Brief Report

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Association of HIV infection with metabolic syndrome among normal or underweight young adults: evidence from the CHART cohort

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SUMMARY Metabolic syndrome (MS) is common among obese people. Little is known about the magnitude and characteristics of MS in people living with HIV (PLWH) in Asian countries in general and China in particular. Using baseline data collected between February 2017 through January 2020 from the Comparative HIV and Aging Research in Taizhou (CHART) cohort in China, we examined MS among 2,227 PLWH and 5,264 matched people without HIV, respectively. MS was defined using the criteria set forth by the International Diabetes Federation (IDF). Approximately 76.7% of PLWH had body mass index (BMI) < 24.0 kg/m^2, significantly higher than people without HIV (50.3%). Among participants with BMI < 24.0 kg/m^2, PLWH had a significantly higher prevalence of MS than people without HIV (20.6% *vs.* 14.5%; aOR: 1.41, 95% CI: 1.19-1.68) overall, and at an age of 18-29 (10.4% *vs.* 3.4%, aOR: 3.49, 95% CI: 1.99-6.11) and 30-44 years (17.3% *vs.* 8.5%, aOR: 2.03, 95% CI: 1.47-2.81), respectively. Among participants with BMI ≥ 24.0 kg/m^2, MS prevalence was not significantly different between PLWH and people without HIV overall, but significantly lower in PLWH than people without HIV for those aged over 60 years (65.9% *vs.* 77.8%, aOR: 0.53, 95% CI: 0.32-0.88). Among PLWH, MS was significantly associated with older age and higher CD4 cell count, and with stavudine (d4T) use only in the group of BMI < 24.0 kg/m^2. Our finding is indicative of a relatively higher risk for early onset of MS among HIV-infected young adults with lower BMI. Research is needed to elucidate the pathogenic mechanism for MS among PLWH.

Keywords metabolic syndrome, body mass index, young adults, HIV infection, China

1. Introduction

Benefited tremendously from antiretroviral therapy (ART) with long life (*1*), people living with HIV (PLWH) increasingly face non-HIV health problems such as metabolic complications including lipodystrophy, dyslipidemia, and insulin resistance (*2*). This cluster of metabolic conditions, combined with elevated blood pressure, is known as metabolic syndrome (MS). Individuals with MS are thought to be more susceptible to cardiovascular disease (CVD) and diabetes mellitus (DM), as well as stroke and cancers (*3-5*).

Many studies have suggested that MS is largely an inflammatory disease. Both adipose tissue (AT) and chemokines or cytokines derived from monocytes contribute to the MS *via* inflammatory pathways (*6*). Among the general population, excessive fat tissue is the main cause of MS development (*7*), and metabolic health often declines as body mass index (BMI) increases. However, the development of MS in PLWH is probably more complex with the coexistence of HIV infection and obesity. Research in developed countries shows that HIV-infected individuals had a high prevalence of being overweight or obesity prior to ART initiation, and 20% progressed to a higher unhealthy weight after ART initiation (*8*). Weight gain after receiving ART, along with HIV infection may accelerate metabolic dysfunction because excessive adipose accumulation and HIV

infection are chronic inflammatory states (*9,10*). Of note, overweight and obesity are not common in all PLWH especially in some Asian countries, where PLWH usually have a relatively low weight compared to the general population ever after ART initiation (*11*). For PLWH with low BMI, the effect of HIV-infection on development of MS is probably not overshadowed by that of excessive adipose tissue.

The global literature has revealed diverse estimates of prevalence of MS among PLWH (*12*). However, there is no definitive conclusion about the association between HIV infection and MS (*13-16*). Meanwhile, data on prevalence and risk factors for MS among PLWH with relatively lower or normal weight are very limited. Therefore, we conducted a cross-sectional study to: *i*) estimate the prevalence of MS and its association with different categories of BMI; *ii*) examine correlates of MS among PLWH in mainland China.

2. Materials and Methods

2.1. Study design and participants

Using baseline data collected between February 2017 through January 2020 from an ongoing cohort known as the "Comparative HIV and Aging Research in Taizhou" (CHART) in Taizhou prefecture, Zhejiang province, east China, we examined MS among 2,227 PLWH and 5,264 individuals without HIV, respectively. The CHART is an ongoing prospective cohort study of HIV and age-related co-morbidities among PLWH and people without HIV; details of baseline characteristics of CHART have been described previously (*17,18*).

