Changes in body mass index and clinical outcomes after initiation of contemporary antiretroviral regimens

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Background: Weight gain is becoming increasingly prevalent amongst people with HIV (PWH) receiving contemporary antiretroviral treatment. We investigated BMI changes and clinical impact in a large prospective observational study.

Methods: PWH aged ≥18 years were included who started a new antiretroviral (baseline) during 2010–2019 with baseline and ≥1 follow-up BMI assessment available. Rates of clinical outcomes (cardiovascular disease [CVD], malignancies, diabetes mellitus [DM] and all-cause mortality) were analysed using Poisson regression to assess effect of time-updated BMI changes (>1 kg/m^2 decrease, ±1 kg/m^2 stable, >1 kg/m^2 increase), lagged by 1-year to reduce reverse causality. Analyses were adjusted for baseline BMI plus key confounders including antiretroviral exposure.

Results: 6721 PWH were included; 72.3% were male, median age 48 years (interquartile range [IQR] 40–55). At baseline, 8.4% were antiretroviral-naive, and 5.0% were underweight, 59.7% healthy weight, 27.5% overweight, and 7.8% were living with obesity. There was an 8.2% increase in proportion of overweight and 4.8% in obesity over the study period (median follow-up 4.4 years [IQR 2.6–6.7]).

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100 CVDs, 149 malignancies, 144 DMs, and 257 deaths were observed with incidence rates 4.4, 6.8, 6.6, 10.6 per 1000 person-years of follow-up, respectively. Compared to stable BMI, >1 kg/m^2 increase was associated with increased risk of DM (adjusted incidence rate ratio [IRR]: 1.96, 95% confidence interval [CI]: 1.36–2.80) and >1 kg/m^2 decrease with increased risk of death (adjusted IRR: 2.33, 95% CI: 1.73–3.13). No significant associations were observed between BMI changes and CVD or malignancies.

Conclusions: A BMI increase was associated with DM and a decrease associated with death.

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Keywords: antiretroviral therapy, body mass index, cardiovascular disease, diabetes mellitus, malignancy, mortality

Introduction

Over the last decade, excess weight gain amongst people with HIV (PWH) receiving contemporary antiretroviral therapy (ART) has become increasingly prevalent. Although initial weight gained following ART commencement can be attributed to the 'return to health' phenomenon where HIV-induced inflammation and catabolic activity is reduced and appetite increases, additional weight gain on ART can lead to elevated risks of comorbidities [1–3] and multimorbidity [4]. Many factors are thought to be linked to this rising incidence of obesity, including lifestyle trends in diet and exercise, changing demographics, increased life expectancy leading to an ageing population [5–7], and growing evidence of an effect of newer antiretrovirals such as integrase strand transfer inhibitors (INSTIs) [5,8–16].

Increases in body mass index (BMI) have been associated with a higher risk for diabetes mellitus (DM) through increased levels of proinflammatory cytokines, fatty acids and other molecules leading to insulin resistance, and with cardiovascular disease (CVD) via increased blood pressure and changes in lipid levels, in both the general population [17–20] and amongst PWH [21–23]. Obesity may also promote cancer, through a multifactorial mechanism, including increased levels of growth factors and sex steroid hormones, and low-grade inflammation [24], and is linked to all-cause mortality [25,26]. Conversely, evidence has also been found for an association between low BMI and CVD, cancer, and mortality in PWH [1].

The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study including multicohort data up to study completion in 2016 found a higher risk for DM with increased BMI but no evidence of a higher CVD risk [27]. Since these data largely predated INSTI use, it is of interest to study these associations with more recent data from adequately powered observational studies.

EuroSIDA provides a large, heterogeneous population of PWH with comprehensive, longitudinal data collected up to the end of 2019, including ART history, co-morbidities, laboratory assessments, and clinical outcomes. Our aims were to assess changes in BMI distribution during the period 2010–2019 and to investigate whether changes in BMI during this time of contemporary ART are associated with long-term health outcomes (CVD, malignancies, DM, all-cause mortality).

Methods

Participants and definitions

EuroSIDA is a large prospective observational cohort study including data from over 23 000 PWH aged ≥18 years in 118 collaborating clinics across 39 countries covering the World Health Organization (WHO) European region and Argentina (https://www.chip.dk/Studies/EuroSIDA) [28]. Participants were enrolled into 11 cohorts from 1994 onwards and data are collected from routine clinic visits on a standardized form sent to the coordinating centre at yearly intervals.

The study aimed to investigate BMI changes during the contemporary ART era. Thus, we included all PWH who started a new antiretroviral to which they had no previous exposure, between 1 January 2010 and 31 December 2019, while under prospective follow-up. This included individuals who either initiated ART for the first time, switched, or added at least one new antiretroviral to an existing regimen. Baseline was the first date of starting a new antiretroviral and date of last follow-up was defined as last clinical visit, withdrawal from the study, or death, prior to the administrative censoring date, 31 December 2019. Baseline BMI was calculated from height at enrolment and latest weight assessment within 1 year prior to baseline. To be eligible for analysis, participants were required to have a baseline BMI, at least one follow-up BMI

assessment, baseline $CD4^+$ cell count and baseline HIV viral load (VL) available.

BMI categories were defined using WHO clinical cut-offs [29] as $<18.5\,kg/m^2$ = underweight, 18.5 to $<25\,kg/m^2$ = healthy weight, 25 to $<30\,kg/m^2$ = overweight, $\geq 30\,kg/m^2$ = living with obesity. BMI changes were calculated relative to baseline BMI at each follow-up assessment and categorized as $>1\,kg/m^2$ decrease, $\pm 1\,kg/m^2$ stable, $>1\,kg/m^2$ increase. These cut-offs were selected in line with the minimum threshold for a BMI change used by the D:A:D study in their analysis of CVD and DM [27].

