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The impact of age on associations between HIV-disease markers (immunological and virological) and systemic markers of metabolic function in therapy naïve HIV-infected subjects in the UK Collaborative HIV Cohort (CHIC)

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BACKGROUND

- It has been suggested that age modifies the impact of HIV on immunological function, with older people experiencing a more rapid decline in CD4 cell count (CD4) following infection with HIV [1,2]
- Whilst an association has been documented between untreated HIV and markers of metabolic function [3], it is unclear whether age modifies this association
- Surrogate markers, such as CD4 cell count and HIV viral load (HIV-VL), are used to guide the management of people living with HIV. However the metabolic impact of HIV may vary at a given CD4 count amongst people of different age groups.

AIMS

- To investigate associations between HIV-VL, CD4 cell count and markers of metabolic function in antiretroviral (ART)-naïve subjects
- To assess whether associations between HIV-disease markers and systemic markers of metabolic function are modified by age.

METHODS

- All ART-naïve subjects from the UK CHIC Study with at least one visit between 1996 and 2011 were included.
- Data were analysed in STATA v 12. Multilevel linear regression models were used to assess the associations between markers of HIV progression (CD4/VL) and the following outcomes: haemoglobin (Hb), albumin (Alb) low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), total cholesterol (TC), triglycerides (TG).
- For each outcome measure, if a measure of the exposure of interest (CD4/ HIV-VL) was measured within 90 days, the exposure/outcome 'pair' was included in the analysis. If a single exposure measure (CD4 or VL) was paired to multiple measures of outcome, all pairs were included.
- Multilevel models used different levels to account for having multiple observations per individual and multiple outcome measures paired with a single exposure measure.
- Co-variates which could confound the associations between the main exposures and outcomes were identified a priori. Each possible confounder was then introduced into the model; those which caused a >10% change in the effect estimate of either of the main exposures with any of the outcomes were included in the adjusted model for all the outcomes, unless we observed colinearity. The final models were therefore adjusted for: CD4, HIV-VL, age, sex and ethnicity
- The strength of evidence of associations between markers of HIV progression and metabolic outcomes were assessed using Likelihood Ratio Tests.
- Age was categorised into the following groups: under 30 years old, 30-50 years old, over 50 years old.
- Age strata specific estimates were calculated for the association between each of the outcomes and CD4 and VL respectively
- The possibility that the associations between markers of HIV progression and metabolic outcomes differed by age strata was assessed through tests of statistical interaction.

RESULTS

Cohort Characteristics

- Data were collected on 15088 subjects. The characteristics of study subjects are shown in Table 1

Table 1: Baseline characteristics of study subjects

Characteristic		n (%) *Observations*		n (%) *Subjects*		
Total number of subjects/observations		27 775	(100)	15088	(100)	
Gender	Male	21 942	(78.9)	11467	(76.0)	
	Female	5833	(21.1)	3621	(24.0)	
Ethnic group	White	15 853	(57.1)	8956	(59.4)	
	Black African	6720	(24.2)	3189	(21.1)	
	Black Other	1581	(5.7)	810	(5.4)	
	South Asian	183	(0.7)	113	(0.8)	
	Other	3438	(12.4)	2020	(13.4)	
Age (years)	<30	5769	(20.8)	3366	(23.1)	
	30-50	19 261	(69.4)	9982	(68.5)	
	>50	2726	(9.8)	1230	(8.4)	
CD4 (cells/µl)	Median (IQR)	27 742		15 071		257 (96-426)
HIV-VL (copies/ml)	Median (IQR)	14 822		8119		4.86 (4.25-5.38)
Haemoglobin (g/dL)	Median (IQR)	27 770		14 579		12.7 (10.6– 14.2)
Albumin (g/L)	Median (IQR)	26 115		13 293		39.0 (33.0 -44.0)
LDL Cholesterol (mmol/L)	Median (IQR)	4896		3937		2.07 (2.00– 3.00)
HDL Cholesterol (mmol/L)	Median (IQR)	6467		4923		1.0 (0.89-1.30)
Total Cholesterol (mmol/L)	Median (IQR)	10 265		7895		4.0 (3.5 – 4.9)
Triglyceride (mmol/L)	Median (IQR)	9616		7640		1.28 (1.00 – 2.00)

RESULTS (continued)

Is there an association between HIV progression and metabolic markers?

- After adjustment, there was persistent evidence that lower CD4 and higher HIV-VL were correlated with lower TC, LDL, Hb and Alb but higher TG levels (table 2).

Table 2. Associations between metabolic markers and markers of HIV disease progression (CD4 cell count and HIV-VL) adjusted for CD4, HIV-VL, age , gender and ethnicity.

