Heseltine, T, Hughes, E, Mattew, J, Murray, S, Ortega-Martorell, S, Olier, I, Dey, D, Lip, GYH and Khoo, S

The association of epicardial adipose tissue volume and density with coronary calcium in HIV-positive and HIV-negative patients

The association of epicardial adipose tissue and CVD in HIV-positive and HIV-negative patients

Thomas Heseltine[1,2,3]

Elen Hughes[3]

Jean Mattew[1]

Scott Murray[3]

Sandra Ortega-Martorell[3,4]

Ivan Olier[3,4]

Gregory Y.H. Lip[3]

Saye Khoo[2]

[1]Department of Cardiology, Royal Liverpool University Hospital, Liverpool UK

[2]Institute of Translational Medicine, University of Liverpool, Liverpool, UK

[3]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool UK

[4]School of Computer Science and Mathematics, Liverpool John Moores University, Liverpool UK

Corresponding Author:

Dr Thomas Heseltine

Email: t.d.f.heseltine@liv.ac.uk

Introduction

Patients living with HIV have an increased risk of developing cardiovascular disease compared to risk matched HIV-negative patients (1). This increased risk is may be driven by several factors. Viral related mechanisms, antiretroviral therapy (ART) and increased prevalence of traditional risk factors (smoking, poor diet, sedentary lifestyle) may act in a synergistic fashion to enhance the atherosclerotic phenotype seen in HIV-positive patients. Viral and accessory viral protein mediated changes attenuate energy transport and storage and may predispose to increased visceral adiposity seen in HIV-positive patients. This is done through the effect on PPAR-γ, a nuclear receptor, that governs the differentiation of pre-adipocytes to mature adipocytes (2). This can lead to increased inflammation and drive the atherosclerotic process (3).

Epicardial adipose tissue (EAT) is becoming increasingly recognised as a potential substrate for CVD risk. It functions as an energy depot for normal cardiac function and has an intimate relationship with the epicardial coronary arteries. It is increasingly recognized that EAT volume and density are strongly associated with CVD (4,5). EAT shares a common microcirculation with the epicardial coronary arteries and can exert influence on vascular biology through adipokine secretion, buffering of fatty acids and inflammatory cytokines. Increasing visceral adiposity can cause fat depots to become lipotoxic and dysfunctional. This can induce a proinflammatory phenotype with secretion of pro-inflammatory cytokines and adipokines. The close anatomical relationship between EAT and the epicardial coronary arteries may indicate a novel substrate for atherogenesis.

EAT is readily quantifiable using non-invasive imaging techniques. Computed tomography (CT) allows accurate quantification of EAT volume and density (6). Higher EAT density has been shown to correlate with smaller dysfunctional adipocytes with poor lipid content and lower expression of PPAR-γ (7). Increased EAT volumes have been shown to be associated with markers of subclinical CVD and cardiac events in HIV-positive populations (8,9). This association has also be demonstrated in general populations. Increased EAT density has also been associated with metrics of CVD on CT but data in HIV-positive populations is lacking.

We sought to investigate the association of EAT volume and density with CVD in HIV-positive and HIV-negative patients using CT datasets.

Methods

We conducted a real-world retrospective analysis to compare the associations of EAT volume and CVD in both HIV positive and HIV negative patients. Data was collected from the Royal Liverpool University Hospital HIV clinical database and CT Coronary Angiography (CTCA) clinical database. Both the HIV and CTCA databases exist for both clinical use and quality improvement purposes and are approved by the host institution's audit committee. All demographic and clinical variables present on the databases were cross checked by the research team using the Trusts electronic patient record (clinical notes). The HIV database includes all patients under follow up with the service. It contains clinical co-morbidities, current and previous medications, anthropometric measurements, blood chemistry and

CVD risk. The HIV database was cross checked for patients that had a received a CT thorax within the last 10 years. The images were inspected by an independent imaging cardiologist for the presence of coronary calcification which was recorded in a binary fashion (yes or no).

The CTCA database contains demographic and clinical variables for all patients referred for cardiac CT (either CAC scoring or CTCA) between July 2019 and December 2019. The majority of patients were referred for the investigation of atypical angina and were considered low to medium risk. The presence of HS had previously been calculated by two independent radiologists and added to the clinical database. Patients were labelled as having coronary calcification if the calcium score was >0.

Clinical variables were collected and checked by reviewing patients case notes, including consultation letters, for prior and current diagnoses. Patients with prior diagnoses of cardiovascular disease (including clinical diagnosis, imaging diagnosis of coronary plaque or coronary event or intervention) were excluded. Patients were also excluded if quantification of coronary calcifications was not possible.

EAT volumes were calculated using automated, deep learning software specifically designed to quantify EAT. Contours were generated by the software along the visceral pericardium from the main pulmonary artery bifurcation to apex of the heart on sequential axial slices. Two operators, specifically trained in EAT volume measurement, were able to adjust the

contours as required. Epicardial fat was defined tissue between the visceral pericardium and myocardium meeting the predefined attenuation thresholds for adipose tissue.

In the HIV-positive group CT datasets, including contrast and non-contrast studies were analysed. For non-contrast enhanced studies attenuation thresholds were set between -190 and -30 Hounsfield Units (HU). For contrast enhanced studies the upper threshold limit was adjusted to 0HU as described in previous work (6). In the HIV-negative group EAT volume was assessed from non-contrast enhanced studies using the aforementioned attenuation thresholds.

Statistical Analysis

Summary statistics were calculated to compare the difference in clinical and demographic covariates between HIV-positive and HIV-negative groups. The prevalence of categorical variables was presented in absolute prevalence and percentages. All data were inspected using graphical representation for normality (histograms and Q-Q plots) and Shapiro-Wilk test. The proportions between categorical variables were compared using Chi Squared test. Continuous variables were presented as means and standard deviations (normal distribution) or median and interquartile ranges (non-normal distribution). The means were compared using an independent t test where normally distributed and Mann-Whitney-U test where non-normally distributed. P-values were considered statistically significant if <0.05. Missing data (<5%) was imputed using a random forest multiple imputation technique.