According to China treatment guidelines, the first-line of HIV treatment regimen for ART-naïve patients consists of two nucleotide reverse-transcriptase inhibitors (NRTIs) including lamivudine (3TC), along with zidovudine (AZT) or stavudine (d4T, replaced with tenofovir disoproxil fumarate [TDF] since 2010), and one non-nucleotide reverse-transcriptase inhibitor (NNRTIs) namely nevirapine (NVP) or efavirenz (EFV). Patients who experience side effects or drug resistance from NNRTIs may receive the two NRTIs mentioned above plus lopinavir (LPV) – a proteinase inhibitor (PI).

The study was approved by the Institutional Review Board of Fudan University School of Public Health, Shanghai, China. All participants have subscribed to the informed consent.

2.2. Data collection

Basic demographic and lifestyle characteristics of all participants were collected using a structured questionnaire, including sex, age, physical activity, smoking status, and alcohol use. Age groups were categorized by cut-offs of 18-29, 30-44, 45-59, and 60 and above according to the previous paper (*17*). Smoking status was classified as "never", "previous" or "current", with current smoking defined as having smoked at least one cigarette in the past 30 days. Regular exercise was defined as having engaged in exercise more than three times per week. Regular alcohol use was defined as often or always drinking alcohol in the past month. HIV-related information (*i.e.*, date of HIV diagnosis, CD4 count, date of ART initiation, and ART regimen) was extracted from the national "Comprehensive Response Information Management System (CRIMS)" for HIV patients in China.

Height, weight, waist circumference, and blood pressure were measured by trained public health workers. Measurement of blood pressure was performed two times 5 minutes apart and the mean value was recorded. BMI calculated as body weight divided by height squared (kg/m^2) was categorized into underweight/normal weight (< 24.0 kg/m^2), or overweight/obese (≥ 24.0 kg/m^2) according to the criteria set forth by the "Working Group on Obesity in China" (*19*). Venous blood samples were collected for glycated hemoglobin (HbA1c) and lipids measurement.

2.3. Definition of metabolic syndrome (MS)

According to the "International Diabetes Federation" (IDF) (*20*), MS is defined as the presence of at least three of the following five components: *i*) an increased waist circumference (Asian males > 90 cm; Asian females > 80 cm); *ii*) blood pressure ≥ 130/85 mmHg or hypertension based on self-report and/or local hospital records; *iii*) raised triglycerides (TG) levels ≥ 150 mg/dL (1.7 mmol/L); *iv*) reduced high density lipoprotein (HDL) < 40 mg/dL (1.03 mmol/L) in males or HDL < 50 mg/dL (1.29 mmol/L) in females; and *v*) elevated level of HbA1c > 5.7 % (*21*) or diabetes based on self-report and/or local hospital records.

2.4. Statistical analysis

All analyses were carried out using Stata 15.0 (Stata Corp., College Station, TX, USA). Descriptive data were expressed as mean with standard deviation, median (IQR) or tabulated as the number and percentage. Differences between groups were assessed by χ^2 test for categorical variables and by *t*-test or Kruskal-Wallis test for continuous variables, where appropriate. Logistic regressions were performed to evaluate the association of HIV-infection and MS within different BMI (< 24.0 or ≥ 24.0 kg/m^2) and age groups. HIV-specific correlates (*e.g.*, CD4) of MS were also examined among PLWH. Variables with $p < 0.200$ in univariate analysis and *a priori* were included in final multivariate analysis.

3. Results and Discussion

A total of 7,491 participants aged 18 to 75 years were

included in this analysis. They were mostly male (73.7%) with a mean age of 44.2 (± 14.3) years. Table 1 shows the demographic, lifestyle, and clinical characteristics of the PLWH (n = 2,227) and their negative counterparts (n = 5,264) stratified by BMI category (< 24.0 or ≥ 24.0 kg/m^2). Compared to people without HIV, PLWH were younger with lower BMI, less likely to be smokers and alcohol users. 76.7% of PLWH had BMI < 24.0 kg/m^2, significantly higher than people without HIV (50.3%). These two groups were significantly different in blood pressure and biochemical characteristics (Table 1). PLWH had a median (IQR) value of current CD4 count of 425 (277-577) count/μL. The median (IQR) duration of HIV infection and ART usage prior to recruitment into the study was 2.3 (0.6-5.1) years and 1.7 (0.4-4.0) years, respectively. Protease inhibitors were used by 28.7% of PLWH, whereas the rest of the sample (71.3%) used NNRTI-based regimens. For past or current use of the NRTI, 6.8% of those with BMI < 24.0 kg/m^2 had used stavudine (d4T), significantly higher than 4.4% among those with BMI ≥ 24.0 kg/m^2 (Table 1).

