Body mass index and leptin are related to cognitive performance over 10 years in women with and without HIV infection

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Abstract

Objective. To determine whether body mass index (BMI) and leptin were longitudinally associated over 10 years with neuropsychological performance (NP) among middle-aged women with HIV (WWH) versus without HIV.

Methods. Women’s Interagency HIV Study (WIHS) participants (301 WWH, 113 women without HIV from Brooklyn, New York City and Chicago had baseline and 10-year BMI (kg/m²) and fasting plasma leptin levels using commercial ELISA (ng/mL); and demographically-adjusted NP T-scores (attention/working memory, executive function (EF), processing speed, memory, learning, verbal fluency, motor function, global) at 10-year follow-up. Multivariable linear regression analyses, stratified by HIV-serostatus, examined associations between BMI, leptin, and NP.

Results. Over 10 years, women (baseline age 39.8+/−9.2 years, 73% Black, 73% WWH) transitioned from average overweight (29.1+/−7.9 kg/m²) to obese (30.5+/−7.9 kg/m²) BMI. Leptin increased 11.4+/−26.4 ng/mL (p<0.0001). Higher baseline BMI and leptin predicted poorer 10-year EF among all women (BMI B=−6.97, 95%CI(−11.5, −2.45) p=0.003; leptin B=−1.90, 95%CI(−3.03, −0.76), p=0.001); higher baseline BMI predicted better memory performance (B=6.35, 95%CI(1.96, 10.7), p=0.005). Greater 10-year leptin increase predicted poorer EF (p=0.004), speed (p=0.029), verbal (p=0.021) and global (p=0.005) performance among all women, and WWH. Greater 10-year BMI increase predicted slower processing speed (p=0.043) among all women; and among WWH, poorer EF (p=0.012) and global (p=0.035) performance.

Conclusions. In middle-aged WIHS participants, 10-year increases in BMI and leptin were associated with poorer performance across multiple NP domains among all and WWH. Trajectories of adiposity measures over time may provide insight into the role of adipose tissue in brain health with aging.

Key Words: Cognition; Leptin; HIV; Women; Overweight; Obesity; Body Mass Index
INTRODUCTION

Improved antiretroviral therapies (ART) transformed HIV infection into a treatable chronic condition, increasing life expectancy among people living with HIV (PLWH).\(^1,2\) Consequently, PLWH may experience concomitant physiological and neuropsychological consequences of aging. These include adverse vascular and metabolic co-morbidities, sometimes due to cumulative ART exposure, and overweight and obesity. In uninfected populations, overweight and obesity during middle-age increase risk for late-life neuropsychological impairment and Alzheimer’s Disease and Related Dementias (ADRD).\(^3,4\)

Leptin is an adipose tissue hormone, positively correlated with body mass index (BMI), and a proposed modulator of BMI and neuropsychological performance (NP) given peripheral and central nervous system (CNS) effects.\(^5-7\) Higher blood leptin levels are associated with lower AD risk within 10 years of clinical onset.\(^8-10\) The relationship between peripheral and brain-derived leptin is unknown. However, leptin promotes hippocampal synaptic plasticity\(^11\) affecting learning and memory,\(^11-14\) aids in satiety regulation, improves insulin sensitivity,\(^15,16\) and acts on the hypothalamus to regulate body weight. Leptin may be dysregulated in HIV-related lypodystrophies.\(^17\)

While several studies examined single BMI measurement associations or BMI trajectories in association with ADRD,\(^3,18\) there are fewer reports on adiposity-related metabolic changes. Given the vascular, metabolic, and lipodystrophic effects of both HIV infection and ART, and a relatively unknown HIV-specific aging process, particularly among Black women, we investigated whether baseline and/or 10-year change in BMI and blood leptin levels were associated with NP in middle-aged women with HIV (WWH) and without HIV infection who were participants in the Women’s Interagency HIV Study (WIHS) Brooklyn and Chicago sites.

Materials and Methods

Standard Protocol Approvals, Registrations, and Patient Consents

WIHS was the largest prospective study of HIV infection in women in the United States.\(^19\) WIHS began in 1994 and initially enrolled 2054 WWH and 1712 women without HIV who were ‘at risk’ demographically-similar women across six sites in San Francisco, Los Angeles, Chicago, Washington DC, Brooklyn and the Bronx, New York City, with two additional enrollment waves in 2001-2002 and 2011-2014. Semiannual WIHS core visits included sociodemographic, behavioral, and clinical
measures including body weight and height. A standardized comprehensive NP battery was administered every two years starting in 2009. A subset of Brooklyn and Chicago WIHS participants (N=414; 301 WWH, 113 women without HIV) had batch testing of fasting plasma leptin levels in 2004-06 (designated as baseline) and 10 years later in 2014-16. Concurrent NP assessments occurred in 2014-16. Those with repeated leptin measures comprise this analytic subsample. The institutional review boards of the Brooklyn and Chicago Cook County Health clinical research sites approved the WIHS research protocol and all participants provided written informed consent.

