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Frailty and subclinical coronary atherosclerosis: The Multicenter AIDS Cohort Study (MACS)

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ABSTRACT

Background and aims: Frailty and cardiovascular disease share many risk factors. We evaluated whether frailty is independently associated with subclinical coronary atherosclerosis and whether any relationships differ by HIV-serostatus.

Methods: We studied 976 [62% HIV-infected] male participants of the Multicenter AIDS Cohort Study who underwent assessment of frailty and non-contrast cardiac CT scanning; of these, 747 men also underwent coronary CT angiography (CCTA). Frailty was defined as having ≥3 of 5 of the following: weakness, slowness, weight loss, exhaustion, and low physical activity. Coronary artery calcium (CAC) was assessed by non-contrast CT, and total plaque score (TPS), mixed plaque score (MPS), and non-calcified plaque score (NCPS) by CCTA. Multivariable-adjusted regression was used to assess the cross-sectional associations between frailty and subclinical coronary atherosclerosis.

Results: Mean (SD) age of participants was 54 (7) years; 31% were black. Frailty existed in 7.5% and 14.3% of HIV-uninfected and HIV-infected men, respectively. After adjustment for demographics, frailty was significantly associated with prevalence of any CAC (CAC>0), any plaque (TPS>0), and mixed plaque (MPS>0) in HIV-uninfected but not in HIV-infected men (p-interaction$_{HIV}$<0.05 for all). Among HIV-uninfected men, after adjustment for cardiovascular risk factors, frailty was significantly associated only with CAC>0 [Prevalence Ratio 1.27 (95%CI 1.02, 1.59)] and TPS>0 [1.19 (1.06, 1.35)]. No association was found for NCPS.

Conclusions: Frailty was independently associated with subclinical coronary atherosclerosis among HIV-uninfected men, but not among HIV-infected men. Further work is needed to ascertain mechanisms underlying these differences and whether interventions that improve frailty (i.e. strength training) can improve cardiovascular outcomes.

1. Introduction

There is a decline in functional status with aging, and for some older adults this can manifest as frailty. Frailty is a state of diminished physiological reserve, which limits adaptability to internal

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and external stressors and increases vulnerability to illness [1–3]. Frailty is typically defined based on the presence of at least three out of five characteristics: weakness, slowness, low physical activity, weight loss, and exhaustion [3,4]. The presence of frailty independently predicts falls, disability, hospitalizations, and all-cause mortality in geriatric patients and in patients infected with the human immunodeficiency virus (HIV) [1–7].

Frailty and cardiovascular disease (CVD) share common risk factors (i.e. increased age, insulin resistance, low-grade inflammation, etc.) but frailty, and even pre-frailty, have been shown to be independent risk factors for incident CVD and mortality [8–11]. In the Cardiovascular Health Study, frailty was associated with increased prevalence of clinical CVD, particularly heart failure, and subclinical CVD including carotid disease, peripheral artery disease, left ventricular hypertrophy, and major electrocardiogram abnormalities, but the association of frailty with prevalence of subclinical *coronary atherosclerosis* was not assessed in that study [12]. Little is known about the association between frailty and subclinical coronary atherosclerosis independent of traditional CVD risk factors. Frailty may be a marker of vascular aging, or may directly contribute to CVD risk through muscle atrophy and increased inflammation [13].

HIV-infected individuals are at increased risk of becoming frail compared to similar-aged (i.e. 50-70 years) HIV-uninfected individuals [14,15]. Highly-active antiretroviral therapy (HAART) has improved survival among HIV-infected individuals, resulting in an increased prevalence of HIV-infected persons surviving into older ages and the emergence of age-related chronic diseases such as CVD in this population [16,17]. HIV-infection has been shown to be associated with an increased risk for both clinical and subclinical coronary artery disease (CAD), independent of traditional CVD risk factors [18,19]. Subclinical atherosclerosis and its progression among HIV-infected individuals is likely due to both traditional CVD risk factors as well as immunologic factors such as CD4 T-lymphocyte count [20]. However, the extent to which the frailty phenotype explains this increased CVD risk among HIV-infected individuals is unknown. HIV-infected individuals with frailty may be at particularly increased risk for CVD compared to similar HIV-uninfected individuals with frailty due to a greater burden of inflammatory markers associated with HIV-infection [21].

The coronary artery calcium (CAC) score measured by non-contrast cardiac CT is a well-established surrogate marker for burden of atherosclerosis and is prognostic of CVD risk [22]. Contrast coronary CT angiography (CCTA) can further define the presence, extent, and composition of coronary plaque and the presence of significant coronary stenosis.

