JAIDS Journal of Acquired Immune Deficiency Syndromes Publish Ahead of Print
DOI: 10.1097/QAI.0000000000001906

Body Mass Index and Cognitive Function among HIV-1 Infected Individuals in China, India and Nigeria.

Jibreel Jumare MBBS, Ph.D[1*], Samer S. El-Kamary MD, MPH[11], Laurence Magder Ph.D[1], Laura Hungerford DVM, Ph.D[1], Anya Umlauf MS[2], Donald Franklin Ph.D[2], Manisha Ghate MBBS, Ph.D[3], Alash'le Abimiku Ph.D[1], Man Charurat Ph.D[1], Scott Letendre MD[2], Ronald J. Ellis MD, Ph.D[2], Sanjay Mehendale MD, MPH[3], William A. Blattner MD[1], Walter Royal III MD[1], Thomas D. Marcotte Ph.D[2], Robert K. Heaton Ph.D[2], Igor Grant MD[2], J. Allen McCutchan MD, MSc[2]

Author affiliations:

[1]University of Maryland School of Medicine, Baltimore, United States, MD 21201

[2]University of California San Diego, School of Medicine, San Diego, United States, CA 92103

[3]National AIDS Research Institute, Pune, Maharashtra, India

*Corresponding author

E-mail: jibreel.jumare@som.umaryland.edu Tel: (410) 706-7192 Fax: (410) 706-1944

Word Count: Abstract (237); Text (1996)

Conflicts of Interest and Source of Funding: WAB is an editor for JAIDS. Other authors have no conflicts to report. This work was supported by National Institutes of Health grant #R01 P30 MH62512-14 (to Igor Grant), National Institute of Mental Health (NIMH) grant #R01 MH78748 (to Thomas D. Marcotte), National Institutes of Health grant #R01 MH086356 (to William A.

Blattner and Walter Royal, III) and by National Institutes of Health Fogarty/AIDS International Training and Research Program grant #2D43TW001041-14 (training support to Jibreel Jumare).

Abstract

Background: Risk of cognitive impairment is increased among persons with high or low body mass index (BMI) in HIV- and HIV+ populations in resource-rich settings. We examined this association among HIV+ patients in three resource-limited settings.

Methods: This secondary analysis included data of 761 HIV+ volunteers pooled from 3 prospective cohort studies conducted in China (n=404; 53%), India (n=200; 26%) and Nigeria (n=157; 21%). World Health Organization (WHO) weight classifications were based on BMI. T scores, adjusted for demographics and practice effects, were derived from a 7-domain neuropsychological battery. Neurocognitive impairment (NCI) was defined as global deficit score (GDS) of ≥ 0.5.

Results: Overall prevalence of NCI at baseline was 27.7% (similar across all cohorts). The overweight/obese and underweight constituted 37.3% and 15.5% of the total participants respectively. In a multivariable logistic regression of pooled longitudinal data, adjusting for clinical and demographic variables, the odds of global neurocognitive impairment were 38% higher among the overweight/obese as compared to normal weight participants (OR: 1.38 [95% CI: 1.1, 1.72]; P=0.005). Similarly, the odds of global neurocognitive impairment were 39% higher among the underweight as compared to normal weight participants (OR: 1.39 [95% CI: 1.03, 1.87]; P=0.029).

Conclusion: Neurocognitive impairment among HIV-1 infected patients was more prevalent in both overweight/obese and underweight than normal weight individuals in three resource-limited settings, confirming observations in resource rich settings. Mechanisms underlying these associations are unclear, but likely differ for underweight and overweight persons.

