Age-specific associations between HIV infection and carotid artery intima-media thickness in China: a cross-sectional evaluation of baseline data from the CHART cohort

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Summary

Background Inconclusive results have been reported in studies evaluating the association between HIV infection and subclinical atherosclerosis. Unsolved issues include whether the increased atherosclerosis burden observed in some studies is attributed to greater prevalence of traditional risk factors or HIV infection. Therefore, we evaluated the association of HIV infection with subclinical atherosclerosis as assessed by carotid artery intima-media thickness, while controlling for the effects of traditional risk factors as operationalised by the Framingham risk score (FRS).

Methods We did a cross-sectional evaluation of data derived from the baseline assessment of the Comparative HIV and Aging Research in Taizhou (CHART) cohort, an ongoing longitudinal study being done in Zhejiang province, China. HIV-positive and HIV-negative individuals aged 18 years and older were recruited between Feb 1, and Dec 10, 2017, and were frequency-matched for age and sex in a 1:2 ratio. Subclinical atherosclerosis was defined as carotid artery intima-media thickness of 780 μm or higher. Logistic regression was used to assess the associations of HIV-positive serostatus and FRS with subclinical atherosclerosis.

Findings 480 of 1425 (36·1%, 95% CI 33·6–38·6) HIV-positive and 784 of 2850 (27·5%, 95% CI 25·9–29·2) HIV-negative individuals had subclinical atherosclerosis (p<0·0001), and these patterns remained significant (adjusted odds ratio [adjOR] 1·72, 95% CI 1·47–2·01) in the adjusted model. After stratifying by age, higher prevalence of subclinical atherosclerosis was observed in HIV-positive than in HIV-negative individuals across the age groups 18–29 years (41 [16·0%] of 256 *vs* 13 [2·5%] of 512, p<0·0001), 30–44 years (128 [24·0%] of 533 *vs* 153 [14·4%] of 1066, p<0·0001), and 45–59 years (182 [46·6%] of 391 *vs* 294 [37·6%] of 782, p=0·0032), but not 60–75 years (163 [66·5%] of 245 *vs* 324 [66·1%] of 490, p=0·912). Significant negative interaction between HIV-positive serostatus and age on subclinical atherosclerosis was observed (p<0·0001). ORs adjusted for age, sex, and FRS were 8·84 (95% CI 4·50–17·34) for the age group 18–29 years, 2·09 (1·59–2·74) for 30–44 years, 1·54 (1·19–1·98) for 45–59 years, and 1·04 (0·75–1·44) for 60–75 years. Among HIV-positive individuals, none of the HIV-specific variables were significantly associated with carotid artery intima-media thickness estimates except for being antiretroviral therapy naive.

Interpretation HIV infection is associated with subclinical atherosclerosis, independent of classic risk factors. The association is stronger at younger ages, suggesting early onset of subclinical atherosclerosis among young adults. These findings highlight the need to modify HIV/AIDS treatment guidelines to incorporate cardiovascular evaluation in China.

Funding China National Science and Technology Major Projects on Infectious Diseases, National Natural Science Foundation of China, and Shanghai Municipal Health and Family Planning Commission.

Lancet HIV 2019

Published Online
October 18, 2019
https://doi.org/10.1016/S2352-3018(19)30263-2

See Online/Comment
https://doi.org/10.1016/S2352-3018(19)30329-7

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Introduction

The success of combination antiretroviral therapy (cART) has transformed HIV infection from a fatal to a chronic disease, with life expectancy among people with HIV approaching that of the general population. Consequently, cardiovascular disease (CVD), including acute myocardial infarction, peripheral arterial disease, and stroke that occur more frequently in the elderly population and often as a result of years of the atherosclerotic process, has emerged as a leading cause of morbidity and mortality in people with HIV.[1–3]

Atherosclerosis is an inflammatory disease in which the immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate lesions in the artery. Chronic inflammation has a central role in the pathogenesis of untreated HIV infection, and is not fully restored by cART. Despite viral suppression, people with HIV show evidence of chronic systematic inflammation.[4] Additionally, both HIV infection and antiretroviral drugs have adverse effects on the metabolic mechanisms that are known to contribute to atherosclerosis. Emerging evidence shows that metabolic comorbidities are

Research in context

Evidence before this study

We searched PubMed with any combination of the keywords "HIV" or "human immunodeficiency virus" and "carotid intima-media thickness", "cIMT", "atherosclerosis", "subclinical atherosclerosis", "coronary plaque", "subclinical carotid atherosclerosis", or "subclinical coronary disease" for all human studies with no language restrictions published before Dec 31, 2018. Conflicting results have been reported in epidemiological studies on the comparison of subclinical atherosclerosis prevalence and incidence between HIV-positive and HIV-negative individuals. Some studies reported higher subclinical atherosclerosis burden in HIV-positive individuals or only in some groups, whereas others found similar or lower burden of subclinical atherosclerosis in HIV-positive individuals. It remains equivocal whether increased atherosclerosis burden observed in some studies is accentuated by greater prevalence of traditional risk factors or accelerated by HIV itself. Few studies have compared subclinical atherosclerosis in a large sample-matched set of HIV-positive and HIV-negative individuals across a wide age range that included age-stratified analysis. In particular, to our knowledge, no large-scale studies have systematically reported the epidemiology of subclinical atherosclerosis burden in China, or even in Asia.

