Higher risk of abdominal obesity, elevated LDL cholesterol and hypertriglyceridemia, but not of hypertension, in people living with HIV: results from the Copenhagen Comorbidity in HIV infection (COCOMO) Study

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Running title: Higher risk of abdominal obesity in PLWH

Key words: HIV-infection, abdominal obesity, elevated LDL cholesterol, hypertension, hypertriglyceridemia

Summary: for a given BMI, HIV infection was associated with an excess risk of abdominal obesity, and this effect was exacerbated by age. PLWH had also higher risk of elevated LDL-C and hypertriglyceridemia, but not of hypertension.

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Abstract

Background: People living with HIV (PLWH) have lower life expectancy than uninfected individuals, partly explained by excess risk of cardiovascular diseases (CVD) and CVD risk factors. We investigated the association between HIV infection and abdominal obesity, elevated LDL cholesterol (LDL-C), hypertriglyceridemia and hypertension, in a large cohort of predominantly well-treated PLWH and matched controls.

Methods: 1,099 PLWH from the Copenhagen Co-morbidity in HIV infection (COCOMO) study and 12,161 age and sex-matched uninfected controls from the Copenhagen General Population Study were included and underwent blood pressure, waist-, hip-, weight-, and height-measurements. Non-fasting blood samples were obtained from all participants. We assessed whether HIV was independently associated with abdominal obesity, elevated LDL-C, hypertriglyceridemia and hypertension using logistic regression models adjusted for known risk factors.

Results: HIV infection was associated with higher risk of abdominal obesity (adjusted odds ratio (aOR): 1.92[1.60-2.30]) for a given BMI, elevated LDL-C (aOR: 1.32[1.09-1.59]), hypertriglyceridemia (aOR 1.76[1.49-2.08]), and lower risk of hypertension (aOR: 0.63[0.54 – 0.74]). The excess odds of abdominal obesity in PLWH was stronger with older age (p-interaction 0.001). Abdominal obesity was associated with elevated LDL-C (aOR: 1.44[1.23-1.69]), hypertension (aOR: 1.32[1.16-1.49]), and hypertriglyceridemia (aOR: 2.12[1.86-2.41]). Low CD4 nadir and duration of HIV infection were associated with the presence of abdominal obesity (aOR: 1.71[1.12-2.62] and aOR: 1.37/5-years[1.11-1.70]).

Conclusions: Abdominal obesity was associated with proaterogenic metabolic factors including elevated LDL-C, hypertension and hypertriglyceridemia and remains a distinct HIV-related

phenotype particularly among older PLWH. Effective interventions to reduce the apparent detrimental impact on cardiovascular risk from this phenotype are needed.

Introduction

With the introduction of combination antiretroviral therapy (cART), people living with HIV (PLWH) have experienced a dramatic improvement in life expectancy [1]. Nonetheless, the observed median survival time from age 50 years is still lower in PLWH than in uninfected individuals [2]. This is partly explained by increased risk of cardiovascular diseases (CVD) [3], the biggest contributor to non-AIDS mortality in PLWH [4], as well as by diseases or traits constituting the metabolic syndrome (abdominal obesity, dyslipidemia, hypertension, and diabetes) [3,5–7].

The redistribution of body fat from the periphery towards the abdomen (fat redistribution syndrome) is a well-known feature of HIV infection, first defined in 1998 [8], and traditionally described as an important complication of old generation antiretroviral treatment [8]. Abdominal obesity has been linked to higher risk of CVD and CVD risk factors in PLWH [9]. Due to new generation cART with fewer metabolic complications, the incidence of fat redistribution syndrome has declined [10]. However, the exact mechanisms behind this condition are still unclear. In addition to cART [11], both host-[11] and viral-associated factors [12] may be involved. Whether fat redistribution syndrome is still involved in the excess risk of CVD in PLWH after the introduction of new antiretroviral regimens, is yet to be determined.

We tested the hypothesis that PLWH had higher prevalence of abdominal obesity, elevated LDL-C, hypertriglyceridemia, and hypertension and that HIV infection was independently associated with these outcomes. For this purpose we i) investigated the prevalence of abdominal obesity, elevated LDL-C, hypertriglyceridemia and hypertension in a large cohort of PLWH (n=1099) compared to matched uninfected individuals (n=12,161), ii) assessed whether HIV infection was independently

associated with risk of abdominal obesity, elevated LDL-C, hypertriglyceridemia, and hypertension, and iii) aimed to identify HIV-associated predictors of these outcomes.