Keywords: HIV-1 BMI Cognitive Function China India Nigeria

INTRODUCTION

The pathogenesis of HIV-associated neurocognitive disorders (HAND) involves interaction of viral, host, treatment, and comorbid factors, but the specific mechanisms remain unclear.[1-3] Among important comorbid factors implicated in cognitive impairment are metabolic disorders like overweight/obesity.[4,5] High body mass index (BMI) is associated with hypertension, diabetes mellitus and metabolic syndrome, which are risk factors for cardiovascular disease and neurocognitive dysfunction.[6-14] Several studies in the general population have linked high and low BMI with increased risk of cognitive impairment.[15-20] The studies that explored this association in the context of HIV infection are mainly in Caucasians from HIV low-burden and resource-rich settings, cross-sectional in design, generally limited in power, and reported variable findings.[21-23]

As HIV patients receive antiretroviral treatment, many gain weight and may become overweight/obese at rates similar to or greater than the general population.[24,25] In fact, one report indicated that overweight/obesity is now more prevalent than wasting among individuals living with HIV/AIDS.[25] Elevated BMI in these patients may increase the risk for neurocognitive impairment.[26] In this study, we examined the association between BMI categories and cognitive

function, utilizing data from three cohort studies conducted in middle income countries in Asia and Africa.

METHODS

Design: This was a secondary analysis of data from three cohort studies conducted in China[27,28], India[29], and Nigeria.[30,31]

Study Participants: Of 761 HIV-1 infected participants in this study, 404 (53%) were from the China study, 200 (26%) from the India cohort, and 157 (21%) from the Nigeria cohort. At enrollment, participants were ≥18 years of age, antiretroviral treatment-naïve in the India and Nigeria studies, and mixed naïve and experienced in the China study. Participants with hepatitis B or C infections (India and China) and substance use (China) were also included. Informed consent was obtained from all participants and study procedures were approved by relevant Institutional Review Boards.

Neuropsychological assessment: A standardized comprehensive 7-domain neuropsychological battery was administered to participants at each study visit. Tests were translated as needed into local languages (China and India). Details of these are described in our other reports.[27,29,31] Mean T-score below 40 in each domain signified impairment for that domain, while global neurocognitive impairment (NCI) was defined as global deficit score (GDS) of ≥ 0.5.[32,33]

Clinical Assessment: Demographic and clinical information were obtained using standardized questionnaires, including general medical assessment at each study visit. Weight and height were used to determine body mass index (BMI), calculated as the ratio of weight (in kilograms [Kg]) to the square of height (in meters squared [m^2]). Weight classifications used were: Underweight: <18.5 kg/m^2; Normal weight: 18.5 to <23 kg/m^2; Overweight/Obese: ≥23 kg/m^2.[34]

Follow-up Schedule: Participants were seen at 6, 12, and 24 months after their baseline assessment in the Nigeria study. For the China and India studies, there were 4 annual visits after enrollment.

Statistical Analyses

Demographic and clinical characteristics were compared between normal weight, overweight and underweight participants, using chi-square, Kruskal-Wallis and analysis of variance (ANOVA) tests, in addition to pairwise comparisons. Generalized linear and generalized estimating equation (with exchangeable correlation structure) models were used for the baseline and longitudinal regression analyses respectively. Conditional logistic regression analyses were also used to assess within-person associations. All statistical analyses were performed using SAS 9.3 (SAS Institute, Inc.).

RESULTS

Baseline Demographic and Clinical Characteristics

The median age of participants was 35 years and about 42% were women. Participants' median number of years of education did not differ significantly between the weight categories (P=0.058). A higher proportion of overweight individuals had hypertension compared to the normal weight or underweight participants (P<0.001). The underweight participants had lower median nadir CD4 count (P=0.048) and hemoglobin level (P<0.001) as well as higher mean plasma $\log_{10}$ HIV RNA (P=0.002) when compared to the other weight categories. Median Beck's depression score was lower among the overweight as compared to normal weight and underweight participants (P=0.001). Overall, the prevalence of global NCI at baseline was 27.7%

(28.5% [China], 26% [India] and 28% [Nigeria]). [Table 1] (See Table 1, Supplemental Digital Content 1).

Association of BMI Categories with Global and Domain-Specific Cognitive Impairment

Baseline: Odds of global neurocognitive impairment (NCI) were 48% higher among the overweight as compared to normal weight participants (OR: 1.48 [95% CI: 0.99, 2.2]) in a multivariable logistic regression analysis. The odds of NCI tended to be higher among the underweight as compared to normal weight participants, but this was not statistically significant (OR: 1.35 [95% CI: 0.80, 2.29]) [Figure 1].

