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Clinical Research

Sarcopenic Obesity Phenotypes in Patients With HIV: Implications for Cardiovascular Prevention and Rehabilitation

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ABSTRACT

Background: We aimed to describe prevalence, incidence, and risk factors for sarcopenic obesity (SO) phenotypes in people living with HIV (PWH) and their association with subclinical cardiovascular disease (CVD).

Methods: Observational, longitudinal study of PWH. A minimum of 1 criterion was necessary to diagnose sarcopenia: weak hand grip (HG), low appendicular skeletal muscle index (ASMI), short physical performance battery (SPPB $<$ 11). Obesity was defined as body mass index

RÉSUMÉ

Contexte : Nous souhaitions décrire la prévalence, l'incidence et les facteurs de risque des phénotypes d'obésité sarcopénique (OS) chez les personnes vivant avec le VIH et leur lien avec les maladies cardiovasculaires sous-cliniques.

Méthodologie : Nous avons mené une étude longitudinale observationnelle auprès de personnes vivant avec le VIH, dans laquelle au moins un 1 critère était nécessaire au diagnostic de la sarcopénie : poignée de main (PM) faible, index ASMI (*appendicular skeletal*

As the world population rapidly ages, it is predicted that, by 2050, approximately 21% will be 60 years of age or older.[1] With the increasing number of older individuals in the population, their health has become a major focus of attention.

One condition that poses a significant threat to this demographic shift is sarcopenia, which involves a decline in skeletal muscle mass, muscle strength, and physical performance.[2] In 2018, the European Working Group on Sarcopenia in Older People (EWGSOP) revised the 2010 consensus definition of sarcopenia that aimed to foster advances in identifying and caring for people with sarcopenia. They also identified diagnostic tools to evaluate muscle mass and strength that contribute to its definition.[3] Sarcopenia is associated with a greater risk of experiencing negative health outcomes such as falls,[4] disability,[5] hospitalization,[6] and mortality.[7] In addition, with aging comes an increase in fat mass and obesity, which are major risk factors for cardiovascular and metabolic diseases.[8,9]

Research has shown that sarcopenia is often accompanied by an increase in adipose tissue, leading to the emergence of a phenotype known as sarcopenic obesity (SO). This condition is considered more severe than either sarcopenia or obesity alone,[10] heightening the risk of developing disabilities, cardiovascular and metabolic diseases, as well as mortality.[11,12] The prevalence of this condition in the general population is influenced by the diagnostic criteria applied to diagnose it, rendering the epidemiology of SO unclear.

This is even more relevant in people living with HIV (PWH) in whom SO prevalence, risk factors for its development, and its association with clinically meaningful endpoints are completely unknown. In this population at high risk of

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(BMI) $\geq$ 30 kg/m^2 or visceral adipose tissue (VAT) $\geq$ 160 cm^2. These variables combined generated 5 SO phenotypes: severe SO: low HG + low ASMI + low SPPB + high BMI; SO1: weak HG + high VAT; SO2: weak HG + high BMI; SO3: low ASMI + high VAT; SO4: low ASMI + high BMI. Subclinical CVD was defined as carotid intima-media thickness (IMT) $\geq$ 1 mm, presence of carotid plaque, or coronary artery calcification (CAC) score $>$ 10.

Results: Among 2379 male PWH 72%, median age was 52 years, median HIV vintage 21 years, and median BMI 24 kg/m^2. Two PWH had severe SO. The prevalence of SO1-SO4 was 19.7%, 3.6%, 20.8% and 0.8%, respectively. Incidence of SO1-SO4 was 6.90, 1.2, 5.6, and 0.29 $\times$ 100 person-years, respectively. SO1 was associated with risk of IMT $\geq$ 1, and SO3 with risk of CAC score $>$ 10.

Conclusions: There was a large variability in incidence and prevalence of SO phenotypes. The presence of SO may have important implications for cardiovascular prevention and cardiac rehabilitation of PWH who suffered events.

muscle index, ou masse musculaire squelettique appendiculaire) bas, SPPB (*short physical performance battery,* ou version courte de la batterie de tests de performance physique) $<$ 11. L'obésité correspondait à un indice de masse corporelle (IMC) $\geq$ 30 kg/m^2 ou à un volume de tissu adipeux viscéral $\geq$ 160 cm^2. Ces variables combinées ont généré 5 phénotypes d'obésité sarcopénique, soit OS sévère : faible PM + index ASMI bas + SPPB bas + IMC élevé; OS1 : faible PM + volume de tissu adipeux viscéral élevé; OS2 : faible PM + IMC élevé; OS3 : index ASMI bas + volume de tissu adipeux viscéral élevé; OS4 : index ASMI bas + IMC élevé. La maladie cardiovasculaire sous-clinique était définie par une épaisseur intima-média de la carotide $\geq$ 1 mm, la présence de plaque dans la carotide ou un score de calcification des artères coronaires (CAC) $>$ 10.