The objective of our study was to characterize the association between expression of the frailty phenotype and subclinical coronary atherosclerosis, and to determine whether there are differences by HIV-serostatus. We hypothesized that frail participants will have increased prevalence of both CAC and any coronary plaque compared to non-frail participants. We also hypothesized that frail HIV-infected men will have more overall plaque and non-calcified plaque than frail HIV-uninfected men.

2. Materials and methods

2.1. Study population

The Multicenter AIDS Cohort Study (MACS) is an ongoing prospective cohort study of HIV-infected and HIV-uninfected men who have sex with men in 4 U.S cities; Baltimore/Washington D.C. Chicago, Los Angeles, and Pittsburgh [23]. Initial enrollment was in 1984–1985 and subsequent enrollments took place in 1987–1991, 2001–2003, and from 2010 onwards. Semi-annual study visits included standardized medical/behavioral interviews, physical examinations, and laboratory measurements. Assessment of frailty status was added to semi-annual visits beginning in 2006.

During the period 2010–2013, the MACS Cardiovascular Ancillary Study (MACS-CVD) recruited eligible men to undergo non-contrast cardiac CT scans and contrast CCTA to determine whether HIV-infected individuals have more coronary atherosclerosis than HIV-uninfected individuals [18,24]. Inclusion criteria for MACS-CVD were being an active MACS participant (with oversampling of HIV-infected men), age 40-70 years, weight <300 lbs. and no prior history of cardiac surgery or percutaneous coronary intervention since these procedures would interfere with the measurement of coronary atherosclerosis. Exclusion criteria for CCTA measurement included atrial fibrillation, chronic kidney disease [estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 within 30 days of the CT) or a history of intravenous contrast allergy.

Study inclusion/exclusion criteria for our analyses are shown in Fig. 1. From the MACS-CVD study population of 1006 participants with a non-contrast cardiac CT, we studied 976 (62% HIV-infected) who had available data on frailty assessed within 2 years before the CT. Of these, 747 men underwent CCTA. The Institutional Review Boards of all participating sites approved the study, and all participants signed informed consent.

2.2. Frailty assessment

MACS collected data on the 5 components of the frailty phenotype [25] which included: (1) weakness (grip strength <20th percentile of HIV-uninfected men); (2) slowness (time to walk 4 m ≥ 80th percentile of HIV-uninfected men; (3) weight loss ("yes" to the question "Since your last visit, have you had an unintentional weight loss of >10 lbs"); (4) exhaustion ("yes" to the question "During past 4 weeks did you have difficulty completing your work or activities due to your physical health" and; (5) low physical activity ("yes" to the question "Does your health limit you from vigorous activities such as running, lifting heavy objects, participating in strenuous sports." [14,26] Frailty was defined as the presence of having at least 3 of these 5 components assessed at the closest visit before the CT within 2 years. The median (IQR) time from frailty assessment to CT scan was -59 (-119, -23) days.

2.3. Covariates

As part of routine MACS visits, study participants were seen every 6 months, and data were collected on CVD risk factors and HIV clinical variables by history, physical examination, and blood tests. For this analysis, we used data collected at the MACS visit closest to the CT.

HIV-related factors measured included plasma HIV RNA levels, $CD4^+$ T-lymphocyte cell counts (CD4) measured by flow cytometry, history of AIDS-defining illness, use of HAART, and duration of HAART. Hepatitis C virus (HCV) infection was defined as either a positive enzyme immunosorbent assay (EIA) for HCV antibody in plasma or serum, or detection of HCV RNA in plasma using a Roche ultrasensitive assay (limit detection of 50 copies/mL). Men who were EIA-positive with undetectable HCV RNA for at least 3 years were considered HCV-uninfected.

Glucose, total cholesterol, and high-density lipoprotein cholesterol (HDL-C), levels were measured from fasting blood samples. Serum creatinine level was measured at each MACS visit and within 30 days prior to CT scanning for participants who had contrast injection; eGFR was determined by the Modification of Diet in Renal Disease equation [27].

