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Body Mass Index and the Risk of Serious Non-AIDS Events

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BACKGROUND

- Several studies have reported an increasing prevalence of overweight /obesity in the treated HIV-positive population (>50% in some settings)[1,2] which may be driven by antiretroviral therapy (ART) and life-style factors.
- High body mass index (BMI) (weight (kg)/ height(m^2)) in the general population has been associated with a range of serious outcomes, including cardiovascular disease (CVD), diabetes, various types of cancer and overall mortality. In contrast, low BMI / being underweight is also associated with adverse outcomes, including mortality.[3-6]
- A detailed assessment of how BMI affects the risk of individual serious non-AIDS events (SNAEs) in HIV-positive individuals will help provide key data to clinicians and patient community on the optimal management of this important modifiable risk factor.

METHODS

Study population: All individuals in the D:A:D cohort who initiated ART, with at least one BMI measurement available on/after time of starting ART (baseline) and at least one year of further follow-up from baseline.

Follow-up: Follow-up commenced from the latter of cohort enrolment, ART initiation or first BMI measurement and ended on the first occurrence of the respective endpoint; follow-up was censored at death, 1st February 2014 or six months after last follow-up visit for those who did not experience an endpoint. Individuals with prior CVD, diabetes or cancers were excluded.

Endpoints: The SNAEs of interest, all centrally adjudicated, were CVD (composite of myocardial infarction/stroke/invasive cardiovascular procedures); diabetes; non-AIDS-defining cancers (NADCs); BMI-related NADCs (composite of cancers known to be associated with BMI in the general population: oesophageal, pancreatic, colon, rectal, breast, endometrium, kidney, thyroid and gallbladder); and all-cause mortality.

Statistics: BMI was included into regression models as a time-updated covariate, lagged by 1 year. BMI was categorised initially using clinically meaningful cut-offs (18.5, 23, 25, 27.5 and 30 kg/m^2) but, for sensitivity analyses, BMI was additionally categorized at the deciles of the distribution.

- As BMI was lagged, i.e. the analyses considered the association between a BMI measurement and clinical events that occurred at least 1 year in the future. This approach was taken to minimise reverse causation which may occur if BMI is adversely affected by the clinical event.
- Poisson regression models were used adjusted for key confounders selected using directed acyclic graphs (DAGs). For the CVD outcome, we also present analysis from models additionally adjusted for variables thought to be on the causal pathway.

Table 1

Baseline characteristics and rates of SNAEs

	BMI (kg/m^2) category						
	<18.5	18.5-23	23-25	25-27.5	27.5-30	>30	Overall
N (%)	1929 (4.7)	17640 (42.9)	9283 (22.6)	6998 (17.0)	2910 (7.1)	2389 (5.8)	41149
Age (years) (mean)	38.8	39.3	40.9	41.8	41.7	41.5	40.4
Male	55.1	72	79.6	80.3	73.1	56.2	73.5
MSM	30.9	46.1	50.5	48.3	38.1	25.9	45
Injecting drug use	24.9	17.1	13.4	11.2	9.9	9.9	14.7
White (%)	47.6	52.5	51.2	50.2	45.9	39.4	50.5
Current smoker (%)	52.3	46	38.3	33.4	28.1	24.7	39.9
Family history of CVD (%)	6.6	6.7	7.1	7.2	5.7	7	6.8
CD4 count/mm^3 (median)	354	406	420	415	427	420	410
Total cholesterol mmol/L (mean)	4.7	4.9	5	5.1	5.2	5.1	4.9
HDL mmol/L (mean)	1.3	1.25	1.19	1.17	1.18	1.18	1.21
Systolic BP (mean)	115	120	124	126	128	129	123
N (IR per 1000 PYFU) events							
CVD	97 (6.7)	578 (4.8)	298(4.6)	242(4.8)	96(4.4)	87(4.9)	1398 (4.8)
Diabetes	33 (2.3)	248 (2)	253 (4)	280 (5.6)	184 (8.5)	209 (12.2)	1207 (4.2)
NADC	95 (7.9)	510 (5.1)	223 (4)	167 (3.8)	82 (4.2)	66 (4.1)	1143 (3.9)
BMI-related NADCs	12 (1)	75 (0.8)	32 (0.6)	31 (0.7)	13 (0.7)	21 (1.3)	184 (0.6)
All-cause mortality in males	260 (33.2)	1138 (13)	443 (8.4)	333 (8.1)	142 (8.7)	102 (10)	2418 (11.2)
All-cause mortality in females	116 (16.7)	256 (7.4)	94 (7.2)	66 (6.2)	33 (5.4)	42 (5.3)	607 (7.6)