Longitudinal: In a multivariable logistic regression, the odds of NCI were 38% higher among the overweight as compared to normal weight participants (OR: 1.38 [95% CI: 1.1, 1.72]). Similarly, the odds of NCI were 39% higher among the underweight compared to normal weight participants (OR: 1.39 [95% CI: 1.03, 1.87]) [Figure 1] (See Table 2, Supplemental Digital Content 1).

The odds of impairment tended to be higher among the overweight as compared to normal weight participants across all cognitive domains. Comparing the underweight to normal weight participants, the odds of impairment were significantly higher for the attention and memory domains, as well as marginally significant for the executive function domain (See Table 2, Supplemental Digital Content 1).

Although differences were seen between the three cohorts, these were not statistically significant (Global P-value for interaction: 0.121). Within cohort associations were statistically significant only for the underweight in the India study (OR: 1.78; P=0.012) and the overweight in the China study (OR: 1.48; P=0.011) (Figure 1).

In conditional logistic regression analyses among participants that experienced changes in weight category and cognitive status, the odds of NCI were higher among the underweight (OR: 2.57; P=0.016) and among the overweight (OR: 2.05; P=0.025), as compared to normal weight participants (See Table 3, Supplemental Digital Content 1).

DISCUSSION

In this study, we found a significantly higher likelihood of neurocognitive impairment among overweight as compared to normal weight participants, in both baseline and longitudinal repeated measures analyses. We also showed a similar association for underweight participants particularly in the longitudinal analysis.

Our findings are consistent with results of other studies in the general population and among HIV-infected populations in resource-rich settings. In a meta-analysis of cohort studies of older adults in the general population, Beydoun and colleagues found evidence of a U-shaped association between BMI and dementia, with dementia risk increased for obese and underweight persons.[35] Anstey et al.[36], in another meta-analysis, showed similar results.

For HIV-infected individuals, McCutchan et al.[21] reported a significantly higher likelihood of neurocognitive impairment as BMI increased in a baseline sub-study of the CHARTER cohort. An even stronger association was found in that study for waist circumference, a better indicator of visceral adiposity, though among a much smaller subset of participants. This relationship was confirmed in another CHARTER study which also showed a greater effect among those with abdominal obesity and those with the highest level of systemic inflammation[23].

In contrast to these observations, some reports describe a seemingly protective role of higher BMI on cognition, an example of the so-called 'obesity paradox'.[37-40] Such contradictory reports may be due partly to methodologic limitations in some of the studies, but more importantly, may be an indication of the limitations of BMI which is a surrogate marker for central adiposity. Nevertheless, the preponderance of evidence, including from systematic reviews and meta-analyses, supports an adverse effect, even though modest, of excess weight on cognition.

Our study found similar effect sizes to studies in the general population with significantly older participants and lengthy follow-up. This similarity may reflect the synergistic effects of HIV and abnormal BMI categories, potentially leading to an earlier onset of cognitive decline. HIV disease is associated with accelerated aging, and may result in earlier occurrence of comorbid conditions and their adverse sequelae.[41]

A number of potential causal pathways have been postulated in the association between overweight/obesity and cognitive dysfunction.[42] First, overweight/obesity has been linked to cardio-metabolic disorders like type-2 diabetes mellitus and hypertension, which are strongly associated with cognitive impairment.[9,43,44] These disorders may potentially play substantial mediating or synergistic role in this relationship.[45]

Second, adipocyte enlargement and proliferation, the histopathologic hallmark of overweight/obesity, is associated with macrophage recruitment and promotion of local and systemic inflammation. This manifests through higher expression of pro-inflammatory cytokines like tumor necrosis factor-alpha [TNF-α], interleukin-6 [IL-6] and monocyte chemotactic protein-1 [MCP-1]. Such cytokines are believed to mediate many of the downstream complications of overweight/obesity.[23,46] Studies have demonstrated associations between these

cytokines and cognitive decline, and this may be due to direct neural damage or the result of induced atherosclerotic changes, also known to interfere with cognitive function.[47-49]

Third, obesity is associated with adipokine changes, including central leptin resistance and reduction in adiponectin levels.[46] Leptin resistance, coupled with associated insulin resistance, may lead to dysregulated neuronal metabolism and dysfunction.[50] Similarly, reduction in adiponectin levels may result in impairment of its anti-inflammatory, anti-hyperglycemic, and anti-atherogenic activity,[51] potentially leading to adverse outcomes that may include cognitive dysfunction.