Linear regression analysis was performed on continuous data and the logit of the probabilities of coronary calcification. Variables were inspected for linear associations. Outliers and influential datapoints were assessed using graphical representation of Cook's distance and plotting the standardized residuals. Multicollinearity was assessed by measuring the variance inflation factors of the covariates.

Multiple logistic regression (LR) models were developed to ascertain the association between coronary calcifications and EAT volumes after adjustment for clinical covariates in the HIV-positive and HIV negative groups. Clinical covariates were added to the model a priori. Further multiple logistic models were developed to assess the influence of lipid subfractions and finally HIV-serostatus as independent predictors of coronary calcifications. Odd ratios (OR) and 95% confidence intervals (95% CI) were used to demonstrate the degree of association.

Multiple linear regression models were developed to assess the association of predictor variables and EAT volume for HIV-positive and HIV-negative groups. In the subgroup analysis models were developed to assess the association with EAT density and predictor variables. The statistical analysis and development of the regression models were performed using RStudio, version 1.3.1056.

Results

A total of 700 patients were included in the analysis. There were 195 HIV positive (27.9%) and 505 HIV-negative (72.1%) patients. The demographic and clinical covariates for the cohort, stratified by HIV-serostatus, are summarised in table 1. Mean age was lower in the HIV-positive group (49.2 versus 57.8, p<0.001) whilst the HIV-positive group had a higher proportion of male sex (75.9% versus 48.1%, p<0.001). The presence of traditional CVD risk factors (hypertension, diabetes, hypercholesterolaemia) was all significantly lower in the HIV-positive group compared to the HIV-negative group (all p<0.001). Current smoking was more prevalent in the HIV positive group whilst ex-smoking status was more prevalent in the HIV-negative group (both p<0.001).

EAT volume was significantly lower in the HIV positive group (68mm3 versus 118.3mm3, p<0.001) whilst the prevalence of HS was significantly higher (31.3% versus 19.6%, p<0.001). Coronary calcifications were higher in the HIV-negative group (58.2% versus 29.2%, p<0.001). BMI was significantly lower in the HIV-positive group (27.3 versus 29.6, p<0.001). There were no significant differences in parameters of the lipid profile (all >0.05).

EAT volume and CVD

Univariate and multivariate predictors of coronary calcification are presented in table 5. In the HIV-positive group after adjustment for CVD risk factors, age, sex, statin use and BMI both EAT volume and HS remained significantly associated with coronary calcification. In the HIV-negative the only significant association in the final model was TC (negatively associated with coronary calcifications).

EAT volume and clinical covariates

Multiple linear regression demonstrated that HS was significantly associated with EAT volume in the HIV-positive group but not in the HIV-negative group after adjustment for sex, age and BMI ($p<0.001$ versus 0.066). There was no significant association with constituents of the lipid panel and EAT volume in the HIV-positive group. In the HIV-negative group TG was the only marker significantly associated with increasing EAT volume ($p=0.009$). There was no significant association with hypertension, diabetes or hypercholesterolaemia in either the HIV-positive or the HIV-negative group. HIV was negatively associated with EAT volume after adjusting for age, sex, BMI and HS ($p<0.001$).

EAT attenuation associations

In the subgroup analysis the association of EAT density with CVD risk predictors was assessed in 79 (40.5%) HIV-positive patients in whom non-contrast CT datasets were available. Associations with EAT density were assessed using linear regression models. Significant univariate predictors of EAT density for the HIV-positive group were ex-smoking ($p=0.039$), statin prescription ($p=0.030$), EAT volume ($p<0.001$) and BMI ($p=0.030$). For the HIV-negative group age ($p<0.001$), male sex ($p=0.043$), statin use ($p=0.024$), EAT volume ($p<0.001$), triglyceride ($p=0.025$) and BMI ($p<0.001$) were significantly associated with EAT density. In the HIV-positive group only EAT volume ($p<0.001$) was significantly associated with EAT density in the multivariate analysis. In the HIV-negative group male sex ($p<0.001$) and EAT volume ($p<0.001$) were significantly associated with EAT density. The correlation

between EAT volume and EAT density was significant in both HIV-positive and HIV-negative groups.

The association of EAT density and coronary calcification was assessed using multiple logistic regression. In both HIV-positive and HIV-negative group EAT density was significant predictor of coronary calcification. After adjusting for age, sex (model 2) and age, sex, HS and EAT volume (model 3) the association became non-significant.

Discussion

In this retrospective analysis, involving 700 participants, we sought to investigate the association of EAT volume and EAT density with coronary calcification in HIV-positive and HIV-negative groups. The principal findings from our study indicate that, after adjustment for traditional CVD risk factors, increasing EAT volume is significantly associated with CVD in HIV-positive individuals but not HIV-negative individuals. Predictors of increasing EAT volume also varied by HIV serostatus. In the HIV-positive group, after adjustment for age, sex and BMI only statin therapy and HS were significantly associated with EAT volume. In the HIV-negative group only TG was significantly associated with EAT volume with HS having a borderline significance (table 3). Furthermore, HIV-positivity had a significant inverse relationship with EAT volume in the regression analysis for the whole cohort (supplementary tables). EAT density was similarly negatively correlated with EAT volume in both groups (HIV-positive: R=-0.65 versus HIV negative: R=-0.68) (figure 2). In unadjusted models EAT density was associated with coronary calcification but this association became

non-significant when adjusted for age, sex and age, sex, HS and BMI. The findings were similar across both groups (figure 1).

In general populations increased EAT volume has been demonstrated to be associated with markers of CVD, independently of traditional CVD risk factors (10,11). It is also significantly associated with adverse outcomes (5). In a recent meta-analysis of over 40,000 subjects Manico et al report a significant association of EAT volume with obstructive stenosis, significant stenosis and adverse outcomes (4).

In HIV-positive populations the association of EAT volume and CVD remains relatively under reported. Crum-Cianflone et al demonstrated EAT volume was independently associated with coronary calcium score >100 in their multivariate analysis in men. In addition, the highest quartile of EAT (>140cm3) was associated with a significant odds ratio of 10.4 (p=0.03) (12). Brener et al published findings from the Multicentre AIDS Cohort Study (MACS) showing that EAT volume was associated with increasing calcium score, any plaque and non-calcified plaque after adjustment for CVD risk factors. Furthermore, HIV-serostatus did not attenuate the association of EAT and coronary plaque (9). Raggi et al assessed the impact of EAT and coronary plaque on all-cause mortality in 843 HIV-positive patients. They found the upper tertile of EAT volume (>93mm3) and calcium score >100 were independently associated with all-cause mortality after 3 years (8).

