Factors associated with obesity in the POPPY Cohort: an observational cross-sectional analysis.

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Abstract.

Objectives: The aims of the study were to describe the prevalence of obesity in the POPPY cohort, to identify demographic, clinical and HIV-specific factors associated with obesity, and to characterize the association between obesity and socio-demographic, clinical, HIV-specific factors and quality-of-life (QoL).

Methods: Cross-sectional analysis of baseline data from the three groups ("older" people with HIV (PWH) aged ≥50 years, "younger" PWH aged <50 years, HIV-negative controls aged ≥50 years) within the POPPY cohort. Obesity was defined as a Body Mass Index (BMI) > 30 Kg/m^2.

Results: 1361 subjects were included, of which 335 (24.6%) were obese. The prevalence of obesity was higher in controls (22.3%) than in older (16.8%) and younger (14.2%) PWH, with no differences between the two groups of PWH. Factors associated with obesity were older age, female gender, black African ethnicity and alcohol consumption. Recreational drug use and a higher current CD4+ T-cell count (in PWH) were associated with lower and higher odds of being obese, respectively. Presence of obesity was associated with worse physical health QoL scores, higher odds of having cardiovascular disease, type 2 diabetes, hypertension but lower odds of having osteopenia/osteoporosis, irrespective of HIV status.

Conclusions: Despite a lower prevalence of obesity in PWH, specific subgroups (women, people of black African origin and older people) were more likely to be obese and negative health consequences of obesity were evident, regardless of HIV status. Whether targeted preventive strategies can reduce the burden of obesity and its complications in PWH remains to be determined.

Introduction

Obesity represents an emerging health problem worldwide. According to the World Health Organization (WHO) 39% of women and men globally were overweight in 2016, with the prevalence of obesity nearly tripling since 1975 [1]. The prevalence of being overweight, defined as a body mass index (BMI) ≥25 kg/m^2, is particularly high in developed countries, with prevalence rates in Ireland and the UK among the highest (>60%) in Europe. Obesity (defined as a BMI ≥30 kg/m^2) is associated with increased all-cause and cardiovascular disease (CVD) mortality in the general population, especially in severely obese subjects (BMI ≥35 kg/m^2) [2].

Antiretroviral therapy (ART) has transformed HIV into a chronic condition with life expectancy of people with HIV (PWH) approaching that of the general population [3]. However, there has been a concomitant increase in non-AIDS related co-morbidities such as CVD and metabolic complications, related to a number of factors, including ageing and immune activation [4]. Moreover, the prevalence of obesity in PWH, including those from low-income countries, is rising [5-12] and several studies have tried to identify risk factors for obesity in this population. While most of the findings from observational studies agree on the existence of associations between obesity and older age, female gender and length of HIV infection [6-9,11,12], reported associations with $CD4^+$ T-cell count and different antiretroviral (ARV) regimens are controversial [6-9,12-17] and few studies have explored associations between ageing and obesity in PWH with appropriate control groups.

The Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY) Study is a multicentre, prospective, observational study initiated in 2013 to assess the clinical outcomes of PWH over the age of 50 in England and Ireland [18]. Given evidence suggesting an accentuated and perhaps accelerated ageing process in PWH [19], the POPPY study aims to describe the burden of clinical conditions in older PWH compared with two demographically similar control groups; younger PWH and older HIV-negative individuals. This cohort provides an opportunity to examine the risk factors for obesity and associated conditions in both PWH and HIV negative subjects that can explore the impact of ageing. The aims of our study were to describe the prevalence of obesity in the POPPY cohort, and to define the associations of demographic, clinical and HIV-specific factors with obesity. These data may help identify potential targets for future research into prevention strategies to avoid the development of obesity and its complications.

Methods

Study design and participants

The characteristics of the POPPY cohort and the eligibility criteria have been described previously [18]. The cohort includes three groups of people: "older" PWH aged ≥50 years, "younger" PWH aged <50 years and HIV-negative controls aged ≥50 years. All subjects were either of white or black African ethnicity and PWH had a history of sexually acquired HIV infection (those with intravenous drug use as a principal transmission risk factor were not included). The younger PWH were frequency-matched with the older PWH in terms of gender, ethnicity, sexual orientation and participating clinic, whereas the HIV-negative controls were frequency-matched with the older PWH on gender, ethnicity, sexual orientation and location, and were recruited in sexual health clinics or through community recruitment strategies. All participants provided written informed consent. The present study is a cross-sectional analysis based on information collected at cohort enrollment (April 2013-February 2016) including only those subjects with available data on BMI.

Data collection.