The prevalence of MS was 35.0% (95% CI: 33.9-36.1) for the entire sample. The global literature is equivocal concerning whether the prevalence of MS is higher among PLWH than in the general population (*15,16,22*). In our study, the overall MS prevalence is lower among PLWH (29.0%, 95% CI: 27.1-30.9) than people without HIV (37.5%, 95% CI: 36.2-38.9), partially due to lower weight and BMI of HIV cases. Nevertheless, a significantly higher risk for MS was observed among PWLH with BMI < 24.0 kg/m^2 than their HIV-negative counterparts (20.6% *vs.* 14.5%; aOR: 1.41, 95% CI: 1.19-1.68, p < 0.001) (Table 2), a finding similar to previous research (*23*).

MS is an age-related morbidity where incidence tends to go up with increased age (*24*). The prevalence of MS increased with age for both PLWH and people without HIV, from 16.0 % at 18-29 years to 39.2% at 60-72 years among PLWH, and from 16.7% to 60.1% correspondingly among people without HIV. Similar patterns were observed among participants within both BMI strata, *i.e.*, BMI < 24.0 kg/m^2 or BMI ≥ 24.0 kg/m^2 (Table 2). Given the effect of BMI (as a moderator) on HIV infection with MS, we statistically contrasted the BMI- and age-specific prevalence of MS among participants with BMI < 24.0 kg/m^2 and BMI ≥ 24.0 kg/m^2, respectively (Figure 1 and Table 2). A higher prevalence of MS was observed among PLWH than

Table 1. Characteristics of PLWH and people without HIV stratified by BMI category

Variables	Total		BMI < 24.0 kg/m^2		p	BMI ≥ 24.0 kg/m^2		p
	HIV+ (n = 2,227)	HIV- (n = 5,264)	HIV+ (n = 1,707)	HIV- (n = 2,645)		HIV+ (n = 520)	HIV- (n = 2,619)	
Male	1,737 (78.0)	3,782 (71.9)	1,332 (78.0)	1,751 (66.2)	< 0.001	405 (77.9)	2031 (77.6)	0.867
Age, yrs	44.1 ± 14.0	44.2 ± 14.4	43.7±14.3	41.8 ± 14.6	< 0.001	45.6 ± 13.1	46.6 ± 13.7	0.090
18-29	438 (19.7)	1,001 (19.0)	367 (21.5)	651 (24.6)	0.003	71 (13.7)	350 (13.4)	0.139
30-44	767 (34.4)	1,808 (34.4)	571 (33.5)	948 (35.8)		196 (37.8)	860 (32.8)	
45-59	652 (29.3)	1,567 (29.8)	487 (28.5)	672 (25.4)		165 (31.7)	895 (34.2)	
60-75	370 (16.6)	888 (16.9)	282 (16.5)	374 (14.1)		88 (16.9)	514 (19.6)	
Smoking status					< 0.001			< 0.001
Never	1,349 (60.6)	2,979 (56.6)	1,025 (60.1)	1,608 (60.8)		324 (62.3)	1371 (52.4)	
Previous	269 (12.1)	498 (9.5)	198 (11.6)	193 (7.3)		71 (13.7)	305 (11.7)	
Current	609 (27.4)	1,787 (34.0)	484 (28.3)	844 (31.9)		125 (24.0)	943 (36.0)	
Regular exercise	801 (36.0)	1,650 (31.3)	624 (36.6)	812 (30.7)	< 0.001	177 (34.0)	838 (32.0)	0.363
Regular alcohol use	207 (9.3)	1,043 (19.8)	159 (9.3)	451 (17.1)	< 0.001	48 (9.2)	592 (22.6)	< 0.001
SBP, mmHg	124.4 ± 15.4	126.8 ± 17.8	123.0 ± 14.6	121.0 ± 16.2	< 0.001	130.0 ± 16.6	132.6 ± 17.4	0.003
DBP, mmHg	76.8 ± 10.2	78.1 ± 17.5	75.8 ± 9.8	74.8 ± 16.7	< 0.001	80.2 ± 10.8	81.4 ± 17.7	0.072
TG, mmol/L	2.16 ± 1.80	2.23 ± 1.76	1.95 ± 1.40	1.71 ± 1.14	< 0.001	2.87 ± 2.60	2.76 ± 2.09	0.375
HDL, mmol/L	1.10 ± 0.34	1.18 ± 0.30	1.12 ± 0.36	1.26 ± 0.32	< 0.001	1.03 ± 0.29	1.09 ± 0.25	< 0.001
HbA1c, %	5.28 ± 0.80	5.71 ± 0.86	5.25 ± 0.77	5.54 ± 0.67	< 0.001	5.37 ± 0.87	5.88 ± 0.99	< 0.001
WC, cm	82.1 ± 7.83	82.5 ± 10.7	79.8 ± 6.6	75.3 ± 7.4	< 0.001	89.6 ± 6.8	89.8 ± 8.3	0.867
BMI, kg/m^2	22.0 ± 3.06	24.2 ± 3.7	20.8 ± 1.9	21.2 ± 1.9	< 0.001	26.1 ± 2.5	27.1 ± 2.6	< 0.001
Metabolic syndrome	646 (29.0)	1,976 (37.5)	351 (20.6)	383 (14.5)	< 0.001	295 (56.7)	1,593 (60.8)	0.082
Current CD4, count/μL[†‡]	425 (277-577)	-	420 (276-571)	-		434 (279-597)	-	0.045
Years since HIV diagnosis[†]	2.3 (0.6-5.1)	-	2.3 (0.6-5.3)	-		2.2 (0.6-4.8)	-	0.408
Duration on ART, yrs[†]	1.7 (0.4-4.0)	-	1.7 (0.4-4.2)	-		1.7 (0.5-3.6)	-	0.192
< 1	913 (41.0)	-	701 (41.1)	-		212 (40.8)	-	0.138
1~ < 3	567 (25.5)	-	419 (24.6)	-		148 (28.5)	-	
≥ 3	747 (33.5)	-	587 (34.4)	-		160 (30.8)	-	
Ever using d4T	139 (6.2)	-	116 (6.8)	-		23 (4.4)	-	0.050
Ever using PIs	640 (28.7)	-	485 (28.4)	-		155 (29.8)	-	0.538