Significant interactions may occur among these potential causal pathways. Studies are needed to characterize the contributions of these factors in the relationship between overweight/obesity and cognitive function.

The observed association between underweight and cognitive impairment probably reflects the effects of advanced HIV disease, which causes both NCI and wasting, a manifestation of the phenomenon of 'confounding by severity'.[52] Another plausible explanation for this association is reverse causality, which refers to weight loss caused by cognitive impairment, as reported in some studies among older adults[16,39] Mechanistically, however, hormonal and metabolic dysregulation, malnutrition, and pro-inflammatory cytokine elaboration in the underweight may have an underlying causal effect on the observed cognitive dysfunction.[53-55]

In this study, the association between underweight and global NCI appears to be driven by deficits in the domains of attention, memory and executive function. Gustafson et al. [22] also found lower performance in executive function and speed of information processing domains among underweight HIV-infected women. Overall, these domains are the most frequently

affected in HIV-related cognitive disorders,[56,57] a further indication that the underweight association may be largely a reflection of the HIV disease process. In contrast, the pattern for overweight/obesity did not appear to preferentially select for particular cognitive domains. Other studies also reported significant findings for virtually all domains.[16,22,58] Therefore, overweight/obese patients exhibit a more diffuse pattern of deficits, possibly indicating a predominantly vascular pathogenic mechanism.[59,60]

This study has some limitations. First, BMI is considered a surrogate marker for visceral adiposity, which is the more likely biological factor involved[21]. Such an indirect measure may be associated with misclassification bias among persons with more widely distributed adipose tissue or high lean body mass.[61] However, such misclassification is expected to be non-differential and would tend to attenuate estimates of association.

Second, about 30% of participants were lost to follow-up by the penultimate study visit, and over half had missing assessment at the final visit. However, those lost did not differ significantly from those retained by baseline impairment status or BMI category up to the penultimate visit. We also found the same estimates of longitudinal association with or without the final study visit. Therefore, the loss to follow-up in this study was unlikely to have introduced significant selection bias.

Another limitation is the recruitment of only English-speaking participants in the Nigeria study and individuals with significant history of injection drug use in the China cohort. These would potentially limit the generalizability of findings but are unlikely to significantly affect the internal validity of the study. The net effect of these selection factors might be an attenuation of estimates when compared to expected effect sizes from a more representative cohort.

Conclusion

We confirmed in a pooled analysis of data for HIV-1 infected persons from China, India and Nigeria the U-shaped relationship of body mass index and cognitive function reported by multiple studies in the general population. Given the global epidemic of overweight/obesity and the similarity in its prevalence among HIV-infected patients treated with antiretroviral drugs and HIV-uninfected populations, overweight/obesity may be an increasing cause of cognitive impairment in both groups globally. Although systemic inflammation constitutes the leading causal hypothesis for this association, further studies are required to define the biological mechanisms involved and to guide development of therapeutic interventions.

ACKNOWLEDGEMENTS: The authors acknowledge the study participants and staff of the primary projects in China, India and Nigeria, staff and management at the individual study sites, National AIDS Research Institute (NARI) India, China CDC/National Center for AIDS (NCAIDS), Peking University, CDC Nigeria, and Institute of Human virology Nigeria.

REFERENCES

1. Ellis RJ, Badiee J, Vaida F, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. *Aids.* 2011;25(14):1747-1751.

2. Burdo TH, Weiffenbach A, Woods SP, Letendre S, Ellis RJ, Williams KC. Elevated sCD163 in plasma but not cerebrospinal fluid is a marker of neurocognitive impairment in HIV infection. *Aids.* 2013;27(9):1387-1395.

3. Marcotte TD, Deutsch R, Michael BD, et al. A concise panel of biomarkers identifies neurocognitive functioning changes in HIV-infected individuals. *J Neuroimmune Pharmacol.* 2013;8(5):1123-1135.