The following long-term clinical outcomes were defined:

- Cardiovascular disease: myocardial infarction, stroke, invasive cardiovascular procedures, CVD-related deaths.
- Malignancies (fatal and non-fatal) excluding precancers, metastatic cancers and basal or squamous cell skin cancer.
- Diabetes mellitus: clinical definition, glucose >11.1 mmol/l (non-fasting limit), HbA1C >6.5% or 48 mmol/l and/or use of antidiabetic drugs/insulin, DM-related deaths.
- All-cause mortality: cause determined by Coding Causes of Death in HIV (CoDe) algorithm [30].

Statistical methods

Participant characteristics were summarized according to baseline BMI category. Changes in the distribution of BMI categories were described over the study period including years where at least 100 participants had an assessment available. If multiple BMI assessments were available for an individual during a 1-year period, the first assessment was used.

Incidence of each clinical outcome per 1000 person-years of follow-up (PYFU) was calculated including PYFU from 1 year after baseline until either diagnosis of the event or censoring date (last follow-up), stratified by change in BMI categories. To reduce potential bias from reverse causation, post-baseline BMI assessments were lagged, meaning that they were only included if they preceded the events by at least 1 year, with a corresponding time lag between baseline and start of follow-up time. For this analysis, all BMI assessments were included with the last observation carried forward (LOCF) so that PYFU were divided into increased, decreased, and stable BMI categories. Participants with a relevant diagnosis prior to baseline, or with <1 year of follow-up and/or no lagged follow-up BMI assessments available prior to the event/censoring were excluded.

Poisson regression was used to compare incidence of each clinical outcome following an increase or decrease in BMI versus stable, and to identify any significant associations ($P < 0.05$). A multivariable model was constructed for each of CVD, malignancies, DM, and all-cause mortality, adjusting for baseline BMI group and potentially confounding factors with $P < 0.1$ from univariable models. Factors tested were gender, ethnicity, HIV transmission risk, region, age, smoking status, family history of CVD, $CD4^+$ cell count and nadir, HIV viral suppression, hepatitis B surface antigen (HBsAg) status, hepatitis C antibody (HCV-Ab) status, liver fibrosis stage, anaemia, liver function tests, ART-naive versus experienced, previous number of antiretrovirals received, current number in regimen, cumulative exposure to INSTIs, NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs), plus prior clinical events and co-morbidities including AIDS, non-AIDS defining cancer, CVD, DM, end-stage liver disease, hypertension, dyslipidaemia, chronic kidney disease (see Table 1 for definitions, Supplemental Digital Content, http://links.lww.com/QAD/C588). If assessments were available over the study period and the factor was not considered to lie on the causal pathway for the endpoint of interest, it was included as a time-updated variable using lagged time points as for BMI. Additional categories were included for unknown/missing data. To test whether the effects of BMI changes were significantly different ($P < 0.1$) according to baseline BMI category, we tested an interaction term in each model.

Sensitivity analyses were performed to investigate the impact of 'return to health'. The main analyses were repeated but adjusted for whether individuals were underweight with a low $CD4^+$ cell count (<350 cells/μl) at baseline, and also in a subset excluding underweight individuals at baseline. As pregnancy data were limited and exact dates unknown, we repeated the analysis excluding those with known pregnancies. Another sensitivity analysis extending the lagging time for BMI to 2 years was performed to allow for a longer sub-clinical disease period. Finally, to explore the effect of outliers with more extreme BMI changes ($>3\,kg/m^2$), increased and decreased BMI were split into further categories.

SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA) was used for all analyses.

Results

Characteristics

Fig. 1 outlines the selection process of 6721 eligible participants from the total 23 005 in EuroSIDA and characteristics are summarized in Table 1. The population consisted of 72.3% males, 85.5% of White/Caucasian ethnicity, and median age was 48 years (interquartile range [IQR]: 40–55). There were 25.2% with injecting drug use (IDU) as main risk for HIV transmission, 38.6% were