Résultats : Parmi les 2 379 personnes vivant avec le VIH, 72 % étaient des hommes, l'âge médian était de 52 ans, la durée médiane du VIH était de 21 ans et l'IMC médian était de 24 kg/m^2. Deux personnes vivant avec le VIH présentaient une obésité sarcopénique sévère. La prévalence des phénotypes OS1 à OS4 était respectivement de 19,7 %, de 3,6 %, de 20,8 % et de 0,8 %. L'incidence des phénotypes OS1 à OS4 était respectivement de 6,90, de 1,2, de 5,6 et de 0,29 $\times$ 100 années-personnes. Le phénotype OS1 était associé à un risque d'épaisseur intima-média $\geq$ 1 mm, et le phénotype SO3 à un risque de score CAC $>$ 10.

Conclusions : L'incidence et la prévalence des phénotypes d'obésité sarcopénique affichaient une grande variabilité. La présence d'obésité sarcopénique pourrait avoir des implications importantes dans la prévention cardiovasculaire et la réadaptation cardiologique des personnes vivant avec le VIH qui ont présenté un événement cardiovasculaire.

atherosclerotic cardiovascular events, both the virus and antiretroviral therapies (ART) have been associated with sarcopenia and obesity. The former has been described in the context of the so-called wasting syndrome in the pre-ART era or as the result of mitochondrial toxicity caused by AZT and the D-drugs (DDI, D4T, DDC) in the early-ART era. The latter has been associated with central fat accumulation (lipohypertrophy), still present in the late-ART era,[13] or as the result of weight gain associated with integrase strand transfer inhibitors (INSTI) and tenofovir alafenamide (TAF) used in contemporary ART regimens.[13-17]

Subclinical cardiovascular disease (CVD) markers such as coronary artery calcification (CAC) and intima-media thickness (IMT) may be meaningful end point associated with SO. They reflect the burden and severity of atherosclerosis in coronary and carotid arteries and are well-known markers of risk of adverse cardiovascular outcomes. The presence of SO and markers of CV risk poses a high level of complexity for prevention of CVD and rehabilitation of PWH.

The objective of the study was to describe the prevalence and incidence of and risk factors for different SO phenotypes and their association with subclinical CVD in consecutive PWH followed at a tertiary HIV centre.

Methods

Study design and subjects

We conducted an observational, longitudinal, and retrospective study in consecutive PWH followed at the Modena HIV Metabolic Clinic (MHMC) from January 2015 to September 2022. In this multidisciplinary tertiary care centre, PWH are screened for chronic comorbidities and geriatric syndromes. Patients routinely undergo total body DEXA for body composition (Hologic, Inc, Marlborough, MA; Technologic Srl, Pontinvrea, Savona, Italy), a hand grip (HG) assessment with a dynamometer and a functional evaluation with Short Physical Performance Test Battery (SPPB). Clinical activities were interrupted from February to October 2020, during the first wave of the COVID pandemic in Italy. PWH were eligible for this study if they had received ART for at least 12 months before inclusion and had been evaluated at least once for the presence of SO.

Lifestyle, medical, surgical history, current and past medications, and HIV and ART history were obtained by interview and chart review. Body composition variables included body mass index (BMI), total and truncal fat, visceral adipose tissue (VAT) measured by DEXA, and computed tomography (CT), limb lean mass and appendicular skeletal muscular index (ASMI).

Physical function variables included HG test and SPPB. HG was assessed with a Jamar dynamometer (Handexer LLC, South El Monte, CA), asking the patient to squeeze the dynamometer tightly with maximum force, then release it. Measurements were made 3 times in each hand, and the average of the 3 measurements was used for analysis.[18] Cutoff points for low hand grip were derived from an equation that takes into consideration age, sex, height, and weight of a US reference population 18 to 85 years of age.[19]