Added value of this study

Our findings provide robust evidence that HIV infection is associated with increased carotid artery thickening, independent of traditional cardiovascular disease (CVD) risk factors. Our data suggest that HIV-positive young adults are susceptible to increased risk of subclinical atherosclerosis even if they did not acquire HIV perinatally. Our study also shows that although no HIV-specific factors were significantly associated with cIMT except for being antiretroviral therapy naive, this does not necessarily imply that HIV infection does not have an effect on carotid intima-media thickness, highlighting the need for additional markers to link HIV infection with subclinical atherosclerosis.

Implications of all the available evidence

Further research is needed to identify additional modifiable factors such as inflammatory markers in evaluating CVD risk for HIV-positive people. Additionally, these results emphasise the need for careful follow-up of atherosclerosis progression among HIV-positive individuals, particularly young adults, and identification of modifiable determinants for prevention. A change in current HIV/AIDS treatment guidelines to incorporate routine cardiovascular evaluation into standard care is recommended for HIV-positive people even at young age.

over-represented in patients with HIV.[5] Exposure to both chronic inflammation and traditional CVD risk factors could accelerate the atherosclerotic process and increase the odds for developing CVD among people with HIV.

The relationship between HIV infection and measures of subclinical atherosclerosis (eg, carotid intima-media thickness [cIMT] and coronary artery calcium) has been widely assessed in cross-sectional and cohort studies mainly from the USA and Europe. Most studies have shown a higher subclinical atherosclerosis burden in people with HIV[6–8] or only in younger age groups.[6,9] However, a few studies found a lower burden of subclinical atherosclerosis in people with HIV,[10,11] including a large study done in Europe.[11] These discrepancies raise the issue whether increased atherosclerosis burden observed in some studies is accentuated by greater prevalence of traditional risk factors in people with HIV or accelerated by HIV itself. Nonetheless, either scenario is an impending health concern that needs to be addressed among people with HIV.[7,11,12] However, most of the previous studies were limited by insufficient sample size, no appropriate HIV-negative individuals for comparision,[8] narrow age range,[7] or no age-stratified analysis,[6] thus limiting the ability to fully evaluate the independent effect of HIV-positive serostatus on subclinical atherosclerosis. A large study[6] reported that higher cIMT values among HIV-positive versus HIV-negative individuals were observed only in people aged 16–29 years but not in older indaviduals,[6] but it was a pooled study in which the HIV-negative individuals were not matched to the cases.

Therefore, to better evaluate the association of HIV infection with subclinical atherosclerosis, we did a cross-sectional analysis of HIV-positive and HIV-negative individuals who participated in the baseline assessment of the Comparative HIV and Aging Research in Taizhou (CHART) cohort in China.[13]

Methods

Study design and participants

CHART is an ongoing prospective cohort study of HIV and age-related comorbidities among HIV-positive and HIV-negative adults being done in local centres for disease prevention and control in Taizhou prefecture, Zhejiang province, China. The reported number of people living with HIV in Taizhou was 2623 at the end of 2017 (appendix p 1). We aimed to enrol 1800–2000 HIV-positive individuals and 3600–4000 HIV-negative individuals (a 1:2 ratio considering the lower incidence of comorbidities in HIV-negative individuals[5,14]). This sample size should provide sufficient power to assess the associations of HIV and other risk factors with age-related comorbidities. The overarching goal is to do standardised screening for age-related comorbidities at baseline and after 3 years, and depending on resources, every 3 years thereafter.

We recruited and enrolled HIV-positive adults aged 18 years or older who live in Taizhou prefecture, when they went to local centres for disease prevention and

See Online for appendix

control for regular follow-up visits for routine care (appendix p 1).[15] Patients unable to participate in the study procedures for any reason (eg, refused to participate or could not read and write to provide consent) were excluded. During the same period, HIV-negative individuals were recruited from six local communities (Yuhuan, Luqiao, Tiantai, Huangyan, Linhai, and Sanmen), which were randomly selected using random sampling within each county or district in Taizhou prefecture (appendix p 1), and were tested if they were HIV seronegative. Enrolment of under-represented age and sex categories among HIV-negative individuals was adjusted to achieve age and sex comparable groups.

We recruited 1770 HIV-positive and 3350 HIV-negative individuals. For the current analysis, using Proc SurveySelect in SAS software (version 9.4; appendix p 2), HIV-positive and HIV-negative individuals were randomly selected from the whole sample (appendix p 2) with available cIMT measurements (1638 HIV positive and 3350 HIV negative) and frequency-matched in a 1:2 ratio according to sex and 5-year age categories.

Written informed consent was obtained from all study participants. The study was approved by the Institutional Review Board of Fudan University School of Public Health, Shanghai, China.

Data collection and measurements

All study participants completed a standardised questionnaire to evaluate demographics, smoking history, and medical history of CVD. Participants had their anthropomorphic measurements (height, weight, waist, and hip circumferences), blood pressure measurement, fasting blood collection for lipid profile, and glycated haemoglobin (HbA_{1c}) testing done. Serum biochemical tests were done with an automated analyser (ADVIA 2400, Siemens Healthcare Diagnostics, Tarrytown, NJ, USA). HbA_{1c} concentrations were measured with an automated glycohaemoglobin analyser (TOSOH G8, Yokkaichi, Mie Prefecture, Japan). HIV-related variables were extracted from the HIV/AIDS Comprehensive Response Information Management System.[16] Nadir CD4 cell count was defined as the lowest CD4 count as recorded.