Very recently Sadouni et al published a cross sectional analysis of asymptomatic HIV-positive and negative patients undergoing cardiovascular CT. The only HIV specific association with EAT volume was duration of non-nucleoside transcriptase inhibitor therapy. They found a significant association with EAT volume and non-calcified plaque volume in 226 participants (entire cohort). In those with any low attenuation plaque (a surrogate for high-risk plaque, n=139) EAT volume increase was the only covariate that retained a significant association after adjustment for CVD risk factors (13).

Work analysing specific plaque morphology and association with EAT volume has been done in general populations (14–16). Non-calcified plaque is considered a vulnerable plaque phenotype and prone to rupture leading to acute coronary syndromes. Yuan et al demonstrated that EAT volume and density were independent predictors of thin cap fibroatheroma (17). HIV-positive patients are thought to have this specific plaque morphology at higher rates compared to HIV-negative individuals (18). Non-calcified plaque is considered metabolically active and is the precursor to mixed and calcified plaque. The associations demonstrated in HIV-positive populations may explain the link between a proinflammatory phenotype and the increased CVD risk seen in this population. Coronary calcification is a surrogate for overall CVD burden and has extensive registry data validating its use in risk prediction in general populations (19). Raggi et al has demonstrated that calcium scores >100 is an independent risk factor for cardiac events in HIV-positive patients (8). In addition, Paerira et al have demonstrated the utility of calcium scores to reclassify individual risk in HIV-positive populations (20).

In the present study both covariates associated with visceral adiposity storage, EAT volume and HS, were significantly associated with coronary calcification in the multivariate analysis (both $p<0.005$). In the HIV-negative group the only significant association with coronary calcium was a negative association of TC (table 2). These results hint at subtle differences in the pathogenesis of coronary artery disease between the two groups. HIV-positive patients have higher rates of visceral adiposity compared to HIV-negative cohorts. We demonstrated a higher proportion of HS in the HIV-positive group, but the mean EAT volume was lower. In addition to EAT volume, HS has been shown to be significantly associated with CVD in HIV populations but has mixed associations in general populations (21,22).

Predictors of EAT volume were similar across both cohorts in our study. Age, sex and BMI were significant univariate predictors in both groups. HS was a significant univariate predictor in both groups but the association became non-significant in the fully adjusted model in the HIV-negative group. Knudson et al compared 587 HIV-positive patients with 587 HIV-negative controls from the observational Copenhagen Comorbidity in HIV infection (COCOMO) study to investigate predictors of pericardial volume. Although the vast majority of pericardial adipose tissue encompasses EAT (and the terms are often used interchangeably) they defined it as all fat between the parietal pericardium and myocardium (23). Simarly to us they found significant associations with male sex, age and BMI. They also found significant associations with dyslipidaemia, former and current smoking after adjustment for age, sex and CVD risk factors including sedentary lifestyle. In contrast to this present study, they found that the HIV-positive group had higher pericardial

volumes then the HIV-negative group. The reasons for this are not clear but may relate to our cohort having a larger BMI (both groups) and higher proportions of females.

Previous studies in general populations demonstrated significant associations with lipids and EAT volume and EAT attenuation (5). Our multivariate analyses did not show any significant association with constituents of the lipid panel and EAT volume or attenuation, aside from a significant negative association of TC with EAT volume (table 3). Statins have been demonstrated to reduce EAT volume and attenuation in general populations (24,25). Our data did not show any association of statin therapy with EAT volume or density. Sadouni et al did reported statin as a significant univariate predictor of EAT volume but this association became non-significant in the fully adjusted model (13).

In our subgroup analysis we assessed the effect of EAT density in both HIV-positive and HIV-negative groups. Lower EAT attenuation has been associated with subclinical CVD in general populations but its effect in HIV-positive cohorts is unknown (10). In our data the mean attenuation was significantly lower in the HIV-negative group. We found that EAT volume was negatively correlated with EAT attenuation in both groups (R=-0.65 for HIV-positive and R=-0.68 for HIV-negative). In the multivariate analysis for HIV-positive patients only EAT volume ($p<0.005$) was associated with lower EAT attenuation whilst male sex ($p<0.005$) and EAT volume ($p<0.005$) was associated in the HIV-negative group. EAT attenuation was a significant univariate predictor of coronary calcification in both groups. In the subsequent adjusted models the association became non-significant (figure 1).

These data may suggest a unique pathophysiological role positive HIV-serostatus on coronary atherogenesis and its link to EAT. HIV-positive patients have been demonstrated to have higher rates of “lean adiposity” compared to matched HIV-negative cohorts (26). The mechanism for this is not fully elucidated but is thought to centre on the viral and ART influence on adipogenesis through the nuclear precursor PPAR-γ (3). These pressures reduce maturation of preadipocytes and increase visceral deposition of triglyceride as remaining adipocytes become hypertrophied and unable to accommodate excess lipid. EAT and hepatic parenchyma are visceral depots for this. The lower EAT volume seen in our HIV-positive group compared to the HIV-negative group may be a consequence of lower EAT storage ability.

Alongside the association of increasing EAT volumes with coronary atherogenesis adipocyte function is increasingly recognised as being important for plaque development. Adipocyte in function can be estimated from attenuation of EAT volume. Adipocyte density decreases (reducing attenuation) as lipid content increases. As adipocyte expansion limits are reached adipocytes become dysfunctional with secretion of proinflammatory cytokines. This in turn may cause fibrosis within fat depots which increases attenuation which may distort / weaken the relationship with EAT attenuation measures and CVD. In a retrospective analysis Liu et al reported higher attenuation of EAT was associated with subclinical CVD. They concluded that their Chinese cohort had lower BMI than typical American or European studies with relatively lower EAT volumes. Fibrotic tissue within the EAT depot would therefore be relatively higher which may be attributable to their finding of higher fat

attenuation being linked to CVD (10). Within our study the HIV-positive group had a significantly lower BMI but negative attenuations were significant univariate predictors of coronary calcifications in both groups. This may suggest race has an important role in EAT expansion and inflammation.

