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Leptin, Adiponectin and Cognition in Middle-aged HIV-infected and Uninfected Women. The Brooklyn Women's Interagency HIV Study

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Abstract

Context: Case-control study of women with and without HIV infection.

Objective: To explore the association of cognition and the adipokines, leptin and adiponectin (total; high molecular weight, HMW), in women with (HIV+) and without HIV (HIV-) infection.

Design: Cross-sectional analyses of adipokines and cognition using linear regression models of log-transformed adipokines, 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, education, CD4 count, diabetes, body mass index (BMI), waist circumference (WC) and race/ethnicity.

Setting: Brooklyn, NY.

Participants: 354 participants (247 HIV+, 107 HIV-), in the Brooklyn Women's Interagency HIV Study (WIHS), average age 38.9 years, with measured levels of leptin and adiponectin (total and high molecular weight, HMW).

Main Outcome Measure: Cognition

Results: Higher levels of leptin were positively associated with worse cognition on the basis of Trails A completion time and SDMT score. Among at risk HIV- women, leptin was associated with worse performance on Trails B. No associations were observed for total or HMW adiponectin.

Conclusion: Blood adipokine levels were measured to provide mechanistic insights regarding the association of adipose with cognitive function. These data suggest that higher levels of leptin, consistent with more adipose tissue, are associated with worse cognitive function in middle age. Monitoring leptin over time and with increasing age in relation to cognition and dementia, may lend insights to the role of adipose tissue in successful body and brain aging among women with HIV infection.

Keywords: Cognition; Adipokine; Leptin; Adiponectin; HIV; Women; Overweight; Obesity

Introduction

Human Immunodeficiency Virus (HIV) infection is one of the most prevalent infectious diseases worldwide. With current therapies, HIV infection has evolved from a fatal infection, to a treatable, chronic condition of aging among older adults [1,2]. In 2012, 50% of all Ryan White HIV/AIDS Program clients were age 45-64 years and older; [3] and data suggest that over half of HIV-infected people in the United States (US) today are age 50 years and older [4]. This increase in life expectancy is necessarily accompanied by concerns about the concomitant physiological, social and mental consequences of aging with chronic HIV infection. Some studies show that HIV infection is synergistic with adverse influences of aging on the immune, endocrine, vascular, and central nervous systems, thereby accelerating the aging process [5,6]. Evaluating these systems in middle-aged HIV infected persons is essential to understanding HIV impact on the natural processes of aging.

In many countries, the advent of ART has been accompanied by an increase in body mass index (BMI). Thus, in contrast to the wasting syndrome that initially characterized HIV infection and AIDS, individuals with HIV infection and on antiretroviral therapies (ART) are overweight and obese. Importantly, overweight and obesity are leading causes of disability and death in the United States and around the world, and are associated with risk of cognitive impairment and late-onset dementia in populations without HIV [7].

During adult life, BMI is a gross indicator of amount of adipose tissue in the human body. This is mainly white adipose tissue, which functions as the largest endocrine organ in the human body by secreting many hormones, peptides and cytokines, some of which are referred to as adipokines [8]. These adipokines are not exclusively secreted by adipose tissue, nor is adipose tissue the primary source of these compounds, however their bioactivity is indisputable [9]. Adipokines affect processes in the periphery and the central nervous system (CNS), and may be dysregulated in individuals with HIV infection, whether on or off ART, perhaps due to lipodystrophies [10]. It is important to try to partition out the bioactive aspects of adipose tissue and their relationship to cognition in individuals with HIV infection. Using blood adipokine levels may be one way to do this.

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Leptin is an adipose tissue hormone that has been most reported in association with dementia and Alzheimer's Disease (AD). Leptin is a 16 kDa protein hormone [11,12] that is primarily secreted by adipose tissue and positively correlated with anthropometric measures [13,14]. Correlations of approximately r=0.7 between BMI and blood leptin levels are observed in adults, even among those with obesity syndromes [15,16]. There have been numerous reports from human population studies showing that higher leptin levels are associated with less cognitive impairment and dementia in later life. The Framingham Heart Study, [17] Study of Osteoporotic Fractures, [18] and Health ABC Study, [19] have all shown leptin levels to be protective for dementia and Mild Cognitive Impairment (MCI), or cognitive decline when measured 4-8.3 years before onset of disease. During this prodromal period, leptin may merely be a marker of adipose tissue since higher levels of BMI have also shown protection for dementia during this period; or leptin may have independent, beneficial effects on the brain and/or reflect neurodegenerative processes. However, it has also been observed that leptin levels 24 years prior to dementia onset are not predictive of dementia risk [15].

Adiponectin is produced solely by adipose tissue and exists as complex multimeric isoforms comprised of High Molecular Weight (HMW), hexamers and trimmers [20]. It is an effective insulin sensitizer, and circulating levels are inversely correlated with insulin resistance, metabolic syndrome, obesity, type 2 diabetes, and cardiovascular diseases. HMW adiponectin or the ratio of HMW adiponectin to total adiponectin may be better indicators of insulin sensitivity than total adiponectin in obesity, diabetes, and cardiovascular disease [20]. Adiponectin modulates inflammatory responses, energy expenditure (CNS and periphery), food intake (CNS), and a number of metabolic processes, including glucose regulation and fatty acid catabolism in the periphery [21]. Adiponectin has also been implicated in cognition and dementia, but data are mixed and available for total adiponectin only. The Framingham Heart Study [22] and the Mayo Clinic Study on Aging (MCSA) [23] have shown mixed associations between total adiponectin and dementia. Framingham reported that higher total adiponectin levels were associated with all-cause dementia and AD risk over a 13 year follow-up; whereas there was no cross-sectional difference by Mild Cognitive Impairment (MCI) status in the MCSA.

In the present study, we determined whether leptin and adiponectin levels are differentially associated with concurrent measures of cognitive performance in women who are HIV+ or HIV- and are participants at the Brooklyn site of the Women's Interagency HIV Study (WIHS). Demographic, cardiovascular, and HIV-related factors were considered as confounders.