Based on prior work, we also considered levels of inflammatory

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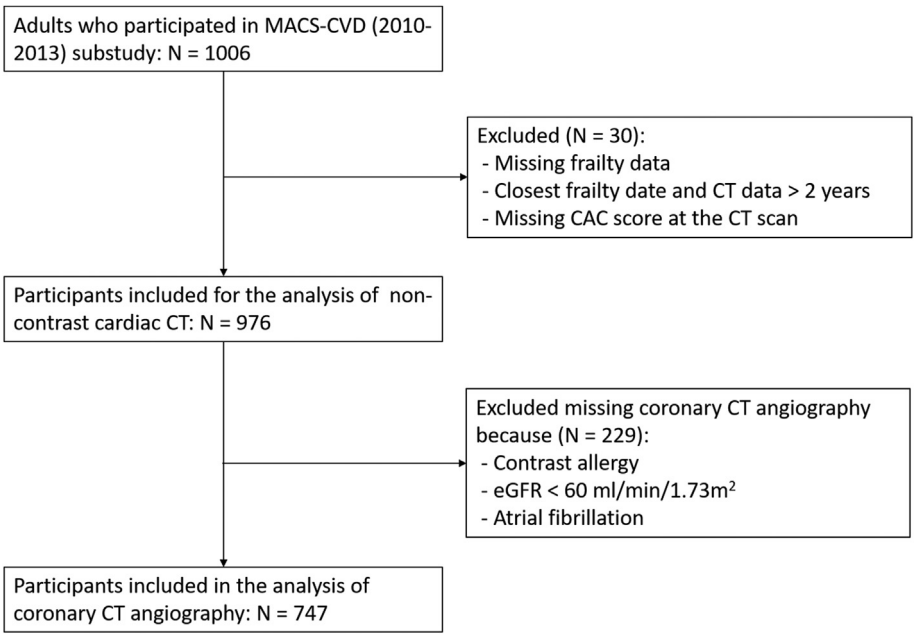

Fig. 1. Participant inclusion and exclusion criteria.

biomarkers that may be potential mediators of the association of frailty and/or HIV-infection with CAD; these included C-reactive protein (CRP), interleukin 6 (IL-6), and levels of the monocyte activation markers of soluble CD14 (sCD14), soluble CD163 (sCD163), and chemokine (C-C motif) ligand 2 (CCL2) [13,21,28,29]. Serum/plasma levels of inflammatory markers were measured in samples collected on the day of CT and stored at −70 °C until the laboratory work was performed at the University of Vermont Laboratory for Clinical Biochemistry Research (Burlington) with assays described previously [28].

2.4. Assessment of coronary atherosclerosis

Cardiac CTs were obtained following procedures as previously described [18,24]. Briefly, participants received a beta-blocker or calcium channel blocker if needed for heart rate control, followed by sublingual nitroglycerin before administration of IV contrast unless contraindicated. CCTA was performed with electrocardiogram-triggered protocols and a median radiation dose of 1.9 mSv (interquartile range, 1.7–2.7 mSv). CT images were analyzed at the core CT reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA) by trained, experienced readers blinded to participants' clinical information.

CAC scores from non-contrast CTs were calculated using the Agatston method [30]. CCTA images were examined to characterize coronary plaque (presence, burden, and composition) and degree of coronary stenosis using the modified 15-segment model of the American Heart Association [31]. Plaque burden was scored as 0 (no plaque), 1 (mild), 2 (moderate), or 3 (severe) in each coronary segment. The presence of coronary stenosis ≥50% was considered obstructive. The total plaque score (TPS) was calculated as the sum of plaque scores across all coronary segments, with a maximum score of 45 [32]. Plaque composition was categorized as non-calcified, mixed, or calcified for each coronary segment. Non-calcified plaque was defined as any discernible structure visualized in the coronary wall with a CT density less than the contrast-enhanced coronary lumen but greater than the surrounding connective tissue in at least 2 planes. Mixed plaque was defined as any structure with <50% calcification of the plaque area. Calcified plaque was defined as any structure with CT attenuation >130 HU that was distinct from the intravascular coronary lumen visualized in at least 2 planes. The non-calcified, mixed, and calcified plaque scores (NCPS, MPS, and CPS) were calculated as the sum of the respective scores across all coronary segments.

2.5. Statistical analysis

For subjects with missing data regarding cardiovascular risk factors, multiple imputation was used [33]. Data were imputed as follows: systolic blood pressure (n = 53); fasting glucose (n = 132); use of lipid-lowering medications (n = 7); total and HDL cholesterol (n = 29); pack-year smoking (n = 6); CRP (n = 46); IL-6 (n = 58); sCD163 (n = 78), sCD14 (n = 83), CCL2 (n = 42), and HCV-serostatus (n = 13). Given their skewed distribution, the inflammatory markers and the plaque scores were log-transformed for analyses.

