

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

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22

23 Abstract

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

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

33 Results: Overall prevalence of NCI at baseline was 27.7% (similar across all cohorts). The
34 overweight/obese and underweight constituted 37.3% and 15.5% of the total participants
35 respectively. In a multivariable logistic regression of pooled longitudinal data, adjusting for
36 clinical and demographic variables, the odds of global neurocognitive impairment were 38%
37 higher among the overweight/obese as compared to normal weight participants (OR: 1.38 [95%
38 CI: 1.1, 1.72]; P=0.005). Similarly, the odds of global neurocognitive impairment were 39%
39 higher among the underweight as compared to normal weight participants (OR: 1.39 [95% CI:
40 1.03, 1.87]; P=0.029).

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

45
46 **Keywords:** HIV-1 BMI Cognitive Function China India Nigeria

47
48 **INTRODUCTION**

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

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

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

66 **METHODS**

67 **Design:** This was a secondary analysis of data from three cohort studies conducted in China^{27,28},
68 India²⁹, and Nigeria.^{30,31}

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

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

81 **Clinical Assessment:** Demographic and clinical information were obtained using standardized
82 questionnaires, including general medical assessment at each study visit. Weight and height were
83 used to determine body mass index (BMI), calculated as the ratio of weight (in kilograms [Kg])
84 to the square of height (in meters squared [m^2]). Weight classifications used were: Underweight:
85 $< 18.5 \text{ kg}/m^2$; Normal weight: 18.5 to $< 23 \text{ kg}/m^2$; Overweight/Obese: $\geq 23 \text{ kg}/m^2$.³⁴

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

89 **Statistical Analyses**

90 Demographic and clinical characteristics were compared between normal weight, overweight
91 and underweight participants, using chi-square, Kruskal-Wallis and analysis of variance
92 (ANOVA) tests, in addition to pairwise comparisons. Generalized linear and generalized
93 estimating equation (with exchangeable correlation structure) models were used for the baseline
94 and longitudinal regression analyses respectively. Conditional logistic regression analyses were
95 also used to assess within-person associations. All statistical analyses were performed using SAS
96 9.3 (SAS Institute, Inc.).

97 **RESULTS**

98 **Baseline Demographic and Clinical Characteristics**

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

107 (28.5% [China], 26% [India] and 28% [Nigeria]). [Table 1] (See Table 1, Supplemental Digital
108 Content 1).

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

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

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

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

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

129 In conditional logistic regression analyses among participants that experienced changes in
130 weight category and cognitive status, the odds of NCI were higher among the underweight (OR:
131 2.57; P=0.016) and among the overweight (OR: 2.05; P=0.025), as compared to normal weight
132 participants (See Table 3, Supplemental Digital Content 1).

133 **DISCUSSION**

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

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

143 For HIV-infected individuals, McCutchan et al.²¹ reported a significantly higher likelihood of
144 neurocognitive impairment as BMI increased in a baseline sub-study of the CHARTER cohort.
145 An even stronger association was found in that study for waist circumference, a better indicator
146 of visceral adiposity, though among a much smaller subset of participants. This relationship was
147 confirmed in another CHARTER study which also showed a greater effect among those with
148 abdominal obesity and those with the highest level of systemic inflammation²³.

149

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

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

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

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

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

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

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

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

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

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

200 This study has some limitations. First, BMI is considered a surrogate marker for visceral
201 adiposity, which is the more likely biological factor involved²¹. Such an indirect measure may be
202 associated with misclassification bias among persons with more widely distributed adipose tissue
203 or high lean body mass.⁶¹ However, such misclassification is expected to be non-differential and
204 would tend to attenuate estimates of association.

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

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

216 **Conclusion**

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

225
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386 **Figure Legend**

387 **FIGURE 1**

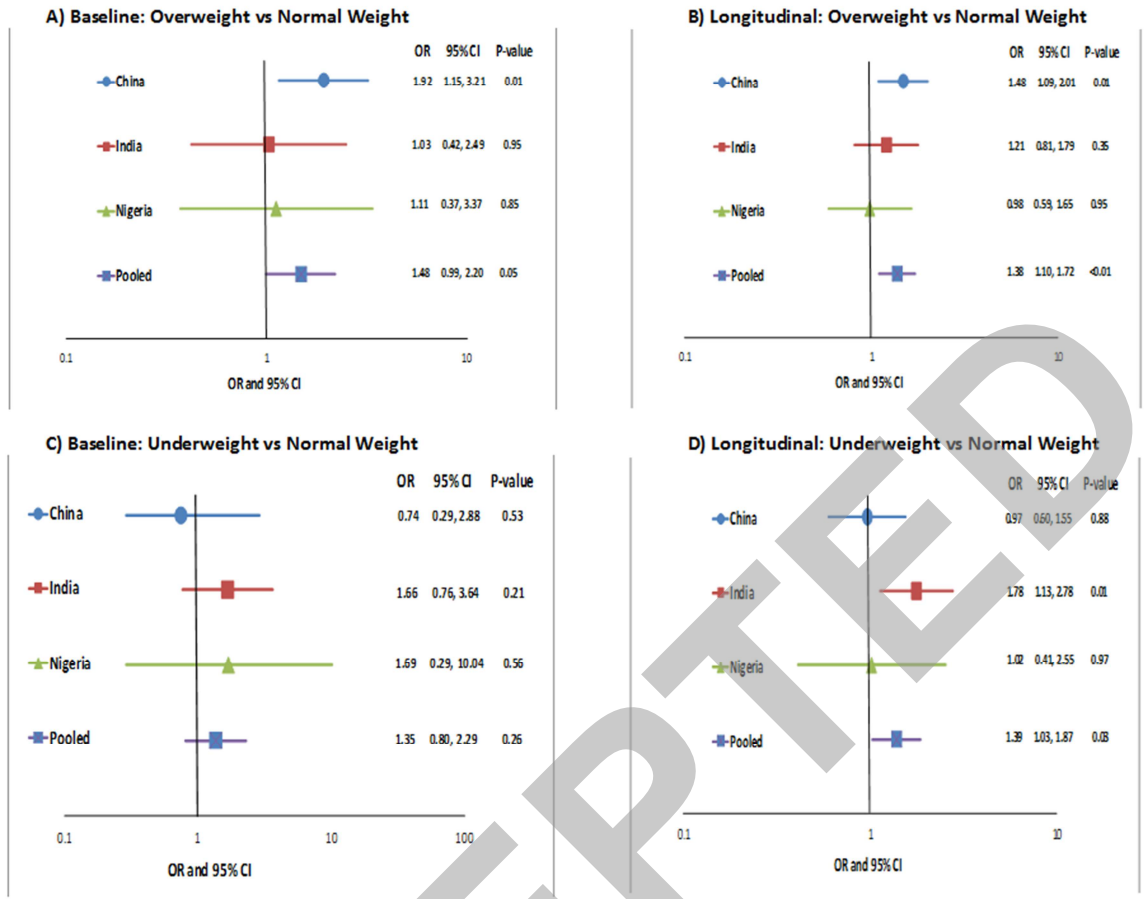
388 Forest plots for baseline and longitudinal association of overweight and underweight with global
389 cognitive impairment. Regression models were adjusted for plasma HIV RNA, CD4 count,
390 Beck's depression score, years of education, age, gender, antiretroviral treatment status,
391 hypertension,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

392 OR: odds ratio; CI: confidence interval

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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 |
| Log₁₀ 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) | | | | | |



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