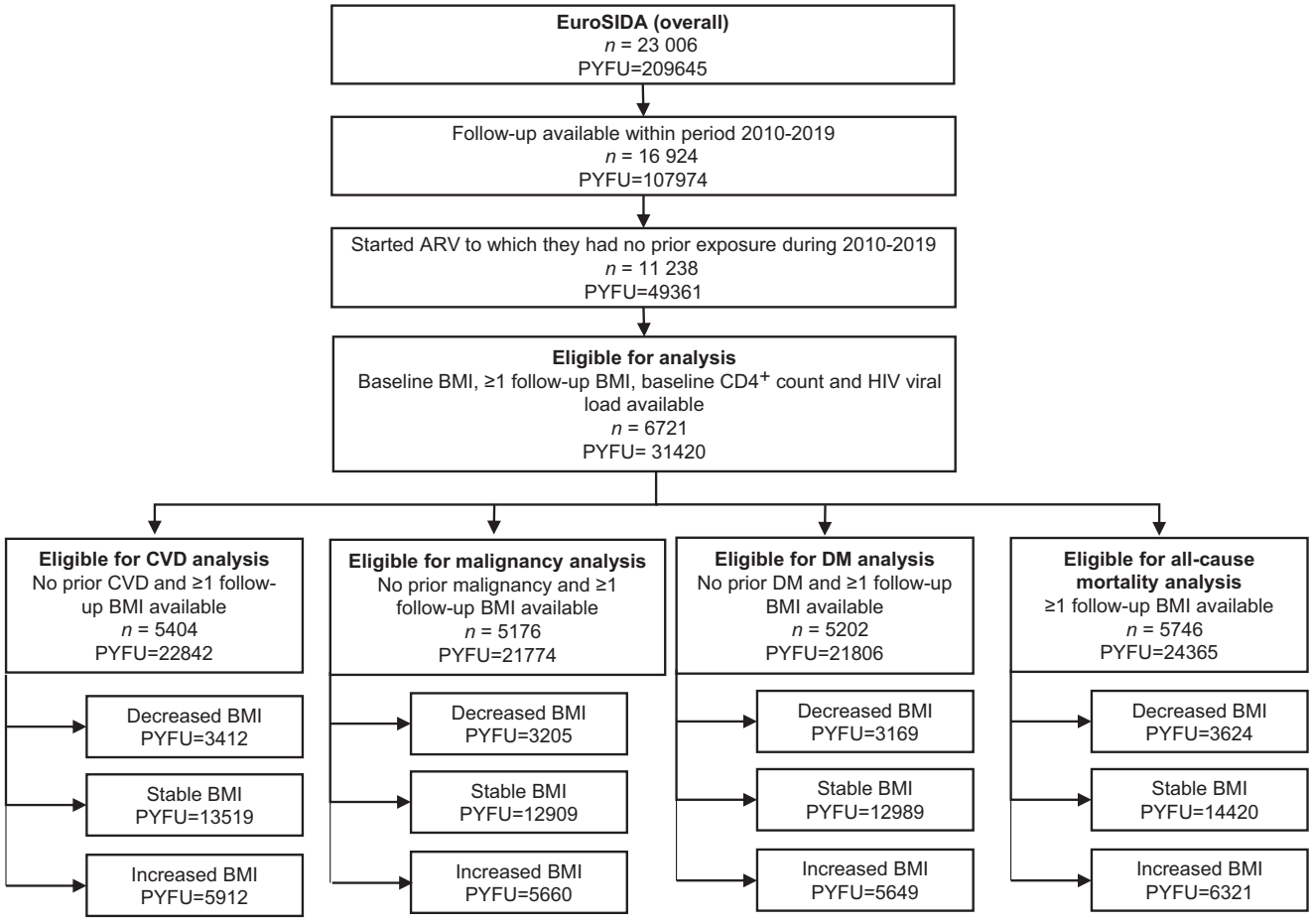

Fig. 1. Flow chart of participants included.

HCV-Ab positive, and 65.9% were current or former smokers, of which the highest frequencies were among those underweight at baseline (34.9% IDU, 52.4% HCV-Ab positive, 78.4% current or former smokers). Median baseline $CD4^+$ cell count was 553 cells/μl (IQR: 371, 760). 65.0% had experienced prior hypertension and 77.4%, dyslipidaemia, which were more prevalent in the higher BMI categories. Demographics were similar between those included and excluded from analyses (Table 2, Supplemental Digital Content, http://links.lww.com/QAD/C589). However, a higher proportion of those included had experienced prior hypertension and dyslipidaemia.

At baseline, 8.4% of patients were ART-naive, 80.6% were on suppressive ART and 11.0% had unsuppressed HIV VL (Table 1). As part of the regimen started at baseline, 41.1% received a PI, 34.7% an NNRTI, and 41.1% an INSTI. 55.3% had a treatment switch during the study period.

Median baseline date was June 2014 (IQR: November 2011, April 2016) and median follow-up was 4.4 years (IQR: 2.6, 6.7) with a median of five weight assessments (IQR: 2, 9) per participant. Total PYFU was 31 420 years, with 19 443 PYFU from 2016 onwards.

BMI changes over time

At baseline, 5.0% were underweight, 59.7% healthy weight, 27.5% overweight, and 7.8% living with obesity. Fig. 2 displays the changes in distribution of BMI categories over time including all individuals with a BMI assessment available during each year (around 14% had missing data each year). Overall, a slightly larger change in BMI distribution was observed in the first year: 4% more overweight/obesity compared to 1–2% per year after that. By the end of the study period, there was an 8.2% increase in proportion of overweight and 4.8% increase in obesity.

Overall, 25.7% experienced a BMI category increase and 15.8%, a decrease, over the whole study period. The median absolute BMI change resulting in one BMI category change was 1.5 kg/m^2 (IQR: 0.8, 2.5), and in two categories was 9.0 kg/m^2 (IQR: 7.3, 11.0).

Clinical outcomes

Incidence rate ratios (IRRs), together with event numbers and incidence rates following increased, stable, or decreased BMI are presented in Fig. 3.

Over 22 843 PYFU, 100 CVD events were observed translating to an incidence of 4.4 [95% confidence