Demographic, socio-economic and clinical information was collected by trained staff using a structured questionnaire, as previously described [20]. Weight and height were measured at the baseline visit, following a standardised protocol across clinical sites. Obesity was defined as a BMI ≥30 kg/m^2, based on the WHO case definition. A history of hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection was defined on the basis of available serological tests or clinical records; information on other medical conditions was reported by the subjects during the interview, including CVD, type 2 diabetes, renal disease, liver disease and hypertension. Co-morbidities were confirmed with the aid of medical notes, healthcare resources use records and list of medications. Osteopenia and osteoporosis were defined as a T-score between -1.0 and -2.5 and a T-score <-2.5, respectively, as assessed with Dual-energy X-ray Absorptiometry (DXA) measuring bone mineral density (BMD) at the lumbar spine and the hip. For each study participant quality of life was assessed during the visit using the Short Form 36 (SF-36) questionnaire [21]. HIV-specific parameters (prior AIDS events, dates and values of all $CD4^+$ and $CD8^+$ T-cell counts and HIV RNA assessments, and a detailed ART history) were derived through linkage with the UK CHIC study and the University College Dublin Infectious Diseases (UCD ID) cohort for subjects recruited in the Republic of Ireland [22,23].

Statistical analysis

Median and interquartile range (IQR) or frequency were used to describe the characteristics of the study participants as appropriate. Overall differences in the prevalence of obesity between the groups were tested for significance using the Chi-squared test.

In order to identify factors associated with obesity in the full study population, a logistic regression analysis was performed, using obesity as the dependent variable and demographic (gender, ethnicity, mode of HIV acquisition/sexual orientation, marital status, educational attainment), lifestyle (smoking status, alcohol consumption, recreational drug use in the past 6 months) and clinical factors (HBV and/or HCV coinfection, number of medications received, use of lipid-lowering drugs (LLD), mental health medications or corticosteroids) as independent variables.

For the purposes of these analyses, the two groups of PWH were combined to allow for HIV status and age to be considered as separate factors. Those variables for which an association with obesity was observed in univariable analysis (with $p<0.1$ used as a threshold for significance), were included simultaneously in a multivariable regression model (multivariable analysis 1). HIV status, age, gender and ethnicity were retained in the model irrespective of their level of significance, considering their supposed importance as factors associated with obesity from previous studies [7-11]. Those variables that remained significantly associated with obesity in multivariable analysis 1 were then included in a second multivariable model that also retained HIV status, age, gender and ethnicity (multivariable analysis 2). In order to test whether the association of risk factors for obesity in multivariable analysis 2 differed between PWH and HIV-negative controls, we added the interaction term for each of these factors (one at the time) with HIV-status in multivariable analysis 2.

Associations of HIV-specific risk factors with obesity were assessed using logistic regression models restricted to PWH with adjustment for risk factors identified in multivariable analysis 2. HIV-related factors considered for these models were: prior AIDS; years since HIV diagnosis and ART start; current and nadir $CD4^+$ T-cell count; years with a $CD4^+$ T-cell count <200 cells/μL; $CD4^+$ T-cell count recovery rate; current $CD4^+$:$CD8^+$ T-cell ratio; HIV RNA $\leq$50 copies/mL; and cumulative exposure to nucleoside reverse transcriptase inhibitors (NRTIs), tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), abacavir/lamivudine, non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and integrase strand transfer inhibitors (INSTIs).

In order to test the robustness of our results, two sensitivity analyses were performed for each model, one using BMI as a continuous variable and the other using presence of class II obesity (BMI ≥35 kg/m^2) as a binary outcome.

Associations of obesity with quality-of-life (QoL, physical and mental health summary scales from the SF-36 questionnaire) and co-morbidities (CVD, type 2 diabetes, renal impairment, liver impairment, hypertension, osteopenia/osteoporosis) were evaluated using a series of median/logistic regression models. For each model, QoL (median regression) or the presence of each co-morbidity (logistic regression) was considered to be the dependent variable, with obesity considered to be the independent variable. Each model also included age, gender and ethnicity as potential confounders. Models were also fit after stratification by HIV-status and the interaction between HIV-status and obesity was included in models to investigate whether the potential role of obesity in these events differed between those with and without HIV.

Results

Study population and prevalence of obesity

Of 1377 individuals recruited to the POPPY cohort, information on BMI was available for 1361 (98.8%) subjects, of whom 689 (50.6%) were older PWH, 372 (27.4%) were younger PWH and 300 (22%) were older HIV-negative controls. Of the 16 subjects for whom BMI data was not available, 10 were older PWH, 2 younger PWH and 4 HIV-negative controls. Included subjects were predominantly male (62.5%), of white ethnicity (75%) and MSM (56.3%). Demographic, lifestyle and clinical characteristics of the three analysed groups are summarized in Table 1. The HIV-negative control group included a higher proportion of female subjects, people of white ethnicity and heterosexuals, whereas PWH were more likely to report recreational drug use in the past 6 months, HBV and HCV co-infection, use of mental health medications and, for the older PWH, use of LLDs.