**Sociodemographic and behavioral measures**

All sociodemographic measures were self-reported and included: date of birth, race (White, Hispanic any race, African-American, or ‘other’, i.e., Native American/Alaskan, Asian/Pacific Islander or other); and highest educational level. Participants were asked about their use of marijuana since last visit.

**Clinical measures**

Body weight and height measures were conducted according to the U.S. National Health and Nutrition Examination Survey (NHANES) III protocol and included body weight (pounds) and body height (inches). Anthropometric measurements were conducted with participants wearing undergarments. Those who conducted the measurements were recertified every two years. Body weight was recorded to the nearest 1.0 pound, and body height was measured to the nearest 1.00 inch. After software conversion of body weight and height to metric units, BMI was calculated as kilograms per meter squared (kg/m²). Categories of BMI included: underweight, <18.5 kg/m²; ‘normal’ or healthy weight, 18.5–24.9 kg/m²; overweight, 25.0–29.9 kg/m²; and obese, ≥30 kg/m².

Systolic (SBP) and diastolic blood pressures (DBP) were obtained and recorded using a standardized protocol with the mean of multiple resting measurements used for analysis. Hypertension was defined as either average measured SBP >140 mm Hg, or DBP >90 mm Hg, or self-reported hypertension with use of prescribed antihypertensive medications. Diabetes mellitus (DM) was determined by fasting glucose ≥126 mg/dl, HbA1C ≥6.5% or self-reported use of anti-diabetic medication.

Menopause status was self-reported and defined according to the Stages of Reproductive Aging Workshop (STRAW)+10 criteria. There are four menopausal status categories: premenopause, early perimenopause, late perimenopause, and postmenopause (natural or surgical).
Leptin measures
Baseline and 10-year leptin levels were measured in batch from stored plasma samples. The latter were collected within two visits (12 months before or after) of NP assessment. Paired longitudinal Brooklyn and Chicago samples were run together. Standards and controls were tested in duplicate using commercial ELISAs (Millipore, Billerica, MA). The intra-assay coefficient of variation (CV%) was 2% and inter-assay CV% was 10%. Undiluted samples were tested and plates were prepared according to protocol. The 7-point standard curve ranged from 0.5–100 ng/mL, the lower and upper limits of detection of the assay, which was appropriate for all samples. Plates were read using a Molecular Devices Plate reader and Softmax Pro data analysis software (Molecular Devices, Sunnyvale, CA). A 4-point logistic (PL) curve fit was used.

HIV-related variables
Laboratory-confirmed HIV status, AIDS diagnosis, CD4 count, HIV viral load, and ART duration and CNS penetration effectiveness (CPE) were considered in analyses of WWH only. CPE scoring for each ART was based on published data regarding the differential abilities of ART to cross the blood-brain barrier. CPE was defined on a 1-4 point scale using the 2010 CPE ranking system, where 4 indicates the highest CNS penetration. The baseline ART regimen CPE sum was subsequently ranked as high (>9), medium (8-9) or low (<8).

Neuropsychological performance
The NP performance battery included the Letter-Number Sequencing (LNS), Trail Making Test Part B (Trails B), Stroop Test (color word, word reading), Hopkins Verbal Learning Test-Revised (HVLT-R), Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association Test (COWAT), Category Fluency Test (Animals), and Grooved Pegboard (GPEG). Performance on these assessments was used to assess seven NP domains: 1) attention/working memory (outcomes: total correct on LNS control and experimental conditions); 2) executive function (outcomes: time to completion on Trails B and Stroop color-word [interference] trial); 3) processing speed (outcomes: total correct on SDMT, time to completion on Stroop word-reading trial); 4) memory (outcome: HVLT-R delayed recall); 5) learning (outcome: total learning across HVLT-R trials); 6) verbal fluency (outcomes: total correct on COWAT and Animals); and 7) fine motor skills (outcomes: total time to completion for each hand on the GPEG).
All timed outcomes were natural log (ln)-transformed to normalize distributions and reverse scored so higher scores represented better performance. Demographically-adjusted T-scores were derived for each outcome based on HIV-seronegative women. These demographic factors include age, education, Wide Range Achievement Test reading subtest (WRAT-3) score, race (African American vs not), and ethnicity (Hispanic vs not). T-scores were used to create domain-specific scores and a global NP score as done in previous WIHS and Multicenter AIDS Cohort Study (MACS) analyses. Global NP performance score was the calculated average of the 7 NP domains.