The distributions of demographic and clinical factors among HIV-infected and HIV-uninfected men by frailty status at the visit closest to the cardiac CT were summarized. We used Poisson regression models with robust variance estimation to determine the prevalence ratios (PR) for the presence of coronary atherosclerosis (i.e. having a respective score >0 for each marker) by frailty status [34]. Multivariable-adjusted linear regression models were also used to assess the association between frailty and burden of disease using log-transformed CAC, TPS, NCPS, and MPS among participants with respective scores >0.

Models were progressively adjusted as follows: Model 1 for demographic variables of age, race, scanning center, pre/post-2001 cohort, and HIV-serostatus. Model 2 (our primary model) included additional adjustment for the CVD risk factors of systolic blood pressure, use of hypertension medications, use of diabetes medications, fasting glucose, total and HDL cholesterol, use of lipid lowering medications, pack-years of smoking and HCV-serostatus. Additionally, we performed a sensitivity analysis (Model 3) that further adjusted for inflammatory biomarkers that may mediate any association between frailty and CVD [13,21,28]. In the HIV-stratified subgroup, we additionally adjusted for HIV-related factors including CD4 cell count, presence of detectable HIV RNA, nadir CD4 cell count, history of AIDS, duration of HIV-infection, duration

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of HAART, and use of HAART (Model 4). Of note, body mass index and physical activity were not included as covariates in any models because weight and activity were part of the definition of the frailty phenotype.

Wald tests were used to formally test for two-way multiplicative interactions of frailty status with HIV-serostatus, in relation to the coronary atherosclerosis, using Model 2. All statistical analyses were performed using Stata 12 (StataCorp Lp, College Station, TX). A p-value of <0.05 was considered to be statistically significant.

3. Results

The characteristics of study participants by HIV-serostatus and by frailty status are displayed in Table 1. Frailty was found in 7.5% and 14.3% of HIV-uninfected and HIV-infected men, respectively. Compared with non-frail men, frail men were more likely to be of black race and have current smoking, hypertension, diabetes, or HCV-infection in both HIV-serostatus groups. Among HIV-infected men, those with frailty were more likely to have had a history of AIDS and a lower (current) mean CD4+T cell count.

The prevalence of coronary atherosclerosis by frailty status for the overall cohort is presented in Table 2. For the overall cohort (nearly two-thirds were HIV-infected), there were no statistically significant associations. However, a statistically significant interaction by HIV-serostatus was seen for the presence of any CAC [CAC>0 (p-interaction = 0.004)], the presence of any plaque [TPS>0 (p-interaction = 0.01)], and the presence of any mixed-plaque [MPS>0 (p-interaction = 0.01)]. Therefore results were stratified by HIV-serostatus.

Among HIV-uninfected men (Table 3), those with frailty (compared to not frail) had a 53% increased prevalence of any CAC (CAC>0) in demographic-adjusted models. This relationship was attenuated slightly but remained significant after further adjustment for traditional CVD risk factors [PR 1.27 (95% CI (1.02, 1.59), Model 2] and after inflammatory markers [1.25 (1.00, 1.58), Model 3]. Frailty was also associated with a 70% increase in the prevalence of significant CAC (CAC>100); however, this association did not persist after adjusting for traditional CVD risk factors. Similarly, frailty was significantly associated with a 29% increase in the prevalence of any coronary plaque (TPS>0) in demographic-

Table 1
Baseline characteristics of study participants by frailty status at the visit closest to cardiac CT scan: The Multicenter AIDS Cohort Study (MACS).[a,b]