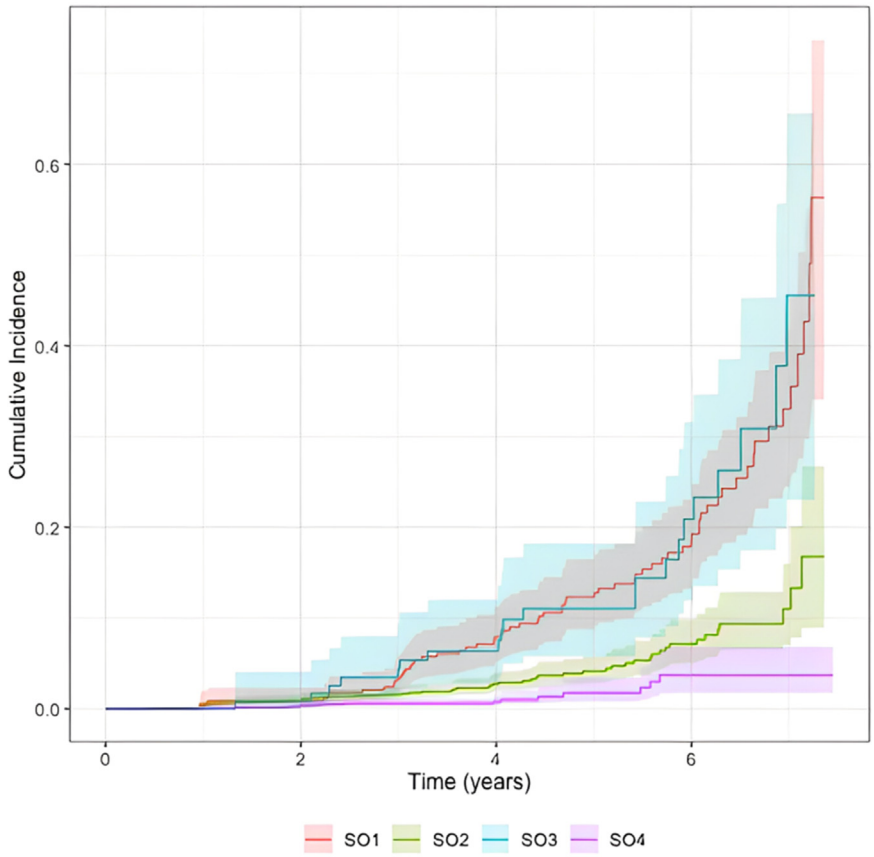

Figure 1. Cumulative incidence plot for all sarcopenic obesity (SO) phenotypes over time. SO1, SO phenotype 1 (weak hand grip [HG] + high visceral adipose tissue [VAT]); SO2, SO phenotype 2 (weak HG + high body mass index [BMI]); SO3, SO phenotype 3 (low appendicular skeletal muscular index [ASMI] + high VAT); SO4, SO phenotype 4 (low ASMI + high BMI).

SPPB consists of a series of tests used to evaluate lower extremity functionality and mobility in older people. It combines scores of gait speed (score: 0-4), balance test (score: 0-4), and chair stand test (score: 0-4). The score ranges from 0 (worst performance) to 12 (best performance). A score < 11 suggests the presence of possible sarcopenia.

Sarcopenia was defined as 1 or more of the following: weak hand grip, adjusted for sex and age; ASMI (l-ASMI) < 7.26 / < 5.45 kg/m^2 for men/women, assessed by DEXA; SPPB score < 11.

The combination of these variables generated 5 different SO phenotypes:

- Severe SO: weak HG + low ASMI + low SPPB + high BMI
- SO1: weak HG + high VAT
- SO2: weak HG + high BMI
- SO3: low ASMI + high VAT
- SO4: low ASMI + high BMI

To calculate the prevalence of each SO phenotype, only the baseline data were considered. Baseline was defined as the first visit in which at least 1 SO phenotype was identified. To describe the population according to presence or absence of SO, PWH were divided into 2 groups: PWH who never developed SO ("never") and PWH who had positive criteria for SO "at least once" over time.

Study outcomes

Subclinical cardiovascular disease was assessed with at least 1 of the following imaging techniques, performed within 6 months from the SO evaluations. Carotid intima-media thickness (cIMT) was measured with high-resolution B-mode ultrasound imaging by trained sonographers. The presence of subclinical carotid atherosclerosis was identified as cIMT $\geq$ 1 mm, presence of plaque, or both. CAC was investigated with multislice computed tomography. Total calcium scores were calculated by an experienced radiologist based on the well-established Agatston methodology.[20] Presence of subclinical atherosclerosis was defined as a CAC score > 10.[21] The choice to perform cIMT or CAC depended exclusively on the availability of the radiology services during the ambulatory clinic visit. The project received approval from the Research Ethics Board of the Area Vasta Nord Regione Emilia-Romagna.

Statistical analysis

Continuous data are presented as mean and standard deviation for normally distributed or median and interquartile range (IQR) for non-normally distributed variables, whereas categorical data are presented as numbers and percentages. The prevalence of each SO phenotype was calculated based on the first visit in which both sarcopenia and obesity were

Table 1. Demographic, anthropometric, HIV-related, and clinical characteristics according to SO1 definition

Characteristics	Never n = 929 (75.2%)	At least once n = 307 (24.8%)	*P*
Age, years, median (IQR)	53 (9)	55 (9)	< 0.001
Sex, n (%)	649 (70%)	277 (90%)	< 0.001
HIV duration, months, median (IQR)	265 (154)	261 (167)	0.60
Nadir CD4 cell count, c/microL median (IQR)	200 (210)	200 (220)	0.40
Current CD4 count, c/microL, median (IQR)	714 (373)	722 (377)	0.60
CD4/CD8 ratio, median (IQR)	0.88 (0.55)	0.84 (0.51)	0.40
Undetectable HIV RNA viral load, n (%)	891 (98%)	294 (98%)	0.40
Physical activity, n (%)	375 (41%)	176 (57%)	< 0.001
Low	453 (49%)	117 (38%)	
Moderate	95 (10%)	14 (4.6%)	
Intense			
Weight, kg, median (IQR)	69 (16)	78 (15)	< 0.001
Waist circumference, cm, median (IQR)	87 (14)	98 (13)	< 0.001
BMI, kg/m^2, median (IQR)	23.5 (4.3)	26.4 (4.4)	< 0.001
Weak grip, n (%)	163 (30%)	137 (68%)	< 0.001
Frailty phenotype, n (%)	267 (48%)	45 (22%)	< 0.001
Fit	272 (49%)	141 (70%)	
Pre-frail	12 (3%)	15 (8%)	
Frail			
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	< 0.001
ASMI, kg/m^2, median (IQR)	6.94 (1.73)	7.42 (1.25)	< 0.001
Men	7.49 (1.23)	7.51 (1.07)	0.30
Women	5.73 (1.02)	5.66 (1.13)	0.90
Frailty index, median (IQR)	0.27 (0.14)	0.31 (0.12)	< 0.001
CVD, n (%)	48 (5.5%)	20 (7.3%)	0.29
ASCVD risk, median (IQR)	5 (7)	8 (9)	< 0.001
Statins, n (%)	107 (12%)	45 (16%)	0.20
VAT, cm^2, median (IQR)	119 (81)	209 (70)	< 0.001
IMT (> 1 mm), at least once, n (%)	71 (19%)	42 (28%)	0.013
CAC (> 10), at least once, n (%)	288 (57%)	109 (62%)	0.3