Statistical analysis

BMI and leptin were ln-transformed to meet normality assumptions before consideration as continuous variables. Paired sample t-tests estimated the differences between baseline and follow-up BMI and leptin measures for all women, and separately for WWH and women without HIV. Multivariable linear regression analyses were performed to examine baseline continuous BMI and leptin in association with NP T-scores at 10-year follow-up. Models were run including all participants, and separately for WWH and women without HIV. Multivariable linear regression analyses were again performed to examine 10-year change in BMI and leptin in association with follow-up NP T-scores.

Potential covariates included cholesterol level, prevalent diabetes, prevalent hypertension as well as use of hypertensive medication, diabetic medication, menopause status, cocaine, alcohol, marijuana, smoking and/or heroin. Of these, prevalent diabetes, prevalent hypertension, and marijuana use were included since they were deemed statistically relevant (p<0.05) in previous univariate analyses of the relationship between adiposity measures - BMI and leptin- and NP in this group of women. Race, ethnicity, WRAT score, education and age were not included as covariates since they were already included in the demographically-adjusted NP T-scores. Analyses including all women were also adjusted for HIV serostatus (WWH versus women without HIV). In analyses of WWH only, we additionally adjusted for baseline CD4 count, HIV viral load and CPE rank (high >9, medium 8-9, low <8). CD4 count and HIV viral load were analyzed as continuous variables. BMI and leptin were not run in the same regression models, since understanding independent contributions of BMI and leptin is difficult due to their high collinearity. Data analyses were conducted using [SAS/STAT] software, Version [9.4] of the SAS System for [SUNY]. Copyright © [2016] SAS Institute Inc. Cary, NC, USA. Results were considered significant at p<0.05.
Results

Baseline demographic, BMI, HIV, and NP characteristics of participants are presented in Table 1. Women were on average 39.8 years old. WWH were approximately 3.1 years older than women without HIV (40.6 years vs 37.5 years, respectively; p=0.005), however educational attainment, a key influencer of NP, did not differ between WWH and women without HIV (Fishers exact test, p=0.85). Most women (74%) self-described as Black (Caribbean Black or African American), 21% had hypertension, and 14% had diabetes. There were no differences by HIV serostatus. More than half of the women (58%) were pre-menopausal, and menopausal status did not differ by HIV-serostatus (Fishers exact test, p=0.12). Most (62%) women were overweight or obese (≥25.0 kg/m²); <5% had a BMI <18.5 kg/m². WWH had, on average, a lower BMI (28.8 +/- 7.5 kg/m²) compared to women without HIV (30.0 +/- 8.9 kg/m²), but this was not significant (p=0.14). Compared to women without HIV, WWH performed poorer on verbal fluency (p=0.02), attention (p=0.002), processing speed (p=0.005), and global (0.003) measures of NP. The anthropometric adiposity measure, BMI, was positively correlated with the metabolic adiposity measure, leptin, in the expected direction and strength (Table 2) among both WWH and women without HIV, and in line with previous reports in non-HIV population samples.3

Over the 10-year period, from mean ages of 40.6 to 50.6 years among WWH and 37.5 to 47.5 years among women without HIV, all women transitioned, on average, from an overweight (29.1 +/- 7.9 kg/m²) to obese (30.5 +/- 7.9 kg/m²) BMI (t=6.00, p<0.0001). Among WWH, average BMI increased from 28.8 +/- 7.5 kg/m² to 30.1 +/- 7.9 kg/m² (t=4.84, p<0.001). Among women without HIV, BMI increased from 30.0 +/- 8.8 kg/m² to 31.5 +/- 8.1 kg/m² (t=3.55, p=0.0006). Correspondingly, average 10-year leptin change from baseline to follow-up was significant in the entire sample (11.4 +/- 26.4 ng/ml, t=8.76 (df=413), p<0.0001); and by HIV status (WWH 12.07 +/- 27.05 ng/ml, t=7.70 (df=297) p<0.0001; women without HIV 9.36 +/- 24.89 ng/ml, t=4.00 (df=112) p=0.0001).