	HIV-uninfected		HIV-infected	
	Non-frail	Frail	Non-frail	Frail
N	346	28	516	86
Demographic factors				
Age, years	55.4 ± 7.4	57.4 ± 7.3	52.5 ± 6.5	54.9 ± 5.8
Race				
Non-Hispanic white	233 (67.3)	16 (57.1)	273 (52.9)	40 (46.5)
Non-Hispanic black	84 (24.3)	9 (32.1)	171 (33.1)	36 (41.9)
Other	29 (8.4)	3 (10.7)	72 (14.0)	10 (11.6)
Frailty measures				
Unintentional weight loss ≥ 10 lb	2 (0.6)	2 (7.1)	9 (1.8)	22 (25.6)
Work/activity difficult due to health	13 (3.8)	23 (82.1)	63 (12.4)	66 (77.6)
Health limits vigorous activities	28 (8.2)	22 (78.6)	40 (7.8)	61 (71.8)
Slowness (time to walk 4 m ≥ 80th percentile)	82 (26.1)	22 (78.6)	148 (32.2)	70 (84.3)
Grip strength test (<20th percentile)	94 (29.4)	19 (73.1)	140 (29.8)	59 (72.0)
CT measures				
CAC score>0	170 (49.1)	23 (82.1)	270 (52.3)	47 (54.7)
Total Agatston CAC score for those with non-zero scores[c]	78 (20–237)	134 (30–269)	67 (20–180)	80 (25–308)
Total plaque score>0[d]	209 (72.8)	15 (100.0)	300 (76.7)	41 (77.4)
Coronary stenosis≥50%[d]	42 (14.6)	2 (13.3)	68 (17.4)	7 (13.2)
Lifestyle and clinical factors				
Smoking status				
Never	90 (26.1)	3 (10.7)	133 (25.9)	18 (20.9)
Former	184 (53.3)	14 (50.0)	229 (44.6)	33 (38.4)
Current	71 (20.6)	11 (39.3)	151 (29.4)	35 (40.7)
History of clinical AIDS	0	0	69 (13.4)	20 (23.3)
CD4 T-lymphocyte cell count/mm^3	922 ± 334	1038 ± 349	624 ± 266	593 ± 302
HIV RNA (viral load) < 200 copies per ml	NA	NA	61 (12.1)	15 (17.9)
Use of HAART	NA	NA	505 (97.9)	82 (95.3)
Duration of HAART, years	NA	NA	14.9 ± 6.8	15.2 ± 7.2
Systolic BP, mmHg	128.2 ± 14.4	129.1 ± 19.7	126.7 ± 15.2	128.7 ± 15.0
Hypertension medication use	102 (29.5)	15 (53.6)	172 (33.3)	46 (53.5)
Hypertension	142 (43.2)	17 (60.7)	235 (47.7)	53 (61.6)
Diabetes	25 (7.9)	9 (36.0)	51 (10.9)	21 (26.6)
Total cholesterol, mg/dl[e]	194.6 ± 38.0	187.7 ± 42.2	188.2 ± 40.3	180.5 ± 47.2
HDL cholesterol, mg/dl[e]	53.5 ± 16.0	45.4 ± 10.1	47.9 ± 15.3	48.7 ± 18.5
Lipid lowering medication use	94 (27.4)	12 (42.9)	175 (34.2)	29 (33.7)
eGFR, ml/min/1.73 m^2				
<60	6 (1.8)	5 (17.9)	28 (5.5)	16 (19.0)
60-<90	176 (51.6)	13 (46.4)	245 (48.4)	29 (34.5)
≥90	159 (46.6)	10 (35.7)	233 (46.0)	39 (46.4)
Hepatitis C virus serostatus	12 (3.5)	5 (17.9)	46 (9.1)	20 (23.5)

[a] AIDS, Acquired Immune Deficiency Syndrome; BP, blood pressure; CT, computed tomography; HIV, human immunodeficiency virus; CAC, coronary artery calcium; HAART, highly-active antiretroviral therapy; eGFR = estimated glomerular filtration rate.
[b] Data are mean ± SD, median (interquartile range) or number (%).
[c] Median (IQR) among those with scores >0.
[d] Coronary CT angiography data measured in a subsample of 747 participants.
[e] To convert total and HDL-C cholesterol from mg/dl to mmol/L, divide by 38.67.

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Table 2
Prevalence ratios[a,b] (95% CI) for coronary artery atherosclerosis by frailty status for all study participants.[c]

	CAC>0	CAC>100	Obstructive coronary stenosis (≥50%)	TPS>0 (any plaque)	NCPS>0	MPS>0
N	510/976	225/976	119/747	566/747	436/747	247/747
Model 1[d]						
No frailty	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Frailty	1.12 (0.96, 1.30)	1.26 (0.94, 1.69)	0.78 (0.42, 1.45)	1.07 (0.96, 1.20)	0.91 (0.73, 1.14)	1.15 (0.86, 1.53)
Model 2[e]						
No frailty	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Frailty	1.01 (0.87, 1.17)	1.05 (0.78, 1.41)	0.73 (0.39, 1.35)	1.03 (0.92, 1.15)	0.87 (0.70, 1.08)	1.07 (0.80, 1.43)
Model 3[f]						
No frailty	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Frailty	0.98 (0.84, 1.14)	0.97 (0.72, 1.31)	0.72 (0.38, 1.35)	1.02 (0.91, 1.14)	0.87 (0.70, 1.09)	1.06 (0.79, 1.42)
p-interaction HIV status[g]	**0.004**	0.15	0.85	**0.01**	0.68	**0.01**