ASCVD, atherosclerotic cardiovascular disease; ASMI, appendicular skeletal muscular index; BMI, body mass index; CAC, coronary artery calcium; CVD, cardiovascular disease; IMT, intima-media thickness; IQR, interquartile range; SO1, sarcopenic obesity phenotype 1 (weak hand grip + high VAT); VAT, visceral adipose tissue.

found, according to the definitions provided here. The cumulative incidence of each SO phenotype was calculated as the new occurrence of SO over time during the study period. As of January 2015, HG assessment was introduced as a routine measurement for all patients attending the MHMC. The incidence of SO during the observational period was calculated in PWH with at least 2 available evaluations without missing data.

The impact of each sarcopenia and obesity phenotype alone and in combination (considering the SO1-SO4 phenotypes) on subclinical CVD was evaluated with Poisson regression models. The severe sarcopenia phenotype (first SO phenotype) was not used in the Poisson models because only 2 patients were affected by it. An interaction term between sarcopenia and obesity was calculated to better assess their impact on the outcome of interest.

The association between outcomes of interest (IMT and CAC) and SO was evaluated considering the rate of each outcome, computed as the number of events over the total number of evaluations per patient, and the percentage of SO-positive evaluations over the follow-up period. Event rate was assessed with a generalized linear model with Poisson distribution using the total number of evaluations as offset. Results are reported as estimates (incidence rate ratio [IRR]) and corresponding 95% confidence interval (95% CI). In this study, an event was defined as any instance in which an abnormal measurement of subclinical CVD was reported during a clinic visit.

All tests were 2-sided, and the statistical significance was set at 5%. The statistical software R (version 4.2.2) was used to analyze the data.

Results

A total of 2379 PWH were evaluated at least once for SO. Median age was 52 (IQR = 10) years, 72% were men. The median time since HIV diagnosis was 21 (IQR = 14.6) years, median current CD4 was 712 (IQR = 366)/μL, and median CD4/CD8 ratio = 0.88 (IQR = 0.55). Sarcopenia and obesity median variables in the whole population were as follows: BMI = 24 (IQR = 4.5), VAT = 147 (IQR = 114) cm^2, ASMI in men = 7.50 (1.15) kg/m^2, ASMI in women = 5.71 (1.09) kg/m^2. Low HG was measured in 538, and SPPB < 11 in 177 PWH. Supplemental Table S1 shows the demographic and clinical characteristics of the entire population.

Severe sarcopenia, defined according to the EWGSOP guidelines, in this large cohort was identified in only 2 patients, both meeting the definition for obesity. Therefore, we considered the combination of less restrictive criteria for sarcopenia and identified 4 different SO phenotypes at baseline: SO1 (weak HG + high VAT) was present in 243 of 1236 PWH in whom variables were evaluated at least once (prevalence: 19.7%; incidence 6.90 × 100 person-years). SO2 (weak HG + high BMI) was present in 79 of 2183 PWH in whom defining variables were measured at least once

Table 2. Demographic, anthropometric, HIV-related, and clinical characteristics according to SO2 definition

Characteristics	Never n = 2052	At least once n = 131	*P*
Age, years, median (IQR)	52 (9)	54 (11)	0.022
Sex, n (%)	1470 (72%)	108 (82%)	0.007
HIV duration, months, median (IQR)	258 (171)	205 (180)	0.001
Nadir CD4 cell count, c/microL, median (IQR)	208 (220)	215 (254)	0.90
Current CD4 count, c/microL, median (IQR)	712 (364)	730 (356)	0.40
CD4/CD8 ratio, median (IQR)	0.88 (0.55)	0.88 (0.64)	0.50
Undetectable viral load, n (%)	1972 (98%)	124 (97%)	0.20
Physical activity, n (%)	905 (44%)	93 (72%)	< 0.001
Low	959 (47%)	32 (25%)	
Moderate	178 (9%)	5 (3%)	
Intense			
Weight, kg, median (IQR)	70 (16)	88 (15)	< 0.001
Waist circumference cm, median (IQR)	89 (14)	108 (11)	< 0.001
BMI, kg/m^2, median (IQR)	23.8 (4.2)	31.0 (3.6)	< 0.001
Weak grip, n (%)	456 (36%)	78 (77%)	< 0.001
Frailty phenotype, n (%)	543 (43%)	15 (15%)	< 0.001
Fit	577 (54%)	77 (77%)	
Pre-frail	35 (3%)	9 (8%)	
Frail			
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	< 0.001
ASMI, kg/m^2, median (IQR)	7.01 (1.70)	7.57 (1.22)	< 0.001
Men	7.45 (1.17)	7.78 (1.08)	< 0.001
Women	5.67 (1.02)	6.35 (1.29)	< 0.001
Frailty index, median (IQR)	0.27 (0.14)	0.33 (0.13)	< 0.001
ASCVD risk, median (IQR)	5 (7)	8 (9)	< 0.001
CVD, n (%)	104 (5.4%)	6 (5.1%)	0.89
Statins, n (%)	193 (10.0%)	17 (14%)	0.024
VAT, cm^2, median (IQR)	142 (105)	239 (66)	< 0.001
IMT (> 1 mm) at least once, n (%)	126 (18%)	16 (32%)	0.011
CAC (> 10) at least once, n (%)	436 (61%)	34 (68%)	0.30