Poorer NP was indicated by a negative (-) unstandardized, adjusted beta (B) coefficient; a positive B coefficient indicated better NP. Higher baseline BMI and leptin predicted poorer executive function (EF) performance 10 years later for all women in multivariable analysis (Table 3) and by HIV status. In contrast, higher baseline BMI was associated with better memory performance at follow-up for all women (B= +6.60, 95%CI (2.32, 10.88) p=0.003) and by HIV status. Change in leptin over 10 years predominated the associations with NP. Among all women, a greater 10-year increase in leptin was associated with poorer EF, processing speed and global NP at 10-year follow-up (Table 4). With stratification by HIV serostatus, these associations were observed among WWH but not women without HIV. WWH additionally showed poorer verbal fluency performance with increasing 10-year leptin. For
all women, a greater 10-year increase in BMI was associated with slower processing speed at follow-up (Table 4). Among WWH only, 10-year increase in BMI was associated with poorer executive function and global performances at follow-up (Table 4). Baseline or change in BMI or leptin measures did not predict any other NP domains (Tables 3 and 4). Changes in BMI or leptin over 10 years were not associated with NP in women without HIV.

**Conclusion**

Among WWH or women without HIV infection, who transitioned from being overweight to obese over a decade, associations between baseline BMI and leptin and NP 10-years later, did not differ by HIV status. Higher baseline BMI and leptin levels were associated with poorer EF at follow-up, but higher baseline BMI was associated with better memory performance. In contrast, increasing BMI and leptin levels over 10 years were associated with poorer NP at follow-up across several neuropsychological domains among all women, and among WWH, specifically poorer EF, processing speed, verbal fluency and global performance. Changes in leptin predominated these associations; changes in BMI were associated with fewer neuropsychological domains. NP assessments are useful in the detection, differential etiologic diagnosis, and management of ADRD syndromes. Neuropsychological deficits associated with AD can be differentiated from age-associated NP decline by quantitative and qualitative differences in episodic memory, semantic knowledge, and some aspects of executive functions. Of note, the WIHS NP battery was created to assess the seven domains (EF, memory, attention, processing speed, verbal fluency, motor, and learning) most influenced by HIV infection, as well as aging.

There are few published repeated anthropometric and metabolic adiposity data among WWH or other at-risk populations to compare our results. A previous Brooklyn WIHS cross-sectional study using a different NP battery at the year 2006 baseline described here, reported that higher leptin levels were associated with poorer EF performance, whereas cross-sectional analyses of anthropometric measures across all WIHS sites, showed that higher BMI was associated with better NP across multiple domains, and lower BMI (<18.5 kg/m²) with worse NP. Studies among middle-aged, predominantly White men with HIV have shown no association between cognition and leptin. Our sample is comprised of primarily Black women. Among uninfected individuals, leptin differences have been observed by race and sex, with serum leptin being higher in women and Blacks. Studies of older adults with Vascular Cognitive Impairment, have reported inverse associations of BMI, but not leptin, with executive function and verbal memory.
Since its discovery in 1994, leptin has been explored in relation to its neuroprotective influence on the brain. Leptin was initially described for its role in feeding, and the homeostatic regulation of energy metabolism. Leptin acts on the arcuate nucleus, a key aggregate of hypothalamic neurons often affected in ADRD. Other mechanisms have been described for the association between leptin and NP but most are cross-sectional and observed in uninfected adults >65 years. Observations in older adults compared to middle age life are mixed. Longitudinally, the Framingham Heart Study reported that leptin was neuroprotective when measured within 8 years of late-onset dementia among adults age >65 years. However, over a 24 year follow-up, a single measure of leptin at mid-life (age 38–60 years) was not associated with late-onset dementia among Swedish elderly. The Framingham Heart Study Third Generation Cohort comprised of over 2200 adults, average age, 40 years, reported a cross-sectional neuroprotective effect of leptin among cognitively intact, non-overweight or obese participants (BMI 18.5-24.9 kg/m²), suggesting that BMI is an effect modifier. Conversely, studies also report inverse cross-sectional associations between leptin and cognition among non-obese adults >65 years. These observations may reflect variations in age, sex, adiposity measures and levels, severity and/or domain of cognitive performance, the presence of preclinical or overt dementia, as well as the temporality of association being explored. There are also differential associations of adiposity measures with brain imaging outcomes, which are correlates of NP. Among adults with cerebral small vessel disease (without dementia), associations vary by study design (cross-sectional versus longitudinal), anthropometric versus metabolic adiposity measures, and neurodegenerative versus vascular brain outcome.