[a] Prevalence ratio was derived from Poisson regression with robust variance.
[b] Statistically significant results are in bold font.
[c] CT, computed tomography; CAC, coronary artery calcium; TPS, total plaque score; MCPS, mixed plaque score.
[d] Model 1: adjusted for demographic factors (age, race, scanning center, pre/post 2001 cohort and HIV status).
[e] Model 2: model 1 + established cardiovascular disease risk factors (systolic blood pressure, use of hypertension medications, use of diabetes medications, fasting glucose, total and HDL cholesterol, use of lipid lowering medications, and pack-years of tobacco smoking) and hepatitis C virus-serostatus.
[f] Model 3: model 2 + inflammatory markers (log-transformed CRP, IL-6, sCD163, sCD14 and CCL2).
[g] *p*-interaction by HIV-status was tested using Model 2.

Table 3
Prevalence ratios[a,b] (95% CI) for coronary artery atherosclerosis by frailty status among HIV-uninfected participants.[c]

	CAC>0	CAC>100	Obstructive coronary stenosis (≥50%)	TPS>0 (any plaque)	NCPS>0	MPS>0
N	193/374	91/374	44/303	225/303	160/303	95/303
Model 1[d]						
No frailty	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Frailty	**1.53 (1.26, 1.87)**	**1.70 (1.10, 2.65)**	0.75 (0.20, 2.79)	**1.29 (1.14, 1.47)**	0.87 (0.50, 1.51)	**1.82 (1.27, 2.59)**
Model 2[e]						
No frailty	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Frailty	**1.27 (1.02, 1.59)**	1.19 (0.75, 1.88)	0.55 (0.17, 1.81)	**1.19 (1.06, 1.35)**	0.81 (0.47, 1.38)	1.49 (0.98, 2.25)
Model 3[f]						
No frailty	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Frailty	**1.25 (1.00, 1.58)**	1.09 (0.66, 1.80)	0.52 (0.14, 1.94)	**1.19 (1.05, 1.36)**	0.87 (0.51, 1.48)	1.50 (0.98, 2.31)

[a] Prevalence ratio was derived from Poisson regression with robust variance.
[b] Statistically significant results are in bold font.
[c] CT, computed tomography; CAC, coronary artery calcium; TPS, total plaque score; MCPS, mixed plaque score.
[d] Model 1: adjusted for demographic factors (age, race, scanning center, pre/post 2001 cohort).
[e] Model 2: model 1 + established cardiovascular disease risk factors (systolic blood pressure, use of hypertension medications, use of diabetes medications, fasting glucose, total and HDL cholesterol, use of lipid lowering medications, pack-years of tobacco smoking) and hepatitis C virus-serostatus.
[f] Model 3: model 2 + inflammatory markers (log-transformed CRP, IL-6, sCD163, sCD14 and CCL2).

adjusted models, which remained significant after adjusting for traditional CVD risk factors [1.19 (1.06, 1.35)] and inflammatory markers [1.19 (1.05, 1.36)]. The association between frailty and prevalence of mixed plaque (MPS>0) seen in demographic-adjusted models [1.82 (1.27, 2.59)] was no longer statistically significant after adjusting for traditional CVD risk factors, but had a similar trend as the less-adjusted model.

Among HIV-infected individuals (Table 4), frailty was not associated with these measures of subclinical coronary atherosclerosis in any models, including after further adjustment for HIV disease related factors such as CD4 count and use of HAART (model 4).

Among men with CAC or plaque scores >0, there were no statistically significant associations of frailty with extent of CAC or plaque burden (Supplemental Table 1) for the overall study population, and no statistically significant interactions by HIV-serostatus.

In Supplemental Table 2, we also examined the associations of the 5 individual components of the frailty phenotype with coronary atherosclerosis among HIV-uninfected men. Some statistically significant associations were noted (i.e. weight loss was associated with CAC>0, muscle weakness was associated with CAC>100, and poor health status associated with the presence of any plaque). However given multiple testing performed, findings for the individual frailty components should be considered exploratory.

4. Discussion

In this large cohort of men who have sex with men, frailty was associated with increased prevalence of any CAC and any coronary plaque among HIV-uninfected men but not among HIV-infected men. This association was independent of both traditional CVD risk factors and levels of potentially mediating inflammatory markers. These results run counter to our hypothesis, that associations between frailty and coronary plaque would be stronger among HIV-infected men, and raise the possibility that there may be other biological mechanisms through which HIV-infected men have higher risk of CAD compared to HIV-uninfected persons [18,19].