(Insert Table 1 here)

Figure 1 shows the distribution of BMI in the three groups. In the cohort overall, median (IQR) BMI was 25.7 (23.3, 28.6) kg/m^2, and in the individual groups was 25.7 (23.4, 28.4), 25.2 (23.0, 27.9) and 26.8 (24.2, 29.5) in older PWH, younger PWH and HIV-negative controls respectively ($p<0.001$, Kruskal-Wallis test). In total, 235 subjects (17.26%) were classified as obese: 115 (16.8%) older PWH, 53 (14.2%) of younger PWH and 67 (22.3%) of HIV-negative controls ($p=0.02$, Chi-squared test). The prevalence of obesity was higher in the HIV-negative control group than in both the older and younger PWH ($p=0.04$ and $p=0.01$, respectively), with no significant difference between the two groups of PWH ($p=0.30$). Of note, the HIV-negative group also included a higher proportion of individuals with class II obesity (BMI ≥35 kg/m^2) than either the older or younger PWH (8.3% versus 4.0% and 2.4%, respectively).

(Insert Figure 1 here)

Factors associated with obesity (Table 2)

In univariable analyses, HIV-positive subjects were less likely to be obese than HIV-negative controls ($p=0.009$). Of the socio-demographic factors, older age, female gender and black African ethnicity were all significantly associated with a higher rate of obesity ($p=0.02$ for age, and $p<0.001$ for gender and ethnicity). A significant association was also found with mode of HIV acquisition/sexuality, with heterosexual subjects being more likely to be obese than men having sex with men (MSM, $p<0.001$), and with marital status, with those who were divorced/widowed or married/in a relationship being more likely to be obese than single subjects ($p<0.001$ and $p=0.02$, respectively). In contrast, no association was seen between obesity and level of education. Ex-smokers and current smokers were both less likely to be obese than non-smokers ($p<0.001$ for smoking status) with a similar association seen for current alcohol and recreational drug users compared to non-users ($p<0.001$ for both). Subjects with a history of HCV infection were less likely to be obese ($p=0.004$), whereas no significant association with obesity was found for HBV infection, number of medications, or use of LLT, mental health medications or steroids.

(Insert Table 2 here)

In the first multivariable analysis (multivariable analysis 1, Table 2), HIV was no longer associated with presence of obesity, with only age ($p=0.05$) and black African ethnicity ($p<0.001$) remaining significantly associated with obesity among the demographic factors. In addition, previous alcohol use was found to be significantly associated with a higher rate of obesity ($p=0.01$ for alcohol consumption) while recreational drug use remained associated with lower rate of obesity. None of the remaining factors were significantly associated with obesity in this multivariable model.

After removing factors that were no longer significantly associated with obesity from the model (multivariable analysis 2, Table 2), black African ethnicity ($p<0.001$), female gender ($p=0.04$), older age ($p=0.04$) but not HIV status remained significantly associated with a higher rate of obesity. In addition, the associations with previous alcohol use and recreational drug use in the past 6 months also remained significantly associated with obesity in this final model. Interaction analyses revealed no evidence that the associations between these factors and obesity differed between those with and without HIV infection (p-values for interaction were 0.44 for age, 0.19 for gender, 0.68 for ethnicity, 0.95 for alcohol consumption and 0.17 for recreational drug use). Furthermore, sensitivity analyses using BMI as a continuous variable and BMI ≥35 kg/m^2 as a binary outcome showed similar associations.

Associations between HIV-specific factors and obesity (Table 3)

Table 3 shows the HIV characteristics associated with obesity in univariable and multivariable models restricted to PWH. In unadjusted models, individuals with a higher $CD4^+$ T-cell count at the POPPY study baseline visit had higher odds of being obese ($p=0.003$), which remained significant ($p<0.001$) after adjusting for factors associated with obesity derived from multivariable analysis 2 (see above). Although no significant associations were observed with any of the other HIV-specific factors, including the CD4:CD8 ratio or cumulative exposure to specific antiretroviral medications, individuals who had experienced a longer time with a $CD4^+$ T-cell count <200 cells/mm^3 were less likely to be obese, albeit of borderline significance ($p=0.06$). Similar results were obtained in a sensitivity analyses using BMI as a continuous variable and BMI ≥35 kg/m^2 as a binary outcome.

(Insert Table 3 here)

Impact of obesity on quality of life and co-morbidities in the whole study cohort: logistic regression analysis.

The median (IQR) SF-36 physical health score was 47.1 (36.9, 54.6) for obese PWH, 53.0 (43.0, 56.4) for non-obese PWH, 52.5 (44.1, 56.4) for obese HIV-negative controls and 55.7 (52.7, 58.1) for non-obese HIV-negative controls. In analyses adjusted for age, gender and ethnicity, obesity was associated with lower physical health scores in both PWH and HIV-negative controls ($p<0.001$; regression coefficient -4.5, 95% CI -6.9, -2.2 for PWH; regression coefficient -3.1, 95% CI -4.8, -1.3 for HIV-negative controls), with no significant differences between the two groups (p=0.31 for the interaction).