ASCVD, atherosclerotic cardiovascular disease; ASMI, appendicular skeletal muscular index; BMI, body mass index; CAC, coronary artery calcium; CVD, cardiovascular disease; IMT, intima-media thickness; IQR, interquartile range; SO2, sarcopenic obesity phenotype 2 (weak hand grip + high BMI); VAT, visceral adipose tissue.

(prevalence: 3.6%; incidence 1.2 × 100 person-years). SO3 (low ASMI + high VAT) was present in 170 of 817 PWH in whom defining variables were assessed at least once (prevalence 20.8%; incidence 5.6 × 100 person-years). Finally, SO4 (low ASMI + high BMI) was present in 17 of 2224 PWH in whom defining variables were assessed at least once (prevalence: 0.76%; incidence 0.29 x 100 person-years). Figure 1 shows the cumulative incidence plot for all SO phenotypes over time.

Demographic, anthropometric, lifestyles, and clinical characteristics are summarized for each SO phenotype in Tables 1-4. The comparison between PWH, with and without each SO phenotype, considers all available observations and not only the baseline data. The column labeled "At least once" refers to PWH in whom SO was identified at any time point from baseline to follow-up. The column "Never" refers to PWH who never had any SO criteria at any time point.

Risk factors for each SO phenotype, including demographics, lifestyle, and clinical characteristics, were assessed with logistic regression analyses and are presented in Table 5. In detail, age at baseline (IRR = 1.04; 95% CI, 1.03-1.05; $P < 0.001$), male sex (IRR = 5.05; 95% CI, 3.45-7.74; $P < 0.001$), and low physical activity (IRR = 1.89; 95% CI, 1.46-2.45; $P < 0.001$) were associated with higher risk of SO1 (Table 5). Age at baseline, male sex, time since HIV infection, and low physical activity were associated with SO2, SO3, and SO4 (Table 5).

Clinical endpoints were markers of subclinical CVD. Specifically, IMT ≥ 1 mm was identified in 240 of 1159 PWH with available assessments, which accounted for a prevalence of 17.2% and an incidence of 2.35 × 100 person-years. CAC > 10 was identified in 691 of 1122 PWH with available assessments, which accounted for a prevalence of 38.1% and an incidence of 5.6 × 100 person-years.

The impact of each sarcopenia and obesity alone and in combination (considering the SO1-SO4 phenotypes) on IMT ≥ 1 mm (Table 6) and CAC score > 10 (Table 7) was evaluated with Poisson regression models. In detail, SO1 phenotype (IRR = 1.05; 95% CI, 1.01-1.09; $P = 0.024$) was associated with risk of IMT ≥ 1 mm, whereas weak grip, high VAT, and the interaction between weak grip and VAT were not (Table 3). Obesity, defined as BMI ≥ 30 kg/m^2 (IRR = 1.13; 95% CI, 1.03-1.22; $P = 0.003$) was associated with IMT ≥ 1 mm, whereas SO2, weak grip, and the interaction between weak grip and BMI were not (Table 6). In the Poisson regression for CAC score > 10, none of the variables in the models was associated with the outcome (Table 7).

Discussion

To the best of our knowledge, this is the first study exploring SO in PWH, a special population at particularly high risk of atherosclerotic cardiovascular events. Although weight gain and obesity are well characterized in these patients, mainly because of the effects of contemporary ART

Table 3. Demographic, anthropometric, HIV-related, and clinical characteristics according to SO3 definition