Materials and Methods

WIHS is an ongoing prospective study of HIV in women [24]. WIHS began in 1994 and enrolled 3766 women across six sites in San Francisco, Los Angeles, Chicago, Washington, DC, Brooklyn and the Bronx. Across all sites, 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. The Brooklyn WIHS site has participated since the WIHS' inception. Three hundred and fifty-four of the participants (247 HIV+, 107 HIV-) enrolled in Brooklyn WIHS had available cognitive test scores.

Demographic measures

All demographic measures were self-reported. Race [24,25] was reported as white, Hispanic, African-American, or 'other' (self-reported as Native American/Alaskan, Asian/Pacific Islander or other). Participants were also asked to report their current smoking status, and use of marijuana, 'crack', cocaine, and heroin.

Clinical measures

Anthropometric measures were conducted according to the U.S. National Health and Nutrition Examination Survey (NHANES) III protocol and included body weight (pounds), body height (inches), waist (WC) and hip circumferences (cm), and BMI (kg/m^2) [26]. 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 1.00 inch. After conversion of body weight and height to metric units, BMI was calculated as kilograms per meter squared (kg/m^2). Categories of BMI included: underweight, <18.5; 'normal' or healthy weight, 18.5-24.9; overweight, 25.0-29.9; and obese, ≥30 kg/m^2 [27]. WC and hip circumference were measured to the nearest 0.5 cm. WHR was calculated as the ratio of WC to hip circumference. Central obesity was defined as WHR >0.85 [28].

Eight hour fasted blood samples were collected and total cholesterol levels were determined as previously described [29]. Systolic (SBP) and diastolic blood pressures (DBP) were recorded using a standardized protocol [30]. Hypertension was defined as either average measured SBP >140 mm Hg, or DBP >90 mm Hg, or a self-reported hypertension with use of antihypertensive medications. Previous myocardial infarction (MI) and diabetes mellitus (DM) were self-reported [24,25].

Adipokine measures

Plasma samples for adipokine analyses were drawn within one visit of cognitive test administration. Standards and controls were tested in duplicate using High Molecular Weight (HMW) adiponectin, total adiponectin, and leptin ELISAs (Millipore, Billerica, MA) [20,31]. For leptin, undiluted samples were tested and plates were prepared according to protocol. The 7-point standard curve ranged from 0.5-100 ng/mL. 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. For HMW adiponectin, samples were digested as directed in the assay protocol using reagents provided in the kit, the 7-point standard curve ranged from 1.5 to 200 ng/mL and samples were tested at a final dilution of 1:200. For total adiponectin, the diluted samples were assayed and plates were prepared according to protocol. The 7-point standard curve range was 1.56-100 ng/mL and tested at a final dilution of 1:500.

HIV-related variables

Methods for determining HIV status, AIDS diagnosis, CD4 count, viral load, and duration of ART use were described previously [24,25,32].

Cognitive tests

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 [29]. 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.

Cognitive Domain	Test
Executive Function	Trails A, Trails B Stroop Interference[63,64]
Speed of Information Processing	Symbol Digit Modalities Test (SDMT)* [65,66] 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 1: Cognitive tests administered in WIHS and corresponding cognitive domains measured [29].

Inclusion criteria

We include all data collected by visit 28, concluding in September 2008 on 354 participants (247 HIV+, 107 HIV-) with data available on both anthropometric and cognitive measures.

Statistical analysis

All adipokines were log-transformed and considered as continuous variables. We estimated leptin resistance via the leptin: BMI [33]. Linear regression analyses were used to examine associations between continuous or categorical log adipokines and cognitive test scores (or time to completion) of Trails A, Trails B, SDMT score, Stroop interference, Stroop Color Naming, and Stroop Word Recall. Regression models were run including all participants, and separately for HIV+ and HIV- individuals.

Several covariates were considered, including: age, race, highest educational level attained, HIV status, ART, CD4 count, CD4 nadir, prevalent DM, SBP, DBP, use of anti-hypertensive medications, blood cholesterol level, current smoking status, and use of marijuana, 'crack', cocaine, and/or heroin. Potential covariates were included if they were significantly associated with cognitive test scores and/or adipokines in age-adjusted models at a level of $p<0.05$. The final models included the following covariates: age, education, race, DM, and BMI. In analyses of women who were HIV+, we also adjusted for current CD4 count. STATA 12 was used for all statistical analyses. Results were considered statistically significant at $p<0.05$.

Results

Both adipokines and cognitive measures were available for 354 Brooklyn WIHS participants (213 HIV+ and 97 HIV- women). Demographic, anthropometric, and health characteristics of the participants are presented in Table 2. HIV+ women were approximately 3.5 years older than HIV- women, however educational attainment, a key influencer of cognitive performance, did not differ between HIV+ and HIV- women. Most (65%) women were overweight or obese (≥25.0 kg/m^2) and the prevalence of central obesity was 60%. Less than 2% of women had a BMI <18.5, probably in concordance with the low prevalence of AIDS among those who were HIV+. HIV+ women had a higher WHR ($P<0.05$) and there was a trend for them ($p<0.10$) to have a lower average BMI, compared to HIV- women. Among published vascular risk factors for cognitive impairment, there were no differences.

Correlations between anthropometric measures and adipokines indicated strong associations in the directions expected (Tables 3 and 4). Leptin was positively, and adiponectin inversely, correlated with anthropometric measures. Notably the correlation coefficients were quite strong for each hormone in line with previous reports in the literature in non-HIV population samples [15]. An exception to this was the correlation between leptin and WHR among HIV+ women. In addition, viral load was correlated with log leptin only after age adjustment; and CD4 count was correlated with all adipokine measures except for the ratio of HMW/total adiponectin.