Table 1. Baseline characteristics

	Baseline BMI				
	Underweight (*N* = 338)	Healthy weight (*N* = 4011)	Overweight (*N* = 1851)	Obesity (*N* = 521)	Total (*N* = 6721)
Age (years), median (IQR)	49 (38, 55)	48 (39, 55)	49 (42, 56)	50 (43, 55)	48 (40, 55)
Sex, *n* (%)					
Male	172 (50.9%)	2869 (71.5%)	1475 (79.7%)	345 (66.2%)	4861 (72.3%)
Female	166 (49.1%)	1142 (28.5%)	376 (20.3%)	176 (33.8%)	1860 (27.7%)
Ethnicity, *n* (%)					
White/Caucasian	277 (82.0%)	3456 (86.2%)	1588 (85.8%)	428 (82.1%)	5749 (85.5%)
Black	6 (1.8%)	131 (3.3%)	106 (5.7%)	44 (8.4%)	287 (4.3%)
Asian	7 (2.1%)	55 (1.4%)	18 (1.0%)	6 (1.2%)	86 (1.3%)
Other/unknown	48 (14.2%)	369 (9.2%)	139 (7.5%)	43 (8.3%)	599 (8.9%)
HIV transmission risk, *n* (%)					
MSM	86 (25.4%)	1544 (38.5%)	786 (42.5%)	168 (32.2%)	2584 (38.4%)
IDU	118 (34.9%)	1088 (27.1%)	392 (21.2%)	94 (18.0%)	1692 (25.2%)
Heterosexual	107 (31.7%)	1144 (28.5%)	552 (29.8%)	223 (42.8%)	2026 (30.1%)
Other/unknown	27 (8.0%)	235 (5.9%)	121 (6.5%)	36 (6.9%)	419 (6.2%)
Smoking status, *n* (%)					
Never	62 (18.3%)	1222 (30.5%)	660 (35.7%)	223 (42.8%)	2167 (32.2%)
Current	203 (60.1%)	1838 (45.8%)	692 (37.4%)	153 (29.4%)	2886 (42.9%)
Former	69 (20.4%)	885 (22.1%)	461 (24.9%)	134 (25.7%)	1549 (23.0%)
Unknown	4 (1.2%)	66 (1.6%)	38 (2.1%)	11 (2.1%)	119 (1.8%)
$CD4^+$ cell count (cells/mm^3), median (IQR)	521 (327, 763)	542 (364, 749)	573 (388, 770)	610 (408, 823)	553 (371, 760)
Hepatitis B, HBsAg[a], *n* (%)					
Positive	15 (4.4%)	211 (5.3%)	113 (6.1%)	30 (5.8%)	369 (5.5%)
Negative	298 (88.2%)	3491 (87.0%)	1598 (86.3%)	451 (86.6%)	5838 (86.9%)
Unknown	25 (7.4%)	309 (7.7%)	140 (7.6%)	40 (7.7%)	514 (7.6%)
Hepatitis C, HCV-Ab [a], *n* (%)					
Positive	177 (52.4%)	1645 (41.0%)	621 (33.5%)	151 (29.0%)	2594 (38.6%)
Negative	156 (46.2%)	2290 (57.1%)	1189 (64.2%)	358 (68.7%)	3993 (59.4%)
Unknown	5 (1.5%)	76 (1.9%)	41 (2.2%)	12 (2.3%)	134 (2.0%)
Prior hypertension [a], *n* (%)	167 (49.4%)	2399 (59.8%)	1373 (74.2%)	430 (82.5%)	4369 (65.0%)
Prior dyslipidaemia [a], *n* (%)	240 (71.0%)	3002 (74.8%)	1528 (82.5%)	435 (83.5%)	5205 (77.4%)
Prior CKD [a], *n* (%)	31 (9.2%)	226 (5.6%)	95 (5.1%)	19 (3.6%)	371 (5.5%)
Prior AIDS, *n* (%)	126 (37.3%)	1115 (27.8%)	461 (24.9%)	118 (22.6%)	1820 (27.1%)
ART experience and HIV viral load (copies/mL) prior to baseline, n (%)					
ART-naive	24 (7.1%)	347 (8.7%)	148 (8.0%)	46 (8.8%)	565 (8.4%)
ART-experienced, VL ≤200	263 (77.8%)	3209 (80.0%)	1523 (82.3%)	421 (80.8%)	5416 (80.6%)
ART-experienced, VL >200	51 (15.1%)	455 (11.3%)	180 (9.7%)	54 (10.4%)	740 (11.0%)
Previously received, *n* (%)					
NRTIs	314 (92.9%)	3646 (90.9%)	1696 (91.6%)	471 (90.4%)	6127 (91.2%)
PIs	268 (79.3%)	2911 (72.6%)	1342 (72.5%)	361 (69.3%)	4882 (72.6%)
NNRTIs	213 (63.0%)	2451 (61.1%)	1134 (61.3%)	322 (61.8%)	4120 (61.3%)
INSTIs	43 (12.7%)	481 (12.0%)	241 (13.0%)	73 (14.0%)	838 (12.5%)
Cumulative exposure (years), median (IQR)					
NRTIs	12 (6, 18)	11 (6, 16)	11 (6, 16)	10 (6, 15)	11 (6, 16)
PIs	7 (3, 12)	7 (4, 13)	8 (4, 12)	7 (4, 11)	7 (4, 12)
NNRTIs	4 (1, 10)	5 (2, 10)	6 (2, 10)	5 (2, 10)	5 (2, 10)
INSTIs	4 (2, 5)	4 (2, 6)	3 (2, 6)	3 (2, 6)	3 (2, 6)
Included in regimen started at baseline, *n* (%)					
NRTIs	293 (86.7%)	3639 (90.7%)	1690 (91.3%)	478 (91.7%)	6100 (90.8%)
PIs	163 (48.2%)	1707 (42.6%)	712 (38.5%)	179 (34.4%)	2761 (41.1%)
NNRTIs	103 (30.5%)	1399 (34.9%)	643 (34.7%)	185 (35.5%)	2330 (34.7%)
INSTIs	154 (45.6%)	1577 (39.3%)	791 (42.7%)	237 (45.5%)	2759 (41.1%)

ART, antiretroviral therapy; CKD, chronic kidney disease; IDU, injecting drug use; INSTIs, integrase strand transfer inhibitors; IQR, interquartile range; MSM, men who have sex with men; *n*, number of participants; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors. Baseline is defined as the date of starting a new antiretroviral to which the person has not previously been exposed between 1 January 2010 and 31 December 2019. [a] See Table 1, Supplemental Digital Content, http://links.lww.com/QAD/C588 for definitions.