Observed increases in leptin and/or BMI over time in association with worse NP among WWH may be influenced by ART, the chronic HIV aging process, or a combination of both. Adjustment for ART CPE did not alter our findings. While increases in adiposity during the middle age transition may not be positive for brain health, higher adiposity may still be protective for the brain among surviving WWH to later life. It will be interesting to observe whether these associations change as WWH age.

This is a sizable study of longitudinal, repeated BMI and leptin measures in association with NP in WWH and women without HIV infection. Strengths include the underrepresented, predominantly Black (African American and Caribbean) sample; use of a clinical, easily obtained anthropometric measure (BMI) that is commonly used to estimate total body adiposity; longitudinal, repeated measures of both anthropometric (BMI) and metabolic (leptin) measures of adiposity; information on menopause status; and a comprehensive NP assessment battery. Limitations include no imaging-based brain or whole body composition measures; lack of other leptin measures (e.g., cerebrospinal fluid leptin levels, leptin...
receptors, leptin resistance); one fasting leptin measure that does not allow consideration of diurnal variation in blood leptin levels; not including both leptin and BMI in the same statistical models due to high collinearity; and lack of comparable baseline NP assessments. Due to multiple comparisons, one must also consider risk for false discoveries. Our analyses were not adjusted for multiple comparisons due to their exploratory nature, however, p-values were <0.005 for some linear regression analysis results. A potential bias is that this was a healthier longitudinal cohort of WWH and at-risk women without HIV. These WWH were highly adherent to their HIV medications, and had low HIV viral loads and high CD4 counts. As with all longitudinal cohort studies, routine follow-up over time may limit the generalizability our results to those who are not enrolled in these rigorous protocols. Finally, our global NP score is study specific, and we do not know how this score relates to clinical ADRD since there are no cohorts today who can address this question given the younger average age of people surviving with HIV infection.

We report promising longitudinal associations of anthropometric and metabolic adiposity measures in association with NP in women with or at risk for HIV infection. These data suggest the need for continued clinical follow-up of these women to determine transitional mid- to late-life metabolic and other effects of adipose tissue on NP and eventually ADRD in HIV. Interventions to reduce body weight and BMI may be particularly relevant in mid-life for maintaining aging brain health.
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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.
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Table 1. Baseline demographic, adiposity, and neuropsychological performance characteristics for all women and by HIV-serostatus (n=414)

| Variable                          | ALL Women Mean (SD) or N (%) | HIV+ Mean (SD) or N (%) | HIV- Mean (SD) or N (%) | P   |
|----------------------------------|-------------------------------|-------------------------|-------------------------|-----|
| Age, years, Mean (SD)            | 39.8 (9.2)                    | 40.6 (8.5)              | 37.5 (10.4)             | 0.005 |
| Race/Ethnicity N (%)             |                               |                         |                         | 0.236 |
| Black/ African American          | 306 (74)                      | 216 (72)                | 88 (78)                 |      |
| Hispanic/ Latinx, any race       | 36 (8)                        | 31 (10)                 | 10 (9)                  |      |
| White                            | 26 (6)                        | 20 (7)                  | 6 (5)                   |      |
| Marijuana Use N (%)              | 89 (21)                       | 59 (20)                 | 30 (27)                 | 0.262 |
| Prevalent Hypertension N (%)     | 83 (20)                       | 64 (21)                 | 19 (17)                 | 0.314 |
| Prevalent Diabetes N (%)         | 61 (14)                       | 45 (15)                 | 16 (14)                 | 0.834 |
| Baseline BMI, kg/m², Mean (SD)   | 29.1 (7.9)                    | 28.8 (7.5)              | 30.0 (8.9)              | 0.142 |
| BMI ≥ 30 kg/ m²                  | 145 (35)                      | 101 (34)                | 44 (39)                 |      |
| BMI 25 – 29.9 kg/m²              | 113 (27)                      | 84 (28)                 | 29 (26)                 |      |
| BMI 18.5 – 24.9 kg/m²            | 139 (34)                      | 101 (33)                | 38 (33)                 |      |
| BMI <18.5 kg/m²                  | 17 (4)                        | 15 (5)                  | 2 (2)                   |      |
| Leptin, ng/mL, Mean (SD)         | 28.4 (26.0)                   | 27.5 (26.6)             | 30.8 (24.3)             | 0.250 |
| Menopausal Status N (%)          |                               |                         |                         | 0.108 |
| Premenopause                     | 242 (59)                      | 165 (40)                | 77 (19)                 |      |
| Early perimenopause              | 51 (12)                       | 40 (10)                 | 11 (3)                  |      |
| Late perimenopause               | 22 (5)                        | 17 (4)                  | 5 (1)                   |      |
| Postmenopause                    | 99 (24)                       | 79 (19)                 | 20 (5)                  |      |
### HIV Variables