The regionality of epicardial attenuation may also be important with increasing evidence supporting the specific role of perivascular adipose tissue attenuation in vascular inflammation. The close relationship of perivascular adipose tissue to epicardial coronary arteries is well described. Proinflammatory cytokines from dysfunctional epicardial adipocytes may drive vascular inflammation in a paracrine manor due to a common microcirculation with the adventia of epicardial coronary arteries. The attenuation of perivascular adipose tissue has been shown to be significantly associated with marker adipocyte size, inflammatory cytokines and PPAR-γ (27). PVAT attenuation using artificial intelligence derived radiomics has been shown to be associated with adverse cardiac events independently of traditional risk factors and calcium scoring (7). Given the proinflammatory phenotype and visceral adiposity seen in HIV-positive groups this understanding of the link between EAT volume and EAT attenuation warrants further investigation.

Limitations and strengths

We acknowledge several limitations to our study. Firstly, assessment of coronary calcium and EAT volumes was performed in some instances on non-dedicated CT datasets of the thorax. These non-dedicated scans had taken place historically for different indications.

Although it us recognised that assessment of EAT volumes and coronary calcification can be performed in a robust manor which is highly correlated to dedicated datasets our datasets were not homogenous. By using non-contrast datasets, we were unable to assess different plaque morphologies. Secondly, by opportunistically selecting patients who had received CT scans of the thorax for alternative indications we may have introduced selection bias into the study. Thirdly, the HIV-negative cohort were a pre-defined group of patients with symptomatic low to medium risk chest pain and this may affect the generalisability of the result. We did not adjust for HIV-specific covariates or ART. However, this study was designed to assess the differences in associations of EAT volume and attenuation between HIV-positive and HIV-negative cohorts.

Despite these limitations our study had several strengths. Our data was extremely well characterised with <5% missing values. This study is unique in the way HS, an important visceral adiposity depot and marker of CVD risk, was assessed with EAT metrics to assess associations with coronary calcification. It is also the first study comparing EAT attenuation between HIV-positive and HIV-negative groups. Future prospective studies are required to ascertain the predictive value of measuring EAT volume, EAT attenuation and EAT regional attenuation including PVAT. The impact of measuring PVAT and regional EAT attenuation is particularly interesting for defining the mechanistic processes driving the heightened CVD risk seen in HIV-positive groups. This study is designed to be hypothesis generating and no causality can be inferred from the retrospective design.

Conclusion

In conclusion, in this retrospective analysis we demonstrated a significant association of EAT volume with coronary calcification in the HIV-positive cohort but not in the HIV-negative group. Drivers of EAT volume differed in each group. This may hint at different mechanistic drivers of coronary atherosclerosis depending on HIV-serostatus. EAT attenuation was significantly associated with coronary calcification in both groups. This emerging field may represent a significant portion of the excess CVD risk seen in HIV-positive groups

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Tables and Figures

Table 1: Summary statistics of covariates stratified by HIV-serostatus.

Stratified by HIV			
	0	1	p
n	505	195	
Age (mean (SD))	57.84 (12.17	49.24 (10.60)	<0.001
Male Sex = 1 (%)	243 (48.1)	148 (75.9)	<0.001
Smoker = 1 (%)	81 (16.0)	57 (29.2)	<0.001
Ex_smoker = 1 (%)	105 (20.8)	7 (3.6)	<0.001
HTN = 1 (%)	218 (43.2)	28 (14.4)	<0.001
DM = 1 (%)	81 (16.0)	5 (2.6)	<0.001
Chol = 1 (%)	184 (36.4)	14 (7.2)	<0.001
Statin = 1 (%)	190 (37.6)	34 (17.4)	<0.001
HS = 1 (%)	99 (19.6)	61 (31.3)	0.001
EAT_V (mean (SD))	118.35 (56.7	68.03 (49.94)	<0.001
TC (mean (SD))	4.64 (1.04)	4.76 (1.11)	0.188
TG (mean (SD))	1.74 (0.80)	1.89 (1.45)	0.096
LDL (mean (SD))	2.40 (0.93)	2.51 (1.08)	0.16
HDL (mean (SD))	1.36 (0.36)	1.34 (0.48)	0.555
BMI (mean (SD))	29.62 (4.68)	27.33 (6.38)	<0.001
Coronary calcium = 1 (%)	294 (58.2)	57 (29.2)	<0.001

Table 2: Univariate and multivariate predictors of coronary calcification

HIV-positive

	Univariate OR	p	Model 1	p	Model 2	p	
Age	1.10	<0.005					
Sex	2.91	0.016					
Smoker	1.48	0.249	2.78	0.015			
Ex-smoker	1.86	0.426	0.92	0.924			
Hypertension	1.42	0.417	0.85	0.738			
Diabetes	1.64	0.595	1.38	0.754			
Hypercholesterolaemia	3.59	0.024	2.15	0.197			
Statin	3.52	<0.005	2.19	0.079			
EAT Volume(10mls)	1.22	<0.005	1.14	<0.005	1.14	<0.005	
HS	4.29	<0.005	3.41	<0.005	3.17	<0.005	
TC	1.16	0.306	1.01	0.953	1.05	0.778	
TG	1.32	0.014	1.26	0.052	1.23	0.142	
LDL	1.12	0.422	1.03	0.839	1.09	0.642	
HDL	0.45	0.037	0.35	0.016	0.43	0.066	
BMI	1.05	0.034					

HS, Hepatosteatosis; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein;

HDL, high density lipoprotein; BMI; body mass index.