Figure 1 a-d

BMI and the risk of SNAEs

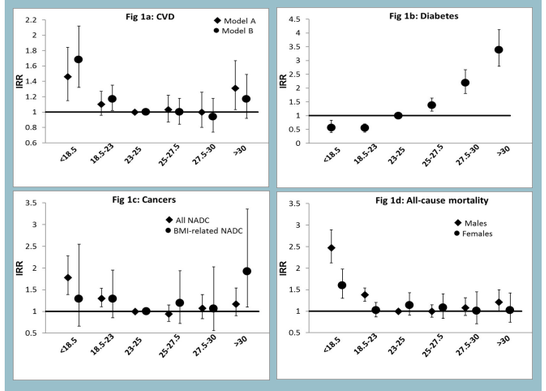

Fig 1: BMI and the risk of SNAEs. Note: All models adjusted for sex, race, mode of HIV transmission, clinical cohort, calendar year and time-updated age, smoking and CD4 count. **Fig 1a**: CVD: **Model A** additionally adjusted for currently being on abacavir, cumulative years on nucleoside reverse transcriptase inhibitors and protease inhibitors. **Model B**: As model A plus additionally adjusted for time-updated (lagged by 1 year) diabetes, total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, systolic and diastolic blood pressure. **Fig 1b**: Models for diabetes adjusted for HCV infection and following time-updated (lagged by 1 year) variables: cumulative years of stavudine, triglycerides, and HDL cholesterol. **Fig 1c and Fig 1d**: Models for cancer and all-cause mortality adjusted for hepatitis B or C co-infection. P for interaction between gender and BMI: <0.001 for all-cause mortality. BMI category of 23-25 was the reference category in all models.

RESULTS

- At total of 41,149 individuals with 295,147 person-years of follow-up (PYFU) were included.
- Participants were largely male (73%) with baseline mean age of 40 years and had a baseline median BMI of 23.3 (interquartile range (IQR): 21.2- 25.7). The median (IQR) time-gap between BMI measurements was 6 (4-9) months.
- A majority of follow-up was in BMI categories of 18.5-23 (41%), 23-25 (22%) and 25-27.5 (17%).
- Smoking appeared to be inversely related to the baseline BMI category.

BMI and SNAEs

- Overall, BMI showed a statistically significant J-shaped relationship with the risk of all SNAEs except diabetes (Table 1 and Figure 1). Overall p- value for the BMI variable in all models was <0.05.
- Low BMI (<18.5 and <23) was consistently associated with the higher risk of all SNAEs (except diabetes) compared to BMI of 23-25. This remained unchanged when the time-updated BMI was lagged by 2 years instead of 1 year (data not shown).
- For diabetes, the relationship with BMI was linear, i.e. increasing risk with increasing BMI, with risk nearly 3.5 times high for BMI >30 vs. BMI of 23-25.
- There was a higher risk of CVD, NADC, and all-cause mortality at BMI levels <18.5 and at 18.5-23 (especially for NADC and all-cause mortality), compared to a BMI at 23-25. High BMI (>30), compared to that of 23-25, was associated with a higher relative risk of CVD, diabetes, BMI-related NADCs and all-cause mortality (especially in males, p-value for interaction between gender and BMI: <0.001).
- Table 2 (analysis by deciles of BMI) and Figure 1 collectively suggest that risk for most SNAEs (except diabetes) at the higher end of BMIs is variable and likely obvious only at levels >30.
- Results were qualitatively similar when BMI was lagged by 2 years (instead of 1 year).