| HIV Variables                                      | Mean (SD)       | --     |
|---------------------------------------------------|-----------------|--------|
| CD4 Count, cells/mL, Mean (SD)                    | 542.1 (302.4)   | --     |
| HIV RNA viral load, copies/mL                     | --              | --     |
| Viral load undetectable <80 copies/mL             | 147 (49)        | --     |
| Viral load median (IQR), detectable, copies/mL    | 5500.0 (20500.0)| --     |
| CPE Score N (%)                                   | --              |        |
| Low <8                                            | 90 (47)         | --     |
| Medium 8-9                                        | 67 (35)         | --     |
| High >9                                           | 33 (17)         | --     |

### NP Assessments, T-score, Mean (SD)

| NP Assessments, T-score, Mean (SD) | Executive 48.8 (10.7) | Memory 47.5 (10.6) | Verbal Fluency 48.7 (9.8) | Learning 47.4 (10.6) | Attention 47.0 (9.9) | Processing Speed 48.8 (9.6) | Motor 48.3 (10.8) | Global 48.1 (6.6) | 50.1 (9.6) | 46.9 (10.3) | 48.0 (9.9) | 46.7 (10.8) | 45.9 (9.8) | 48.0 (9.9) | 47.7 (10.9) | 47.3 (6.9) | 49.7 (6.5) | 0.167 | 0.146 | 0.023 | 0.082 | 0.002 | 0.005 | 0.095 | 0.003 |
|----------------------------------------|---------------------|-------------------|--------------------------|----------------------|---------------------|--------------------------|-------------------|-------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|

Variables reported as N (%) were analyzed with Chi-Square tests. Variables reported as Mean (SD) were analyzed using independent sample t-tests.

CPE, CNS Penetration Effectiveness; T-scores are demographically adjusted for age, education, Wide Range Achievement Test reading subtest (WRAT-3) score, race (African American vs not), and ethnicity (Hispanic vs not).
Table 2. Pearson correlation coefficients between baseline adiposity and HIV measures in all women and by HIV status. The Women’s Interagency HIV Study Brooklyn and Chicago Clinical Research Sites

|                          | ALL WOMEN n = 414 | HIV + n=301 | HIV- n=114 |
|--------------------------|--------------------|-------------|-------------|
|                          | r (p-value)        | r (p-value) | r (p-value) |
| Body weight x leptin     | 0.53 (<0.0001)    | 0.52 (<0.0001) | 0.59(<0.0001) |
| Body height x leptin     | 0.08 (0.10)       | 0.10 (0.09)  | 0.03 (0.75)  |
| BMI x leptin             | 0.77 (<0.0001)    | 0.77 (<0.0001) | 0.78(<0.0001) |
| HIV Viral load x leptin  | -0.01 (0.9)       | --          | --          |
| HIV Viral load x ln leptin| -0.02 (0.80)   | --          | --          |
| CD4 x leptin             | -0.05 (0.40)      | --          | --          |
| CD4 x ln leptin          | -0.06 (0.31)      | --          | --          |

* adiposity measures are natural log transformed
Table 3. Linear regression models associating baseline (2006) plasma leptin and BMI measures with neuropsychological performance by domain 10-years later in all women and stratified by HIV status. The Women’s Interagency HIV Study Brooklyn and Chicago Clinical Research Sites.