Model 1: Age, Sex, BMI

Model 2: Age, Sex, BMI, Smoker, HTN, DM, Chol, Statin

HIV negative

	Univariate OR	p	Model 1	p	Model 2	p
Age	1.11	<0.005				
Sex	1.90	<0.005				
Smoker	1.27	0.345	1.87	0.031		
Ex-smoker	1.57	0.050	1.71	0.042		
Hypertension	1.84	<0.005	1.08	0.733		
Diabetes	2.16	<0.005	1.18	0.580		
Hypercholesterolaemia	1.90	<0.005	1.46	0.092		
Statin	3.17	<0.005	1.77	0.014		
EAT Volume(10mls)	1.12	<0.005	1.05	0.089	1.04	0.104
HS	1.07	0.757	0.85	0.549	0.81	0.444
TC	0.60	<0.005	0.76	0.010	0.75	0.012
TG	0.91	0.421	1.10	0.493	1.06	0.699
LDL	0.67	<0.005	0.81	0.070	0.83	0.115
HDL	0.83	0.464	0.53	0.050	0.55	0.056
BMI	1.05	0.022				

Model 1: Age, Sex, BMI

Model 2: Age, Sex, BMI, Smoker, HTN, DM, Chol, Statin

Table 3: Univariate and multivariate predictors of EAT volume

HIV-positive

	Univariate	Model 1	Model 2
Age	<0.005*	<0.005*	-
Male Sex	<0.005*	<0.005*	-
Smoker	0.443	0.800	0.753
Ex-smoker	0.016*	0.034*	0.104
Hypertension	0.115	0.212	0.747
Diabetes	0.262	0.322	0.401
Hypercholesterolaemia	0.173	0.204	0.772
Statin	<0.005*	<0.005*	0.048*
TC	0.109	0.175	0.449
TG	0.154	0.345	0.931
LDL	0.254	0.265	0.385
HDL	0.116	0.151	0.276
HS	<0.005*	<0.005*	<0.005*
BMI	<0.005*	-	-

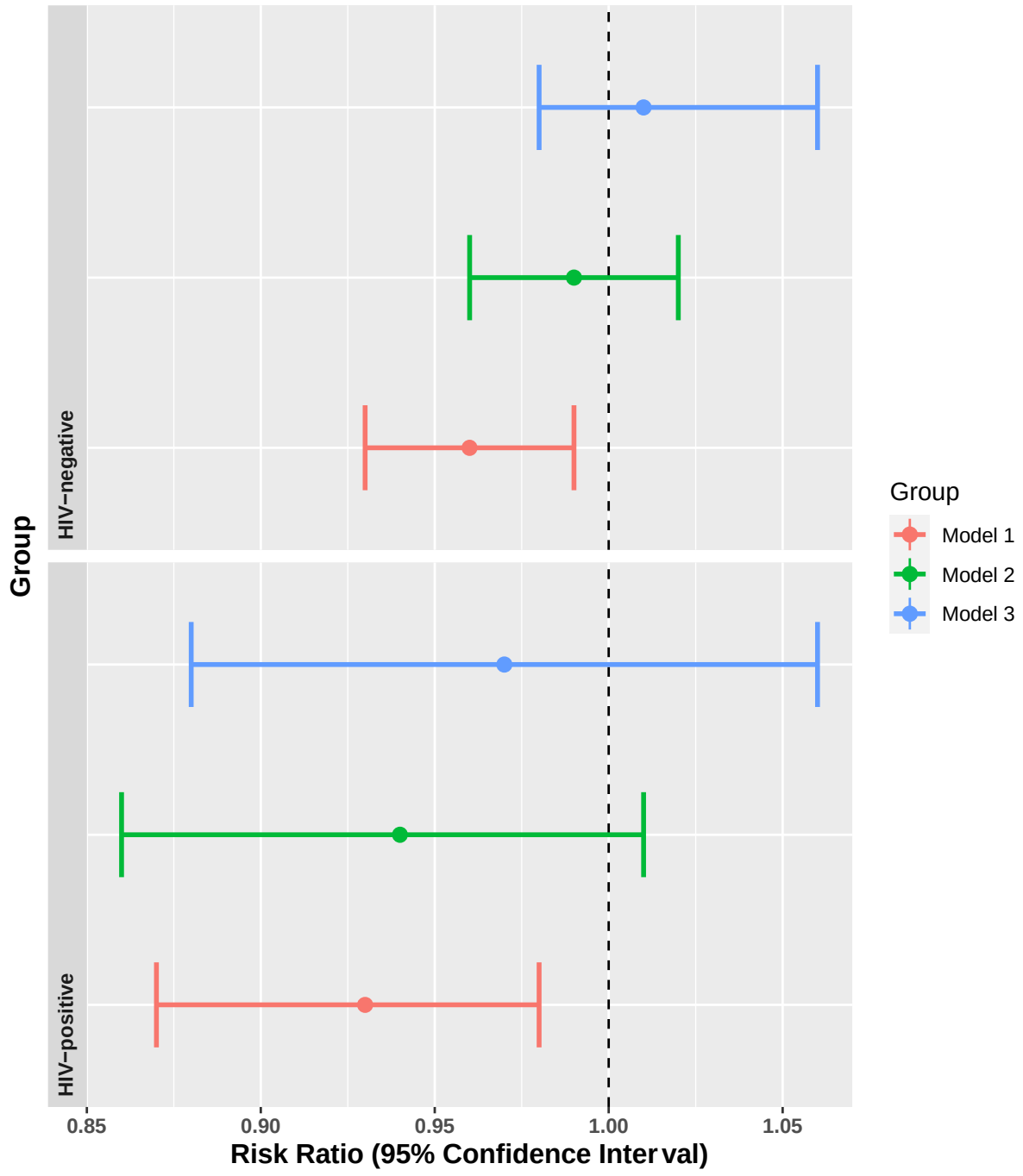
HIV-negative

	Univariate	Model 1	Model 2
Age	<0.005	<0.005*	-
Male Sex	<0.005	<0.005*	-
Smoker	0.858	0.484	0.193
Ex-smoker	0.356	0.187	0.187
Hypertension	<0.005	0.030*	0.593
Diabetes	<0.005	0.005*	0.183
Hypercholesterolaemia	0.319	0.643	0.187
Statin	<0.005	<0.005*	0.45
TC	<0.005	<0.005*	0.576
TG	0.006	0.104	<0.005
LDL	<0.005	<0.005*	0.111
HDL	0.132	0.546	0.5
HS	<0.005	0.032*	0.067
BMI	<0.005	-	-