CONCLUSIONS

- Low BMI preceding an event by at least 1-2 years was associated with an increased risk of CVD, cancers and all cause mortality.
- Risk of SNAEs (except diabetes) only started to increase at very high levels of BMI (>30), with minimal increased risk even at BMIs of 25-30.
- Data are limited by fewer participants (and therefore low power) at extremes of BMI, especially at values above 30 kg/m^2. Also there are limitations of BMI as a marker of body weight/fat.
- Further work is needed to assess short term increases and decreases in BMI and risk of SNAEs.

References: 1. Chen et al, 2013; BMJ 347:f5446; **2**. Achhra et al for the DAD study group, 2015, HIV Med **3**.Bays et al, 2007, Int J Clin Pract; 61(5): 737–747; **4**.Renehan et al, 2008, Lancet 371: 569–78; **5**.Gonzalez et al, 2010; N Engl J Med; 363:2211-9; **6**.Petoumenos et al for the DAD study group, 2012, J Int AIDS Soc, 15(2): 17426.

Table 2

BMI deciles and risk of SNAEs

	CVD		Diabetes	NADC		All-cause mortality	
BMI decile	Model A	Model B		All NADCs	BMI-related NADCs	Males	Females
1 (≤ 19.5)	1.56 (1.24 to 1.96)	1.74 (1.38 to 2.20)	0.78 (0.56 to 1.10)	1.37 (1.07 to 1.75)	1.15 (0.59 to 2.24)	2.12 (1.73 to 2.60)	1.13 (0.86 to 1.47)
2 (≤ 20.8)	1.32 (1.04 to 1.67)	1.41 (1.11 to 1.79)	0.57 (0.40 to 0.83)	1.60 (1.26 to 2.03)	1.73 (0.92 to 3.25)	1.31 (1.05 to 1.64)	0.74 (0.52 to 1.05)
3 (≤ 21.7)	1.12 (0.88 to 1.43)	1.17 (0.91 to 1.49)	0.75 (0.53 to 1.05)	0.96 (0.73 to 1.25)	1.01 (0.49 to 2.06)	1.16 (0.92 to 1.46)	0.73 (0.49 to 1.10)
4 (≤ 22.5)	1.10 (0.86 to 1.41)	1.12 (0.88 to 1.44)	0.92 (0.67 to 1.27)	0.96 (0.74 to 1.26)	0.76 (0.35 to 1.65)	1.05 (0.83 to 1.33)	1.02 (0.70 to 1.50)
5 (≤ 23.4)	1	1	1	1	1	1	0.72 (0.45 to 1.14)
6 (≤ 24.2)	1.12 (0.88 to 1.43)	1.10 (0.87 to 1.41)	1.41 (1.05 to 1.88)	0.86 (0.65 to 1.13)	0.91 (0.44 to 1.88)	0.91 (0.72 to 1.16)	1.05 (0.70 to 1.59)
7 (≤25.2)	1.08 (0.85 to 1.38)	1.06 (0.83 to 1.35)	1.64 (1.23 to 2.17)	0.96 (0.74 to 1.26)	1.10 (0.55 to 2.20)	0.80 (0.62 to 1.03)	0.84 (0.53 to 1.32)
8 (≤ 26.5)	1.12 (0.88 to 1.43)	1.06 (0.83 to 1.36)	1.94 (1.48 to 2.55)	0.89 (0.68 to 1.16)	1.32 (0.68 to 2.57)	0.84 (0.65 to 1.08)	0.74 (0.46 to 1.20)
9 (28.7)	1.08 (0.84 to 1.39)	1.00 (0.78 to 1.28)	2.50 (1.92 to 3.26)	0.77 (0.58 to 1.02)	0.85 (0.41 to 1.77)	0.88 (0.69 to 1.13)	0.89 (0.58 to 1.37)
10 (>28.7)	1.30 (1.01 to 1.67)	1.16 (0.90 to 1.49)	4.20 (3.25 to 5.43)	1.02 (0.78 to 1.34)	1.53 (0.81 to 2.89)	1.09 (0.84 to 1.40)	0.74 (0.50 to 1.10)

Results are IRRs (95% CI)

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