| Model                      | ALL            |              | WWH            |              | Women Without HIV |              |
|----------------------------|----------------|--------------|----------------|--------------|-------------------|--------------|
|                             | N Beta (95%CI) | p            | N Beta (95%CI) | p            | N Beta (95%CI)    | p            |
| Executive Function          |                |              |                |              |                   |              |
| Baseline leptin            | 358 -1.90 (-3.03, -0.76) | 0.001 | 258 -1.63 (-3.01, -0.76) | 0.020 | 100 -2.92 (-5.02, -0.81) | 0.007 |
| Baseline BMI               | 355 -6.97 (-11.50, -2.45) | 0.003 | 255 -5.71 (-11.3, -0.26) | 0.045 | 99 -10.6 (-18.20, -2.87) | 0.008 |
| Memory                     |                |              |                |              |                   |              |
| Baseline leptin            | 360 0.49 (-0.64, 1.62) | 0.393 | 257 0.48 (-0.78, 1.74) | 0.451 | 101 0.74 (-1.80, 3.28) | 0.564 |
| Baseline BMI               | 356 6.35 (1.96, 10.70) | 0.005 | 254 5.17 (0.16, 10.20) | 0.043 | 100 9.29 (0.29, 18.30) | 0.043 |
| Learning                   |                |              |                |              |                   |              |
| Baseline leptin            | 362 0.21 (-0.92, 1.34) | 0.720 | 258 0.48 (-0.84, 1.80) | 0.477 | 102 -0.24 (-2.54, 2.05) | 0.837 |
| Baseline BMI               | 358 3.49 (-0.93, 7.90) | 0.121 | 255 2.92 (-2.36, 8.20) | 0.277 | 101 5.12 (-3.12, 13.40) | 0.220 |
| Attention                  |                |              |                |              |                   |              |
| Baseline leptin            | 340 -0.74 (-1.80, 0.33) | 0.175 | 244 -0.94 (-2.18, 0.30) | 0.135 | 95 -0.23 (-2.46, 1.88) | 0.794 |
| Baseline BMI               | 336 0.10 (-4.17, 4.37) | 0.963 | 241 -1.81 (-6.90, 3.23) | 0.484 | 94 5.28 (-2.52, 13.10) | 0.182 |
| Processing Speed           |                |              |                |              |                   |              |
| Baseline leptin            | 365 -0.48 (-1.49, 0.53) | 0.350 | 261 -0.36 (-1.58, 0.87) | 0.564 | 102 -0.99 (-2.83, 0.85) | 0.290 |
| Baseline BMI               | 361 0.09 (-3.90, 4.08) | 0.964 | 258 0.71 (-4.22, 5.65) | 0.776 | 101 -1.44 (-8.17, 5.30) | 0.673 |
| Verbal Fluency             |                |              |                |              |                   |              |
| Baseline leptin            | 361 0.01 (-1.01, 1.04) | 0.978 | 259 0.26 (-0.96, 1.49) | 0.670 | 100 -0.84 (-2.83, 1.15) | 0.404 |
|                  | Baseline BMI |      |      |      |      |      |      |      |      |      |
|------------------|--------------|------|------|------|------|------|------|------|------|------|
|                  | 357          | 0.81 | (3.24, 4.86) | 0.881 | 256 | 0.93 | (3.99, 5.87) | 0.708 | 99  | -0.47 | (-6.69, 7.63) | 0.897 |
| **Motor**        |              |      |      |      |      |      |      |      |      |      |
| Baseline leptin  | 361          | 0.10 | (-1.23, 1.04) | 0.868 | 258 | 0.60 | (-0.73, 1.93) | 0.375 | 102 | -2.04 | (-4.34, 0.25) | 0.080 |
| Baseline BMI     | 357          | -0.003 | (-4.47, 4.46) | 0.999 | 255 | 2.30 | (-3.04, 7.65) | 0.397 | 101 | -5.49 | (-13.8, 2.85) | 0.194 |
| **Global**       |              |      |      |      |      |      |      |      |      |      |
| Baseline leptin  | 366          | -0.33 | (-1.05, 0.39) | 0.363 | 261 | -0.13 | (-0.98, 0.72) | 0.764 | 103 | -0.92 | (-2.36, 0.51) | 0.203 |
| Baseline BMI     | 362          | 0.633 | (-2.22, 3.49) | 0.662 | 258 | 0.75 | (-2.69, 4.20) | 0.667 | 102 | 0.43  | (-4.77, 5.62) | 0.870 |

Note. All models are adjusted for prevalent diabetes, prevalent hypertension, marijuana use and HIV status at baseline visit. Beta represents an adjusted, unstandardized coefficient. NP assessments are reverse scored and a higher beta indicates better NP. WWH models are additionally adjusted for baseline CD4 count, viral load and CPE rank (High, medium, low). * = all adiposity measures are ln transformed.
Table 4. Linear regression models associating 10-year changes in plasma leptin and BMI measures with neuropsychological performance by domain at 10-year follow-up in all women and by HIV infection status. The Women's Interagency HIV Study Brooklyn and Chicago Clinical Research Sites.