Body-mass index (BMI) was calculated. The cutoff waist-to-hip ratio for abdominal obesity was 0·90 for men and 0·85 for women. Current smoking was defined as having smoked one or more cigarettes in the last 30 days. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, or diastolic blood pressure of 90 mm Hg or higher, or previous clinical diagnosis of hypertension. Dyslipidaemia was defined as total cholesterol 5·2 mmol/L or higher, LDL cholesterol 3·4 mmol/L or higher, or triglycerides 1·7 mmol/L or higher. Diabetes was defined as HbA_{1c} 6·5% or higher or previous clinical diagnosis. Aggregate CVD risk was evaluated by the 10-year risk of CVD from the Framingham Heart Study.[17] The Framingham risk score (FRS) is based on an algorithm derived from a 10-year predicted risk of CVD estimate comprised of age, sex, total cholesterol, HDL cholesterol, smoking history, blood pressure, and diabetes.[18] 10-year CVD FRS was classified as low (<10%), intermediate (10–20%), or high risk (>20%).

	HIV-positive (n=1425)	HIV-negative (n=2850)	p value
Age (years)	44·3 (14·1)	44·4 (14·0)	0·8590
Sex			
Female	341 (23·9%)	682 (23·9%)	..
Male	1084 (76·1%)	2168 (76·1%)	1·0000
Smoking	..	..	<0·0001
Never	868 (60·9%)	1534 (53·8%)	..
Past	171 (12·0%)	283 (9·9%)	..
Current	386 (27·1%)	1033 (36·3%)	..
BMI (kg/m^2)	22·0 (3·0)	24·0 (3·7)	<0·0001
<18·5	152 (10·7%)	150 (5·3%)	..
18·5–23·9	939 (65·8%)	1334 (46·8%)	..
≥24	334 (23·4%)	1366 (47·9%)	..
WHR above the cutoff	697 (48·9%)	1361 (47·8%)	0·4750
Dyslipidaemia	863 (60·6%)	2006 (70·4%)	<0·0001
Total cholesterol (mmol/L)	4·7 (4·2–5·4)	5·1 (4·5–5·8)	<0·0001
LDL cholesterol (mmol/L)	2·4 (1·9–2·9)	2·8 (2·3–3·4)	<0·0001
Triglycerides (mmol/L)	1·7 (1·2–2·7)	1·9 (1·2–2·8)	<0·0001
HDL cholesterol (mmol/L)	1·1 (0·9–1·3)	1·1 (1·0–1·4)	<0·0001
Diabetes	84 (5·9%)	302 (10·6%)	<0·0001
HbA_{1c} (% of total Hb)	5·1% (4·8–5·5)	5·5% (5·3–5·8)	<0·0001
Previous clinical diagnosis	51 (3·6%)	210 (7·4%)	<0·0001
Hypertension	289 (20·3%)	845 (29·7%)	<0·0001
SBP (mm Hg)	124 (115–132)	123 (113–134)	0·8489
DBP (mm Hg)	76 (70–82)	76 (69–83)	0·5291
Previous clinical diagnosis	116 (8·1%)	529 (18·6%)	<0·0001
FRS (10-year CVD risk)	5·8 (2·3–14·0)	6·9 (2·4–16·5)	0·0012
<10%	945 (66·3%)	1749 (61·4%)	..
10–20%	264 (18·5%)	512 (18·0%)	..
>20%	216 (15·2%)	589 (20·6%)	..
HIV transmission mode*			
Sexual	1403 (98·5%)	..	..
IDU or others	22 (1·5%)	..	..
Years since HIV diagnosis	2·8 (0·8–5·5)	..	..
Years on cART			
ART naive	105 (7·4%)	..	..
<3 years	784 (55·0%)	..	..
≥3 years	536 (37·6%)	..	..
Nadir CD4 count <200 cells per μL	635 (44·6%)	..	..
Current CD4 count (cells per μL)	434 (300–602)	..	..
HIV RNA <200 copies per mL†	993 (89·5%)	..	..
Past or current ritonavir-boosted lopinavir use	76 (5·3%)	..	..

Data are n (%), mean (SD), or median (IQR). BMI=body-mass index. cART=combination antiretroviral therapy. CVD=cardiovascular diseases. DBP=diastolic blood pressure. FRS=Framingham risk score. HbA_{1c}=glycated haemoglobin. IDU=injection drug use. SBP=systolic blood pressure. WHR=waist-to-hip ratio. ART=antiretroviral therapy *None were infected through mother-to-child transmission. †Only 1109 patients had available data for HIV RNA because RNA is assayed every 1 year in HIV-positive patients on antiretroviral therapy but not assessed at baseline according to China ART guidelines. Therefore, there are missing values for some patients who were on treatment for less than a year.