In contrast, the median SF-36 mental health scores were 52.6 (41.7, 57.7) for obese PWH, 50.9 (41.6, 57.0) for non-obese PHW, 55.2 (48.0, 58.3) for obese HIV-negative controls and 56.8 (52.0, 59.2) for non-obese HIV-negative controls, with no significant associations observed between obesity and mental health scores (p=0.54 for PWH and p=0.30 for HIV-negative controls) and no differences between the two groups (p=0.11 for the interaction).

Regarding co-morbidities (Table 4), in both PWH and HIV negative controls, presence of obesity was associated with increased CVD ($P<0.01$ for both groups), type 2 diabetes ($p<0.01$ for both) and hypertension ($p<0.001$ for both), with no significant differences in the observed associations with obesity between the two groups. Obese subjects also had a lower likelihood of having osteopenia/osteoporosis at both the lumbar spine (p=0.02 for PWH and p=0.002 for controls) and hip ($p<0.001$ for PWH and p=0.007 for controls), with no between-group differences in the associations with obesity. No association between obesity and renal disease was observed in either group. While obese PWH had higher odds of having liver disease than non-obese PWH (p=0.003). no similar association between obesity and liver disease was seen in HIV-negative controls, although the difference in effect estimates between the two groups was not statistically significant. The associations remained similar in sensitivity analyses with BMI as a continuous variable and when using BMI ≥35 kg/m^2 as the outcome.

(Insert Table 4 here)

Discussion.

In this large cohort of older and younger PWH compared with a representative control group of older HIV negative participants, we demonstrated a lower prevalence of obesity in PWH compared to HIV-negative subjects. However, we also observed negative health consequences of obesity in both PWH and controls that include an increased risk of prevalent co-morbidities as well as impacts on physical function. Given the fact that these co-morbidities and lower QoL measures are both more prevalent in PWH, these results suggest an important contribution of obesity to co-morbidities in PWH.

Other observational studies have shown lower BMI values in PWH and identified female gender, black African ethnicity and age as risk factors for obesity [5,7-11,25-28]. However, BMI values at diagnosis and rates of obesity in PWH have increased over the years [5,25-27], and a recent study from Denmark showed a higher prevalence of abdominal obesity, as defined by the waist-hip ratio, in PWH compared to controls, suggesting that fat distribution might be different in PWH [8]. Of note, the fact that HIV was no longer associated with lower odds of being obese in the multivariable model might suggest that the prevalence of obesity in the three groups was predominantly influenced by other demographic factors, such as gender and ethnicity, considering the fact that the HIV-negative group had a significantly higher proportion of white subjects and females, compared to PWH (see Table 1). Other socio-economic factors that have been previously linked to an increased risk of obesity are low income/educational level, being married, alcohol consumption and having quit smoking, whereas being MSM, current cigarette smoking and recreational drug use have been associated with lower odds of being obese [15,30-38]. Our findings of a lower odds of being obese in current smokers and recreational drug users are in line with the published literature, although we did not recruit individuals with a history of injection drug use as a HIV transmission risk factor, which may have impacted somewhat on this association. On the other hand, the association between previous alcohol use, but not current use, and an increased risk of obesity in our cohort might have been influenced by other factors, such as the amount of alcohol consumed when the participant was drinking or the reasons why the person had discontinued drinking, none of which were recorded as part of the interview. Finally, differences in body image perception and cultural background between the various groups (i.e. MSM vs black African women) should be considered when interpreting these results.

Considering clinical factors, a high prevalence of obesity in patients with HCV infection has been previously reported [39]. However, no significant association with viral hepatitis (HBV/HCV) was observed in our cohort, although this might have been influenced by the lack of information about the infection status, whether chronic or resolved. Moreover, even though LLD are frequently used in obese people for the treatment of dyslipidaemia [40], and both corticosteroids and antidepressants have been associated with weight gain [41,42], we observed no association between the use of these medications and prevalent obesity, potentially as a consequence of the different rates of LLD use between the three groups, and the overall small numbers reporting use of corticosteroids and antidepressants.

When obesity was considered as a risk factor for co-morbidities, prevalent obesity was associated with significant health outcomes, as shown by the higher odds of having CVD, type 2 diabetes and hypertension in our cohort, irrespective of HIV status. PWH have nearly a doubled risk of myocardial infarction and a higher risk of other co-morbidities such as diabetes and renal and liver disease [3,4,43-46]. The negative health outcomes associated with obesity in our cohort suggest its important contribution to the development of co-morbidities, which is particularly relevant in PWH, given the higher prevalence of co-morbidities in this population. The lack of any association between renal and liver diseases and obesity might be explained by the small number of subjects experiencing these complications in our cohort. Obesity was associated with lower odds of having osteopenia/osteoporosis irrespective of HIV status, in line with what is known from literature about the effect of a higher fat mass on the axial and appendicular bone remodelling [47]. Finally, obesity was associated with lower physical health, as assessed by the SF-36 scale, in line with previous studies showing an association between obesity and lower quality of life [48]. A previous analysis from the POPPY cohort showed an association between pain and pain-related healthcare use and worse QoL scores in PWH, especially in the older population [49]. Taken together these findings suggest the existence of a mutual relationship between co-morbidities and QoL in obese PWH, where obesity could have an impact on QoL through an increased burden of co-morbidities and/or vice versa.

