7.1%)	423	28 (6.6%)	0.736
Total Cholesterol (mg/dl)	1689	175.6 (40.9)	1195	175.5 (42.3)	494	175.8 (37.4)	0.872

* Either SBP $\geq$ 140, DBP $\geq$ 90, self-reported hypertension, or taking anti-hypertensive medication.

Table 3

Body Mass Index (BMI) category in relation to cognitive test scores: the Women's Interagency HIV Study (WIHS).

		BMI category (kg/m ²)				
		<18.5	18.5-24.9	25-29.9	30	
		Beta ^a (95% CI) p-value	referent	Beta (95% CI) p-value	Beta (95% CI) p-value	
Executive Function						
Trails A						
HIV+	Crude ^b	8.13 (2.63, 13.63)	0.0	-0.35 (-2.71, 2.01)	0.47 (-1.80, 2.75)	
		0.004		0.771	0.797	
HIV-	Adjusted ^c	8.62 (3.40, 13.83)	0.0	-0.32 (-2.66, 2.02)	-0.53 (-2.82, 1.76)	
		0.001		0.79	0.649	
HIV+	Crude	-8.04 (-20.42, 4.33)	0.0	-0.45 (-3.90, 3.00)	1.02 (-2.04, 4.08)	
		0.202		0.797	0.513	
HIV-	Adjusted	-7.81 (-20.05, 4.44)	0.0	-1.54 (-5.08, 2.01)	-0.36 (-3.61, 2.88)	
		0.211		0.394	0.826	
Trails B						
HIV+	Crude	18.89 (1.74, 36.04)	0.0	-5.33 (-12.71, 2.04)	-6.38 (-13.46, 0.70)	
		0.031		0.156	0.078	
HIV-	Adjusted	17.66 (1.77, 33.54)	0.0	-5.59 (-12.73, 1.55)	-7.84 (-14.78, -0.91)	
		0.029		0.125	0.027	
HIV+	Crude	-16.87 (-56.55, 22.80)	0.0	11.12 (-0.02, 22.26)	2.45 (-7.50, 12.40)	
		0.404		0.050	0.629	
HIV-	Adjusted	-14.83 (-52.94, 23.28)	0.0	7.11 (-4.01, 18.22)	-2.86 (-13.08, 7.37)	
		0.445		0.210	0.583	
Stroop Interference						
HIV+	Crude	1.61 (-14.81, 18.04)	0.0	2.29 (-3.89, 8.47)	5.83 (0.02, 11.65)	
		0.847		0.467	0.049	
HIV-	Adjusted	2.11 (-12.87, 17.09)	0.0	2.41 (-3.36, 8.18)	5.17 (-0.40, 10.73)	
		0.782		0.413	0.069	

		BMI category (kg/m2)			
		<18.5	18.5-24.9	25-29.9	30
		Beta ^a (95% CI) p-value	referent	Beta (95% CI) p-value	Beta (95% CI) p-value
HIV-	Crude	-7.51 (-40.07, 25.04)	0.0	6.33 (-2.60, 15.26)	5.69 (-2.20, 13.59)
	Adjusted	-10.47 (-41.28, 20.34)	0.0	4.12 (-4.59, 12.83)	3.06 (-4.77, 10.88)
		0.650		0.164	0.157
		0.504		0.353	0.442
Speed of Information Processing					
Symbol Digit Modalities Test (SDMT)					
HIV+	Crude	-5.44 (-9.60, -1.28)	0.0	0.28 (-1.49, 2.06)	0.50 (-1.21, 2.21)
	Adjusted	-5.54 (-9.32, -1.75)	0.0	0.29 (-1.39, 1.98)	1.53 (-0.12, 3.18)
		0.010		0.755	0.565
		0.004		0.732	0.070
HIV-	Crude	5.62 (-4.69, 15.94)	0.0	0.80 (-2.10, 3.69)	1.06 (-1.50, 3.62)
	Adjusted	4.95 (-4.29, 14.18)	0.0	0.588	0.417
		0.285		0.245	0.052
		0.293			
Stroop Color Naming					
HIV+	Crude	-0.78 (-11.10, 9.53)	0.0	-0.18 (-4.05, 2.68)	0.67 (-2.95, 4.29)
	Adjusted	0.07 (-9.45, 9.59)	0.0	0.925	0.715
		0.882		0.40 (-3.24, 4.05)	0.35 (-3.14, 3.84)
		0.988		0.828	0.844
HIV-	Crude	3.63 (-13.58, 20.83)	0.0	3.06 (-1.62, 7.74)	7.21 (3.06, 11.37)
	Adjusted	2.53 (-13.27, 18.63)	0.0	0.199	0.001
		0.679		1.51 (-3.01, 6.03)	5.20 (1.12, 9.27)
		0.757		0.512	0.013
Learning and Memory					
Stroop Word Recall					
HIV+	Crude	1.27 (-7.02, 9.56)	0.0	-0.02 (-3.11, 3.08)	1.49 (-1.41, 4.39)
	Adjusted	0.764		0.990	0.314
		1.70 (-5.55, 8.96)	0.0	0.54 (-2.23, 3.31)	0.95 (-1.71, 3.61)
		0.645		0.704	0.483