Associations with cognitive test scores (Table 5), revealed that higher

Characteristic	ALL (n=354)		HIV+ (n=247)		HIV- (n=107)		
	N	*Mean (SD)/n(%)*	N	*Mean (SD)/n(%)*	N	*Mean (SD)/n(%)*	*p-value*
Age	354	38.9 (9.1)	247	40.0 (8.6)	107	36.4 (9.8)	<0.001
Race	354		247		107		0.465
White		31 (8.7%)		24 (9.7%)		7 (6.5%)	
African American (AA)		280 (79.0%)		193 (78.2%)		87 (81.5%)	
Non-white, non-AA Hispanic		34 (9.6%)		23 (9.3%)		11 (10.2%)	
Other		9 (2.7%)		7 (2.8%)		2 (1.8%)	
Highest education	354		247		107		0.285
Grades 7-11		124 (35.1%)		91 (36.8%)		33 (31.1%)	
Completed HS		127 (36.0%)		88 (35.6%)		39 (26.8%)	
Some college		86 (24.4%)		58 (23.5%)		28 (26.4%)	
4-yr degree		14 (3.9%)		10 (4.1%)		4 (3.8%)	
attend/ complete grad school		2 (0.6%)		0		2 (1.9%)	
CD4 count, need log			245	518.3 (323.4)			
Viral load			244	27,619 (140,879)			
Leptin (ng/ml)	353	30.8 (29.7)	246	29.0 (28.7)	107	34.8 (31.7)	0.091
HMW Adiponectin (ng/ml)	348	5074.8 (5009.7)	244	5283.7 (5488.1)	104	4584.5 (3626.0)	0.234
Total Adiponectin (ng/ml)	354	6998.5 (3873.6)	247	7035.6 (4124.2)	107	6912.9 (3238.1)	0.785
HMW/Total Adiponectin	348	0.68 (0.36)	244	0.70 (0.39)	104	0.63 (0.30)	0.115
BMI (kg/m^2)	349	29.2 (7.9)	245	28.8 (7.3)	104	30.3 (9.1)	0.091
<18.5		6 (1.7%)		5 (2.0%)		1 (1.0%)	
18.5-24.9		115 (33.0%)		83 (33.9%)		32 (30.8%)	
25.0-29.9		104 (29.8%)		75 (30.6%)		29 (27.9%)	
≥30.0		124 (35.5%)		82 (33.5%)		42 (40.4%)	
WHR	264	0.88 (0.08)	180	0.89 (0.08)	84	0.85 (0.07)	<0.001
>0.85		157 (59.5%)		119 (66.1%)		38 (45.2%)	0.002
Waist Circumference, WC (cm)	266	91.1 (16.2)	181	90.9 (15.3)	85	91.3 (17.8)	0.821
Marijuana Use since last visit	354	64 (18.1%)	247	41 (16.6%)	107	23 (21.5%)	0.294
Any indicator of hypertension*	354	127 (35.9%)	247	94 (38.1%)	107	33 (30.8%)	0.119
Total Cholesterol (mg/dl)	354	176.8 (36.5)	247	175.4 (37.4)	107	180.1 (34.1)	0.265
Diabetes mellitus (yes)	312	15 (4.8%)	217	9 (4.2%)	95	6 (6.3%)	0.401
*Either SBP ≥ 140, DBP ≥90, self-reported hypertension, or taking anti-hypertensive medication.							

Table 2: Demographic and health characteristics of Brooklyn WIHS participants with adipokine and cognitive measures.

leptin levels were associated with longer time to completion of Trails A in both HIV+ and HIV- women after multivariate adjustment (Model 2). Similar associations were also observed for Trails B performance, but only among those without HIV infection. Also observed was an inverse association of leptin with SDMT among women without HIV infection. There were no linear associations observed for total or HMW adiponectin. Calculated leptin resistance was not informative (data not shown).

Conclusion

Among women at mid-life with HIV infection for at least 10 years, cross-sectional associations between cognition and adipokines (leptin, total adiponectin and HMW adiponectin), were observed for tests of executive function for leptin only, in which case higher leptin levels were associated with worse performance. This is in contrast to some of our findings concerning anthropometric measures – BMI, WC, or WHR – and cognition in WIHS, where there appeared to be an association between higher levels of adiposity (suggesting higher leptin levels) and better performance on certain cognitive tests, as well as lower adiposity (BMI <18.5 kg/m^2) and worse performance [16]. This is also in contrast to published observations for leptin in non-HIV populations suggesting protection via leptin, albeit at older ages. Interestingly, and as a type of validation, similar correlations between BMI and adipokine levels were observed here in mid-life for women with or at risk for HIV infection in Brooklyn WIHS as have been observed in other epidemiologic studies for non-HIV populations [15]. Given potential aberrations in fat metabolism, such as lipodystrophies, that are observed in HIV, this was deemed somewhat surprising. Also of note, a BMI of 40-59 kg/m^2 (9.7% of women; max BMI, 59 kg/m^2) brought substantial heterogeneity in leptin levels in the sample. The association of leptin with BMI was no longer linear (data not shown); the highest isolated leptin levels were observed; and there was vague evidence of leptin resistance at BMI >50 kg/m^2, since leptin levels plateaued as BMI continued to increase. Attempts to estimate this phenomenon via calculation of leptin:BMI did not lend further insight into this theory.

To our knowledge, published data on leptin and/or adiponectin

	BMI					Waist Circumference					WHR				
		crude		age-adjusted			crude		age-adjusted			crude		age-adjusted	
	n	*r*	*p-value*	*r*	*p-value*	*n*	*r*	*p-value*	*r*	*p-value*	*n*	*r*	*p-value*	*r*	*p-value*
Log Leptin	348	0.706	<0.0001	0.707	<0.0001	265	0.699	<0.0001	0.709	<0.0001	263	0.156	0.011	0.182	0.003
HMW adiponectin	343	-0.294	<0.0001	-0.298	<0.0001	262	-0.334	<0.0001	-0.345	<0.0001	260	-0.265	<0.0001	-0.303	<0.0001
Total adiponectin	349	-0.260	<0.0001	-0.266	<0.0001	266	-0.314	<0.0001	-0.325	<0.0001	264	-0.282	<0.0001	-0.321	<0.0001
HMW/total adiponectin ratio	343	-0.292	<0.001	-0.292	<0.0001	262	-0.263	<0.0001	-0.263	<0.0001	260	-0.206	<0.001	-0.213	<0.001

Table 3: Correlations between anthropometric measures and adipokines: Brooklyn WIHS.