Materials and Methods

Study population

The Copenhagen comorbidity in HIV infection (COCOMO) study is a longitudinal cohort study with the aim of assessing the burden of non-AIDS comorbities in PLWH. Inclusion criteria were a positive HIV test and age ≥18 years. Between March 2015 and December 2016, 1,099 participants were enrolled in COCOMO study, representing more than 40% of the PLWH population residing in Copenhagen area. The procedures for recruitment and data collection have been described elsewhere [13].

12,161 uninfected individuals were recruited from the Copenhagen General Population Study (CGPS). CGPS is an ongoing population study initiated in 2003 including more than 100,000 individuals residing in the greater Copenhagen area [14–17]. Of all the residents, 25% of those aged 20-40 years and 100% of the >40 years old are invited to participate (response rate ≈ 45%). Ethical approval was obtained by the Regional Ethics Committee of Copenhagen (COCOMO: H-15017350; CGPS: H-KF-01-144/01). Written informed consent was obtained from all participants.

Uninfected controls were frequency matched with PLWH by gender and five age year strata, and 14 randomly selected controls were identified for every woman and most men with HIV. For men aged 25-50 it was only possible to identify three to eleven controls in each 5-year age interval, due to differences in the age- and sex-distribution between the HIV and the control population (Supplementary Figure 2).

Clinical assessments

Information about participants´ demographics, physical activity, educational level, smoking, and medication were collected using identical structured questionnaire in COCOMO and CGPS participants. Data regarding HIV infection were obtained from review of medical charts of COCOMO participants [13].

All examinations were performed by trained clinic staff, using identical protocols in both groups.

Waist and hip measurements and body mass index (BMI) calculations were performed according to WHO guidelines [18].

Blood pressure (BP) was measured on the left arm after 5 minutes rest with the subject in sitting position, using an automatic Digital Blood Pressure Monitor [19].

Non-fasting venous blood was collected and analyzed for LDL-C, triglycerides, total cholesterol, HbA1c, and glucose. Blood samples from both COCOMO and CGPS participants were analyzed at Herlev Hospital, Copenhagen [13].

Outcome definitions

According to WHO guidelines, abdominal obesity was defined as waist-hip ratio ≥ 0.90 for men and ≥ 0.85 for women [18].

According to ACC/AHA guidelines elevated LDL-C was defined as LDL ≥ 4.14mmol/l and/or lipid lowering therapy[20]. As sensitivity analysis, a cutoff of LDL ≥ 3.00mmol/l according to European guidelines was used [21].

According to Joint National Committee guidelines, hypertension was defined as anti-hypertensive treatment and/or as having ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic BP values [22].

Hypertriglyceridemia was defined as triglycerides ≥ 2mmol/l and/or lipid lowering therapy [21].

Metabolic syndrome was defined using a slightly modified version of the harmonized metabolic syndrome definition [17,23]. These criteria are depicted in Table 1.

Statistical analysis

Continuous variables were reported as median (interquartile range, IQR), while categorical variables as percentage and frequency. Different groups were compared with t-tests or Mann Whitney U test for continuous data that had normal or non-normal distribution, respectively, and chi square/Fisher's tests for categorical data.

Multivariable logistic models were fitted to test associations between HIV infection and the outcomes of interest. Unadjusted and adjusted odds ratios (OR/aOR) and 95% confidence intervals [CIs] were computed. Covariates included in the model were: age, gender, smoking (current-, former-, never smoker), origin (Scandinavian, other EU, Middle-East and Indian sub-continent, other), educational level (none, short, vocational, middle length, university), physical activity (inactive, moderately inactive, moderately active, very active), BMI, and abdominal obesity.

Separate models for PLWH were fitted to assess associations between HIV-related variables and each outcome. Two different models were considered: in model 1, abdominal obesity was used as dependent variable. Independent variables included in model 1 were: age, gender, smoking, physical activity, origin, education, BMI, current CD4, CD4 nadir < 200, current viral load <40 copies, time since HIV infection and cART initiation, hepatitis-C co-infection.

Model 2 was used when testing elevated LDL-C, hypertriglyceridemia, and hypertension as dependent variables. Independent variables included in the model were: model 1 + abdominal obesity.

As sensitivity analyses, the associations between HIV infection and abdominal obesity and elevated LDL-C, respectively, were explored in multivariable logistic regression models stratified both by present/previous didanosine(ddI)/stavudine(d4T)/zidovudine(AZT) exposure (yes vs. no) and cART initiation date (before and after 2005), separately. This arbitrary and a priori-defined cut-off aims to represent the time-point for shift to newer anti-retroviral regimens characterized by fewer metabolic side effects. As further sensitivity analysis, when testing the association between HIV infection and hypertension, logistic regression analyses were performed using all COCOMO participants and 3 randomly selected CGPS participants for every PLWH, matched using gender and five years age strata, thus eliminating sex and age differences between the two groups (Supplementary Table1). As exploratory analysis, the association between HIV infection and the presence of metabolic syndrome was analyzed. Finally, in order to evaluate the possible impact of a lower threshold when defining elevated LDL-C, the association between HIV infection and elevated LDL-C was also tested using as cut-off ≥ 3.00 mmol/l [21]. In all sensitivity analyses, the same covariates as in the primary analyses were included in the models.