		BMI category (kg/m2)			
		<18.5	18.5-24.9	25-29.9	30
		Beta ^a (95% CI) p-value	referent	Beta (95% CI) p-value	Beta (95% CI) p-value
HIV-	Crude	3.15 (-12.04, 18.35) 0.683	0.0	1.79 (-2.35, 5.94) 0.395	4.67 (1.00, 8.36) 0.013
	Adjusted	2.37 (-11.31, 16.06) 0.733	0.0	0.22 (-3.62, 4.07) 0.909	2.89 (-0.58, 6.36) 0.102

^aA positive beta coefficient indicates a positive relationship between anthropometric measure and cognitive test score. For all tests except SDMT, a positive relationship indicates worse cognitive performance with higher level of anthropometric measure. Thus, in fully adjusted models, a BMI < 18.5 kg/m² is related to longer Trails A completion among HIV+ compared to those with a BMI within the normal range of 18.5-24.9; a BMI 30 kg/m² is related to a shorter Trails A completion time.

^bCrude models adjust for age.

^cMultivariate models adjust for the covariates: age, WRAT, race, insulin, and any drug use.

Table 4
Waist circumference category related to cognitive test scores: the Women's Interagency HIV Study (WIHS)

		Waist circumference category (cm)	
		<80	88
		referent	Beta (95% CI) p-value
<i>Executive Function</i>			
Trails A			
HIV+			
	Crude	0.0	-1.21 (-4.13, 1.72)
			-0.24 (-4.26, 3.79)
	Adjusted	0.0	0.417
			0.907
			0.26 (-2.96, 3.48)
			0.194
			0.875
HIV-			
	Crude	0.0	-1.79 (-4.72, 1.14)
			-0.66 (-4.73, 3.41)
	Adjusted	0.0	0.231
			0.748
			-3.04 (-5.48, -0.60)
			-0.89 (-4.27, 2.49)
			0.015
			0.606
Trails B			
HIV+			
	Crude	0.0	-7.19 (-16.37, 1.98)
			-8.19 (-15.74, -0.65)
	Adjusted	0.0	0.124
			0.033
			-10.98 (-19.92, -2.04)
			-10.95 (-18.43, -3.46)
			0.016
			0.004
HIV-			
	Crude	0.0	3.66 (-8.76, 16.08)
			1.95 (-8.02, 11.91)
	Adjusted	0.0	0.562
			0.701
			0.91 (-11.29, 13.12)
			-3.16 (-13.32, 6.99)
			0.883
			0.540
Stroop Interference			
HIV+			
	Crude	0.0	0.59 (-6.94, 8.12)
			6.36 (0.14, 12.58)
	Adjusted	0.0	0.878
			0.045
			0.54 (-6.55, 7.63)
			5.50 (-0.49, 11.50)
			0.881
			0.072