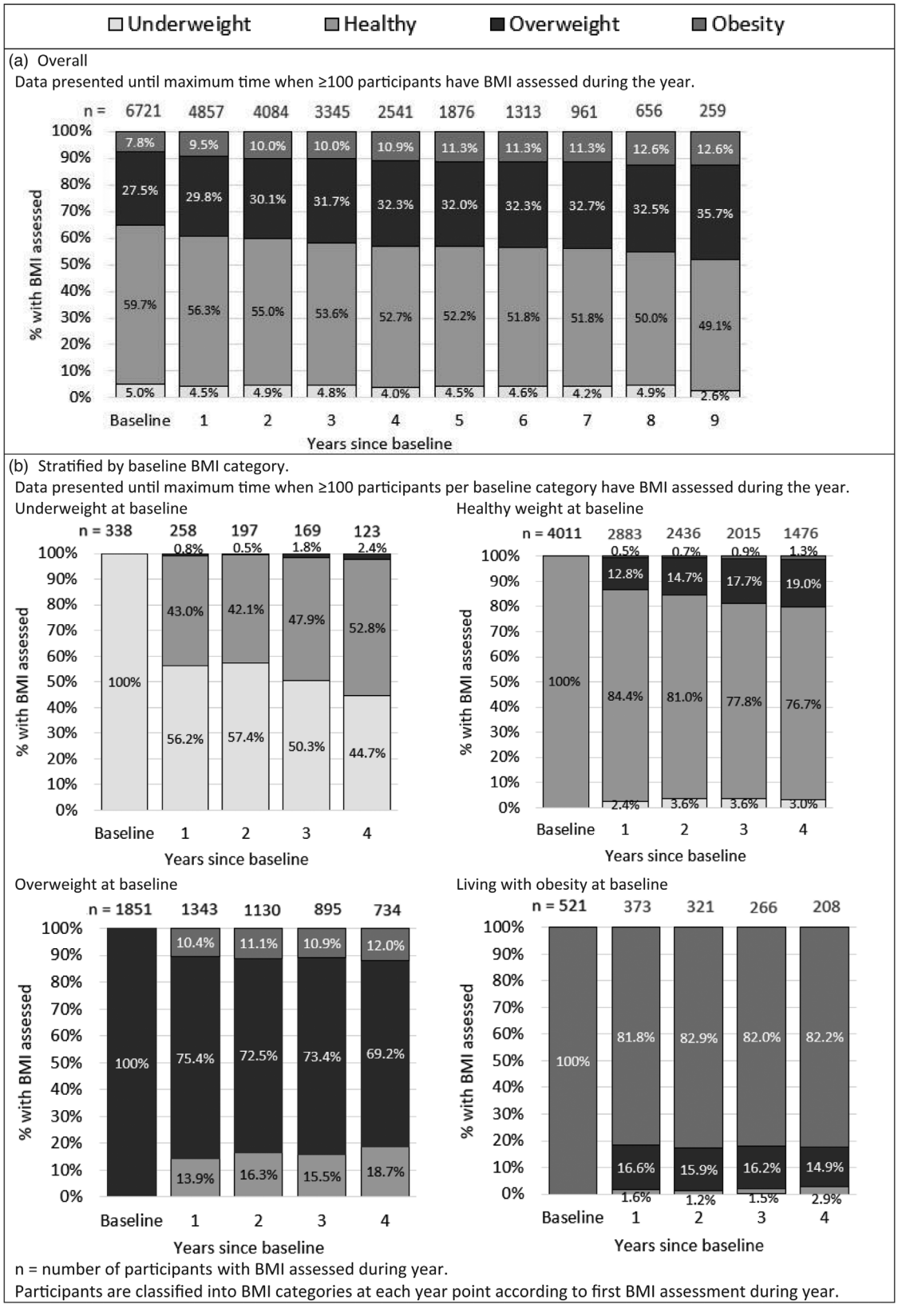

Fig. 2. Distribution of BMI categories over time.