Interaction between age and HIV-status was tested in multivariable logistic analysis models with abdominal obesity, elevated LDL-C, hypertriglyceridemia, and hypertension as dependent variables, respectively. In these analyses, age was grouped into quartiles.

A P-value <0.05 was considered statistically significant. Analyses were conducted in R (V.3.3.0).

Results

Demographics

1,099 COCOMO and 12,161 CGPS participants were included. Characteristics of the participants are shown in Table 1. HIV-specific characteristics of COCOMO participants are shown in Table 2.

Abdominal obesity in PLWH and uninfected controls

PLWH had lower BMI compared to uninfected controls (Table 1). In contrast, PLWH had higher prevalence of abdominal obesity (63.5% vs 59.8%, p-value 0.018) (Table 1). In logistic regression analyses, HIV infection was associated with the presence of abdominal obesity (OR: 1.17[1.03–1.34] and aOR 1.92[1.60-2.30]) (Table 3). This result was reproduced when including all controls and PLWH who initiated cART before 2005 (n=514, aOR: 2.84[2.18-3.73]), and when including all controls and PLWH who started cART after 2005 (n=544, aOR: 1.28[1.01-1.72]) (Supplementary Figure 1). Comparable results were obtained when stratifying PLWH according to ddI/d4T/AZT exposure (Supplementary Table2).

The association between abdominal obesity and HIV increased as persons aged ($p<0.0001$, test for interaction), from an adjusted odds ratio of 1.46[1.06-2.00] in those aged 20-45 years to 2.75[1.75-4.73] in those aged 60-89. A plot representing this interaction is shown in Figure 1.

Abdominal obesity was associated with elevated LDL-C, hypertriglyceridemia, and hypertension in uni- and multivariable logistic regression analyses (Table 3).

Elevated LDL-C, hypertriglyceridemia, and hypertension in PLWH and uninfected controls

PLWH had lower LDL-C but higher prevalence of current lipid-lowering treatment compared to uninfected controls (Table 1). No difference was found in prevalence of elevated LDL-C (24.0% vs 22.7%, p-value 0.358) (Table 1). HIV infection was associated with elevated LDL-C in multivariable (aOR: 1.32[1.09-1.59]) only after adjusting for BMI (Table 3). Furthermore, time of initiation of cART had effect on the association between HIV infection and elevated LDL-C (cART initiation before 2005, aOR: 1.74[1.37-2.19] and cART initiation after 2005, aOR: 0.80[0.58-1.09]). Comparable results were found when stratifying PLWH according to ddI/d4T/AZT exposure (Supplementary Table 2). No association between HIV infection and elevated LDL-C was found when defining this outcome as LDL ≥ 3.00 mmol/l (OR: 0.87[0.74-1.02]).

The association between HIV infection and elevated LDL-C was different in younger and older persons (p-interaction 0.033). While there was no significant association between HIV and elevated LDL-C in those aged 20-52, a positive association was found in persons aged 52-60 (aOR: 1.66[1.16-2.38]), and 60-89 (aOR: 1.32[0.94-1.84]), without however reaching statistical significance in the latter.

PLWH had lower systolic blood pressure (SBP) and lower diastolic blood pressure (DBP) compared to uninfected controls and no difference in prevalence of current anti-hypertensive treatment was found (Table 1). PLWH had lower prevalence of hypertension compared to uninfected controls (43.9% vs 57.9%, p-value <0.001) and negative association was found between HIV infection and the presence of hypertension (OR: 0.57[0.50-0.65] and aOR: 0.63[0.54 – 0.74]) (Table 3). These results were reproduced in sensitivity analyses, using 3 age- and gender-matched uninfected

controls for every COCOMO participant in order to achieve a perfect sex and age matching (aOR: 0.70[0.57-0.87]).

PLWH had higher concentration of triglycerides and higher prevalence of hypertriglyceridemia compared to uninfected controls (Table1). HIV infection was associated with higher risk of hypertriglyceridemia (OR: 1.53[1.35–1.75] and aOR 1.76[1.49-2.08]).