4. Clark US, Cohen RA. Brain dysfunction in the era of combination antiretroviral therapy: implications for the treatment of the aging population of HIV-infected individuals. *Curr Opin Investig Drugs.* 2010;11(8):884-900.

5. Nath A, Schiess N, Venkatesan A, Rumbaugh J, Sacktor N, McArthur J. Evolution of HIV dementia with HIV infection. *Int Rev Psychiatry.* 2008;20(1):25-31.

6. Wright EJ, Grund B, Robertson K, et al. Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons. *Neurology.* 2010;75(10):864-873.

7. Adamu H MA, Liman HM, Isah MD, Jega MR and Chijioke A. Prevalence of Obesity, Diabetes Type 2 and Hypertension among a Sampled Population from Sokoto Metropolis-Nigeria. *British Journal of Medicine & Medical Research.* 2014;4(10):2065-2080.

8. Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. *Eur J Pharmacol.* 2008;585(1):97-108.

9. van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. *Biochim Biophys Acta.* 2009;5:470-481.

10. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. *Jama*. 2004;292(18):2237-2242.

11. Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. *Circulation.* 2008;117(13):1658-1667.

12. Bennasar-Veny M, Lopez-Gonzalez AA, Tauler P, et al. Body adiposity index and cardiovascular health risk factors in Caucasians: a comparison with the body mass index and others. *PLoS One.* 2013;8(5).

13. Wang SK, Ma W, Wang S, Yi XR, Jia HY, Xue F. Obesity and its relationship with hypertension among adults 50 years and older in Jinan, China. *PLoS One.* 2014;9(12).

14. Luft VC, Schmidt MI, Pankow JS, et al. Chronic inflammation role in the obesity-diabetes association: a case-cohort study. *Diabetol Metab Syndr.* 2013;5(1):1758-5996.

15. Cournot M, Marquie JC, Ansiau D, et al. Relation between body mass index and cognitive function in healthy middle-aged men and women. *Neurology.* 2006;67(7):1208-1214.

16. Sabia S, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A. Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study. *Am J Clin Nutr.* 2009;89(2):601-607.

17. Gunstad J, Lhotsky A, Wendell CR, Ferrucci L, Zonderman AB. Longitudinal examination of obesity and cognitive function: results from the Baltimore longitudinal study of aging. *Neuroepidemiology.* 2010;34(4):222-229.

18. Dahl A, Hassing LB, Fransson E, et al. Being overweight in midlife is associated with lower cognitive ability and steeper cognitive decline in late life. *J Gerontol A Biol Sci Med Sci.* 2010;65(1):57-62.

19. Hassing LB, Dahl AK, Pedersen NL, Johansson B. Overweight in midlife is related to lower cognitive function 30 years later: a prospective study with longitudinal assessments. *Dement Geriatr Cogn Disord.* 2010;29(6):543-552.

20. Nilsson LG, Nilsson E. Overweight and cognition. *Scand J Psychol.* 2009;50(6):660-667.

21. McCutchan JA, Marquie-Beck JA, Fitzsimons CA, et al. Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. *Neurology.* 2012;78(7):485-492.

22. Gustafson DR, Mielke MM, Tien PC, et al. Anthropometric measures and cognition in middle-aged HIV-infected and uninfected women. The Women's Interagency HIV Study. *J Neurovirol.* 2013;19(6):574-585.

23. Sattler FR, He J, Letendre S, et al. Abdominal obesity contributes to neurocognitive impairment in HIV-infected patients with increased inflammation and immune activation. *J Acquir Immune Defic Syndr.* 2015;68(3):281-288.

24. Crum-Cianflone N, Tejidor R, Medina S, Barahona I, Ganesan A. Obesity among patients with HIV: the latest epidemic. *AIDS Patient Care STDS.* 2008;22(12):925-930.

25. Amorosa V, Synnestvedt M, Gross R, et al. A tale of 2 epidemics: the intersection between obesity and HIV infection in Philadelphia. *J Acquir Immune Defic Syndr.* 2005;39(5):557-561.

26. McArthur JC, Brew BJ. *HIV-associated neurocognitive disorders: is there a hidden epidemic?* Vol 24: AIDS. 2010 Jun 1;24(9):1367-70. doi: 10.1097/QAD.0b013e3283391d56.; 2010.