Characteristic	Never n = 626	At least once n = 191	*P*
Age, years, median (IQR)	53 (8)	57 (9)	< 0.001
Male sex, n (%)	439 (70%)	176 (92%)	< 0.001
Time since HIV diagnosis, years, median (IQR)	260 (141)	291 (121)	0.004
Nadir CD4 cell count, c/microL, median (IQR)	200 (203)	163 (197)	0.005
Current CD4 count, c/microL, median (IQR)	713 (388)	713 (420)	0.12
CD4/CD8 ratio, median (IQR)	0.93 (0.57)	0.81 (0.54)	0.006
Undetectable HIV RNA viral load, n (%)	598 (98%)	183 (99%)	0.50
Physical activity, n (%)	267 (43%)	107 (56%)	< 0.001
Low	298 (48%)	77 (41%)	
Moderate	60 (9%)	6 (3%)	
Intense			
Weight, kg, median (IQR)	70 (18)	75 (13)	< 0.001
Waist circumference, cm, median (IQR)	88 (16)	95 (10)	< 0.001
BMI, kg/m^2, median (IQR)	24.2 (4.8)	24.7 (3.7)	0.084
Weak grip, n (%)	120 (36%)	49 (37%)	0.80
Frailty phenotype, n (%)	155 (47%)	30 (23%)	< 0.001
Fit	166 (50%)	98 (75%)	
Pre-frail	10 (3%)	3 (2%)	
Frail			
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	0.036
ASMI, kg/m^2, median (IQR)	7.29 (1.84)	6.86 (1.05)	0.002
Men	7.65 (1.12)	6.91 (0.95)	< 0.001
Women	5.72 (1.14)	5.27 (0.78)	0.14
Frailty index, median (IQR)	0.29 (0.13)	0.31 (0.11)	< 0.001
CVD, n (%)	32 (5.5%)	17 (9.7%)	0.05
ASCVD risk, median (IQR)	5 (7)	10 (12)	< 0.001
Statins, n (%)	66 (11%)	36 (20%)	0.002
VAT, cm^2, median (IQR)	124 (93)	195 (80)	< 0.001
IMT (> 1mm), at least once, n (%)	62 (21%)	25 (25%)	0.40
CAC (> 10), at least once, n (%)	210 (54%)	94 (71%)	< 0.001

ASCVD, atherosclerotic cardiovascular disease; ASMI, appendicular skeletal muscular index; BMI, body mass index; CAC, coronary artery calcium; CVD, cardiovascular disease; IMT, intima-media thickness; IQR, interquartile range; SO3, sarcopenic obesity phenotype 3 (low ASMI + high VAT); VAT, visceral adipose tissue.

drugs, sarcopenia has been overlooked. In a previous report from the same cohort, using sequential DXA scans in 839 women and 1759 men, we described a steady decline in appendicular lean mass during a follow-up of 10 years.[22]

In this study, we initially described "severe sarcopenia" according to the 2018 revised consensus definition of the EWGSOP.[3] This restrictive definition comprises anthropometric (ASMI) and functional (HG and SPPB) variables to best identify people at higher risk of adverse health outcomes. Contrary to our expectations, in this large cohort, only 2 PWH met the EWGSOP criteria, and both were obese. Hence, these criteria may not be helpful to identify SO in PWH and specifically in patients attending the MHMC. We may speculate that as the "severe sarcopenia" construct was developed for older geriatric patients, these individuals are poorly represented in HIV cohorts. In addition, we cannot exclude a population selection bias at the MHMC, in consideration of the mobility issues affecting PWH with sarcopenia that may limit referral to our clinic.

We further described the recurrence of the 4 SO phenotypes in PWH attending the MHMC on a yearly basis. All SO occurrences accumulated during follow-up, with an incidence rate decreasing in the following order: SO1, SO3, SO2, and SO4. This observation suggests that SO will increase in the future—in particular, the SO1 and SO2 phenotypes—in parallel with the aging of PWH.

A few issues regarding the SO definition criteria deserve discussion. ASMI is a variable derived from appendicular lean mass assessed with DEXA. This technology cannot discriminate the presence of fat infiltration in the muscles, and fat is therefore included in the mass computation. Also, HG cutoffs are less well standardized in a relatively young population. A BMI $\geq$ 30 kg/m^2, which was chosen to define obesity, is much less common in PWH compared with the general Italian population. Nevertheless, this may not be true in other geographic areas. Finally, increased visceral adiposity has been shown to be associated with exposure to older ART regimens and low CD4 cell counts.[23]

Older age, male gender, and sedentary lifestyle were common risk factors across all SO phenotypes, whereas an association with HIV clinical characteristics was present in SO2, SO3, and SO4. Time since HIV diagnosis was identified as a specific risk factor for these 3 phenotypes, presumably in collinearity with age and longer exposure to detectable HIV viremia. We still cannot exclude that immune-virologic variables may affect SO, but to a lesser extent than age, sex and sedentary lifestyle, which drive all SO phenotypes. Admittedly, in these analyses, neither current nor cumulative exposure to different antiretroviral therapies was explored. Instead, our data support the notion that physical activity may be a very important intervention to help prevent SO in PWH and potentially reduce CV events. The importance of accurate characterization and identification of various SO phenotypes rests on the ability to design appropriate rehabilitation programs. The WHO guidelines on physical activity and sedentary behaviours quote specific

Table 4. Demographic, anthropometric, HIV-related, and clinical characteristics according to SO4 definition