The association between HIV status and both hypertension and hypertriglyceridemia was similar across different age groups (p-interaction 0.39 and 0.09, respectively).

In exploratory analysis, HIV infection was associated with increased risk of metabolic syndrome (OR 1.68[1.39-2.03]).

HIV-related predictors of abdominal obesity, elevated LDL-C, hypertriglyceridemia, and hypertension

Low CD4 nadir and duration of HIV infection were associated with the presence of abdominal obesity (aOR: 1.71[1.12-2.62] and aOR: 1.37 per 5 years[1.11-1.70], respectively) (Figure 2).

Low CD4 nadir and duration of cART were positively associated with the presence of elevated LDL-C (aOR: 1.67[1.09-2.55] and aOR: 1.56 per 5 years[1.17–2.09]) and hypertension (aOR: 1.60[1.10-2.34] and aOR: 1.29 per 5 years[1.00-1.66], respectively) (Figure 2).

Duration of cART was associated with the presence of hypertriglyceridemia (aOR: 1.32 per 5 years[1.04–1.70]).

Discussion

The redistribution of body fat towards the abdomen is associated with increased risk of CVD in PLWH [24] and was classically described as a serious, yet obsolete complication of HIV infection, due to its association with old generation cART [10]. In this study we found that abdominal obesity remains a distinct HIV-related phenotype in particular among older PLWH. Furthermore, abdominal obesity was associated with elevated LDL-C, hypertriglyceridemia, and hypertension. Our results suggest a link between HIV and proaterogenic metabolic factors, partly mediated by abdominal obesity.

CVD is the leading contributor to non-AIDS morbidity and mortality in PLWH [4]. Mechanisms behind the increased risk of CVD in PLWH, however, are not fully elucidated. The fat redistribution syndrome that characterized the early stages of HIV epidemic [8] was a serious complication of old generation antiretroviral treatments, due to its association with CVD risk factors [24]. After the introduction of cART with minor metabolic side-effects, the incidence of fat redistribution syndrome among PLWH has declined [10,25], and so has the attention towards this condition. In this study, however, PLWH had higher prevalence of abdominal obesity compared to uninfected controls, despite having lower BMI. Furthermore, HIV infection was associated with increased risk of abdominal obesity, also after stratifying PLWH according to cART initiation date (pre and post 2005). These results suggest that either HIV *per se* or modern cART may contribute to fat redistribution syndrome as this remains a problem even in contemporary treated PLWH. However, higher risk of abdominal obesity observed in PLWH with initiation of cART prior to 2005, supports a more harmful effect of old generation cART on abdominal fat distribution compared to newer regimens.

Interestingly, for a given BMI the association between HIV infection and abdominal obesity was exacerbated by age. Ageing is known to cause fat tissue redistribution from subcutaneous to intra-abdominal compartments [26]. This is mainly due to systemic inflammation and dysdifferentiation of pre-adipocytes into a pro-inflammatory, senescent-like and tissue remodeling state, which leads to imbalance between lipolysis and lipogenesis [27].Similar cascade of events is described in HIV-associated fat redistribution syndrome [28], where both host and HIV-specific factors are involved [12,28]. In accordance with previous literature [29], we described associations between low CD4 nadir, duration of HIV infection and the presence of abdominal obesity. Low CD4 nadir may be considered an indirect measure of the length of ongoing viral replication [30]. A prolonged exposure to viral proteins may interfere directly with lipogenesis, by inhibiting PPAR-gamma receptor activity in adipocytes [12]. We hypothesize that age- and HIV-associated fat redistribution syndromes are characterized by parallel yet interconnected pathways that amplify each other, leading to a synergistic interaction between aging and HIV infection in causing abdominal obesity in PLWH. This interaction, together with the association found between abdominal obesity and elevated LDL-C, hypertriglyceridemia and hypertension, may partly explain the increased risk of premature CVD in PLWH [31].

Dyslipidemia has been described to be associated with increased risk of CVD in PLWH [3]. Consistent with previous literature [3], we found that HIV infection was associated with higher risk of hypertriglyceridemia and, after adjusting for BMI, elevated LDL-C. However, when considering only PLWH initiating treatment after 2005, no evidence of association between HIV infection and elevated LDL-C was found. Although power for this analysis was lower than in primary analyses, this result may be due to the exposure to different antiretroviral regimes introduced prior to and after 2005, the latter being characterized by fewer metabolic side effects compared to older

generation cART. While having declined in the last decade [25], the prevalence of lipid metabolism disturbances and abdominal obesity still remains high in PLWH and warrants continued attention.