27. Heaton RK, Cysique LA, Jin H, et al. Neurobehavioral effects of HIV infection among former plasma donors in rural China: Neurobehavioral effects of HIV in rural China. *Journal of neurovirology.* 2008;14(6):536-549.

28. Day TRC, Smith DM, Heaton RK, et al. Subtype Associations with HIV Associated Neurocognitive Disorder in China. *Journal of neurovirology.* 2016;22(2):246-250.

29. Ghate M, Mehendale S, Meyer R, et al. The effects of anti-retroviral treatment initiation on cognition in HIV-infected individuals with advanced disease in Pune, India. *Journal of neurovirology.* 2015;21(4):391-398.

30. Royal W, 3rd, Cherner M, Burdo TH, et al. Associations between Cognition, Gender and Monocyte Activation among HIV Infected Individuals in Nigeria. *PLoS One.* 2016;11(2):e0147182.

31. Jumare J, El-Kamary SS, Magder L, et al. Plasma HIV RNA level is associated with neurocognitive function among HIV-1-infected patients in Nigeria. *Journal of neurovirology.* 2018.

32. Blackstone K, Moore DJ, Franklin DR, et al. Defining neurocognitive impairment in HIV: deficit scores versus clinical ratings. *Clin Neuropsychol.* 2012;26(6):894-908.

33. Carey CL, Woods SP, Gonzalez R, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *J Clin Exp Neuropsychol.* 2004;26(3):307-319.

34. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet.* 2004;363(9403):157-163.

35. Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obes Rev.* 2008;9(3):204-218.

36. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obes Rev.* 2011;12(5):23.

37. Qizilbash N, Gregson J, Johnson ME, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. *The Lancet Diabetes & Endocrinology.* 2015;3(6):431-436.

38. Kim S, Kim Y, Park SM. Body Mass Index and Decline of Cognitive Function. *PLoS One.* 2016;11(2):e0148908.

39. Suemoto CK, Gilsanz P, Mayeda ER, Glymour MM. Body mass index and cognitive function: the potential for reverse causation. *International journal of obesity (2005).* 2015;39(9):1383-1389.

40. Hainer V, Aldhoon-Hainerova I. Obesity paradox does exist. *Diabetes Care.* 2013;36(2):dcS13-2023.

41. Smith RL, de Boer R, Brul S, Budovskaya Y, van Spek H. Premature and accelerated aging: HIV or HAART? *Frontiers in Genetics.* 2012;3:328.

42. Dahl AK, Hassing LB. Obesity and cognitive aging. *Epidemiol Rev.* 2013;35:22-32.

43. Kotsis V, Stabouli S, Papakatsika S, Rizos Z, Parati G. Mechanisms of obesity-induced hypertension. *Hypertens Res.* 2010;33(5):386-393.

44. Alosco ML, Spitznagel MB, Cohen R, et al. Obesity and cognitive dysfunction in heart failure: the role of hypertension, type 2 diabetes, and physical fitness. *Eur J Cardiovasc Nurs.* 2015;14(4):334-341.

45. Wolf PA, Beiser A, Elias MF, Au R, Vasan RS, Seshadri S. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. *Curr Alzheimer Res.* 2007;4(2):111-116.

46. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. *Am J Clin Nutr.* 2006;83(2):461S-465S.

47. McAfoose J, Baune BT. Evidence for a cytokine model of cognitive function. *Neurosci Biobehav Rev.* 2009;33(3):355-366.

48. Allan SM, Rothwell NJ. Cytokines and acute neurodegeneration. *Nat Rev Neurosci.* 2001;2(10):734-744.

49. Silvestrini M, Gobbi B, Pasqualetti P, et al. Carotid atherosclerosis and cognitive decline in patients with Alzheimer's disease. *Neurobiology of aging.* 2009;30(8):1177-1183.

50. Paz-Filho G, Wong ML, Licinio J. The procognitive effects of leptin in the brain and their clinical implications. *Int J Clin Pract.* 2010;64(13):1808-1812.