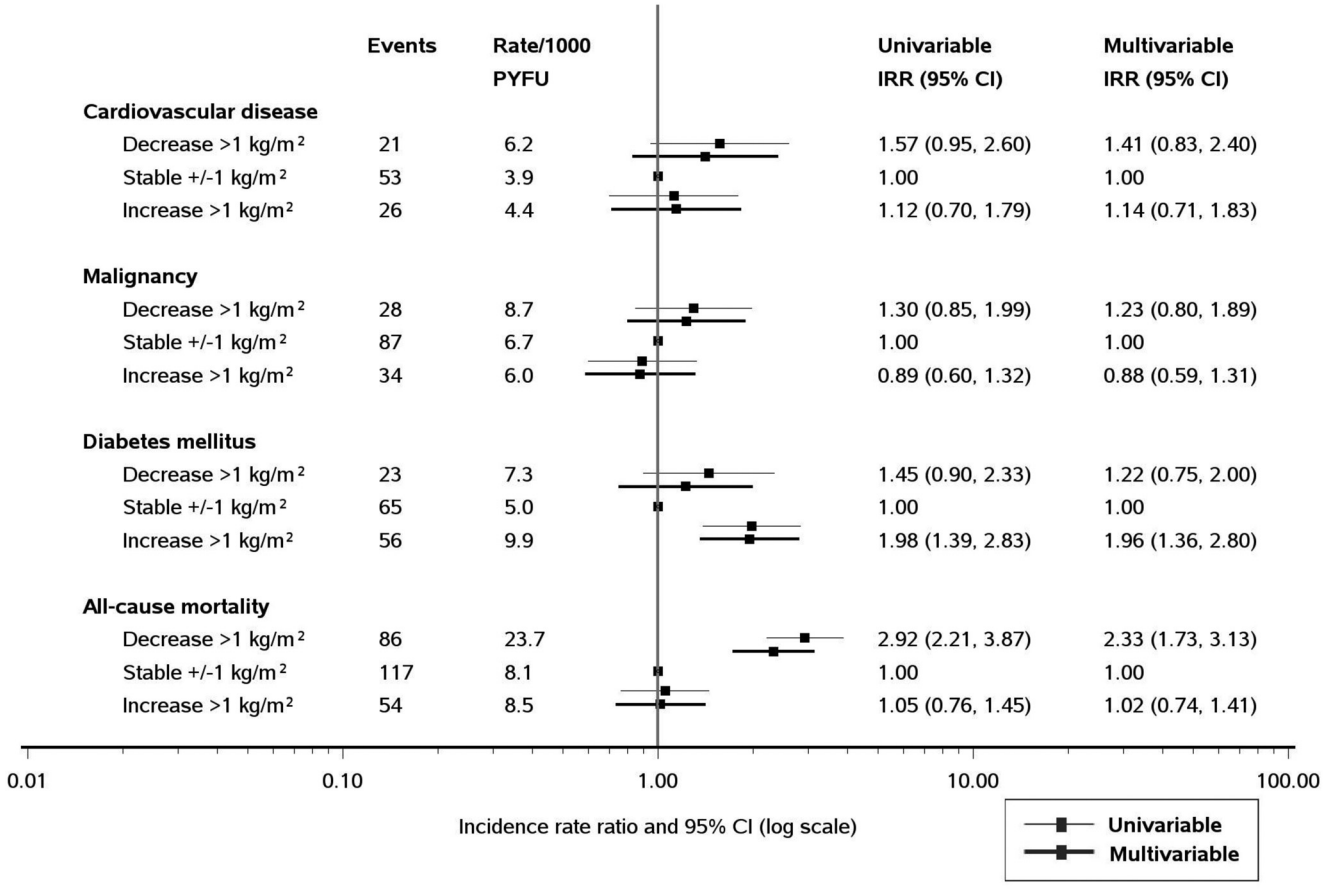

Fig. 3. Incidence rate ratios (IRRs) for clinical outcomes according to changes from baseline in BMI. Multivariable Poisson regression models include time-updated changes in BMI (reference group: stable BMI), baseline BMI group, and factors with $P < 0.1$ from univariable models, including gender, region, age, prior hypertension and dyslipidaemia at baseline, time-updated previous number of antiretrovirals received, current number in regimen, cumulative exposure to NRTIs and INSTIs, chronic kidney disease (CKD), plus other confounders related to but not considered to lie on the causal pathway for the particular clinical outcome: cardiovascular disease (CVD) – baseline liver function tests (LFTs), prior diabetes mellitus (DM) at baseline, and time-updated cumulative exposure to PIs, smoking status, liver fibrosis, anaemia, and end-stage liver disease (ESLD). Malignancy – baseline family history of CVD, ART-naive vs. experienced, whether had HIV viral suppression at baseline, prior DM at baseline, and time-updated cumulative exposure to PIs, smoking status, $CD4^+$ cell count, liver fibrosis, anaemia, and ESLD. DM – ethnicity, baseline LFTs, family history of CVD, prior CVD at baseline, and time-updated cumulative exposure to PIs, non-AIDS defining cancer (NADC). All-cause mortality – HIV transmission risk group, baseline LFTs, ART-naive vs. experienced, whether had HIV viral suppression at baseline, prior CVD, NADC, and DM, and time-updated smoking status, $CD4^+$ cell count, hepatitis B surface antigen (HBsAg) status, hepatitis C antibody (HCV-Ab) status, liver fibrosis, anaemia, ESLD, and AIDS-defining disease.

interval (CI): 3.6, 5.3] per 1000 PYFU. After adjustment for baseline BMI and potential confounders detailed in Fig. 3, no significant associations were observed between BMI changes and CVD, IRRs: 1.41 (95% CI: 0.83, 2.40) and 1.14 (95% CI: 0.71, 1.83) for decreased and increased BMI versus stable BMI, respectively.

One hundred and forty-nine malignancies (including 10 AIDS-defining and 50 previously identified as BMI-related [31]) were observed during 21 774 PYFU with incidence 6.8 (95% CI: 5.8, 8.0) per 1000 PYFU. Most common malignancies were anal ($n = 21$), lung ($n = 17$), prostate ($n = 14$), liver ($n = 11$), and bladder ($n = 11$). No significant associations were found between BMI changes and malignancies, adjusted IRRs: 1.23 (95% CI: 0.80, 1.89) and 0.88 (95% CI: 0.59, 1.31) for decreased and increased BMI versus stable, respectively.

There were 144 cases of DM over 21 806 PYFU with incidence 6.6 (95% CI: 5.6, 7.8) per 1000 PYFU. No association was found between decreased BMI and rate of DM, adjusted IRR: 1.45 (95% CI: 0.90, 2.33). However, there was a significant association with increased BMI versus stable, adjusted IRR: 1.96 (95% CI: 1.36, 2.80).

Over 24 365 PYFU, there were 257 deaths with causes including malignancy ($n = 69$), chronic viral hepatitis ($n = 26$), AIDS-defining disease ($n = 25$), CVD-related