Model 1: BMI

Model 2: Age, sex, BMI

Figure 1: The association of EAT density with coronary calcification



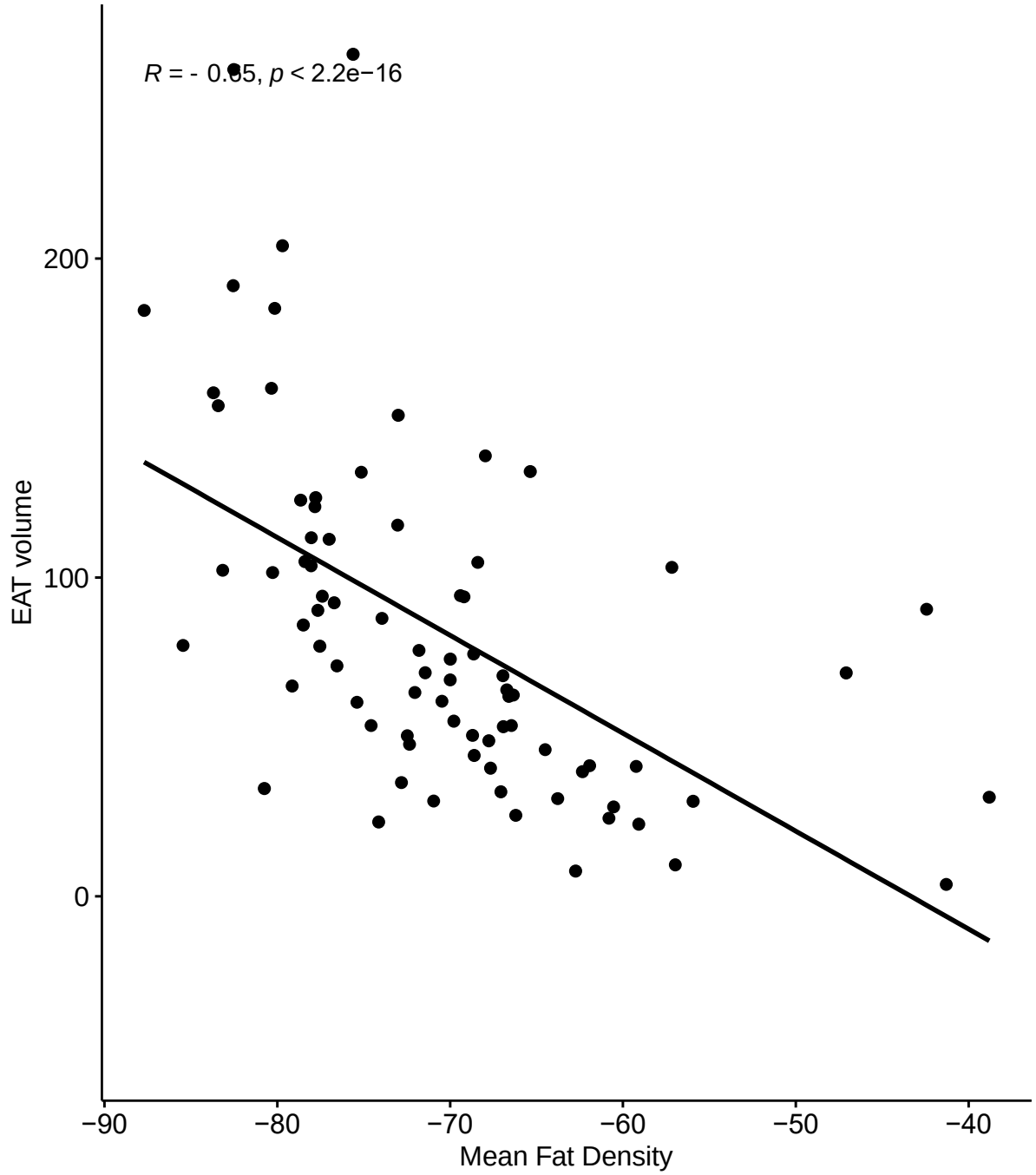
Model 1: Univariate

Model 2: Adjusted for age and sex

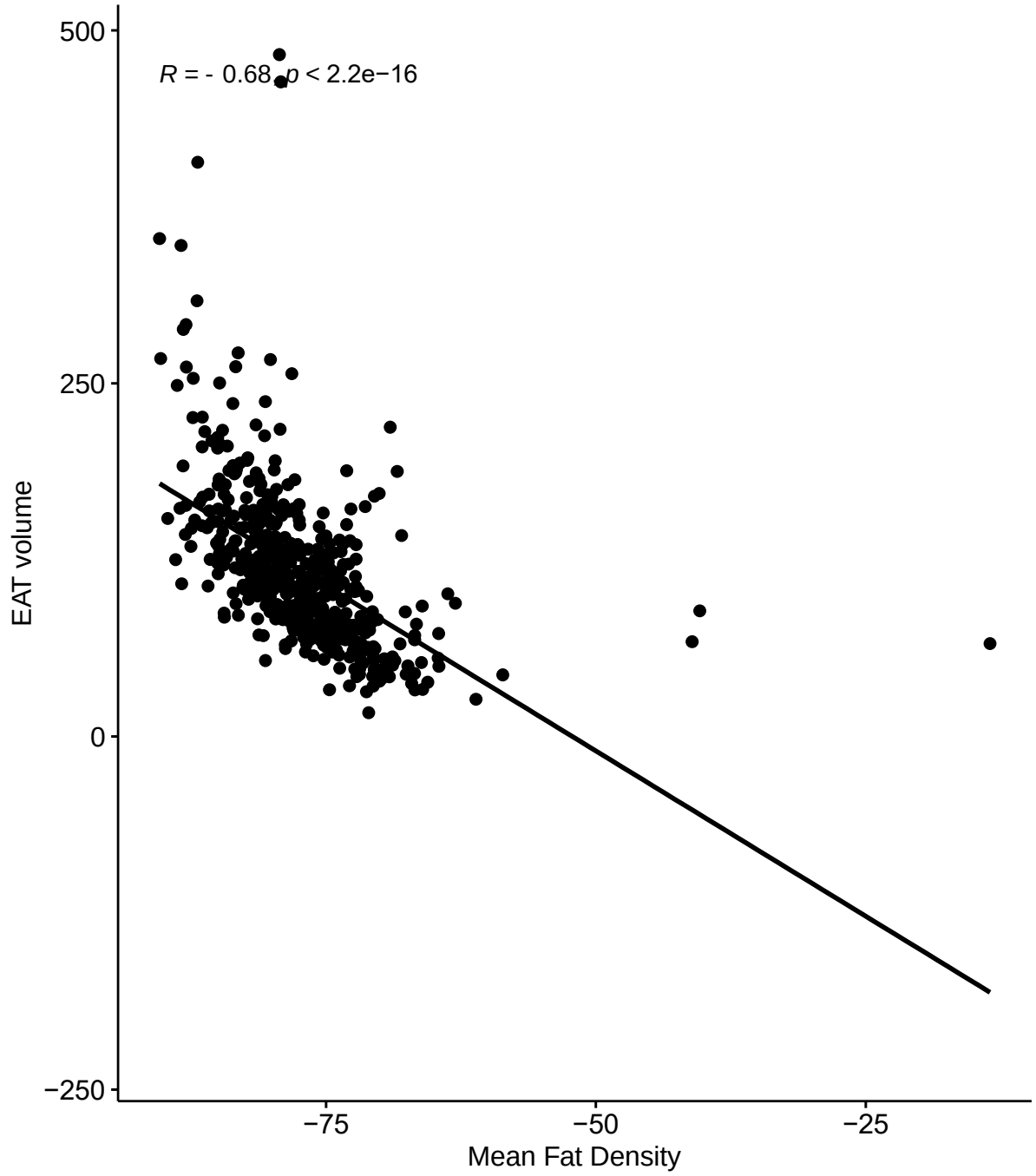
Model 3: Adjusted for age, sex, HS and BMI