Table: **Baseline characteristics**

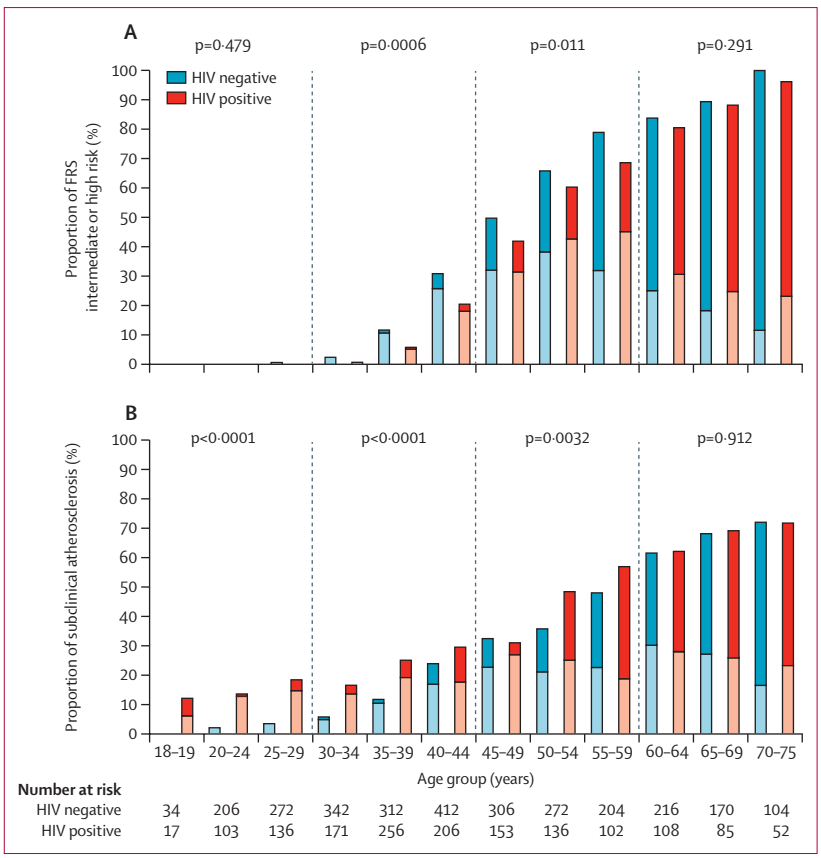


Figure 1: **Prevalence of Framingham intermediate and high-risk categories (A) and subclinical atherosclerosis (B) across age groups in HIV-positive and HIV-negative participants**
(A) Filled bars show participants with high CVD risk, lighter lined bars show participants with intermediate CVD risk. (B) Filled bars show participants with cIMT more than 1000 μm, lighter lined bars show participants with cIMT of 780–1000 μm. p values compare the combined proportions of Framingham intermediate and high-risk categories and cIMT of 780–1000 and >1000 μm) between HIV-positive and HIV-negative participants within four age groups (18–29 years, 30–44 years, 45–59 years, and 60–75 years) using χ^2 test, or Fisher's exact test when appropriate. cIMT=carotid intima-media thickness. CVD=cardiovascular disease risk. FRS=Framingham risk score.

cIMT was imaged using a high-resolution B-mode ultrasound machine with 10 MHz multi-frequency linear transducer (LOGIQ P5 pro, General Electric Medical Company, USA). A standardised protocol was used for image and procedures. Specifically, the carotid arteries on the left side of the neck were examined while patients laid supine with their head slightly tilted to the contralateral of the examined side to enhance adequate visualisation of the vessels. Following the Mannheim criteria,[19] cIMT measurements were done during evaluation on the far wall of the distal common carotid artery within 1 cm from the bifurcation over a segment of carotid of about 1 cm and free of plaque with a clearly identified double-line pattern. The sound waves were beamed perpendicularly to the arteries to show the two parallel echogenic lines, which corresponds to the lumen-intima and media-adventitia. The IMT is the distance between the leading edge of the first bright line on the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface). Mean IMT values were recorded. For quality control, all measurements were done by one trained and certified sonographer who had a cardiac sonographer certificate and at least 5 years' experience, and simultaneously reviewed by the other senior certified sonographer who had at least 10 years' experience at all sites.

Subclinical carotid atherosclerosis was defined as a cIMT of 780 μm or more, according to a previous observation that showed a healthy adult reaches a cIMT of 780 μm on average at the age of 76 years.[20] A higher cutoff value of cIMT of more than 1000 μm was also used; both values have been associated with increased CVD risk in the general population.[21]

Statistical analysis

Group comparisons were assessed using χ^2 test, Fisher's exact test, Student's *t* test, or Wilcoxon rank-sum test when appropriate. Logistic regression was done to analyse the association of HIV-positive serostatus and FRS with subclinical atherosclerosis (cIMT ≥780 μm). We examined effect modification by age of the association between HIV-positive serostatus and cIMT by including the interaction term in the model. Subsequently, models were adjusted for age, sex, and FRS (or HIV serostatus) depending on which association was examined. In addition to aggregate analysis, we did stratified analyses by HIV serostatus and age groups as appropriate. Furthermore, analysis on HIV-specific and ART-specific factors for subclinical atherosclerosis in the stratum of HIV-positive participants were done. Sensitivity analysis was done to assess the robustness of the results by raising the cIMT cutoff point to more than 1000 μm and treating cIMT as a continuous variable, respectively. A p value of less than 0·05 was used to define statistical significance. Analysis was done with SAS software (version 9.11).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In the final analysis we included 1425 HIV-positive individuals (1084 [76·1%] men) and 2850 HIV-negative individuals (2168 [76·1%] men) who were recruited between Feb 1, and Dec 10, 2017. The mean age was 44·3 years (SD 14·0). Among HIV-positive individuals, the median duration of known HIV infection was 2·8 years (IQR 0·8–5·5), and 1220 (92·6%) were receiving cART. HIV-positive individuals had fewer major CVD risk factors such as current smoking, hypertension, diabetes, and dyslipidaemia, than HIV-negative individuals (all p<0·05; table). These resulted in overall lower median FRS values (p=0·001) and a lower number of patients with intermediate and high CVD risk (p=0·002) among HIV-positive versus HIV-negative individuals (table).