51. Ohashi K, Ouchi N, Matsuzawa Y. Anti-inflammatory and anti-atherogenic properties of adiponectin. *Biochimie.* 2012;94(10):2137-2142.

52. Salas M, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. *Am J Epidemiol.* 1999;149(11):981-983.
53. Gustafson D. Adiposity indices and dementia. *Lancet Neurol.* 2006;5(8):713-720.
54. Grunfeld C, Feingold KR. Metabolic disturbances and wasting in the acquired immunodeficiency syndrome. *N Engl J Med.* 1992;327(5):329-337.
55. Kotler DP. Cachexia. *Ann Intern Med.* 2000;133(8):622-634.
56. Reger M, Welsh R, Razani J, Martin DJ, Boone KB. A meta-analysis of the neuropsychological sequelae of HIV infection. *J Int Neuropsychol Soc.* 2002;8(3):410-424.
57. Woods SP, Moore DJ, Weber E, Grant I. Cognitive Neuropsychology of HIV-Associated Neurocognitive Disorders. *Neuropsychology Review.* 2009;19(2):152-168.
58. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. *Int J Obes Relat Metab Disord.* 2003;27(2):260-268.
59. Nguyen JCD, Killcross AS, Jenkins TA. Obesity and cognitive decline: role of inflammation and vascular changes. *Frontiers in Neuroscience.* 2014;8:375.
60. Gorelick PB, Scuteri A, Black SE, et al. Vascular Contributions to Cognitive Impairment and Dementia. *A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association.* 2011;42(9):2672-2713.
61. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes.* 2008;32(6):959-966.

386 **Figure Legend**

387 **FIGURE 1**

388 Forest plots for baseline and longitudinal association of overweight and underweight with global
389 cognitive impairment. Regression models were adjusted for plasma HIV RNA, CD4 count,
390 Beck's depression score, years of education, age, gender, antiretroviral treatment status,
391 hypertension, diabetes mellitus and IV drug use.
392 OR: odds ratio; CI: confidence interval

TABLE 1: Baseline Demographic and Clinical Characteristics

	All N=761	Normal Weight N=359	Underweight N=118	Overweight N=284	P
Age (years), Median (IQR)	35 (9)	35 (9)	33.5 (7)	36 (9)	0.001[K]
Gender, Female n (%)	318 (41.8)	125 (34.8)	44 (37.3)	149 (52.5)	<0.001[F]
Education (years), Median (IQR)	9 (5)	9 (4)	9 (3)	9 (6)	0.058[K]
Hypertension, n (%)	102 (13.6)	36 (10.2)	5 (4.3)	61 (21.6)	<0.001[F]
***Nadir CD4 cell count/µL, Median (IQR)**	285 (275)	263 (273)	212.5 (304.5)	293.5 (253)	0.048[K]
Hemoglobin g/dl	12.9 (2.8)	13.3 (2.6)	11.7 (2.4)	13.1 (2.6)	<0.001[K]
Log_{10} Plasma HIV RNA copies/ml, Mean (SD)	3.88 (1.27)	3.81 (1.28)	4.24 (1.13)	3.74 (1.3)	0.002[A]
Beck's Depression Score, Median (IQR)	9 (14)	11 (16)	10 (13)	7 (13)	0.001[K]
Global cognitive Impairment, n (%)					
Overall	211 (27.7)	87 (24.2)	33 (28)	91 (32)	0.093[F]
China	115 (28.5)	59 (24.9)	8 (18.6)	48 (38.7)	0.008[F]
India	52 (26.0)	19 (22.4)	22 (33.9)	11 (22)	0.233[F]
Nigeria	44 (28.0)	9 (24.3)	3 (30)	32 (29.1)	0.827[F]
Study Population, n (%)					
China	404 (53.1)	237 (66)	43 (36.4)	124 (43.7)	<0.001[F]
India	200 (26.3)	85 (23.7)	65 (55.1)	50 (17.6)	
Nigeria	157 (20.6)	37 (10.3)	10 (8.5)	110 (38.7)	
[K]Kruskal-Wallis [F]Fisher's test [A]ANOVA					
IQR: interquartile range; SD: standard deviation; N: number of participants; *Baseline CD4 (Nigeria cohort)