Characteristic	Never n = 2193	At least once n = 31	*P*
Age, years, median (IQR)	52 (9)	56 (13)	0.041
Male sex, n (%)	1561 (71%)	28 (90%)	0.019
Time since HIV diagnosis, months, median (IQR)	255 (173)	165 (231)	0.042
Nadir CD4 cell count, c/microL, median (IQR)	210 (220)	249 (200)	0.70
Current CD4 count, c/microL, median (IQR)	715 (367)	688 (379)	0.50
CD4/CD8 ratio, median (IQR)	0.88 (0.55)	0.87 (0.61)	0.70
Undetectable HIV RNA viral load, n (%)	2123 (99%)	30 (100%)	0.90
Physical activity, n (%)	990 (45%)	22 (71%)	0.018
Low	1003 (46%)	8 (26%)	
Moderate	189 (9%)	1 (3%)	
Intense			
Weight, kg, median (IQR)	70 (17)	87 (16)	< 0.001
Waist circumference, cm, median (IQR)	89 (15)	108 (6)	< 0.001
BMI, kg/m^2, median (IQR)	24.0 (4.3)	30.6 (1.7)	< 0.001
Weak grip, n (%)	449 (37%)	13 (65%)	0.011
Frailty phenotype, n (%)	505 (42%)	3 (15%)	0.080
Fit	665 (55%)	16 (80%)	
Prefrail	38 (3%)	1 (5%)	
Frail			
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	0.10
ASMI, kg/m^2, median (IQR)	7.13 (1.72)	7.06 (0.56)	0.70
Men	7.51 (1.17)	7.07 (0.47)	0.008
Women	5.71 (1.09)	5.31 (0.78)	0.90
Frailty index, median (IQR)	0.27 (0.14)	0.35 (0.16)	< 0.001
CVD, n (%)	108 (5.1%)	4 (13%)	0.11
ASCVD risk, median (IQR)	5 (7)	9 (16)	0.003
Statins, n (%)	200 (9.6%)	7 (24%)	0.019
VAT, cm^2, median (IQR)	159 (113)	195 (98)	0.30
IMT (> 1mm) at least once, n (%)	139 (18%)	5 (42%)	0.052
CAC (> 10) at least once, n (%)	454 (61%)	9 (75%)	0.40

ASCVD, atherosclerotic cardiovascular disease; ASMI, appendicular skeletal muscular index; BMI, body mass index; CAC, coronary artery calcium; CVD, cardiovascular disease; IMT, intima-media thickness; IQR, interquartile range; SO4, sarcopenic obesity phenotype 4 (low ASMI + high BMI); VAT, visceral adipose tissue.

interventions for PWH to fight obesity and sarcopenia.[24] Nevertheless, it is unclear whether rehabilitation interventions for SO are simply the sum of the interventions for sarcopenia and for obesity, or if specifically designed programs will be necessary.

Chung et al.[25] showed a significant association of SO with CAC in 1282 subjects, independent of traditional risk factors for coronary artery disease (including age, sex, systemic hypertension, diabetes mellitus, and dyslipidemia). This suggests that sarcopenia and obesity may potentiate each other to induce the development of atherosclerotic coronary artery disease, eventually leading to adverse cardiovascular events..

In our study, only 2 of the 4 SO phenotypes showed a statistical association with IMT and CAC: SO1 was associated with IMT and SO3 with CAC. Both SO phenotypes include VAT as an obesity criterion. This is in line with our previous report in 583 PHW in which ectopic fat—including VAT but not general adiposity measures—were associated with CAC.[26] Interestingly, both in SO1 and SO3, single measures of sarcopenia and obesity were not significantly associated with

Table 5. Poisson models for predictors of different sarcopenic obesity phenotypes

	Sarcopenic obesity 1 (weak grip + VAT)			Sarcopenic obesity 2 (weak grip + BMI)		
Variable	IRR	95% CI	*P*	IRR	95% CI	*P*
Age at baseline	1.04	1.03-1.05	< 0.001	1.02	1.01-1.04	0.003
Male sex	5.05	3.45-7.74	< 0.001	2.84	1.89-4.44	< 0.001
Current CD4 cell count	1.00	1.00-1.00	0.20	1.00	1.00-1.00	0.50
CD4/CD8 ratio	0.98	0.77-1.23	0.90	1.13	0.83-1.50	0.40
Baseline time since HIV infection	1.00	0.99-1.02	0.40	0.97	0.95-0.98	< 0.001
Low physical activity	1.89	1.46-2.45	< 0.001	5.90	4.02-8.83	< 0.001
	Sarcopenic obesity 3 (ASMI + VAT)			Sarcopenic obesity 4 (ASMI + BMI)		
Variable	IRR	95% CI	*P*	IRR	95% CI	*P*
Age at baseline	1.05	1.04-1.07	< 0.001	1.06	1.03-1.10	< 0.001
Male sex	4.95	3.02-8.77	< 0.001	3.49	1.38-11.7	0.02
Current CD4 cell count	1.00	1.00-1.00	0.40	1.00	1.00-1.00	0.90
CD4/CD8 ratio	0.94	0.67-1.27	0.70	1.44	0.79-2.37	0.20
Baseline time since HIV infection	1.02	1.01-1.04	0.01	0.95	0.92-0.99	0.005
Low physical activity	1.77	1.26-2.49	0.001	8.43	3.48- 23.2	< 0.001

ASMI, appendicular skeletal muscular index; BMI, body mass index; CI, confidence interval; IRR, incidence rate ratio; VAT, visceral adipose tissue.