Hypertension is a major CVD risk factor [32], and the possible association between HIV infection and hypertension has been widely studied, with contradictory results [5,33–38]. PLWH have been described to have lower [33,34], comparable [35,36], and higher [5,37,38] prevalence of hypertension compared to uninfected controls. In contrast to our predefined hypothesis, we found that PLWH had lower prevalence of hypertension, and that HIV infection was associated with lower risk of hypertension, even in the sensitivity analysis performed. Of note, the prevalence of hypertension in CGPS was high (57.9%), as described in previous studies [14,19], yet comparable to other Danish general population studies [39]. Due to the size of cohorts included in this study and the overlapping recruitment area between the two groups, we do not believe that sample size or geographical differences explain the findings. There is no obvious biological mechanism that could explain why HIV infection should protect against hypertension, and we suggest that the association found between HIV infection and low risk of hypertension may be due to confounding factors we were not able to account for. It is worth noticing that this finding was mainly driven by undiagnosed and thus untreated hypertension, which may represent a more pronounced white-coat effect in the uninfected population, less exposed to hospital environment compared to PLWH.

HIV was associated with increased odds of abdominal obesity, which was associated with elevated LDL, hypertriglyceridemia, and hypertension. In turn, HIV was associated with increased odds for both elevated LDL and hypertriglyceridemia. As discussed above, PLWH had lower odds of

hypertension. In contrast with the direct and detrimental impact that HIV *per se* and cART have been described to have on both fat tissue and lipid metabolism [28], the effect of HIV on hypertension may be predominantly indirect, mediated by several factors including abdominal obesity, which may result in weaker associations.

The main limitation to the present study is that PLWH and uninfected controls were included in two different centers, University of Copenhagen – Rigshospitalet and University of Copenhagen – Herlev Hospital, respectively. The use of different equipment at the two sites may have led to minor methodologic differences that we were not able to account for. However, the same model of equipment was used in both centers and all the investigations were performed by trained medical staff following identical protocols. Minor differences in age and gender found between the two populations may explain part of the differences in the prevalence of the outcomes. However, a possible confounding effect of these variables was reduced by adjusting for, among the others, age and gender in multivariable analyses.

To our knowledge, this is the largest study to report data regarding abdominal obesity, elevated LDL-C, hypertriglyceridemia, and hypertension in PLWH and uninfected controls. Adjusting for lifestyle and demographic factors, we were able to investigate the effect of HIV infection and to reduce the effect of possible confounders.

In conclusion, our study suggests that abnormal fat distribution and abdominal obesity remains a prominent feature of contemporarily treated PLWH and may contribute to continued excess risk of premature CVD in this population, given both the deleterious interaction found between HIV infection and ageing in causing abdominal obesity and its association with elevated LDL-C, hypertriglyceridemia, and hypertension. Renewed attention by the medical community towards

the abdominal obesity phenotype, and innovative interventions targeting this condition are therefore needed in order to reduce the risk of CVD in PLWH.

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Conflict of interest

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Table 1. Demographic and clinical characteristics of the study population