ART, antiretroviral therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL, high density lipoprotein; HbA1c, glycated hemoglobin; WC, waist circumference; BMI, body mass index; d4T, stavudine; PIs, Protease Inhibitors. p-value for chi-square test or Kruskal-Wallis test, where it is appropriate. [†]Median (interquartile range); [‡]16 observations were missing.

Table 2. Association of HIV Infection with Metabolic Syndrome by BMI Category and Age groups

Age Groups[†]	BMI < 24.0 kg/m^2			BMI ≥ 24.0 kg/m^2		
	MS Prevalence (%)	aOR (95% CI)	*p*	MS Prevalence (%)	aOR (95% CI)	*p*
18-29	5.9 (60/1,018)	3.49 (1.99-6.11)	< 0.001	42.0 (177/421)	1.25 (0.74-2.10)	0.405
30-44	11.9 (180/1,519)	2.03 (1.47-2.81)	< 0.001	53.8 (568/1,056)	1.01 (0.73-1.38)	0.964
45-59	23.6 (273/1,159)	1.25 (0.94-1.66)	0.122	64.6 (685/1,060)	0.78 (0.55-1.10)	0.155
60-75	33.7 (221/656)	0.80 (0.57-1.13)	0.207	76.1 (458/602)	0.53 (0.32-0.88)	0.014
Total[‡]	16.9 (734/4,352)	1.41 (1.19-1.68)	< 0.001	60.1 (1888/3,139)	0.88 (0.72-1.07)	0.189

BMI, Body Mass Index; MS, metabolic syndrome ; aOR, adjusted Odds Ratio. [†]Adjusted for gender, smoking status, exercise and alcohol use for each age-specific subgroup. [‡]Adjusted for age, gender, smoking status, exercise and alcohol use for the total sample.