	Log Leptin			Log Adiponectin			Log Total Adiponectin			Log Total/HMW Adiponectin Ratio		
	n	r	p-value	n	r	p-value	n	r	p-value	n	r	p-value
BMI - HIV+												
crude	244	0.708	<0.0001	242	-0.316	<0.0001	245	-0.271	<0.0001	242	-0.235	0.0002
age-adjusted	244	0.706	<0.0001	242	-0.314	<0.0001	245	-0.264	<0.0001	242	-0.241	0.0002
BMI – HIV-												
crude	104	0.707	<0.0001	101	-0.484	<0.0001	104	-0.277	0.004	101	-0.452	<0.0001
age-adjusted	104	0.697	<0.0001	101	-0.478	<0.0001	104	-0.281	0.004	101	-0.446	<0.0001
WC - HIV+												
crude	180	0.695	<0.0001	179	-0.315	<0.0001	181	-0.312	<0.0001	179	-0.196	0.009
age-adjusted	180	0.699	<0.0001	179	-0.316	<0.0001	181	-0.313	<0.0001	179	-0.196	0.009
WC– HIV-												
crude	85	0.720	<0.0001	83	-0.489	<0.0001	85	-0.351	0.001	83	-0.412	0.0001
age-adjusted	85	0.721	<0.0001	83	-0.473	<0.0001	85	-0.355	0.001	83	-0.384	0.0004
WHR - HIV+												
crude	179	0.085	0.259	178	-0.335	<0.0001	180	-0.332	<0.0001	178	-0.205	0.006
age-adjusted	179	0.112	0.136	178	-0.349	<0.0001	180	-0.360	<0.0001	178	-0.204	0.007
WHR – HIV-												
crude	84	0.419	0.0001	82	-0.497	<0.0001	84	-0.398	0.0002	82	-0.388	0.0003
age-adjusted	84	0.402	0.0002	82	-0.485	<0.0001	84	-0.413	0.0001	82	-0.355	0.001
Viral load												
crude	243	-0.125	0.052	241	0.079	0.220	244	0.089	0.168	241	0.042	0.518
age-adjusted	243	-0.128	0.046	241	0.081	0.212	244	0.096	0.137	241	0.040	0.542
CD4												
crude	272	0.146	0.016	268	-0.159	0.009	273	-0.169	0.005	268	-0.099	0.107
age-adjusted	272	0.144	0.018	268	-0.159	0.009	273	-0.167	0.006	268	-0.101	0.101
Nadir CD4												
crude	221	0.062	0.357	219	-0.058	0.394	222	-0.047	0.486	219	-0.053	0.432
age-adjusted	221	0.040	0.551	219	-0.054	0.427	222	-0.010	0.885	219	-0.078	0.250

Table 4. Correlations between anthropometric measures and adipokines by HIV infection status: Brooklyn WIHS.