General characteristics	PLWH n = 1,099	Controls n = 12,161	P
Age median, (IQR)	50.1 (42.8 - 58.0)	52.2 (45.7 - 61.0)	< 0.001
Gender male, % (n)	85.3 (937)	81.4 (9,893)	0.001
Origin, % (n)			< 0.001
Scandinavia	72.9 (788)	89.3 (10,734)	
Other Europe	11.9 (129)	6.9 (826)	
Middle East and Indian sub-continent	1.8 (19)	3.1 (376)	
Other	13.4 (145)	0.7 (90)	
Smoking status, % (n)			< 0.001
Never smoker	33.6 (369)	48.0 (5,839)	
Current smoker	28.8 (317)	13.0 (1,580)	
Ex-smoker	34.0 (374)	38.5 (4,679)	
Educational level, % (n)			< 0.001
None	11.6 (119)	7.0 (456)	
Short	9.9 (102)	7.6 (490)	
Vocational	29.3 (301)	34.3 (2,221)	
Middle length	22.7 (233)	28.6 (1,849)	
University	26.5 (272)	22.5 (1,457)	
Physical activity, % (n)			< 0.001
Inactive	8.8 (90)	5.5 (670)	
Moderately inactive	35.0 (357)	32.4 (3,914)	
Moderately active	42.4 (432)	49.0 (5,924)	
Very active	13.7 (140)	13.1 (1,582)	
Blood Pressure			
Hypertension, yes, % (n)	43.9 (451)	57.9 (6,953)	< 0.001
Anti-hypertensive treatment, yes, % (n)	17.0 (171)	15.4 (1,834)	0.192
SBP, mmHg, median (IQR)	129 (119 - 141)	138 (127 - 152)	< 0.001
DBP, mmHg, median (IQR)	79 (73 - 87)	85 (78 - 93)	< 0.001
Lipids			
Elevated LDL-C, yes, % (n)	24.0 (229)	22.7 (2,649)	0.358
Hypertriglyceridemia, yes, % (n)	48.7 (478)	38.2 (4,494)	< 0.001
Anti-dyslipidemic treatment, yes, % (n)	14.0 (142)	10.6 (1,266)	0.001
LDL-C, mmol/l, median (IQR)	2.7 (2.2 – 3.4)	3.0 (2.4 – 3.6)	< 0.001
Triglycerides, mmol/l, median (IQR)	1.7 (1.2 – 2.7)	1.5 (1.0 – 2.5)	< 0.001
Glucose metabolism			
Anti-diabetic treatment, yes, % (n)	3.2 (32)	3.0 (358)	0.811
HbA1c, mmol/mol, median, (IQR)	34.0 (31.7-36.6)	35.1 (33.0 – 37.4)	< 0.001
Glucose, mmol/L, median (IQR)	5.0 (4.5 – 5.5)	5.0 (4.6 – 5.5)	0.109
Abdominal obesity, yes, % (n)	63.5 (674)	59.8 (7,236)	0.018
Waist circumference, cm, median (IQR)	93 (86-102)	93 (85-101)	0.143
Hip circumference, cm, median (IQR)	101 (96-106)	102 (98-107)	< 0.001
Metabolic syndrome, yes, % (n)	37.8 (338)	35.0 (4024)	0.092
hsCRP, mg/dl, median (IQR)	1.2 (0.6 – 2.5)	1.0 (0.5 – 1.9)	< 0.001
BMI, median (IQR)	24.6 (22.4-27.1)	26.0 (23.8-28.7)	< 0.001
BMI WHO categories, % (n)			< 0.001
Underweight, < 18.5	2.7 (29)	0.5 (56)	
Normoweight, 18.5 – 24.9	52.8 (576)	37.7 (4,569)	
Overweight, 25 – 29.9	34.8 (380)	44.9 (5,444)	
Obese, ≥ 30	9.7 (160)	16.9 (2,050)	

Abbreviations: People living with HIV, PLWH; systolic blood pressure, SBP; diastolic blood pressure, DBP; low density lipoprotein cholesterol, LDL-C; glycated hemoglobin, HbA1c; high sensitivity CRP, hsCRP; body mass index, BMI; interquantile range, IQR.

In exploratory analysis, metabolic syndrome was defined as minimum three of the following: 3 or more of the following 5:(1)waist circumference ≥ 94cm in men and ≥ 80cm in women, (2) SBP ≥ 130mmHg and/or DBP ≥85mmHg and/or antihypertensive treatment, (3) non-fasting plasma triglyceride ≥ 1.693mmol/l, (4)HDL ≤ 1.036mmol/l in men and ≤ 1.295mmol/l in women, (5)self-reported diabetes and/or antidiabetic treatment and/or plasma glucose ≥11.1mmol/l [18].

Table 2. HIV-specific variables for PLWH included in the study

Characteristics	**PLWH n=1,099**
Transmission mode, % (n)	
Heterosexual	21.6 (235)
IDU	1.5 (16)
MSM	71.2 (775)
Other	5.8 (63)
Current CD4, median (IQR)	690 (520-890)
Current CD4 group, % (n)	
<200	1.8 (20)
200-349	5.5 (60)
350-500	15.2 (165)
>500	77.5 (842)
CD4 nadir < 200, % (n)	42.0 (450)
CD4/CD8 ratio, median (IQR)	0.8 (0.6 – 1.1)
cART, yes, % (n)	98.4 (1078)
Current viral load < 50, % (n)	94.7 (1030)
Years since HIV infection, years, median (IQR)	13.7 (6.9 - 21.3)
Years since cART initiation, years, median	10.5 (5.2, 17.3)
HCV-RNA, yes, % (n)	5.3 (58)

Abbreviations: intravenous drug use, IDU; male-to-male sex, MSM, combined antiretroviral therapy, cART; hepatitis C virus, HCV

Table 3. HIV infection as independent risk factor for abdominal obesity, elevated LDL-C, hypertriglyceridemia, and hypertension