		Waist circumference category (cm)		
		<80	80-87.9	88
	referent	Beta (95% CI)	p-value	Beta (95% CI) p-value
HIV-	Crude	0.0	-0.07 (-10.57, 10.44)	6.03 (-2.77, 14.83)
	Adjusted	0.0	-3.32 (-13.49, 6.86)	0.179
			0.522	0.497
<i>Speed of Information Processing</i>				
<i>Symbol Digit Modalities Test</i>				
HIV+	Crude	0.0	1.76 (-0.44, 3.96)	1.30 (-0.50, 3.11)
	Adjusted	0.0	0.116	0.156
			2.56 (0.47, 4.64)	2.61 (0.86, 4.36)
			0.016	0.070
HIV-	Crude	0.0	0.80 (-2.10, 3.69)	1.06 (-1.50, 3.62)
	Adjusted	0.0	0.157	0.064
			0.245	0.052
<i>Stroop Color Naming</i>				
HIV+	Crude	0.0	-2.30 (-6.91, 2.31)	0.24 (-3.56, 4.05)
	Adjusted	0.0	0.328	0.901
			-1.58 (-5.91, 2.74)	-0.27 (-3.92, 3.38)
			0.473	0.885
HIV-	Crude	0.0	2.30 (-3.04, 7.63)	5.65 (1.16, 10.14)
	Adjusted	0.0	0.398	0.014
			0.72 (-4.32, 5.76)	3.50 (-0.86, 7.87)
			0.779	0.115
<i>Learning and Memory</i>				
<i>Stroop Word Recall</i>				
HIV+	Crude	0.0	0.62 (-3.12, 4.37)	0.62 (-2.47, 3.70)
	Adjusted	0.0	0.744	0.696
			1.57 (-1.73, 4.87)	-0.40 (-3.18, 2.38)
			0.349	0.776

		Waist circumference category (cm)	
		<80	80-87.9
		88	
		referent	Beta (95% CI) p-value
HIV-	Crude	0.0	0.77 (-3.97, 5.50)
			3.29 (-0.69, 7.28)
Adjusted			0.750
			0.104
		0.0	-0.98 (-5.25, 3.28)
			1.16 (-2.54, 4.85)
			0.650
			0.538

^a A positive beta coefficient indicates a positive relationship between anthropometric measure and cognitive test score. For all tests except SDMT, a positive relationship indicates worse cognitive performance with higher level of anthropometric measure. For example, in fully adjusted models, a waist circumference 88 cm is related to longer Trails A completion among HIV+ compared to a waist circumference of < 80 cm.

^b Crude models adjust for age.

^c Multivariate models adjust for the covariates: age, WRAT, race, insulin, and any drug use.

Table 5

WHR category by cognitive test scores: the Women's Interagency HIV Study (WIHS).

		WHR category			
		<0.85	0.85 - < 0.90	0.90 - <0.95	0.95+
referent		Beta (95% CI)	p-value	Beta (95% CI)	p-value
Beta (95% CI)		p-value			
Executive Function					
Trails A					
HIV +					
Crude	0.0	0.09 (-2.68, 2.86)		-0.18 (-2.95, 2.59)	0.21 (-2.95, 2.98)
		0.951		0.897	0.885
Adjusted	0.0	-0.43 (-3.15, 2.28)		-1.57 (-4.34, 1.21)	-1.52 (-4.35, 1.32)
		0.754		0.269	0.294
HIV -	Crude	0.69 (-2.84, 4.21)		0.80 (-2.97, 4.56)	1.51 (-2.34, 5.36)
		0.702		0.678	0.442
Adjusted	0.0	-0.15 (-3.72, 3.42)		-0.64 (-4.51, 3.24)	0.20 (-3.80, 4.19)
		0.933		0.747	0.923
Trails B					
HIV +					
Crude	0.0	0.34 (-1.35, 2.03)		0.72 (-1.00, 2.44)	0.08 (-1.66, 1.81)
		0.695		0.410	0.929
Adjusted	0.0	-6.85 (-15.17, 1.48)		-5.19 (-13.68, 3.30)	-4.88 (-13.62, 3.86)
		0.107		0.231	0.274
HIV -	Crude	0.75 (-10.09, 11.59)		8.88 (-2.63, 20.38)	14.31 (2.48, 26.14)
		0.892		0.130	0.018
Adjusted	0.0	-2.42 (-13.13, 8.28)		4.33 (-7.18, 15.84)	11.03 (-0.93, 22.98)
		0.657		0.460	0.071
Stroop Interference					
HIV +					
Crude	0.0	6.64 (-0.66, 13.94)		-2.79 (-9.96, 4.38)	-0.06 (-7.17, 7.04)
		0.075		0.445	0.986
Adjusted	0.0	4.70 (-2.09, 11.49)		-4.20 (-10.92, 2.51)	-2.92 (-9.86, 4.02)
		0.174		0.219	0.409
HIV -	Crude	5.12 (-4.01, 14.25)		10.31 (-0.04, 20.66)	8.18 (-1.83, 18.19)