	All			HIV+			HIV-		
Log Adipokine	**n**	**b(95% CI)**	**p-value**	**n**	**b(95% CI)**	**p-value**	**n**	**b(95% CI)**	**p-value**
Trails A									
Leptin									
Model 1	353	0.90 (-0.63, 2.42)	0.248	246	0.77 (-1.20, 2.74)	0.444	107	**2.26 (0.05, 4.46)**	**0.045**
Model 2	306	**3.16 (0.97, 5.35)**	**0.005**	215	**2.96 (0.12, 5.81)**	**0.041**	91	**4.84 (1.58, 8.11)**	**0.004**
HMW adiponectin									
Model 1	348	-1.35 (-3.81, 1.10)	0.279	244	-0.91 (-4.01, 2.18)	0.561	104	-2.91 (-6.59, 0.78)	0.121
Model 2	302	-2.13 (-4.84, 0.58)	0.123	213	-1.98 (-5.32, 1.37)	0.245	89	-1.49 (-6.32, 3.34)	0.541
Total adiponectin									
Model 1	354	2.30 (-0.91, 5.51)	0.160	247	2.32 (-1.66, 6.30)	0.251	107	1.68 (-3.53, 6.89)	0.523
Model 2	307	1.05 (-2.44, 4.55)	0.554	216	2.77 (-1.73, 7.26)	0.227	91	-2.71 (-8.61, 3.18)	0.363
HMW adiponectin/total adiponectin ratio									
Model 1	348	-1.35 (-3.81, 1.10)	0.279	244	-0.91 (-4.01, 2.18)	0.561	104	-2.91 (-6.59, 0.78)	0.121
Model 2	302	-3.55 (-8.48, 1.39)	0.159	213	-3.77 (-9.71, 2.18)	0.213	89	-2.85 (-12.13, 6.43)	0.542
Trails B									
Leptin									
Model 1	352	1.64 (-3.26, 6.53)	0.512	245	-0.94 (-7.39, 5.52)	0.776	107	**8.29 (1.50, 15.08)**	**0.017**
Model 2	305	**7.67 (0.75, 14.58)**	**0.030**	214	4.86 (-4.01, 13.74)	0.281	91	**15.48 (4.50, 26.44)**	**0.006**
HMW adiponectin									
Model 1	347	0.85 (-7.05, 8.76)	0.832	243	2.49 (-7.62, 12.61)	0.628	104	-4.48 (-16.10, 7.13)	0.446
Model 2	301	-2.11 (-10.58, 6.36)	0.624	212	-2.58 (-12.81, 7.65)	0.619	89	-3.48 (-19.77, 12.80)	0.671
Total adiponectin									
Model 1	353	6.94 (-3.37, 17.26)	0.186	*246*	12.59 (-0.37, 25.55)	0.057	107	-8.69 (-24.80, 7.42)	0.287
Model 2	306	4.51 (-6.40, 15.42)	0.416	*215*	12.42 (-1.31, 26.16)	0.076	91	-18.22 (-37.64, 1.21)	0.066
HMW adiponectin/total adiponectin ratio									
Model 1	347	0.85 (-7.05, 8.76)	0.832	243	2.49 (-7.62, 12.61)	0.628	104	-4.48 (-16.10, 7.13)	0.446
Model 2	301	-3.14 (-18.57, 12.29)	0.689	212	-2.48 (-20.65, 15.69)	0.788	89	-16.21 (-47.31, 14.90)	0.303
Symbol Digit Modalities Test (SDMT)									
Leptin									
Model 1	348	0.37 (-0.75, 1.49)	0.515	242	0.73 (-0.66, 2.13)	0.303	106	-0.80 (-2.71, 1.10)	0.405
Model 2	302	-1.01 (-2.53, 0.50)	0.190	212	-0.33 (-2.18, 1.52)	0.727	90	**-3.22 (-5.96, -0.48)**	**0.022**
HMW adiponectin									
Model 1	343	-0.33 (-2.12, 1.46)	0.716	240	-0.26 (-2.43, 1.90)	0.810	103	-0.28 (-3.50, 2.93)	0.862
Model 2	298	0.38 (-1.48, 2.25)	0.686	210	0.52 (-1.63, 2.68)	0.633	88	-1.42 (-5.44, 2.60)	0.485
Total adiponectin									
Model 1	349	-0.83 (-3.17, 1.51)	0.486	243	-1.28 (-4.08, 1.52)	0.370	106	0.47 (-3.97, 4.90)	0.835
Model 2	303	0.46 (-1.93, 2.85)	0.706	213	-0.67 (-3.58, 2.23)	0.649	90	3.94 (-0.87, 8.75)	0.107
HMW adiponectin/total adiponectin ratio									
Model 1	343	-0.33 (-2.12, 1.46)	0.716	240	-0.26 (-2.43, 1.90)	0.810	103	-0.28 (-3.50, 2.93)	0.862
Model 2	298	0.16 (-3.23, 3.56)	0.925	210	0.35 (-3.50, 4.21)	0.856	88	-0.80 (-8.56, 6.96)	0.837
Stroop -- Color									
Leptin									
Model 1	313	1.64 (-0.23, 3.51)	0.086	215	2.12 (-0.30, 4.55)	0.086	98	1.07 (-1.81, 3.96)	0.463
Model 2	274	1.58 (-1.14, 4.30)	0.254	189	1.51 (-2.00, 5.03)	0.397	85	0.61 (-3.67, 4.89)	0.777
HMW adiponectin									
Model 1	308	0.55 (-2.54, 3.64)	0.726	213	-0.14 (-3.93, 3.65)	0.944	95	2.13 (-3.20, 7.46)	0.430
Model 2	270	-0.08 (-3.40, 3.24)	0.963	187	-1.48 (-5.55, 2.60)	0.475	83	2.13 (-3.95, 8.21)	0.487
Total adiponectin									
Model 1	314	-2.36 (-6.37, 1.65)	0.248	216	-2.47 (-7.40, 2.45)	0.324	98	-1.75 (-8.78, 5.28)	0.623
Model 2	275	-3.86 (-8.24, 0.50)	0.083	190	-4.04 (-9.58, 1.50)	0.152	85	-2.00 (-9.54, 5.55)	0.600
HMW adiponectin/total adiponectin ratio									
Model 1	308	-0.06 (-3.25, 3.14)	0.973	213	-0.14 (-3.93, 3.65)	0.944	95	2.13 (-3.20, 7.46)	0.430
Model 2	270	1.99 (-4.27, 8.25)	0.532	187	-0.59 (-8.14, 6.97)	0.879	83	7.58 (-4.03, 19.19)	0.197
Stroop -- Word									
Leptin									
Model 1	314	1.12 (-0.44, 2.69)	0.158	216	1.91 (-0.05, 3.87)	0.056	98	-0.07 (-2.75, 2.60)	0.956

Model 2	275	0.85 (-1.44, 3.13)	0.467	190	0.96 (-1.86, 3.78)	0.503	85	-0.07 (-4.29, 4.16)	0.975
HMW adiponectin									
Model 1	309	0.60 (-1.98, 3.19)	0.647	214	0.70 (-2.37, 3.77)	0.653	95	0.09 (-4.85, 5.03)	0.972
Model 2	271	0.66 (-2.13, 3.46)	0.640	188	0.23 (-3.05, 3.50)	0.891	83	0.79 (-5.23, 6.80)	0.796
Total adiponectin									
Model 1	315	-1.41 (-4.76, 1.94)	0.408	217	-0.71 (-4.70, 3.28)	0.726	98	-3.77 (-10.23, 2.69)	0.250
Model 2	276	-2.24 (-5.93, 1.44)	0.231	191	-1.52 (-5.98, 2.95)	0.503	85	-4.12 (-11.52, 3.27)	0.270
HMW adiponectin/total adiponectin ratio									
Model 1	309	0.25 (-2.37, 2.87)	0.850	214	0.70 (-2.37, 3.77)	0.653	95	0.09 (-4.85, 5.03)	0.972
Model 2	271	1.12 (-4.15, 6.40)	0.676	188	0.72 (-5.34, 6.78)	0.815	83	0.33 (-11.25, 11.91)	0.955
Stroop -- Interference									
Leptin									
Model 1	308	**4.67 (1.54, 7.79)**	**0.004**	211	**4.90 (0.96, 8.84)**	**0.015**	97	3.93 (-1.46, 9.31)	0.151
Model 2	271	4.12 (-0.27, 8.51)	*0.066*	187	4.53 (-0.91, 9.98)	0.102	84	3.66 (-4.66, 11.97)	0.384
HMW adiponectin									
Model 1	303	-1.02 (-6.28, 4.24)	0.703	209	-1.37 (-7.65, 4.90)	0.667	94	-0.28 (-10.26, 9.69)	0.955
Model 2	267	-0.41 (-5.80, 4.98)	0.882	185	-3.05 (-9.44, 3.35)	0.348	82	7.33 (-4.25, 18.91)	0.211
Total adiponectin									
Model 1	309	-0.27 (-7.08, 6.54)	0.938	212	2.63 (-5.46, 10.73)	0.522	97	-7.71 (-20.90, 5.48)	0.249
Model 2	272	0.29 (-6.84, 7.43)	0.936	188	2.26 (-6.44, 10.96)	0.609	84	-6.70 (021.40, 8.01)	0.367
HMW adiponectin/total adiponectin ratio									
Model 1	303	-1.85 (-7.21, 3.51)	0.498	209	-1.37 (-7.66, 4.90)	0.667	94	-0.28 (-10.26, 9.69)	0.955
Model 2	267	-1.24 (-11.37, 8.89)	0.810	185	-4.83 (-16.58, 6.91)	0.418	82	10.62 (-12.04, 33.27)	0.353
Model 1 adjusts for age									
Model 2 adjusts for age, education, race, BMI, diabetes. Models of HIV+ also included current CD4 count.									