Table 6. Impact of each sarcopenia and obesity phenotype alone and in combination (SO phenotypes) on IMT > 1 mm evaluated with Poisson regression models; the interaction term between sarcopenia and obesity was also assessed

Sarcopenic obesity 1 (weak grip + VAT)				Sarcopenic obesity 2 (weak grip + BMI)			
Variable	IRR	95% CI	*P*	Variable	IRR	95% CI	*P*
Weak grip + VAT (SO1)	1.05	1.01-1.09	0.024	Weak grip + BMI (SO2)	1.04	0.95-1.12	0.30
Weak grip	0.97	0.90-1.05	0.50	Weak grip	1.02	0.98-1.06	0.40
VAT	0.99	0.95-1.04	0.80	BMI	1.13	1.03-1.22	0.003
Weak grip × VAT (interaction)	1.01	1.00-1.02	0.20	Weak grip × ASMI (interaction)	0.99	0.97-1.00	0.11
Sarcopenic obesity 3 (ASMI + VAT)				Sarcopenic obesity 4 (ASMI + BMI)			
Variable	IRR	95% CI	*P*	Variable	IRR	95% CI	*P*
ASMI + VAT (SO3)	1.02	0.97-1.07	0.40	ASMI + BMI (SO4)	1.12	0.88-1.31	0.20
ASMI	0.99	0.93-1.05	0.80	ASMI	1.01	0.97-1.05	0.50
VAT	0.99	0.94-1.05	0.80	BMI	1.07	0.99-1.14	0.07
ASMI × VAT (interaction)	1.00	1.00-1.01	0.11	ASMI × BMI (interaction)	1.01	0.98-1.02	0.50

ASMI, appendicular skeletal muscular index; BMI, body mass index; CI, confidence interval; IMT, intima-media thickness; IQR, interquartile range; IRR, incidence rate ratio; VAT, visceral adipose tissue.

IMT and CAC, and only the combination of the 2 reached statistical significance, suggesting that these 2 phenotypes identify a condition more severe than either sarcopenia or obesity alone. Further studies may be needed to explore how skeletal muscle communicates with ectopic fat in the complex networking involving chemokines and myokines, as well as the central and peripheral nervous system. This will allow the exploration of the connection between exercise and cardiovascular disease and may contribute to the understanding of a potential mechanism by which physical inactivity affects the process of metabolic diseases.[27]

Limitations

Some study limitations must be acknowledged. The first, and likely most important limitation, was the small number of PWH in geriatric or older-old age who would presumably have a higher SO prevalence. The inconstant availability of the radiology service to perform imaging for subclinical CVD may have inserted a selection bias. In this regard, immortal time bias cannot be excluded, as in some cases subclinical CVD might have been missed as IMT or CAC were not measured. Because of the COVID-19 pandemic, the MHMC in 2020 and 2021 experienced a loss to follow-up, as all nonurgent outpatient services were rendered inoperative during the lockdown. There were too few major adverse cardiac events (MACE) among patients in each SO phenotype, and we cannot prove that the associations we showed are predictive of long-term catastrophic events. Finally, this was a single- centre study, and our results might not be applicable to other clinical settings. However, this paper may raise the awareness of the medical community about the presence of several phenotypes of SO in PWH, which may become highly prevalent in this special population in the future

Conclusions

The incidence and prevalence of different SO phenotypes showed a large variability among PWH followed at 1 tertiary centre. Some of the phenotypes were associated with subclinical CVD. Future studies will be needed to explore the relationship between HIV and SO and their correlation with atherosclerotic cardiovascular events. The presence of SO and its association with markers of risk pose a special challenge for preventive and rehabilitation programs directed at reducing the risk of events and improving the outcome of those who suffered one.

Ethics Statement

The project received approval from the Research Ethics Board of the Area Vasta Nord Regione Emilia-Romagna.

Table 7. Impact of each sarcopenia and obesity phenotype alone and in combination (SO phenotypes) on CAC score > 10 evaluated with Poisson regression models; the interaction term between sarcopenia and obesity was also assessed

Sarcopenic obesity 1 (weak grip + VAT)				Sarcopenic obesity 2 (weak grip + BMI)			
Variable	IRR	95% CI	*P*	Variable	IRR	95% CI	*P*
Weak grip + VAT (SO1)	1.01	0.99-1.03	0.40	Weak grip + BMI (SO2)	1.02	0.98-1.05	0.40
Weak grip	1.01	0.97-1.04	0.60	Weak grip	0.99	0.97-1.01	0.50
VAT	1.02	1.00-1.05	0.02	BMI	1.00	0.96-1.04	0.90
Weak grip × VAT (interaction)	1.00	0.99-1.00	0.50	Weak grip × ASMI (interaction)	1.00	1.00-1.01	0.60
Sarcopenic obesity 3 (ASMI + VAT)				Sarcopenic obesity 4 (ASMI + BMI)			
Variable	IRR	95% CI	*P*	Variable	IRR	95% CI	*P*
ASMI + VAT (SO3)	1.03	1.01-1.05	0.01	ASMI + BMI (SO4)	1.03	0.96-1.10	0.30
ASMI	1.00	0.97-1.02	0.70	ASMI	1.01	0.99-1.03	0.30
VAT	1.01	0.98-1.03	0.60	BMI	1.01	0.98-1.05	0.40
ASMI × VAT (interaction)	1.00	1.00-1.01	0.12	ASMI × BMI (interaction)	1.00	0.99-1.01	0.80

ASMI, appendicular skeletal muscular index; BMI, body mass index; CAC, coronary artery calcium; CI, confidence interval; IRR, incidence rate ratio; VAT, visceral adipose tissue.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This was an observational, longitudinal, and retrospective study using deidentified data; therefore, the institutional review board (IRB) did not require that consent be obtained from each patient.

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Supplementary Material

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