Regarding HIV-specific factors, we observed significant associations between higher current CD4+ T-cell count and prevalent obesity. Previous studies have provided contrasting evidence regarding the association between $CD4^+$ T-cell count and obesity, with some studies describing a low nadir $CD4^+$ T-cell count as a risk factor for obesity [6-8], and others showing a higher prevalence of obesity in subjects with higher pre-ART $CD4^+$ T-cell counts [9,12,13]. The association between higher $CD4^+$ T-cell count and obesity might be a consequence of improved general health leading to increased fat accumulation in people with a better immunological status. While ART initiation is associated with weight gain [50], the role of the different classes of ARV drugs in the development of obesity is less clear. Some studies suggest an increased risk of weight gain with early generation ARV drugs, especially thymidine analogue NRTI (tNRTI) and some PIs [6,7,12-15], while more recent studies have linked greater weight gain with initiation of ART containing INSTI [29], newer PIs and tenofovir alafenamide (TAF) [51]. However, it is still unclear to what extent the weight gain observed arises as a consequence of immune reconstitution following ART initiation or the effect of specific ARVs [17,18]. Recent findings from a large randomised trial showed a significantly greater weight gain in female subjects following initiation of dolutegravir combined with either TAF or TDF, as compared to men, suggesting gender influences on body fat changes associated with dolutegravir [52]. Moreover, a recent large cohort study enrolling predominantly white subjects, showed no differences in mean weight gain in those who switched to an INSTI based regimen, compared to those who did not change ART, although black women experienced the highest weight gain (>10% from baseline), thus pointing towards a possible higher susceptibility to INSTI-associated weight increase in specific ethnic groups [53]. The lack of any association between different ARVs and obesity in our study might have been influenced by the characteristics of our population, considering that whilst a considerable proportion of PWH had a history of exposure to tNRTI (49.3%) and older PIs (60.3%) and, at the time of data collection, a relatively small proportion had been exposed to INSTIs (and only 3.7% to second generation INSTI) and TAF.

Our study has some limitations. Firstly, the absence of a young control group might represent a limit in understanding the additional effect of HIV infection on the development of co-morbidities in younger subjects. Moreover, information on co-morbidities was derived during the interview and might have been influenced by subjects' misconceptions about their health status, although this would only have affected previously unrecorded health problems, since the study staff had access to healthcare records. Another limitation is the use of BMI for the definition of obesity, which does not take into account abdominal obesity (of greater clinical relevance in terms of CVD risk), even though BMI is generally accepted as the standard measurement to define this condition. Finally, the design of the study as a cross-sectional analysis limits our ability to draw conclusions with regards to causality or the direction of associations between supposed risk factors and obesity.

In conclusion, although our study shows that HIV was not an independent risk factor for obesity in the POPPY cohort, specific subgroups such as women, people of black African origin and older subjects were at greater risk of obesity, and the negative health consequences of obesity in terms of higher prevalence of co-morbidities and worse physical function on QoL were consistently observed regardless of HIV status. Given the higher prevalence of co-morbidities, especially in older in PWH, these data point to the importance of addressing obesity in strategies aimed at reducing the impact of non-AIDS complications as PWH age.

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Figure 1. Distribution of BMI categories in the three demographic groups in the POPPY cohort. Obesity was defined as a Body Mass Index (BMI) ≥ 30 Kg/m^2. Overweight was defined as a BMI ≥ 25 Kg/m^2. Underweight was defined as a BMI <18.5 kg/m^2. PWH: People With HIV.