480 (36·1%, 95% CI 33·6–38·6) of 1425 HIV-positive and 784 (27·5%, 25·9–29·2) of 2850 HIV-negative individuals had subclinical atherosclerosis (p<0·0001), and these patterns remained significant after adjusting for age, sex, and FRS (adjusted odds ratio [aOR] 1·72, 95% CI 1·47–2·01). Similarly, HIV-positive individuals had higher mean cIMT values than did HIV-negative individuals (715 µm *vs* 667 µm; p<0·0001), and mean cIMT values remained significant higher after adjusting for age, sex, and FRS, with an adjusted difference of 54·4 µm (95% CI 40·2–68·5).

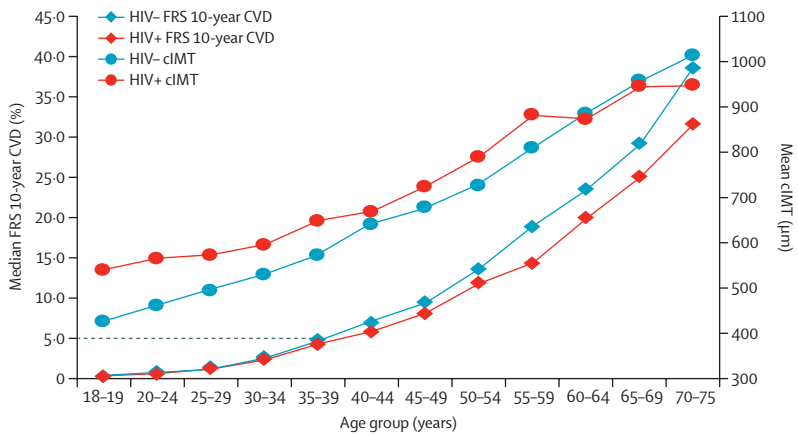
Compared with HIV-negative individuals, HIV-positive individuals had similar prevalence of being in combined intermediate and high FRS categories in the 18–29 year age group, but lower prevalence of being in intermediate and particularly high-risk categories of FRS in the 30–44 year, 45–59 year, and 60–75 year age groups, showing larger differences at older ages (figure 1). Similar trends were observed for major CVD risk factors by HIV serostatus across age groups (appendix pp 3, 4). By contrast, significantly higher proportions of subclinical atherosclerosis were observed in HIV-positive than in HIV-negative participants in age groups 18–29 years (16·0% [41 of 256], 95% CI 11·5–20·5 *vs* 2·5% [13 of 512], 95% CI 1·2–3·9; p<0·0001), 30–44 years (24·0% [128 of 533], 20·4–27·9 *vs* 14·4% [153 of 1066], 12·2–16·5; p<0·0001) and 45–59 years (46·6% [182 of 391], 41·6–51·5 *vs* 37·6% [294 of 782], 34·2–40·1; p=0·0032), but not at 60–75 years (66·5% [163 of 245], 60·6–72·4 *vs* 66·1% [324 of 490], 61·9–70·3; p=0·912), highlighting larger differences at younger ages (figure 1). Further comparison of average cIMT and FRS values across age groups in HIV-positive and HIV-negative individuals showed similar patterns (figure 2).

A negative interaction of HIV-positive serostatus and age on subclinical atherosclerosis was observed in the multivariable model adjusting for age, sex, and FRS ($p_{interaction}$<0·0001), showing an attenuated effect of HIV-positive serostatus on subclinical atherosclerosis as age of individual increased. Specifically, HIV infection was associated with subclinical atherosclerosis, independent of sex and FRS, in age groups 18–29 years (aOR 8·84, 95% CI 4·50–17·34), 30–44 years (aOR 2·09, 1·59–2·74), and 45–59 years (aOR 1·54, 1·19–1·98), but not in 60–75 years (aOR 1·04, 0·75–1·44; figure 3A). In sensitivity analysis using a higher cIMT cutoff point of 1000 µm for subclinical atherosclerosis or treating cIMT as a continuous variable, similar findings were observed (figure 3B).

We assessed the associations of FRS with various cIMT estimates across age groups in HIV-positive and HIV-negative individuals. FRS was less likely to be significantly associated with various cIMT estimates among HIV-positive than among HIV-negative individuals (figure 4). Specifically, the unadjusted associations between FRS and subclinical atherosclerosis were significant among HIV-negative individuals overall and in all age groups but only significant among the HIV-positive individuals overall and age groups 30–44 years and 45–59 years but not in age groups 18–29 years and 60–75 years. In age-adjusted and sex-adjusted analysis these associations were significant only among HIV-negative individuals in age groups 18–29 years and 30–44 years and HIV-positive individuals in the 45–59 year age group (figure 4A). Considering that prevalence of cIMT higher than 1000 µm increases rapidly in people older than 45 years, in the sensitivity analysis using cIMT higher than 1000 µm as the outcome, the associations with FRS among HIV-negative individuals were significant overall and across all age groups in both univariable and multivariable models, but were significant only among HIV-positive individuals in age groups 30–44 years and 45–59 years (figure 4B). In the second sensitivity analysis treating cIMT as a continuous variable, similar results were observed (figure 4C).

Similarly, only age, sex, and hypertension were significantly associated with any cIMT estimate in age-adjusted and sex-adjusted models, whereas a number of factors (ie, age, sex, smoking, BMI, hypertension, dyslipidaemia, and diabetes) were significantly associated with cIMT estimates (appendix p 5).