Table 5. Leptin and adiponectin in association with cognitive test score, by HIV infection status: Brooklyn WIHS.

levels in association with cognition among those with HIV infection have been reported from the Charter Study [34] and the Multicenter AIDS Cohort Study (MACS) [35]. The Charter Study conducted a metabolic substudy that included 52 cognitively impaired and 78 unimpaired HIV+ women and men, at the average age of 46 years. Average leptin levels did not differ between cognitively impaired versus unimpaired. The MACS, which includes men only, conducted an analysis of leptin and adiponectin in 509 HIV+ (average age: 55 years) and 271 HIV- (average age: 53 years). There was, once again, no association between cognition and leptin levels. However, among HIV+ men, higher adiponectin levels were associated with worse cognitive test scores. Thus, observations spanning the average ages of 39-55 years in women and men from Charter, the WIHS, and the MACS, do not support a protective role of leptin for cognition among adults with HIV infection. However, as adiponectin is a marker of inflammation, [36-41] perhaps higher levels of this adipokine, especially among older adults (i.e., MACS participants) and/or men specifically, may be informative.

In relationship to leptin, a null finding with cognition in mid-life may be expected as most published data on the association between leptin and dementia have been collected in late life, [21] when the average age at baseline was 74-83 years, much older than our sample. Another report has shown that over a 24 year follow-up period, mid-life (age 38-60 years) leptin levels were not associated with late life dementia [15]. Based on these findings in old age, it has been suggested that leptin may be a cognitive enhancer when given at the time of cognitive impairment or dementia, [42] and, in light of these findings, influence appears to be temporal in relation to dementia onset. It will be interesting to observe whether there is a late life role for leptin in HIV infected women as the WIHS cohort ages.

There is much mechanistic evidence for a role of peripheral leptin and the brain. Leptin is one of the adipokines most studied in association with brain structure and function, and has been found to have numerous effects on brain development [43] and potentially on brain health in cognition and aging. Peripheral leptin enters the central nervous system and interacts with specific areas of the brain such as the hypothalamus and hippocampus [44]. However, besides leptin transport into the cerebrospinal fluid (CSF) via leptin receptor a (LepRa), and a second, not yet characterized, transport mechanism, [45] several studies indicate that leptin is also produced in the brain, for example in the hypothalamus, cortex and cerebellum [46,47].

Leptin regulates food intake and energy expenditure, improves insulin sensitivity, facilitates lipolysis, and inhibits lipogenesis [48,49]. In addition, leptin plays a permissive role in neuroendocrine immune function [48]. Leptin affects hypothalamic function, and learning and memory processes controlled by the hippocampus [43,50-52]. Experimental data show that leptin, and other adipose tissue compounds, interact directly with hypothalamic nuclei, such as the arcuate nucleus, and regulate energy expenditure and food intake through production of orexigenic (NPY, agrp) and anorectic (aMSH) peptides [53,54]. In addition, leptin appears to facilitate pre- and postsynaptic transmitter release and sensitivity, respectively, in hippocampal CA1 neurons [51]. This translates to improved performance related to spatial learning and memory function. Leptin may even shape the hypothalamus in the earliest stages of development and enhance cognition [43]. Since most data suggest leptin to be positive for the brain, it is unclear as to why the findings reported here, in women with HIV, are observed. Either higher leptin and/or adiposity levels in later life occur as a part of the aging process and are truly protective for the brain, or they are a response to earlier brain injury to which these data would attest. There is a dearth of data in HIV-infected adults.

Adiponectin is a visceral adiposity marker and is moderately inversely correlated with BMI (compared to leptin for example), and blood-brain barrier (BBB) transport mechanisms are unclear. Thus

blood levels may not provide an adequate indication of potential interactions between adiponectin and the brain [55]. Studies evaluating adiponectin in association with dementia, have only reported on total adiponectin levels. Isolating HMW adiponectin and the smaller adiponectin fragments can present problems in the laboratory and inter- and intra-assay variability can be high [20].

While adiponectin is produced solely by adipose tissue, its receptors are not [56]. The peripheral effects of adiponectin are mediated mainly via 2 receptors, AdipoR1 and AdipoR2. Expression of these receptors is reported in adipose, brain, ovaries, endometrium, and placenta [57]. Both AdipoR1 and AdipoR2 are widely found throughout the CNS in brain microvessels, hippocampus, hypothalamus and brainstem in humans [58-60]. However, because there is a 1000-fold lower cerebrospinal fluid (CSF)/serum adiponectin ratio observed in humans, [59] the origin of brain adiponectin is debated. Trimeric and low molecular weight adiponectins are detectable in the CSF of humans and rodents [61,62]. In combination with a lack of HMW adiponectin observed in CSF, this may imply that only smaller forms of adiponectin cross the BBB [61,62].

This is a large study of adipokines 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 adiposity. The primary limitations include a limited battery of cognitive tests, no body composition measures, and cross-sectional analyses. Due to multiple comparisons, one must also consider risk for false discoveries; and our analyses were not adjusted for multiple comparisons. Observed p-values were <0.005 for most correlations between adipokines and anthropometric factors and for some of the regression analyses. However, this is one of the first reports of promising biomarkers of adiposity and cognition in women with or at risk for HIV infection. 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 eventually dementia in HIV, measured as BMI and as adipokines, particularly leptin.

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Disclosure Statement

The authors have nothing to disclose.