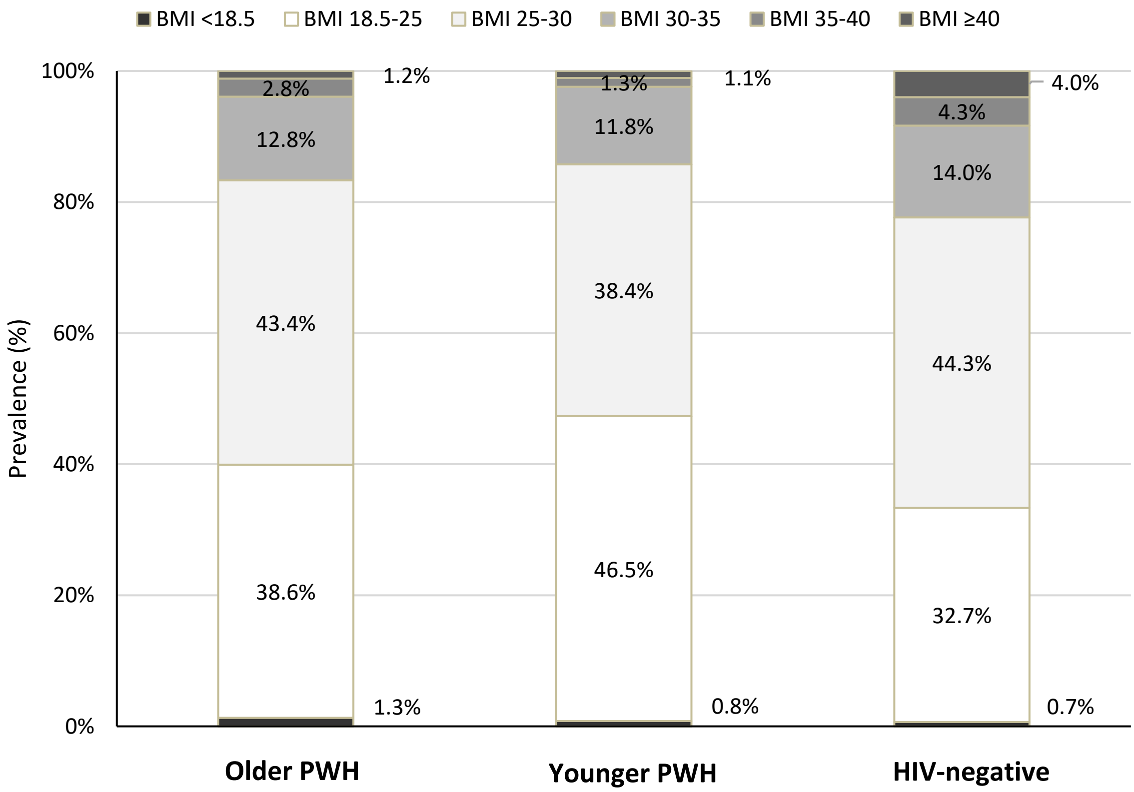

Table 1. Baseline demographic, lifestyle and clinical characteristics of PWH aged ≥50 years and <50 years, and HIV-negative study participants aged ≥50 years. PWH: People With HIV. MSM: Men who have Sex with Men. GCSE: General Certificate of Secondary Education.

n (%) or median (interquartile range, IQR)		**PWH ≥50 (n=689)**	**PWH <50 (n=372)**	**≥50 HIV-negative (n=300)**
Gender	Male	606 (88.0%)	301 (80.9%)	192 (64.0%)
	Female	83 (12.0%)	71 (19.1%)	108 (36.0%)
Age [years]		57 (53, 62)	43 (38, 48)	58 (54, 63)
Ethnicity	Black-African	94 (13.6%)	74 (19.9%)	30 (10.0%)
	White	595 (86.4%)	298 (80.1%)	270 (90.0%)
Sexual orientation/mode of HIV acquisition	MSM/homosexual	542 (78.7%)	267 (71.8%)	142 (47.3%)
	Heterosexual	147 (21.3%)	105 (28.2%)	158 (52.7%)
Education	No qualifications	73 (10.6%)	29 (7.8%)	22 (7.3%)
	O levels/GCSEs/A level (or equivalent)	209 (30.3%)	116 (31.2%)	81 (27.0%)
	University	291 (42.2%)	172 (46.2%)	145 (48.3%)
	Other/Not known	116 (16.8%)	55 (14.8%)	52 (17.3%)
Marital status	Single	325 (47.2%)	193 (51.9%)	91 (30.3%)
	Married/In a relationship	291 (42.2%)	166 (44.6%)	163 (54.3%)
	Divorced/widowed	73 (10.6%)	13 (3.5%)	46 (15.4%)
Alcohol consumption	No alcohol use	55 (8.0%)	32 (8.6%)	18 (6.0%)
	Previous alcohol use	87 (12.6%)	38 (10.2%)	23 (7.7%)
	Current alcohol use	547 (79.4%)	302 (81.2%)	259 (86.3%)
Smoking status	Never smoked	267 (38.9%)	159 (43.0%)	137 (46.0%)
	Ex-smoker	263 (38.3%)	102 (27.6%)	119 (39.9%)
	Current smoker	156 (22.7%)	109 (29.5%)	42 (14.1%)
Recreational drug use (past 6 months)		175 (25.4%)	129 (34.7%)	43 (14.3%)
Hepatitis B infection		127 (18.5%)	54 (14.5%)	20 (6.7%)
Hepatitis C infection		59 (8.6%)	33 (8.9%)	2 (0.7%)
Number of co-medications		6 (4, 9)	4 (3, 6)	1 (0, 3)