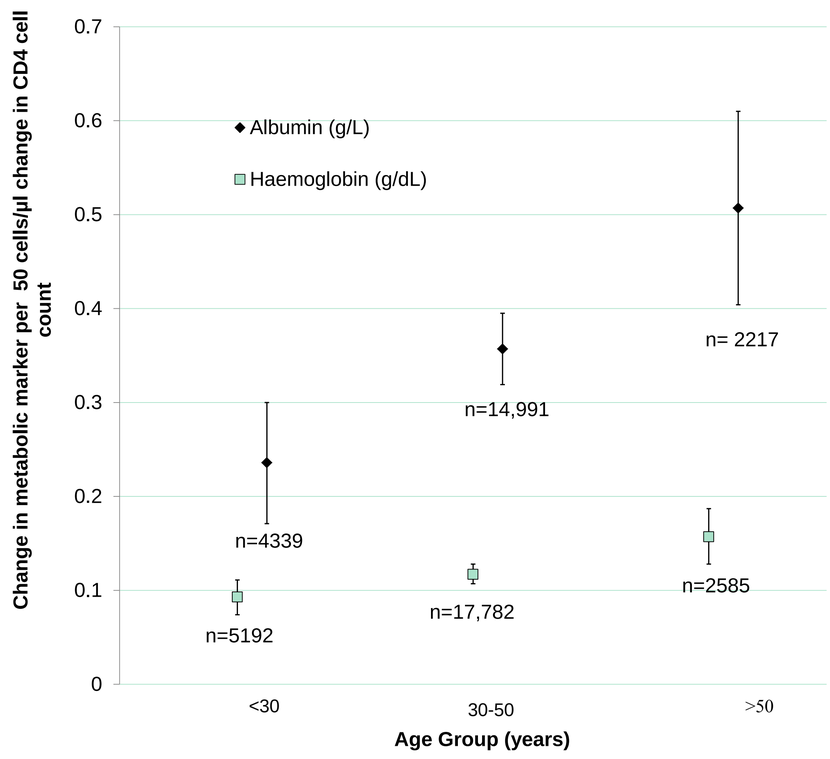
Exposure		Albumin (g/L) β (95% CI)	Haemoglobin (g/dL) β (95% CI)	Cholesterol (mmol/L) β (95% CI)	LDL Cholesterol (mmol/L) β (95% CI)	HDL Cholesterol (mmol/L) β (95% CI)	Triglyceride (mmol/L) β (95% CI)
CD4		**0.34** (0.31 0.38)	**0.12** (0.11 0.12)	**0.02** (0.02 0.03)	**0.02** (0.01 0.03)	**0.03** (0.02 0.05)	**-0.01** (-0.02 0.00)
HIV-VL		**-0.45** (-0.52 -0.37)	**-0.29** (-0.34 -0.24)	**-0.21** (-0.26 -0.17)	**-0.05** (-0.07 -0.03)	**0.04** (-0.02 0.10)	**0.06** (0.01 0.11)
Gender	Male	**1**	**1**	**1**	**1**	**1**	**1**
	female	**-2.11** (-2.51 -1.71)	**-1.86** (-1.96 -1.75)	**0.20** (0.11 0.30)	**0.05** (-0.06 0.16)	**0.01** (-0.12 0.15)	**-0.12** (-0.23 -0.02)
Age (years)	<30	**1**	**1**	**1**	**1**	**1**	**1**
	30-50	**-1.06** (-1.39 -0.74)	**-0.17** (-0.26 -0.08)	**0.32** (0.24 0.40)	**0.25** (0.15 0.34)	**-0.06** (-0.17 0.05)	**0.26** (0.17 0.35)
	>50	**-3.40** (-3.93 -2.88)	**-0.61** (-0.75 -0.46)	**0.41** (0.29 0.53)	**0.35** (0.20 0.49)	**-0.23** (-0.40 -0.06)	**0.27** (0.13 0.40)
Ethnic group	White	**1**	**1**	**1**	**1**	**1**	**1**
	Black (African)	**-1.53** (-2.13 -0.93)	**-0.68** (-0.85 -0.52)	**0.08** (-0.06 0.22)	**0.22** (0.05 0.40)	**-0.05** (-0.26 0.16)	**-0.20** (-0.36 -0.05)
	Black (Other)	**-1.43** (-1.84 -1.03)	**-0.93** (-1.04 -0.82)	**-0.03** (-0.13 0.06)	**0.01** (-0.10 0.12)	**-0.16** (-0.30 -0.02)	**-0.23** (-0.33 -0.12)
	South Asian	**-0.05** (-1.54 1.43)	**-0.33** (-0.77 0.11)	**0.40** (0.04 0.76)	**0.99** (0.48 1.50)	**0.92** (0.49 1.36)	**1.01** (0.59 1.42)
	Other	**-0.14** (-0.55 0.26)	**-0.21** (-0.33 -0.10)	**-0.08** (-0.17 0.02)	**-0.05** (-0.18 0.07)	**0.16** (0.03 0.30)	**-0.04** (-0.15 0.06)

β represents the impact of a 50 cells/µl increase in CD4 or 1 log increase in HIV-VL on the specified metabolic marker. The influence of other exposures is given in comparison to the baseline exposure status for that group. CI: Confidence Interval

Does age modify the effect of HIV progression on metabolic markers?

- In the adjusted analysis there was evidence that age modified the associations between: CD4 and Hb (interaction p=0.001); and CD4 and Alb (interaction p<0.001). The impact of CD4 on haemoglobin and albumin levels increased with older age (Figure 1).
- There was no evidence in the adjusted analysis that age modified the association between CD4 and either TC, LDL, HDL or TG; or the association between HIV-VL and any of the markers of metabolic function.

Figure 1. *Age-specific affect of CD4 count on albumin and haemoglobin after adjusting for HIV-VL, gender and ethnicity. 'n' = number of observations in each age strata.*



DISCUSSION AND FUTURE ANALYSES

- We present evidence that the associations between CD4 cell count, and both haemoglobin and albumin levels are modified by age. Older people experience a greater decline in haemoglobin and albumin levels for a given decrease in CD4 cell count compared to their younger counterparts.
- The lack of evidence that age modified the impact of HIV-VL on metabolic function may be explained by the theory that HIV-VL is a less accurate measure of HIV progression than CD4 cell count.
- Untreated HIV is associated with increased risk of cardiovascular disease; however data from our cohort suggest that HIV progression is associated with reduced total cholesterol and LDL cholesterol. Therefore these indicators of cardiovascular risk may be less accurate predictors amongst people living with HIV.
- As previously documented[3] markers of HIV progression were associated with inhibition of most anabolic function; however reduced CD4 and raised HIV-VL was associated with increased triglyceride levels suggesting the influence of HIV on triglyceride is mediated by a different pathway.

References:

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