References

1. Kirk JB, Goetz MB (2009) Human immunodeficiency virus in an aging population, a complication of success. J Am Geriatr Soc 57: 2129-2138.
2. Vance DE, McGuinness T, Musgrove K, Orel NA, Fazeli PL (2011) Successful aging and the epidemiology of HIV. Clin Interv Aging 6: 181-192.
3. US Department of Health and Human Services (2014) Health Resources and Services Administration, HIV/AIDS Bureau, Rockville, MD.
4. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN (2013) Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One 8: e81355.
5. Nguyen N, Holodniy M (2008) HIV infection in the elderly. Clin Interv Aging 3: 453-472.
6. Kalayjian RC, Landay A, Pollard RB, Taub DD, Gross BH (2003) Age-related immune dysfunction in health and in human immunodeficiency virus (HIV) disease: association of age and HIV infection with naive CD8+ cell depletion, reduced expression of CD28 on CD8+ cells, and reduced thymic volumes. J Infect Dis 187: 1924-1933.
7. Gustafson DR, Luchsinger JA (2013) High adiposity: risk factor for dementia and Alzheimer's disease? Alzheimers Res Ther 5: 57.
8. Esteve Ràfols M (2014) Adipose tissue: cell heterogeneity and functional diversity. Endocrinol Nutr 61: 100-112.
9. Lehr S, Hartwig S, Sell H (2012) Adipokines: a treasure trove for the discovery of biomarkers for metabolic disorders. Proteomics Clin Appl 6: 91-101.
10. Sweeney LL, Brennan AM, Mantzoros CS (2007) The role of adipokines in relation to HIV lipodystrophy. AIDS 21: 895-904.
11. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L (1994) Positional cloning of the mouse obese gene and its human homologue. Nature 372: 425-432.
12. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, et al. (1995) Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1: 1155-1161.
13. Friedman JM, Halaas JL (1998) Leptin and the regulation of body weight in mammals. Nature 395: 763-770.
14. Lissner L, Karlsson C, Lindroos AK, Sjöström L, Carlsson B, et al. (1999) Birth weight, adulthood BMI, and subsequent weight gain in relation to leptin levels in Swedish women. Obes Res 7: 150-154.
15. Gustafson DR, Bäckman K, Lissner L, Carlsson L, Waern M, et al. (2012) Leptin and dementia over 32 years-The Prospective Population Study of Women. Alzheimers Dement 8: 272-277.
16. Gustafson DR, Mielke MM, Tien PC, Valcour V, Cohen M, et al. (2013) Anthropometric measures and cognition in middle-aged HIV-infected and uninfected women. The Women's Interagency HIV Study. J Neurovirol 19: 574-585.
17. Lieb W, Beiser AS, Vasan RS, Tan ZS, Au R, et al. (2009) Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. JAMA 302: 2565-2572.
18. Zeki Al Hazzouri A, Stone KL, Haan MN, Yaffe K (2013) Leptin, mild cognitive impairment, and dementia among elderly women. J Gerontol A Biol Sci Med Sci 68: 175-180.
19. Holden KF, Lindquist K, Tylavsky FA, Rosano C, Harris TB, et al. (2009) Serum leptin level and cognition in the elderly: Findings from the Health ABC Study. Neurobiol Aging 30: 1483-1489.
20. Sinha MK, Songer T, Xiao Q, Sloan JH, Wang J, et al. (2007) Analytical validation and biological evaluation of a high molecular-weight adiponectin ELISA. Clin Chem 53: 2144-2151.
21. Kiliaan AJ, Arnoldussen IA, Gustafson DR (2014) Adipokines: a link between obesity and dementia? Lancet Neurol 13: 913-923.
22. van Himbergen TM, Beiser AS, Ai M, Seshadri S, Otokozawa S, et al. (2012) Biomarkers for insulin resistance and inflammation and the risk for all-cause dementia and alzheimer disease: results from the Framingham Heart Study. Arch Neurol 69: 594-600.
23. Roberts RO, Geda YE, Knopman DS, Boeve BF, Christianson TJ, et al. (2009) Association of C-reactive protein with mild cognitive impairment. Alzheimers Dement 5: 398-405.

24. Bacon MC, von Wyl V, Alden C, Sharp G, Robison E (2005) The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. Clin Diagn Lab Immunol 12: 1013-1019.

25. Barkan SE, Melnick SL, Preston-Martin S, Weber K, Kalish LA, et al. (1998) The Women's Interagency HIV Study. WIHS Collaborative Study Group. Epidemiology 9: 117-125.

26. Justman JE, Hoover DR, Shi Q, Tan T, Anastos K, et al. (2008) Longitudinal anthropometric patterns among HIV-infected and HIV-uninfected women. J Acquir Immune Defic Syndr 47: 312-319.

27. Diet and Health (1989) Implications for Reducing Chronic Disease Risk, National Academy Press, Washington, D.C.

28. Croft JB, Keenan NL, Sheridan DP, Wheeler FC, Speers MA (1995) Waist-to-hip ratio in a biracial population: measurement, implications, and cautions for using guidelines to define high risk for cardiovascular disease. J Am Diet Assoc 95: 60-64.

29. Crystal HA, Weedon J, Holman S, Manly J, Valcour V, et al. (2011) Associations of cardiovascular variables and HAART with cognition in middle-aged HIV-infected and uninfected women. J Neurovirol 17: 469-476.

30. Mansoor A, Althoff K, Gange S, Anastos K, Dehovitz J, et al. (2009) Elevated NT-pro-BNP levels are associated with comorbidities among HIV-infected women. AIDS Res Hum Retroviruses 25: 997-1004.

31. García-Jiménez S, Bernal Fernández G, Martínez Salazar MF, Monroy Noyola A, Toledano Jaimes C, et al. (2015) Serum leptin is associated with metabolic syndrome in obese Mexican subjects. J Clin Lab Anal 29: 5-9.

32. Kaplan RC, Kingsley LA, Gange SJ, Benning L, Jacobson LP, et al. (2008) Low CD4+ T-cell count as a major atherosclerosis risk factor in HIV-infected women and men. AIDS 22: 1615-1624.