| Model              | ALL                          | WWH                          | Women Without HIV |
|--------------------|------------------------------|------------------------------|--------------------|
|                    | N                | Beta (95% CI)   | p     | N          | Beta (95% CI)   | p     | N          | Beta (95% CI)   | p     |
| Executive Function |                 |                          |       |             |                          |       |             |                          |       |
| 10y Leptin Change  | 359              | -0.05 (-0.09, -0.01) | 0.018 | 258        | -0.08 (-0.13, -0.02) | 0.004 | 100        | 0.01 (-0.07, 0.09) | 0.811 |
| 10y BMI Change     | 332              | -0.17 (-0.43, 0.09)  | 0.198 | 236        | -0.42 (-0.75, -0.09) | 0.012 | 95         | -0.41 (-0.04, 0.87) | 0.074 |
| Memory             |                 |                          |       |             |                          |       |             |                          |       |
| 10y Leptin Change  | 360              | 0.02 (-0.07, 0.02)    | 0.254 | 257        | -0.03 (-0.08, 0.02)   | 0.237 | 101        | -0.01 (-0.10, 0.08) | 0.826 |
| 10y BMI Change     | 333              | -0.09 (-0.34, 0.16)   | 0.493 | 235        | -0.15 (-0.44, 0.14)  | 0.318 | 96         | -0.07 (-0.60, 0.45) | 0.782 |
| Learning           |                 |                          |       |             |                          |       |             |                          |       |
| 10y Leptin Change  | 362              | -0.02 (-0.07, 0.02)   | 0.252 | 258        | -0.03 (-0.08, 0.02)   | 0.238 | 102        | -0.005 (-0.09, 0.08) | 0.913 |
| 10y BMI Change     | 335              | -0.07 (-0.32, 0.18)   | 0.592 | 235        | -0.19 (-0.50, 0.12)  | 0.226 | 97         | 0.02 (-0.46, 0.50)  | 0.932 |
| Attention          |                 |                          |       |             |                          |       |             |                          |       |
| 10y Leptin Change  | 340              | -0.03 (-0.07, 0.01)   | 0.101 | 244        | -0.04 (-0.08, 0.01)   | 0.123 | 95         | -0.02 (-0.10, 0.05) | 0.520 |
| 10y BMI Change     | 315              | -0.10 (-0.35, 0.15)   | 0.417 | 224        | -0.20 (-0.50, 0.10)   | 0.196 | 90         | 0.07 (-0.43, 0.56)  | 0.785 |
| Processing Speed   |                 |                          |       |             |                          |       |             |                          |       |
| 10y Leptin Change  | 365              | -0.04 (-0.08, -0.01)  | 0.025 | 261        | -0.05 (-0.10, -0.010) | 0.029 | 102        | -0.04 (-0.10, 0.03) | 0.295 |
| 10y BMI Change     | 338              | -0.23 (-0.47, -0.01)  | 0.043 | 239        | -0.25 (-0.55, 0.04)   | 0.087 | 97         | -0.25 (-0.64, 0.13) | 0.196 |
| Verbal Fluency     |                 |                          |       |             |                          |       |             |                          |       |
| 10y Leptin Change  | 361              | -0.04 (-0.07, 0.001)  | 0.053 | 259        | -0.05 (-0.10, -0.01)  | 0.021 | 100        | -0.02 (-0.09, 0.05) | 0.598 |
| 10y BMI Change     | 334              | -0.12 (-0.36, 0.11)   | 0.305 | 237        | -0.12 (-0.42, 0.16)   | 0.401 | 95         | -0.25 (-0.67, 0.17) | 0.244 |
| Motor              |                 |                          |       |             |                          |       |             |                          |       |
| 10y Leptin Change  | 361              | -0.03 (-0.07, 0.01)   | 0.138 | 258        | -0.04 (-0.09, 0.01)   | 0.109 | 102        | -0.01 (-0.09, 0.07) | 0.791 |
|                      | 10y BMI Change | 10y Leptin Change | 10y BMI Change |
|----------------------|----------------|-------------------|----------------|
| n                    | 335            | 366               | 339            |
| BMI Change           | -0.13 (-0.38, 0.13) | -0.03 (-0.06, -0.01) | -0.12 (-0.29, 0.04) |
| Global              |                |                   |                |
| n                    | 237            | 261               | 239            |
| BMI Change           | -0.24 (-0.56, 0.07) | -0.05 (-0.08, -0.01) | -0.22 (-0.42, -0.02) |
| BMI                 | 0.335          | 0.011             | 0.149          |
| Change              | 0.129          | 0.005             | 0.035          |
|                  |                |                   |                |
| Note. All models are adjusted for prevalent diabetes, prevalent hypertension, marijuana use and HIV status. Beta represents an adjusted, unstandardized coefficient. NP assessments are reverse scored and a higher beta indicates better NP. WWH models are additionally adjusted for CD4 count, viral load and CPE rank (High, medium, low). |
| * = all adiposity measures are ln transformed |