Figure 2: Correlation between EAT volume and EAT density in HIV positive and HIV negative groups.

HIV-Positive

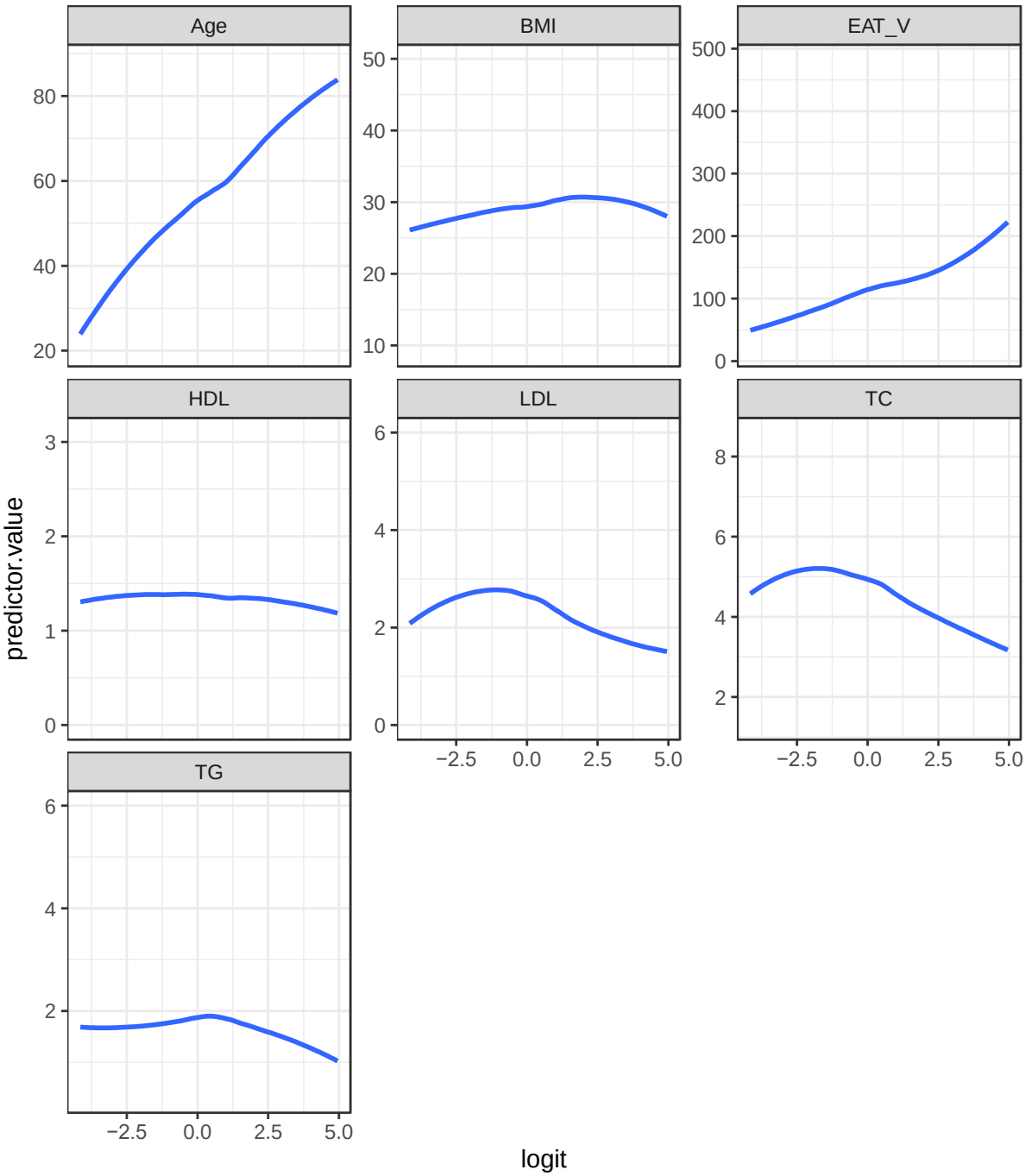


HIV-negative



Supplementary Tables and Figures

Association of continuous covariates with logit odds of coronary calcification in the HIV-negative group.



Association of continuous covariates with logit odds of coronary calcification in the HIV-positive group.