On lipid lowering therapy	167 (24.2%)	18 (4.8%)	37 (12.3%)
On mental health medications	86 (12.5%)	42 (11.3%)	13 (4.3%)
On steroids	44 (6.4%)	9 (2.4%)	21 (7.0%)

Table 2: Odds ratio (OR, with 95% CI) obtained from univariable and multivariable regression models to investigate associations between obesity and socio-demographics, lifestyle factors and HIV-status/group. Both multivariate models included HIV status, age, gender and ethnicity. MSM: Men who have Sex with Men. GCSE: General Certificate of Secondary Education. * Number of medications: total number of medications used by the subject, including ART for PWH. ** Mental health medications include all drugs used to treat mental illnesses (i.e. anti-psychotics, anti-depressants, mood stabilisers)

	Univariable analysis		***Multivariable analysis 1***		***Multivariable analysis 2***	
	OR (95%CI)	***p***	***OR (95%CI)***	***p***	***OR (95%CI)***	***p***
HIV-positive (vs. HIV-negative)	0.65 (0.48, 0.90)	0.009	0.81 (0.55, 1.20)	0.29	0.74 (0.52, 1.08)	0.11
Age (per 10 years older)	1.18 (1.03, 1.36)	0.02	1.18 (1.00, 1.39)	0.05	1.20 (1.02, 1.41)	0.03
Female gender (vs. male)	3.04 (2.23, 4.15)	<0.001	1.42 (0.88, 2.32)	0.16	1.55 (1.04, 2.29)	0.03
Black African ethnicity (vs. white)	4.29 (3.08, 5.97)	<0.001	2.77 (1.67, 4.64)	<0.001	3.25 (2.13, 4.96)	<0.001
Heterosexual (vs. MSM)	3.21 (2.41, 4.29)	<0.001	1.15 (0.66, 1.94)	0.61		
Marital status (vs. single)		0.002		0.37		
Married/In a relationship	1.45 (1.07, 1.97)		1.27 (0.91, 1.76)			
Divorced/widowed	2.17 (1.38, 3.41)		1.16 (0.69, 1.93)			
Education (vs. university degree)		0.35				
No qualifications	0.97 (0.57, 1.65)	0.90				
A levels/O levels/GCSEs	1.19 (0.85, 1.66)	0.31				
Other/Unknown	1.39 (0.94, 2.05)	0.10				
Smoking status (vs. never smoked)		<0.001		0.16		
Ex-smoker	0.70 (0.52, 0.96)		0.95 (0.68, 1.35)			
Current smoker	0.37 (0.24, 0.56)		0.64 (0.39, 1.01)			
Alcohol consumption (vs. no alcohol use)		<0.001		0.01		0.02
Previous alcohol use	0.97 (0.55, 1.70)		1.91 (1.02, 3.62)		1.89 (1.03, 3.54)	
Current alcohol use	0.46 (0.29, 0.73)		1.00 (0.60, 1.74)		1.04 (0.62, 1.78)	
Recreational drug use in past 6 months	0.34 (0.23, 0.52)	<0.001	0.62 (0.39, 0.97)	0.04	0.54 (0.34, 0.83)	0.006
History of Hepatitis B Infection	1.18 (0.81, 1.73)	0.39				
History of Hepatitis C Infection	0.43 (0.20, 0.89)	0.02	0.75 (0.32, 1.53)	0.46		
Number of medications* (vs. 0)		0.67				
1-4	0.99 (0.60, 1.65)	0.97				
5-9	1.04 (0.62, 1.73)	0.89				
10+	1.31 (0.72, 2.41)	0.38				
On lipid lowering drugs	1.36 (0.95, 1.94)	0.11				
On mental health medications**	1.21 (0.78, 1.88)	0.39				

On steroids	1.46 (0.83, 2.56)	0.18

Table 3: Odds ratio (with 95% CI) obtained from univariable and adjusted regression model to investigate associations between obesity and HIV-specific factors in PWH (n=1061). * Adjusted for age, gender, ethnicity, alcohol consumption and recreational drug use. NRTIs: Nucleoside Reverse-Transcriptase Inhibitors. TDF: tenofovir disoproxil fumarate. FTC: emtricitabine. ABC: abacavir. 3TC: lamivudine. NNRTIs: Non-Nucleoside Reverse-Transcriptase Inhibitors. PIs: Protease Inhibitors. INSTI: Integrase Strand Transfer Inhibitors.