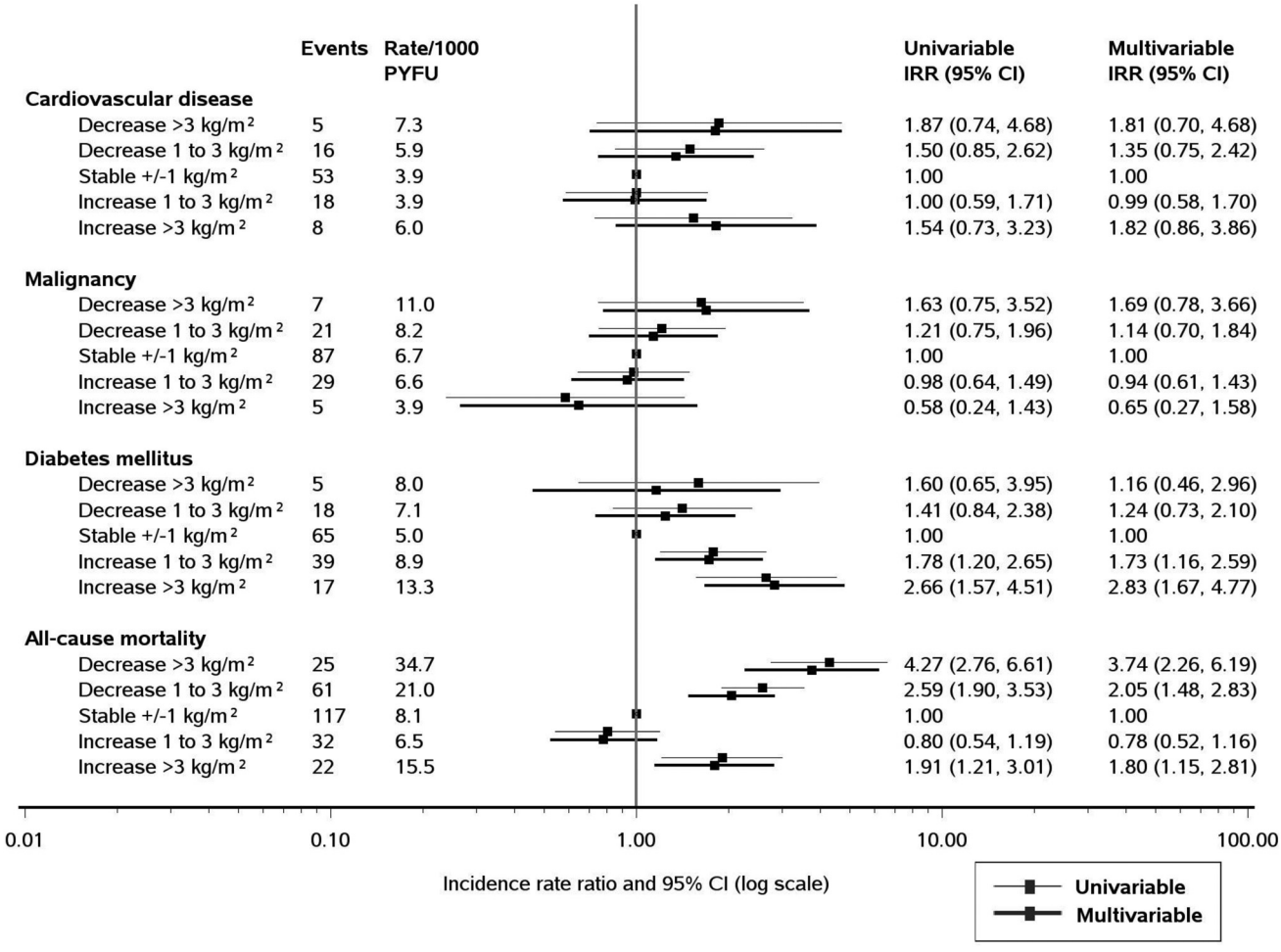

Fig. 4. Incidence rate ratios for clinical outcomes according to changes from baseline in BMI (exploratory analysis with five categories for change in BMI). Multivariable Poisson regression models include time-updated changes in BMI (reference group: stable BMI), baseline BMI group, and factors as described for Fig. 3.

($n = 19$), plus 63 unknown. Incidence was 10.6 (95% CI: 9.3, 11.9) per 1000 PYFU. Decreased BMI had a significant association with all-cause mortality, adjusted IRR: 2.33 (95% CI: 1.73, 3.13), but increased BMI did not, IRR: 1.02 (95% CI: 0.74, 1.41). Comparing causes of death between decreased and stable BMI showed slightly more malignancies (33% and 27%, respectively), and equal proportions of AIDS-defining disease (12%) and unknown causes (22%).

There were no significant interactions between change in BMI and baseline BMI category for any clinical outcome.

Additional analyses

A sensitivity analysis excluding baseline underweight individuals did not impact on results. The subgroup of underweight individuals with a low $CD4^+$ cell count (<350 cells/μl) at baseline was small ($n = 95$, 1.4%) with few clinical events (1 CVD, 5 malignancies, 0 DM, 17 deaths). Consequently, it was only possible to adjust for this in a sensitivity analysis for all-cause mortality and results were unchanged. Excluding 65 individuals with pregnancies gave consistent findings. Extending the lagging time for BMI to 2 years also did not affect the outcomes; the IRR for all-cause mortality, decreased versus stable BMI, was slightly lower but remained significant (1.58, 95% CI: 1.07, 2.32) and for increased versus stable BMI, was slightly higher but still not significant (1.23, 95% CI: 0.87, 1.74).

Fig. 4 displays the results when the increased and decreased BMI categories were split further, noting the small numbers of events per group. No significant differences versus stable BMI were observed for CVD or malignancy but there was some indication of a more pronounced effect in the outlier groups. The significantly higher incidence of DM following increased BMI was present for both 1 to 3 kg/m^2 and >3 kg/m^2 categories but was also more pronounced in the outlier group. Both decreased BMI categories were significantly associated with all-cause mortality but >3 kg/m^2 showed a higher rate. A significant association following increased BMI

>3 kg/m^2 (IRR: 1.80, 95% CI: 1.15, 2.81) was also found that was not detected in the main analysis when combined with 1 to 3 kg/m^2.

Discussion

In this prospective observational study of 6721 PWH across the WHO European region and Argentina, during the period 2010–2019, we observed some increase in proportion of overweight individuals and obesity. We found a BMI increase of >1 kg/m^2 was associated with an increased risk of DM and a decrease of >1 kg/m^2 was associated with all-cause mortality after adjustment for baseline BMI category and other confounders, but no association for CVD or malignancies.

Prevalence of obesity has been increasing in PWH [5,6,32,33], and may be linked to high fat diets, limited exercise, changing demographics in an ageing population, and potentially an effect of newer antiretroviral agents [5–16]. Our data showed an overall increase of overweight individuals and obesity by 2019 of 8.2% and 4.8%, respectively. The increase was slightly higher during the first year after starting a new antiretroviral than subsequent years. 'Return to health' in those underweight, ART-naive, or ART-experienced with unsuppressed VL at baseline, could be a contributing factor; however, these subsets were relatively small. Another factor could be active weight loss after an initial weight gain on treatment, through lifestyle changes or treatment switches due to awareness of potential risks of comorbidities.