Among HIV-positive individuals only, no significant associations of transmission route, years since HIV diagnosis, nadir CD4 cell count, current CD4 cell count, ART status, past or current lopinavir or ritonavir use, and



Age group (years)	18–29	30–44	45–59	60–75
HIV+ *vs* HIV–: n	256 *vs* 512	533 *vs* 1066	391 *vs* 782	245 *vs* 490
◆ FRS, p value	0·006	0·005	0·0004	0·002
FRS HIV+ (median, IQR)	1·0 (0·6–1·4)	4·2 (2·4–6·4)	1·1 (6·6–17·0)	13·3 (7·4–22·0)
FRS HIV– (median, IQR)	1·1 (0·6–1·9)	4·6 (2·4–8·2)	13·3 (7·4–22·0)	28·7 (16·4–47·8)
● cIMT, p value	<0·0001	<0·0001	0·0002	0·321
cIMT HIV+ (mean, SD)	568 (167)	640 (207)	789 (267)	915 (287)
cIMT HIV– (mean, SD)	477 (130)	586 (183)	730 (253)	938 (309)

Figure 2: **Mean cIMT estimates (SD) and median FRS (IQR) across age groups in HIV-positive and HIV-negative participants**
p values compare the FRS and cIMT values between HIV-positive and HIV-negative participants across four age groups (18–29 years, 30–44 years, 45–59 years, and 60–75 years) using *t* test and Wilcoxon rank-sum test when appropriate. FRS=Framingham risk score. cIMT=carotid intima-media thickness. HIV+=HIV positive. HIV–=HIV negative. CVD= cardiovascular disease.

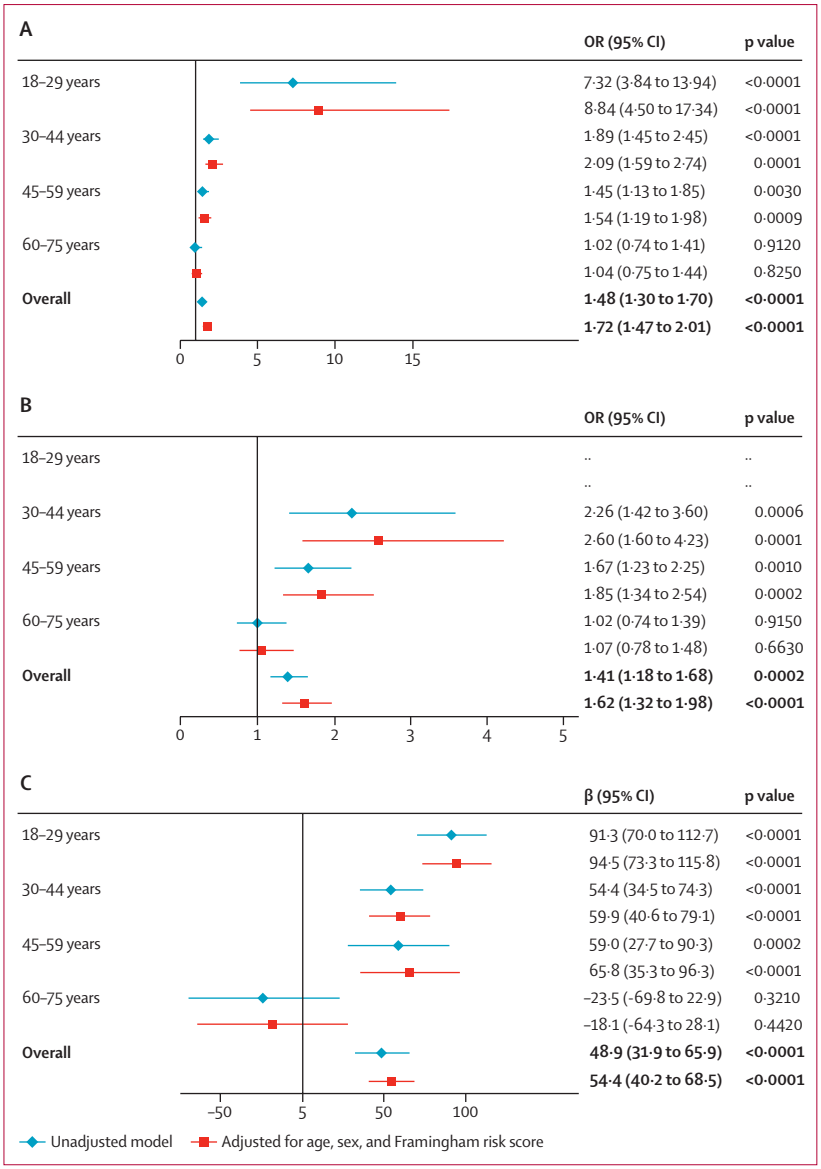


Figure 3: **Regression models examining the associations of HIV infection with various cIMT estimates overall and across age groups**

(A) Subclinical atherosclerosis (cIMT ≥780 μm). (B) cIMT more than 1000 μm. (C) cIMT as a continuous variable. cIMT=carotid intima-media thickness. OR=odds ratio.

HIV RNA less than 200 copies per mL with various cIMT estimates were observed; however, in an age-adjusted, sex-adjusted, and FRS-adjusted model treating cIMT as a continuous variable, being ART naive was significantly associated with cIMT (appendix p 6). Of note, in the analysis using cIMT higher than 1000 μm as the outcome, years since HIV diagnosis was positively associated with subclinical atherosclerosis (appendix p 6).

Discussion

In our matched cross-sectional study, prevalence of subclinical atherosclerosis was significantly higher among HIV-positive individuals than among matched HIV-negative individuals, independent of traditional CVD risk factors. Furthermore, we identified a negative interaction between HIV-positive serostatus, age, and subclinical atherosclerosis. Specifically, the associations are stronger at younger ages than at older ages possibly because of lower traditional CVD risk grouped by FRS. However, none of the HIV-specific variables are significantly associated with cIMT estimates except for being ART naive. To our knowledge, this is the largest study comparing subclinical atherosclerosis measured as cIMT between HIV-positive and HIV-negative individuals in Asia.