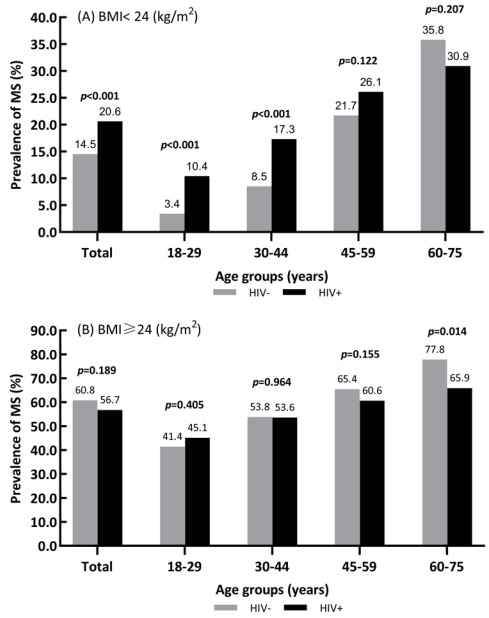

Figure 1. Prevalence of metabolic syndrome across age groups in PLWH and people without HIV. (A) the comparison among individuals with BMI < 24.0 kg/m^2; **(B)** the comparison among individuals with BMI ≥ 24.0 kg/m^2. The *p*-values were obtained from multivariable logistic regression models adjusted for age, gender, smoking status, alcohol use and exercise.

people without HIV within the age group of 18-29 years (10.4% *vs.* 3.4%, aOR: 3.49, 95% CI: 1.99-6.11); 30-44 years (17.3% *vs.* 8.5%, aOR: 2.03, 95% CI: 1.47-2.81); and 45-59 years (26.1% *vs.*21.7%, aOR: 1.25, 95% CI: 0.94-1.66). The positive association of HIV infection with MS is evident at younger ages, possibly because the influence of aging itself surrenders to the impact of HIV infection on MS at a younger age. Besides aging itself, the effect of HIV infection might also be overshadowed by the effect of prevalent traditional risk factors on MS, which therefore render the insignificant association of HIV infection and MS in older age groups.

However, no significant difference in the presence of MS was observed among PLWH and their negative counterparts with BMI ≥ 24.0 kg/m^2 within age groups 18-29 and 30-44, which might correlate with the role of fat tissue in the development of MS. Excessive fat is a major cause of MS for both the general population and PLWH. However, adipose tissue not only acts as a storage and secretion organ involved in energy regulation and metabolism, but also functions as an immune regulator involved in many biological processes (*25,26*). Accordingly, the harmful nature of the HIV virus itself and/or use of ART may somehow be covered by the impact of excessive adipose tissue (*27*), which might lead to a similar prevalence of MS in PLWH comparable to the general population among the overweight or obese group. Nonetheless, we observed a lower prevalence of MS among overweight or obese PLWH within the 60-75 age group. As the development of MS in PLWH is the result of the interplay between traditional risk factors, viral load, and type of ART usage (*28*), it is possible that diverse factors are involved in this complex biological process that then lead to this phenomenon. The reasons remain to be investigated.

In PLWH (Table 3), factors significantly associated with MS in individuals with BMI < 24.0 kg/m^2 included all older age groups, current CD4 ≥ 500 count/μL and ever using d4T. In individuals with BMI ≥ 24.0 kg/m^2, a significantly increased risk was only observed in 45-59 and 60-75 age groups, as well as in current CD4 ≥ 500 count/μL. The overall findings on MS among PLWH are consistent with those often observed in the general population where MS risks increase with age (*24*), although no sex difference was observed in our study.

Similar to previous studies (*29*), no significant association of duration of HIV infection and duration on ART with MS was observed in this study. Considering some ART regimens have a hyperlipidemic effect, the combination of antiretroviral drugs (ARVs) rather than the duration on ART and HIV infection may exert more effects on MS. Given that stavudine (d4T) could induce lipodystrophy and central fat gain (*30*), it is not surprising that ever using d4T is associated with MS. It is noted that such association was only significant among the underweight or normal weight PLWH after adjustment for other covariates, which suggests the potential impact of fat accumulation itself on MS among overweight or obese patients. While the use of PIs for treatment might increase risks for MS (*13*), higher prevalence of MS was only observed among underweight or normal weight

Table 3. Logistic Regression Analysis of Factors Associated with Metabolic Syndrome among PLWH