Increases in BMI have previously been associated with CVD in both the general population [18–20] and among PWH [21,22]. The D:A:D study, which included around 25% EuroSIDA participants and data up to 2016, did not find evidence of an association between overall BMI increases and higher risk of CVD across all baseline BMI categories, but found a higher risk with decreased BMI especially at low baseline BMI, potentially explained by less aggressive disease prevention interventions in this group [27]. Similarly, we found no association with increased BMI in our analysis including data up to 2019. Our estimated rate for decreased compared to stable BMI was also higher (around 40%), but the result was not significant.

In an earlier D:A:D analysis, a non-linear (J-shaped) association was found between BMI and CVD, where low (<18.5 kg/m^2) and high BMI (>30 kg/m^2) were associated with an increased risk [23]. Our results in Fig. 4 show some indication of a similar non-linear association for larger BMI increases and decreases. However, further follow-up and more events are needed to increase precision of our estimates and to determine whether there is a true association.

No significant association was found between change in BMI and incidence of malignancies. In previous research, high BMI was linked to BMI-related non-AIDS-defining cancer (NADC), and low BMI was associated with NADC [1]. We observed a wide range of cancers, similar to other HIV cohort studies [34], but did not have sufficient power to investigate differences between types of malignancy, some of which may have no association or an inverse association with BMI change.

It is well established that weight gain is associated with a higher risk of DM, a known risk factor for CVD and CKD [35,36], both in the general population [17,20] and among PWH [21,22,27]. Our results showing a significantly higher rate of DM for increased BMI supported this. The exploratory analysis indicated a linear relationship for increases of 1–3 kg/m^2 and >3 kg/m^2, consistent with the previous findings in D:A:D [27].

No association was found in our main analysis between increases of >1 kg/m^2 in BMI and all-cause mortality, but when BMI changes were split further, the estimated death rate for >3 kg/m^2 increased BMI compared to stable was 80% higher and statistically significant. There were significant associations with both decreased BMI groups, and the incidence was higher for >3 kg/m^2 decreases. We did not find a significant interaction between change in BMI and baseline BMI category, suggesting that these effects of BMI changes were similar regardless of BMI at the start of our study period. Further investigation of deaths occurring during decreased BMI identified two overweight/obese individuals who died of chronic viral hepatitis and three overweight who died from a malignancy.

In the general population, high BMI and very low BMI have been linked to a higher risk of all-cause mortality [25,26]. The D:A:D study found a relationship between low BMI and mortality in PWH and considered that those with intermediate BMI tend to have greater muscle mass, exercise capacity, and greater fat stores, which may give them a survival advantage. Additionally, while a decrease in BMI in overweight/obese individuals is often a 'healthy' event, poor appetite or unexplained weight loss can be an early indicator of serious illness. Although our analysis lagged BMI measurements by 1 year, symptoms of disease leading to death may have started earlier than this and bias from reverse causation cannot be ruled out. Lagging measurements by 2 years instead, the estimated IRR for decreased BMI was slightly reduced (but still significant), indicating that this may partly explain the result.

The main strengths of our study were that we could analyse a large, heterogeneous population over a 10-year period, with consistent data collection, extensive quality assurance and data monitoring, and low rates of loss to follow-up (15% in our analysis). However, there are some

limitations inherent to cohort research. EuroSIDA is non-interventional and collects data from routine clinic visits and therefore has variation in frequency, timing, and methods of assessments. Waist-to-hip ratio may provide better accuracy in measuring weight gain but is not routinely available in EuroSIDA. During our study period, individuals typically had one or two weight assessments per year, which may not have been frequent enough to study short-term fluctuations in BMI and consequently we may be less likely to detect a significant effect. However, with over 30 000 PYFU, we had opportunity to study long-term effects of BMI changes. There were also missing data, but we considered these to be missing at random and applied a LOCF approach for analysing clinical outcomes.

Although the statistical models adjusted for known, measured potential confounders, residual confounding or confounding by indication cannot be excluded. Data on behavioural factors (diet, exercise, level of alcohol consumption) were not collected in EuroSIDA. Data on pregnancies [37], thyroid disease, substance use, depression and psychiatric illness including use of antidepressants and antipsychotics were collected inconsistently over time and between clinics.

Regular enrolment of new cohorts from all European regions helps to ensure that EuroSIDA is representative of the current PWH population. However, there is a risk of selection bias. In particular, 4000 HIV/HCV-co-infected participants were selectively recruited for one cohort to meet research objectives, resulting in a high proportion of both HCV and IDU. Our population consists of relatively few females, consistent with surveillance data of PWH in the EU [38], and participants of non-white ethnicity, which meant we were unable to study the impact of BMI changes in these groups. We also restricted to participants on newer regimens with BMI available and found a higher proportion of prior hypertension and dyslipidaemia in this group, which could be explained by a higher chance of switching regimens and having weight monitored more closely.

In conclusion, we observed some overall increase in proportions of PWH overweight or living with obesity by the end of our study period. An increase in BMI was associated with a higher rate of DM, consistent with previous research, and a decrease in BMI was linked to higher rate of all-cause mortality, which may be explained by declining health over a long period and potentially by differences in disease prevention interventions according to BMI. No significant association was found between BMI changes and CVD, although there was some indication of a potentially higher rate for decreased BMI. There was also no association with malignancies, but this included a variety of different cancers. We determined that longer follow-up and additional events would be needed to confirm these results.

Our findings including data up to 2019 support previous research into the clinical impact of weight change. Further research from large cohort studies is required to study the effects of particular antiretroviral agents or types of regimen, which was out of scope for our study. Such data could aid decision-making and patient advice for persons receiving HIV treatment.

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Conflicts of interest

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