	Abdominal obesity		**Elevated LDL-C**		**Hypertriglyceridemia**		**Hypertension**	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
HIV, yes vs no	1.17*** [1.03-1.34]	1.92*** [1.60-2.30]	1.08 [0.92-1.26]	1.32** [1.09-1.59]	1.53*** [1.35–1.75]	1.76*** [1.49-2.08]	0.57*** [0.50-0.65]	0.63*** [0.54-0.74]
Sex, male vs female	3.50*** [3.19-3.84]	3.37*** [2.88-3.95]	1.94*** [1.72-2.20]	1.40*** [1.16-1.69]	3.34*** [2.99-3.74]	2.45*** [2.08-2.90]	2.50*** [2.28-2.74]	2.21*** [1.84-2.45]
Age, per five years	1.92*** [1.85-1.99]	1.79*** [1.69-1.90]	1.32*** [1.29-1.35]	1.27*** [1.23-1.31]	1.19*** [1.17-1.21]	1.10*** [1.07-1.13]	1.35*** [1.33-1.38]	1.30*** [1.27-1.34]
Abdominal obesity, yes vs no	-	-	3.00*** [2.73-3.32]	1.44*** [1.23-1.69]	4.51*** [4.15-4.90]	2.12*** [1.86-2.41]	2.84*** [2.64-3.06]	1.32*** [1.16-1.49]

Multivariable models have been adjusted for HIV infection, sex, age, BMI, physical activity, origin, education level, abdominal obesity (except when abdominal obesity was used as dependent variable), and smoking status.
P-values significance: *, < 0.05; **, < 0.01; ***, < 0.001

Figure 1. Predicted probability of abdominal obesity according to age in normoweight uninfected controls and PLWH

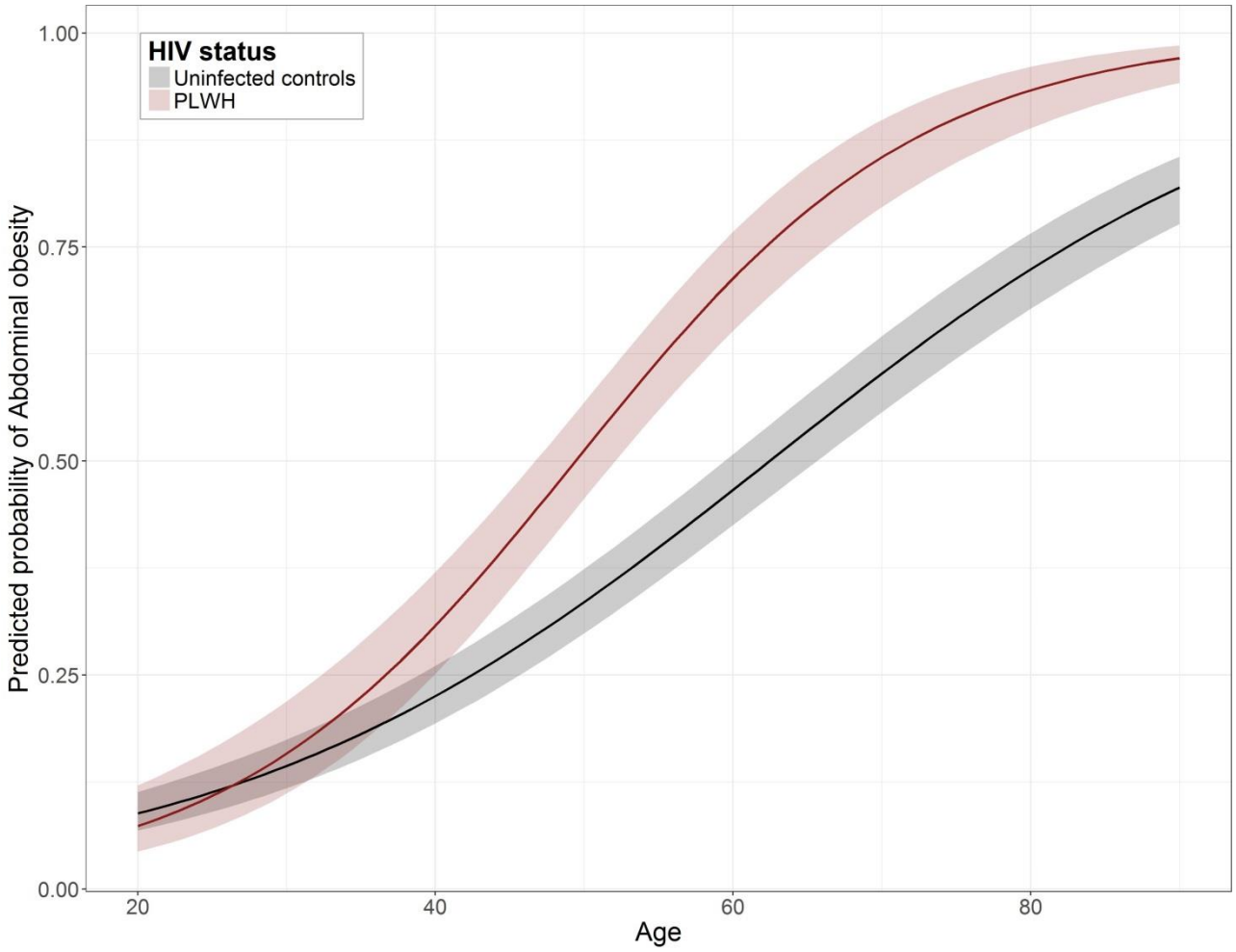
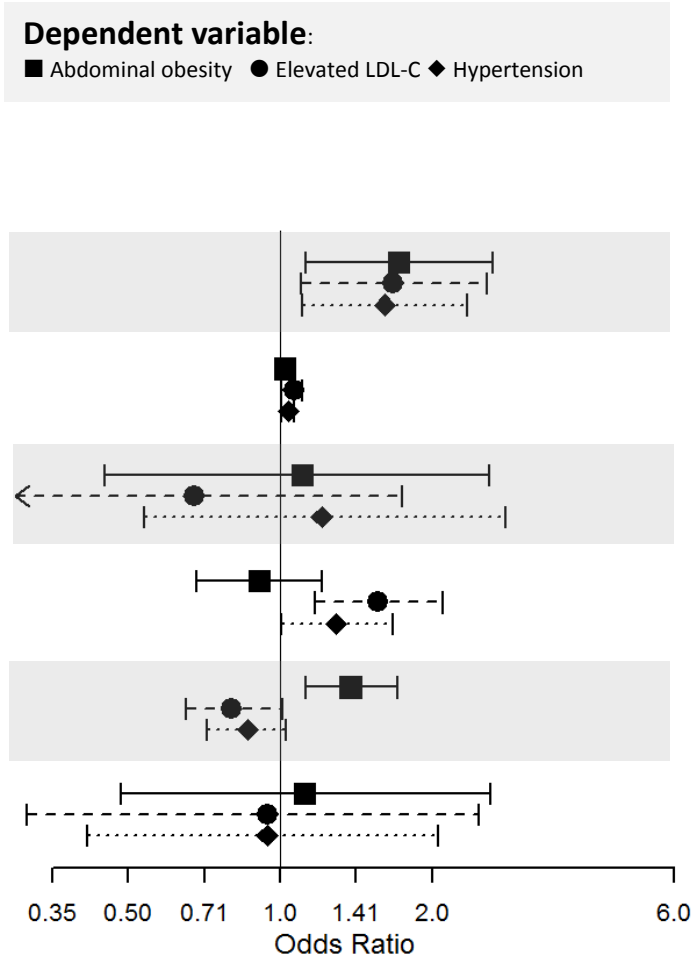