Our study is the first large study, to our knowledge, to evaluate associations between frailty and subclinical coronary atherosclerosis using both non-contrast cardiac CTs and CCTA, and the first undertaken among HIV-infected participants. Only one study to date has evaluated associations between frailty and CAC [35]. That was a small study of 42 institutionalized elderly adults (29 frail and 13 non-frail), and demonstrated no differences in CAC between frailty-defined groups. However, our study adds to existing literature by focusing on non-institutionalized adults in a larger community sample.

The effect of frailty on CVD, if causal, could be explained in part

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Table 4
Prevalence ratios[a] (95% CI) for coronary artery atherosclerosis by frailty status among HIV-infected participants.[b]

	CAC>0	CAC>100	Obstructive coronary stenosis (≥50%)	TPS>0 (any plaque)	NCPS>0	MPS>0
N	317/602	134/602	75/444	341/444	276/444	152/444
Model 1[c]						
No frailty	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Frailty	0.99 (0.82, 1.20)	1.11 (0.76, 1.62)	0.81 (0.41, 1.61)	1.01 (0.87, 1.16)	0.92 (0.72, 1.16)	0.95 (0.65, 1.39)
Model 2[d]						
No frailty	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Frailty	0.91 (0.75, 1.11)	0.95 (0.64, 1.40)	0.78 (0.39, 1.57)	0.97 (0.84, 1.12)	0.88 (0.69, 1.11)	0.90 (0.62, 1.31)
Model 3[e]						
No frailty	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Frailty	0.89 (0.73, 1.08)	0.88 (0.59, 1.29)	0.83 (0.41, 1.67)	0.96 (0.83, 1.11)	0.88 (0.69, 1.12)	0.90 (0.61, 1.32)
Model 4[f]						
No frailty	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)	Reference (1)
Frailty	0.88 (0.70, 1.09)	0.80 (0.51, 1.23)	0.78 (0.38, 1.59)	0.96 (0.82, 1.11)	0.85 (0.66, 1.09)	0.87 (0.58, 1.33)

[a] Prevalence ratio was derived from Poisson regression with robust variance.
[b] CT, computed tomography; CAC, coronary artery calcium; TPS, total plaque score; MCPS, mixed plaque score; AIDS = acquired immunodeficiency virus; HAART, highly active anti-retroviral therapy.
[c] Model 1: adjusted for demographic factors (age, race, scanning center, pre/post 2001 cohort).
[d] Model 2: model 1 + established cardiovascular disease risk factors (systolic blood pressure, use of hypertension medications, use of diabetes medications, fasting glucose, total and HDL cholesterol, use of lipid lowering medications, pack-years of tobacco smoking, and estimated GFR), and hepatitis C virus-serostatus.
[e] Model 3: model 2 + inflammatory markers (log-transformed CRP, IL-6, sCD163, sCD14 and CCL2).
[f] Model 4: Model 3 + HIV-related factors (CD4 cell count, presence of detectable HIV RNA, nadir CD4 cell count, history of AIDS, duration of HIV-infection, duration of HAART, and use of HAART).

by the increased risk of central adiposity, disturbances in long-term glucose control, and increased inflammation seen in frailty [29,36–38]. Studies have shown that elevated inflammatory markers are prevalent in older, frail adults and may play an important role, directly or indirectly, in the pathogenesis of frailty [13,39]. Also, prior work from MACS has demonstrated that higher levels of inflammatory markers and immune activation were associated with increased coronary atherosclerosis [21,28] and with frailty [29]. However, we found that among HIV-uninfected men that the association of frailty with the presence of CAC and any coronary plaque remained statistically significant even after adjusting for these key inflammatory markers. This suggests that frailty may be associated with CAD through mechanisms other than increased inflammation in the HIV-uninfected population, with the caveats that one single measurement of the inflammatory markers may not reflect historical/long-term burden, and that these particular markers may not capture all of the full inflammatory milieu.

As previously reported, HIV-infected individuals were more likely to be frail compared to HIV-uninfected individuals [14,15]. However, we did not identify an association between frailty and subclinical coronary atherosclerosis in HIV-infected men. As shown previously [14], frailty may be more transient in HIV-infected persons, and perhaps this differential expression is the reason for the difference in its association with coronary atherosclerosis. Previous work from MACS revealed HIV-infected men were more likely to have non-calcified plaque than HIV-uninfected men [18,40]. However, we did not find any association of frailty with NCPS regardless of HIV-serostatus. Calcification of coronary plaque implies a longer duration of coronary disease whereas non-calcified plaque is generally younger plaque than calcified plaque. This may be why frailty, a process that generally develops over time and is associated with aging, was associated more strongly with CAC than with NCPS in our study even after adjustment for age.