		WHR category			
<0.85		0.85 - < 0.90	0.90 - < 0.95	0.95+	
referent	Beta (95% CI) p-value	Beta (95% CI) p-value	Beta (95% CI) p-value	Beta (95% CI) p-value	
Speed of Information Processing					
Symbol Digit Modalities Test					
HIV+ Crude	0.0	0.49 (-1.58, 2.57)	1.00 (-1.08, 3.08)	0.75 (-1.34, 2.84)	
		0.642	0.344	0.482	
Adjusted	0.0	1.41 (-0.52, 3.33)	2.58 (0.60, 4.56)	2.58 (0.55, 5.60)	
		0.153	0.011	0.013	
HIV- Crude	0.0	0.77 (-2.16, 3.69)	1.05 (-2.07, 4.16)	-1.06 (-4.25, 2.13)	
		0.606	0.509	0.513	
Adjusted	0.0	1.83 (-0.84, 4.49)	1.07 (-1.80, 3.95)	0.13 (-2.85, 3.11)	
		0.179	0.464	0.930	
Stroop Color Naming					
HIV+ Crude	0.0	1.00 (-3.45, 5.44)	-2.92 (-7.29, 1.45)	-1.45 (-5.76, 2.87)	
		0.659	0.190	0.510	
Adjusted	0.0	0.56 (-3.57, 4.69)	-2.44 (-6.51, 1.63)	-1.97 (-6.16, 2.23)	
		0.789	0.239	0.358	
HIV- Crude	0.0	3.05 (-1.64, 7.74)	3.83 (-1.48, 9.14)	4.92 (-0.23, 10.08)	
		0.202	0.156	0.061	
Adjusted	0.0	1.28 (-3.14, 5.71)	2.61 (-2.42, 7.64)	3.13 (-1.78, 8.04)	
		0.568	0.308	0.211	
Learning and Memory					
Stroop Word Recall					
HIV+ Crude	0.0	1.88 (-1.73, 5.48)	-2.02 (-5.56, 1.52)	0.06 (-3.44, 3.56)	
		0.307	0.262	0.972	
Adjusted	0.0	1.23 (-1.91, 4.37)	-2.08 (-5.17, 1.02)	-1.16 (-4.36, 2.03)	
		0.442	0.189	0.474	
HIV- Crude	0.0	4.25 (0.13, 8.36)	1.21 (-3.44, 5.86)	4.17 (-0.35, 8.69)	

		WHR category			
		<0.85	0.85 - < 0.90	0.90 - <0.95	0.95+
	referent	Beta (95% CI) p-value	Beta (95% CI) p-value	Beta (95% CI) p-value	Beta (95% CI) p-value
Adjusted	0.0	2.47 (-1.26, 6.19) 0.043	-0.01 (-4.24, 4.22) 0.609	2.52 (-1.61, 6.65) 0.071	
		0.193	0.995	0.230	

^a A positive beta coefficient indicates a positive relationship between anthropometric measure and cognitive test score. For all tests except SDMT, a positive relationship indicates worse cognitive performance with higher level of anthropometric measure. For example, in fully adjusted models, a WHR > 0.95 is related to shorter Trails A completion time among HIV+ compared to those with a 'healthy' WHR of <0.85.

^b Crude models adjust for age.

^c Multivariate models adjust for the covariates: age, WRAT, race, insulin, and any drug use.