Our finding that HIV infection is independently associated with subclinical atherosclerosis is consistent with previous studies linking HIV infection with subclinical atherosclerosis and CVD events.[6–8,14] However, other studies have not found an association.[10,11] Our results are robust because the association of HIV infection with subclinical atherosclerosis is more evident at younger ages, possibly because the low prevalence of traditional risk factors among young adults renders the effect of HIV infection on subclinical atherosclerosis more obvious. Similarly, the weaker or even disappeared associations in older age groups could be because the effect of HIV infection on subclinical atherosclerosis might be overshadowed by the very high prevalence of traditional risk factors and thereby their larger effects on atherosclerosis. Our results might further explain the discrepancy across previous studies showing that significant associations are generally observed in studies in which HIV-positive individuals have either more or similar traditional risk factors[6–8] or in young age groups.[6]

A notable finding is that 16% of HIV-positive individuals aged between 18 and 29 years had subclinical atherosclerosis. This finding is seldom observed among the HIV-negative individuals from the same age group. Although early onset of subclinical atherosclerosis has been previously observed in young adults with perinatally or early acquired HIV,[22–24] it is of note that none of our HIV-positive young adults were infected through the mother-to-child route, and few were at intermediate and high risk for CVD as evaluated by FRS. The reasons remain to be investigated. However, these findings suggest the possibility that HIV-positive young adults are at risk of early onset of subclinical atherosclerosis even though they do not acquire HIV perinatally. Because there is insufficient literature examining the progression of subclinical atherosclerosis among HIV-positive young adults using a longitudinal design, it remains unclear whether they are subsequently at risk of accelerated progression to CVD events and what factors can affect the progression.

Furthermore, because our data show that traditional CVD risk factors such as FRS are significantly associated with cIMT estimates among HIV-negative individuals, research on CVD risk equations developed for use in the general population are likely to underestimate CVD risk

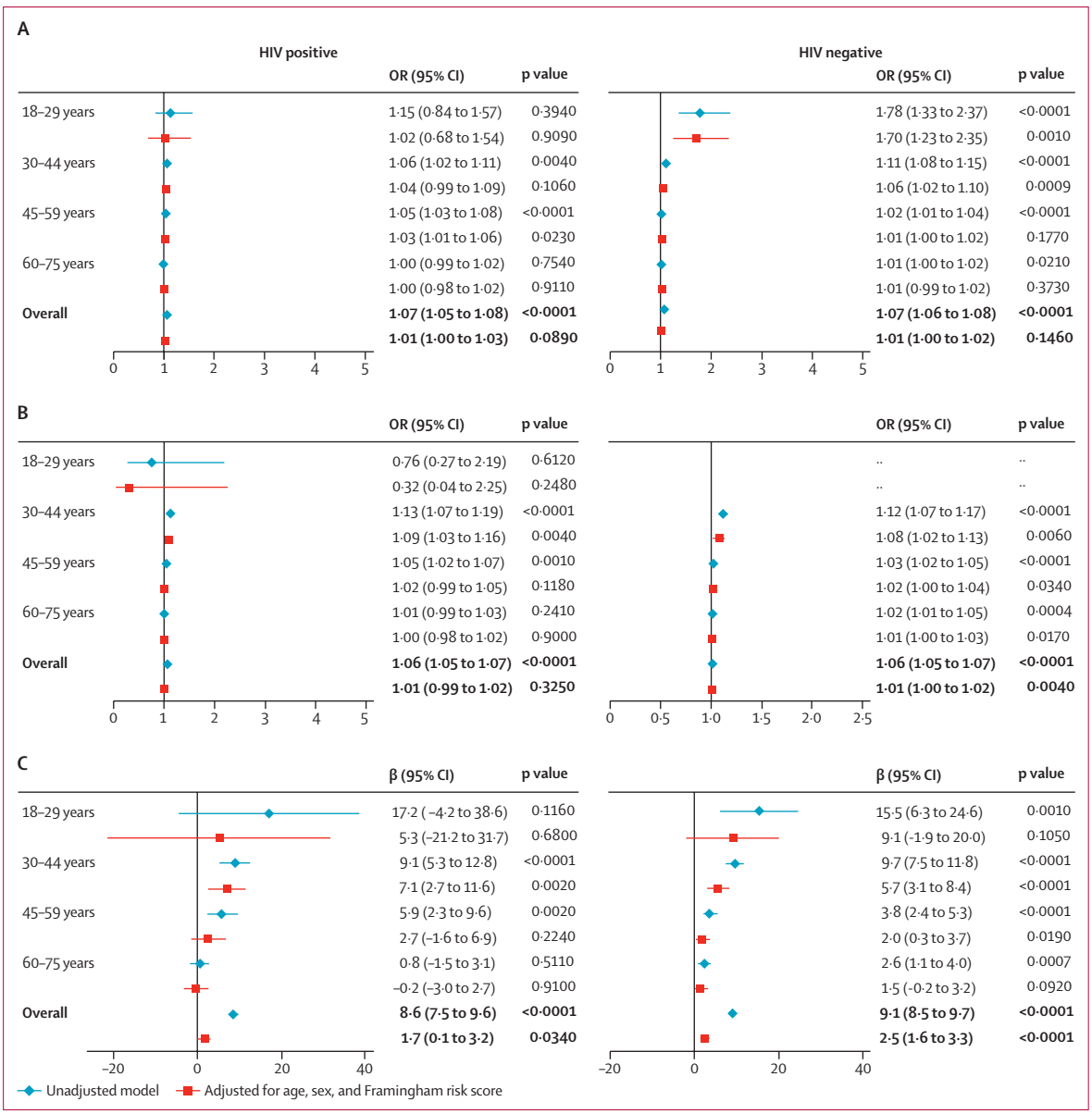


Figure 4: **Regression models examining the associations of Framingham risk score with various cIMT estimates overall and across age groups**
(A) Subclinical atherosclerosis (cIMT ≥780 μm). (B) cIMT more than 1000 μm. (C) cIMT as a continuous variable. cIMT=carotid intima-media thickness. OR=odds ratio.