The present study has many strengths including the use of the well-characterized MACS cohort, the careful assessment of frailty status at regular intervals across many years, and the ability to examine not only CAC but also the different types of coronary plaque and plaque severity. Additionally, we were able to evaluate our hypotheses in a population of HIV-infected individuals, a subgroup who are at increased risk for CVD beyond that conferred by traditional risk factors [18,19] and for whom there is a need to better understand their unique risk.

Nonetheless, the findings of our study should be considered in the context of several limitations. MACS contains only men, so the present findings may not apply to women. Additionally, our study might have been underpowered given that only 12% of our 976 participants were frail. In utilizing a cross-sectional study design, we cannot determine temporal relationships and causation. Although there are plausible biologic mechanisms by which frailty could directly contribute to coronary risk, the association between frailty and coronary atherosclerosis among HIV-uninfected men could also be due to residual confounding by other comorbidities such as chronic obstructive pulmonary disease, osteoporosis, depression and hypovitaminosis D, all of which are significantly more prevalent among frail individuals [8,41–44].

Our study evaluated frailty using the well-established definition of the Frailty Phenotype described by Fried et al. [25] However, this concept was first developed in the Cardiovascular Health Study of older adults (aged >65 years), a cohort with mean age at least 10 years older than our study population (MACS). This might limit the sensitivity and specificity of this tool in our study population. Nonetheless, the Frailty Phenotype has been previously well-characterized in the MACS cohort and is associated with increased immune activation, age, and other co-morbidities [14,29]. There are other instruments that can be used to measure frailty including the Frailty Index described by the Rockwood group (which incorporates 37 age-related health variables), and the Edmonton Frailty Scale [7,44]. Yeoh et al. found that the prevalence of frailty and its associations with comorbidities among HIV-infected men differed slightly depending on which definition was used, but frailty by any of these definitions was associated with a poorer quality of life [7]. Prior work by Guaraldi et al. has suggested the Frailty Index might have stronger associations with nadir CD4 count, falls, and disability among HIV-infected individuals compared to the Frailty Phenotype definition [44].

There is also a possibility of reverse causation, in which the presence of coronary disease could lead to frailty, but this is less likely in our study because these men had subclinical coronary atherosclerosis and not clinical CAD that required revascularization. It is important to note that in the Pro.V.A. Study, a phenotype of "pre-frailty" was shown to precede the development of clinical CVD

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events, supporting a causal role [8]. Furthermore, there is additional evidence that the relationship between frailty and CVD may actually be bi-directional - a phenomenon where the presence of one condition may worsen or accelerate the development of the other. Thus, targeting patients at an earlier stage in this process, such as those with pre-frailty or those with subclinical coronary atherosclerosis, for preventive interventions may potentially break this vicious cycle [45].

In summary, we found that frailty was associated with subclinical coronary atherosclerosis independent of traditional CVD risk factors and levels of inflammatory markers among HIV-uninfected men, but not among HIV-infected men, a group in whom frailty was more common. Further work is needed to identify mechanisms accounting for these associations and differences by HIV-serostatus, and whether interventions that improve frailty status (such as strength training) can improve cardiovascular outcomes.

Conflict of interest

The authors report no financial or personal conflicts of interest related to the topic of work. Unrelated to this work, Dr. Michos has received an honorarium from Siemens Diagnostics. Dr. Brown has served as a consultant to Gilead Sciences, Merck, BMS, EMD-Serono, and Theratechnologies. Dr. Jacobson had served as a consultant to BMS. Dr. Budoff has received research funds from GE Healthcare. Dr. Palella has served as a consultant and speaker for Gilead Sciences, Janssen Pharmaceuticals, Merck and Co. and BMS. No other authors report any conflicts.

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Author contributions

Mr. Korada designed the research, under the mentorship of Dr. Michos, and he drafted the first manuscript. Dr. Zhao was the analyst for the study; she generated all of the results tables and contributed equally to Mr. Korada in authorship. Dr. Post obtained the NIH funding for that supported the MACS-CVD2 ancillary study. Dr. Budoff interpreted the cardiac CT scans for the study (MACS CT Core Lab). Drs. Tibuakuu, Brown, Jacobson, Guallar, Bolan, Palella, Margolick, Martinson, Budoff, and Post all reviewed the manuscript and provided critical scientific input. Mr. Korada, Dr. Zhao, and Dr. Michos take primary responsibility for final content. Additionally, this manuscript draft has been approved by the MACS Executive Committee.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2017.08.026.

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