Figure 2. HIV-specific predictors for abdominal obesity, elevated LDL cholesterol, and hypertension



Variable	Abdominal obesity aOR (95% CI)	Elevated LDL-C aOR (95% CI)	Hypertension aOR (95% CI)
CD4 nadir < 200 cells/ml, yes	1.71 (1.12-2.62)	1.67 (1.09-2.55)	1.60 (1.10-2.34)
Current CD4, per 50 cells	1.02 (0.98-1.05)	1.06 (1.00-1.10)	1.03 (1.00-1.06)
VL < 50, yes	1.10 (0.45-2.58)	0.67(0.28-1.74)	1.20 (0.54-2.77)
cART duration, per year	0.91 (0.68-1.21)	1.56 (1.17-2.09)	1.29 (1.00-1.66)
HIV duration, per year	1.37 (1.11-1.70)	0.80(0.65-1.00)	0.86 (0.71-1.02)
HCV, yes	1.12 (0.48-2.60)	0.94 (0.31-2.46	0.94 (0.41-2.05)

Figure legends

Figure 1.

Predicted probabilities for the presence of abdominal obesity in normoweight people living with HIV (PLWH) and controls were calculated using a logistic regression model that included an interaction term between HIV infection and age, age, BMI = 22, sex = "male", origin = "Scandinavian", smoking status = "Former smoker", physical activity = "Moderately active", education level = "Vocational".

Figure 2.

Adjusted odds Ratios (aOR) from multivariable logistic regression analyses with abdominal obesity, elevated LDL cholesterol, and hypertension as dependent variables, respectively. All the models were adjusted for: age, gender, smoking, physical activity, origin, education, abdominal obesity (except when using abdominal obesity as dependent variable), BMI, current CD4, CD4 nadir, current viral load, time since HIV infection, time since cART initiation, hepatitis C (HCV) co-infection.