33. Lee JH, Reed DR, Price RA (2001) Leptin resistance is associated with extreme obesity and aggregates in families. Int J Obes Relat Metab Disord 25: 1471-1473.

34. McCutchan JA, Marquie-Beck JA, Fitzsimons CA, Letendre SL, Ellis RJ (2012) Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. Neurology 78: 485-492.

35. Lake JE, Vo QT, Jacobson LP, Sacktor N, Miller EN, et al. (2015) Adiponectin and interleukin-6, but not adipose tissue, are associated with worse neurocognitive function in HIV-infected men. Antivir Ther 20: 235-244.

36. Ahonen TM, Saltevo JT, Kautiainen HJ, Kumpusalo EA, Vanhala MJ (2012) The association of adiponectin and low-grade inflammation with the course of metabolic syndrome. Nutr Metab Cardiovasc Dis 22: 285-291.

37. Bonnet E (2010) New and emerging agents in the management of lipodystrophy in HIV-infected patients. HIV AIDS (Auckl) 2: 167-178.

38. Li L, Wu LL (2012) Adiponectin and interleukin-6 in inflammation-associated disease. Vitam Horm 90: 375-395.

39. Longenecker CT, Dunn W, Jiang Y, Debanne SM, McComsey GA (2013) Adipokines and vascular health in treated HIV infection: an obesity paradox? AIDS 27: 1353-1356.

40. Scotece M, Conde J, López V, Lago F, Pino J, et al. (2014) Adiponectin and leptin: new targets in inflammation. Basic Clin Pharmacol Toxicol 114: 97-102.

41. Upadhyaya S, Kadamkode V, Mahammed R, Doraiswami C, Banerjee G (2014) Adiponectin and IL-6: Mediators of inflammation in progression of healthy to type 2 diabetes in Indian population. Adipocyte 3: 39-45.

42. Carro EM (2009) Therapeutic approaches of leptin in Alzheimer's disease. Recent Pat CNS Drug Discov 4: 200-208.

43. Harvey J, Shanley LJ, O'Malley D, Irving AJ (2005) Leptin: a potential cognitive enhancer? Biochem Soc Trans 33: 1029-1032.

44. Peiser C, McGregor GP, Lang RE (2000) Binding and internalization of leptin by porcine choroid plexus cells in culture. Neurosci Lett 283: 209-212.

45. Schulz C, Paulus K, Lehnert H (2010) Adipocyte-brain: crosstalk. Results Probl Cell Differ 52: 189-201.

46. Morash B, Li A, Murphy PR, Wilkinson M, Ur E (1999) Leptin gene expression in the brain and pituitary gland. Endocrinology 140: 5995-5998.

47. Wiesner G, Vaz M, Collier G, Seals D, Kaye D, et al. (1999) Leptin is released from the human brain: influence of adiposity and gender. J Clin Endocrinol Metab 84: 2270-2274.

48. Blüher S, Mantzoros CS (2009) Leptin in humans: lessons from translational research. Am J Clin Nutr 89: 991S-997S.

49. Abizaid A, Horvath TL (2008) Brain circuits regulating energy homeostasis. Regul Pept 149: 3-10.

50. Davidson TL, Kanoski SE, Walls EK, Jarrard LE (2005) Memory inhibition and energy regulation. Physiol Behav 86: 731-746.

51. Oomura Y, Aou S, Fukunaga K (2010) Prandial increase of leptin in the brain activates spatial learning and memory. Pathophysiology 17: 119-127.

52. Fewlass DC, Noboa K, Pi-Sunyer FX, Johnston JM, Yan SD, et al. (2004) Obesity-related leptin regulates Alzheimer's Abeta. FASEB J 18: 1870-1878.

53. Kishi T, Elmquist JK (2005) Body weight is regulated by the brain: a link between feeding and emotion. Mol Psychiatry 10: 132-146.

54. Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, et al. (2004) Adiponectin acts in the brain to decrease body weight. Nat Med 10: 524-529.

55. Drolet R, Bélanger C, Fortier M, Huot C, Mailloux J, et al. (2009) Fat depot-specific impact of visceral obesity on adipocyte adiponectin release in women. Obesity (Silver Spring) 17: 424-430.

56. Kang KH, Higashino A, Kim HS, Lee YT, Kageyama T (2009) Molecular cloning, gene expression, and tissue distribution of adiponectin and its receptors in the Japanese monkey, Macaca fuscata. J Med Primatol 38: 77-85.

57. Angelidis G, Dafopoulos K, Messini CI, Valotassiou V, Tsikouras P, et al. (2013) The emerging roles of adiponectin in female reproductive system-associated disorders and pregnancy. Reprod Sci 20: 872-881.

58. Qiu G, Wan R, Hu J, Mattson MP, Spangler E, et al. (2011) Adiponectin protects rat hippocampal neurons against excitotoxicity. Age (Dordr) 33: 155-165.

59. Kos K, Harte AL, da Silva NF, Tonchev A, Chaldakov G, et al. (2007) Adiponectin and resistin in human cerebrospinal fluid and expression of adiponectin receptors in the human hypothalamus. J Clin Endocrinol Metab 92: 1129-1136.

60. Wilkinson M, Brown R, Imran SA, Ur E (2007) Adipokine gene expression in brain and pituitary gland. Neuroendocrinology 86: 191-209.

61. Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S (2007) Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell Metab 6: 55-68.

62. Kusminski CM, McTernan PG, Schraw T, Kos K, O'Hare JP (2007) Adiponectin complexes in human cerebrospinal fluid: distinct complex distribution from serum. Diabetologia 50: 634-642.

63. Stroop J (1935) Studies of interference in serial verbal reaction. J Experimental Psychology 18: 643-662.

64. COMALLI PE Jr, WAPNER S, WERNER H (1962) Interference effects of Stroop color-word test in childhood, adulthood, and aging. J Genet Psychol 100: 47-53.

65. Smith A (1982) Symbol Digit Modalities Test (SDMT). Manual (revised), Western Psychological Services, Los Angeles.

66. Lezak M, Howieson DB, Loring DW (2004) Neuropsychological Assessment, 4th edition, Oxford University Press, New York.