Variables	BMI < 24.0 kg/m^2				BMI ≥ 24.0 kg/m^2			
	cOR (95%CI)	*p*	aOR (95% CI)	*p*	cOR (95% CI)	*p*	aOR (95% CI)	*p*
Male	1.13 (0.85-1.49)	0.394	0.97 (0.71-1.32)	0.834	1.37 (0.89-2.09)	0.150	1.33 (0.83-2.12)	0.232
Age, yrs								
18-29	1		1		1		1	
30-44	1.82 (1.22-2.71)	0.003	1.80 (1.19-2.71)	0.005	1.41 (0.82-2.43)	0.220	1.43 (0.81-2.51)	0.214
45-59	3.05 (2.06-4.52)	< 0.001	3.10 (2.06-4.64)	< 0.001	1.88 (1.07-3.29)	0.028	1.97 (1.09-3.54)	0.024
60-75	3.86 (2.54-5.88)	< 0.001	4.07 (2.63-6.31)	< 0.001	2.36 (1.24-4.48)	0.009	2.41 (1.24-4.67)	0.009
Smoking status								
Never	1		1		1		1	
Previous	1.51 (1.07-2.14)	0.021	1.20 (0.82-1.76)	0.353	1.49 (0.87-2.54)	0.143	1.60 (0.91-2.81)	0.106
Current	0.96 (0.73-1.26)	0.754	0.86 (0.63-1.16)	0.314	1.03 (0.68-1.56)	0.886	1.13 (0.72-1.77)	0.590
Regular exercise	1.00 (0.78-1.27)	0.969	-		1.09 (0.76-1.58)	0.629	-	
Regular alcohol use	0.93 (0.62-1.40)	0.727	-		1.18 (0.64-2.17)	0.589	-	
Current CD4, count/μL								
< 200	1		1		1		1	
200-500	0.85 (0.59-1.22)	0.376	0.93 (0.64-1.35)	0.705	1.29 (0.75-2.21)	0.361	1.50 (0.85-2.63)	0.162
≥ 500	1.20 (0.84-1.73)	0.311	1.49 (1.02-2.19)	0.041	1.65 (0.97-2.83)	0.067	2.03 (1.15-3.60)	0.015
Years since HIV diagnosis								
< 1	1		-		1			
1~< 3	0.74 (0.53-1.05)	0.093	-		0.95 (0.61-1.50)	0.831	-	
≥ 3	1.16 (0.89-1.51)	0.262	-		1.04 (0.69-1.55)	0.861	-	
Duration on ART, yrs†								
< 1	1		1		1		1	
1 ~ < 3	0.91 (0.67-1.24)	0.551	0.99 (0.71-1.38)	0.947	0.81 (0.53-1.24)	0.336	0.81 (0.51-1.27)	0.349
≥ 3	1.21 (0.92-1.58)	0.167	0.97 (0.71-1.33)	0.868	0.96 (0.63-1.46)	0.848	1.01 (0.63-1.61)	0.979
Ever using d4T	2.45 (1.65-3.65)	< 0.001	2.31 (1.47-3.62)	< 0.001	0.69 (0.30-1.59)	0.380	0.60 (0.24-1.48)	0.269
Ever using PIs	1.08 (0.83-1.39)	0.571	1.19 (0.90-1.58)	0.228	1.21 (0.83-1.77)	0.327	1.25 (0.82-1.90)	0.298

Variables with $p < 0.200$ in univariate analysis were included in multivariate regression. All models were adjusted for gender and age. cOR, crude Odds Ratio; aOR, adjusted Odds Ratio; BMI, Body Mass Index; ART, Antiretroviral Therapy; d4T, Stavudine; PIs, Protease Inhibitors. †The variable 'years since diagnosis' was not included in multivariate regression for collinearity with duration on ART.

patients.

Using baseline data from an ongoing, large-scale cohort of PLWH and people without HIV, we provide some of the first empirical evidence on MS and HIV in mainland China. Our findings not only reinforce the role of HIV infection in the pathogenesis of MS, but also suggest the effect of modifications of BMI and age involved in MS in a study population.

Our study had some limitations. Due to the cross-sectional nature of this study, we cannot determine the temporal relationship between HIV infection and MS. Body composition measured by computed tomography (CT) or magnetic resonance imaging (MRI) may be a more appropriate indicator for metabolic status, which was not available in this study. However, CT and MRI are not applicable in source-limited areas compared with simple BMI. Also, information on potential confounding factors that may influence MS such as dietary habits and meditation use were not available during the study period. Nonetheless, our data are likely to be generalizable or heuristic as is from a large-scale cohort with PLWH and people without HIV within a diverse age range.

In conclusion, this study provides evidence that HIV infection is significantly associated with MS, especially among normal or underweight young Chinese. Our finding is indicative of the risk of early onset of MS among HIV-infected young adults with lower BMI. Research is warranted to elucidate the pathogenic mechanisms for MS among PLWH.

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