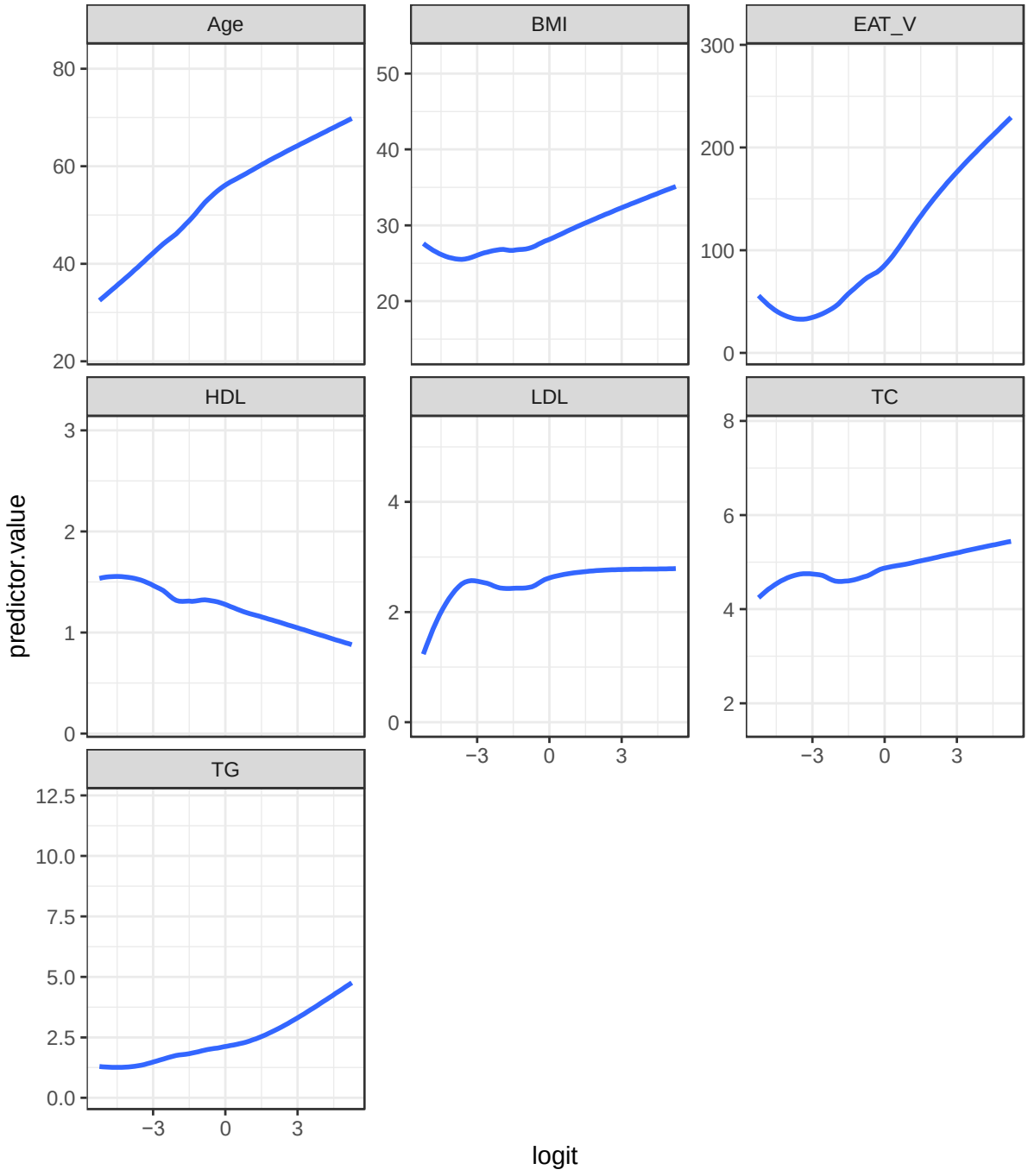


Table 3: Multiple linear regression for the association of clinical covariates and EAT volume in HIV-negative patients.

	Coefficient	Std Error	P value	Significance
Intercept	-5.61	1.36	<0.005	*
Age	0.11	0.01	<0.005	*
Male Sex	0.75	0.25	<0.005	*
Smoker	0.79	0.31	0.011	*
Ex Smoker	0.81	0.29	<0.005	*
Hypertension	-0.01	0.23	0.957	
DM	-0.05	0.34	0.898	
Dyslipidaemia	0.24	0.27	0.371	
Statin	0.39	0.28	0.160	
Hepatosteatosis	-0.31	0.30	0.289	
TC	-0.61	0.28	0.030	*
TG	0.18	0.20	0.374	
LDL	0.36	0.41	0.317	
HDL	0.02	0.03	0.349	
BMI	0.03	0.03	0.349	

Table 3: Multiple linear regression for the association of clinical covariates and EAT volume in HIV-positive patients.

	Coefficient	Std Error	P value	Significance
Intercept	-8.20	2.05	<0.005	*
Age	0.09	0.02	<0.005	*
Male Sex	0.71	0.62	0.249	
Smoker	0.80	0.46	0.085	
Ex Smoker	0.01	1.01	0.993	
Hypertension	-0.73	0.67	0.278	
DM	-0.47	1.11	0.669	
Dyslipidaemia	1.06	0.75	0.158	
Statin	0.10	0.64	0.882	
Hepatosteatosis	0.88	0.43	0.040	*
TC	-1.07	1.00	0.281	
TG	0.75	0.53	0.153	
LDL	1.10	0.97	0.256	
HDL	0.67	1.16	0.564	
BMI	0.02	0.04	0.593	

Table 4: Multiple linear regression for the association of clinical covariates and EAT volume in the whole cohort.

	Coefficient	Std Error	P value	Significance
Intercept	-6.43	1.08	<0.005	*
Age	0.11	0.01	<0.005	*
Male Sex	0.74	0.22	<0.005	*
Smoker	0.75	0.25	<0.005	*
Ex Smoker	0.70	0.27	0.010	*
Hypertension	-0.09	0.22	0.663	
DM	-0.11	0.32	0.728	
Dyslipidaemia	0.29	0.25	0.233	
Statin	0.34	0.25	0.176	
Hepatosteatosis	0.09	0.24	0.712	
TC	-0.60	0.27	0.026	*
TG	0.29	0.16	0.071	
LDL	0.45	0.27	0.096	
HDL	-0.28	0.36	0.444	
BMI	0.02	0.02	0.225	
HIV	-0.57	0.27	0.035	*