in the HIV-positive individuals.[25] The D:A:D group have developed the CVD risk equation on the basis of covariates derived from a large cohort study of HIV-positive patients, including exposure to HIV medications and traditional risk factors.[26] However, a recent cohort study evaluated the performance of four commonly used algorithms (eg, FRS, DAD, SCORE-NL, and PCE) among HIV-positive individuals, concluding that all CVD risk prediction algorithms did reasonably well; however, in patients with a low predicted CVD risk clinicians should be aware of the risk being somewhat underestimated.[27] Additional risk markers might need to be identified in developing CVD risk equations for HIV-positive individuals. Emerging evidence suggests that chronic inflammation might have a vital role in the pathogenesis of atherosclerosis in the context of treated HIV infection;[28] therefore, evaluation of inflammatory markers and their inclusion in CVD risk equations could provide a better identification of patients at risk of CVD. This will be the focus of our next research on the CHART cohort.

Although we observe that HIV infection is independently associated with increased subclinical atherosclerosis, in terms of HIV-specific factors, only known duration of HIV infection and not using cART are associated with higher cIMT values. This reinforces the role of HIV infection per se and not ART in the pathogenesis of

subclinical atherosclerosis.[28] Although suppressive cART does not eliminate chronic inflammation caused by HIV infection, it reduces the inflammation and then has a protective effect on atherosclerosis. Reduced progression of cIMT has been also reported in treated HIV infection with viral load suppression.[29] We did not observe an association between nadir CD4 cell count and subclinical atherosclerosis, partly because most of our participants initiated ART shortly after their diagnosis of HIV infection. In another study of mainly HIV-positive women, cIMT was associated with cardiovascular but not ++HIV-related factors.[8] These findings suggest that beyond general HIV-specific and ART-specific factors (eg, CD4 counts and treatment duration), inflammatory or other factors could be important in the link between HIV infection and subclinical atherosclerosis, and for predicting the risk of CVD.

By contrast, a study in Malawi reported higher prevalence of obesity, hypertension, dyslipidaemia, and diabetes among HIV-positive people than among HIV-negative people.[5] The authors found that both groups had similar traditional CVD risk, as well as FRS, at young ages but HIV-negative individuals had a significantly lower risk at older ages. The possible reasons could include poor economic status, high burden of psychological stress, relatively short duration of ART, and their dietary habits. Our study is similar to a large-scale cross-sectional study in Europe showing that HIV-positive and HIV-negative participants have similar FRS.[11]

The strengths of our study include it being a large-scale study of subclinical atherosclerosis among HIV-positive and HIV-negative individuals in Asia, its matched design and age-stratified analysis, and that it allows the evaluation of the independent effect of HIV infection on subclinical atherosclerosis. Nevertheless, our study had several limitations. First, the cross-sectional design does not allow us to examine the effect of HIV infection on progression of subclinical atherosclerosis. Second, HIV-positive individuals who are irregularly retained in care and are less adherent to ART are less likely to be enrolled and they might have increased burden of subclinical atherosclerosis because of lower adherence. Third, only left cIMT was evaluated, which tends to be slightly higher than right cIMT. Nonetheless, one study[30] reports no significant difference between left and right IMT measurements for both the manual and automated measurements and suggests that the measurement of IMT on one side only is enough. Therefore, our observed association should not be severely affected. Additionally, although cIMT as a reliable prognostic marker of clinical CVD outcomes has been well established in the general population, it remains to be investigated in HIV-positive individuals.

In conclusion, our findings provide evidence that HIV infection is associated with increased carotid artery thickening, independent of traditional risk factors. Such association is stronger at younger ages, which suggests a risk of early onset of subclinical atherosclerosis among HIV-positive young adults. Further research is needed to identify modifiable determinants for prevention and additional markers for CVD prediction among HIV-positive individuals. Our findings are important for HIV care in China, where cardiovascular screening and prevention are not part of routine HIV care. A change in HIV/AIDS treatment guidelines to incorporate routine cardiovascular evaluation into standard care is recommended for HIV-positive individuals even at a young age.

Contributors

YD and NH proposed and developed the research question, designed the statistical analyses, and wrote the first draft of the report. HL, YD, and NH designed and monitored the study. HL, CN, XQ, Xiaochen C, Xiaoxiao C, WS, and XL contributed to data collection. YH provided expert knowledge. All authors have seen and contributed to the final version of the report.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was supported by the China National Science and Technology Major Projects on Infectious Diseases (grant 2018ZX10721102-004), the National Natural Science Foundation of China (grant 81872671, 81803291), and partially supported by Shanghai Municipal Health and Family Planning Commission (grant GWTD2015S05, 15GWZK0101). We acknowledge Frank Y Wong from Florida State University, Tallahassee, FL, USA, and Vincent C Marconi from Emory University, Atlanta, GA, USA, for critical comments and editorial assistance.

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