	Median (IQR) or n (%)	**Unadjusted OR (95% CI)**	**p**	**Adjusted* OR (95%CI)**	***p***
Years since HIV diagnosis (per 5-year)	13.2 (7.8, 20.4)	0.96 (0.86, 1.06)	0.39	0.96 (0.85, 1.08)	0.50
Current $CD4^+$ T cell count (per 100 cells/μL higher)	625 (475, 811)	1.08 (1.03, 1.14)	0.003	1.12 (1.06, 1.19)	<0.001
Nadir $CD4^+$ count (per 100 cells/μL higher)	202 (102, 308)	0.99 (0.89, 1.09)	0.85	1.09 (0.98, 1.21)	0.12
Years with $CD4^+$ count <200 cells/mm^3 (per year)	0.0 (0.0, 0.7)	0.95 (0.87, 1.03)	0.21	0.91 (0.82, 1.00)	0.06
$CD4^+$ count recovery rate (per 100 cells/mm^3/year)	0.25 (0.07, 0.49)	1.10 (0.94, 1.26)	0.19	1.11 (0.94, 1.28)	0.17
Current $CD4^+$:$CD8^+$ T cell ratio (per 1-log higher)	0.73 (0.50, 1.02)	1.12 (0.77, 1.63)	0.67	1.05 (0.71, 1.57)	0.80
HIV RNA <50 copies/ml	953 (90.2%)	0.88 (0.51, 1.50)	0.64	0.87 (0.50, 1.59)	0.64
Prior AIDS diagnosis	308 (29.0%)	1.12 (0.78, 1.60)	0.55	0.89 (0.61, 1.30)	0.56
Cumulative exposure to NRTIs (per year)	8.5 (4.3, 14.0)	0.99 (0.96, 1.02)	0.55	0.99 (0.96, 1.03)	0.59
Cumulative exposure to TDF/FTC (per year)	4.8 (2.3, 6.7)	1.02 (0.95, 1.10)	0.56	1.04 (0.97, 1.13)	0.28
Cumulative exposure to ABC/3TC (per year)	3.4 (1.3, 6.9)	0.97 (0.90, 1.05)	0.51	0.98 (0.89, 1.06)	0.57
Cumulative exposure to NNRTIs (per year)	5.7 (2.4, 10.2)	1.00 (0.97, 1.04)	0.83	1.01 (0.96, 1.05)	0.81
Cumulative exposure to PIs (per year)	6.0 (2.5, 10.5)	0.97 (0.93, 1.01)	0.19	0.97 (0.92, 1.01)	0.15
Cumulative exposure to INSTI (per year)	1.4 (0.4, 3.2)	1.03 (0.84, 1.23)	0.79	1.01 (0.81, 1.24)	0.94

Table 4: Odds ratio (with 95% CI) obtained from regression model to investigate associations of obesity with co-morbidities (each co-morbidity considered as the outcome of a separate regression model with adjustment for age, gender and ethnicity) in PWH and HIV-negative controls. *128 PWH and 40 HIV-negative did not have spine BMD measurement; 153 PWH and 36 HIV-negative did not have hip BMD measurement. Values reported as number of subjects experiencing the event in the population (percentage). PWH: People With HIV. CVD: Cardiovascular Disease. BMD: Bone Mineral Density.

	PWH (n=1061)				HIV-negative (n=300)				
Outcome	**n/N (%) of obese with outcome**	**n/N (%) of non-obese with outcome**	**OR (95% CI)**	**p**	**n/N (%) of obese with outcome**	**n/N (%) of non-obese with outcome**	**OR (95% CI)**	**p**	**p int**
Any CVD	103/168 (61.3%)	369/893 (41.3%)	2.41 (1.66, 3.53)	<0.001	38/67 (56.7%)	81/233 (34.8%)	2.54 (1.41, 4.64)	0.002	0.90
Type 2 diabetes	14/168 (8.3%)	32/893 (3.6%)	1.76 (0.84, 3.52)	0.12	8/67 (11.9%)	4/233 (1.7%)	6.19 (1.76, 24.81)	0.006	0.08
Hypertension	67/168 (39.9%)	162/893 (18.1%)	2.91 (1.96, 4.31)	<0.001	26/67 (38.8%)	38/233 (16.3%)	3.02 (1.57, 5.77)	<0.001	0.81
Spine BMD T-score < -1*	45/146 (30.8%)	327/787 (41.6%)	0.66 (0.44, 0.97)	0.04	8/62 (12.9%)	68/198 (34.3%)	0.29 (0.12, 0.62)	0.003	0.08
Hip BMD T-score < -1*	21/142 (14.8%)	267/766 (34.9%)	0.36 (0.21, 0.58)	<0.001	2/58 (3.5%)	43/206 (20.9%)	0.14 (0.02, 0.48)	0.008	0.24
Renal disease	2/168 (1.2%)	25/893 (2.8%)	0.32 (0.05, 1.16)	0.14	1/67 (1.5%)	5/233 (2.2%)	0.58 (0.03, 4.05)	0.64	0.71
Liver disease	20/168 (11.9%)	63/893 (7.1%)	1.78 (0.99, 3.07)	0.04	1/67 (1.5%)	5/233 (2.2%)	0.62 (0.03, 4.36)	0.68	0.40