Cardiovascular risk score associations with frailty in men and women with or at risk for HIV

Mark H. Kuniholm[a], Elizabeth Vásquez[a], Allison A. Appleton[a], Lawrence Kingsley[b], Frank J. Palella[c], Matthew Budoff[d], Erin D. Michos[e], Ervin Fox[g], Deborah Jones[h], Adaora A. Adimora[i], Igho Ofotokun[j], Gypsyamber D'souza[f], Kathleen M. Weber[k], Phyllis C. Tien[l], Michael Plankey[m], Anjali Sharma[n] and Deborah R. Gustafson[o]

Objective: To understand the relationship between cardiovascular disease (CVD) risk and frailty among men (MWH) and women living with HIV (WWH), or at risk for HIV.

Design: We considered 10-year coronary heart disease and atherosclerotic CVD risk by Framingham risk score (FRS, 2001 National Cholesterol Education Program Adult Treatment Program III) and Pooled Cohort Equations (PCE, 2013 American College of Cardiology/American Heart Association) in relation to the Fried Frailty Phenotype (FFP) in the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS).

Methods: FFP was ascertained in MACS from 2004 to 2019 and in WIHS from 2005 to 2006 and 2011–2019. FFP score at least three of five components defined frailty. Repeated measures logistic regression (both cohorts) and Cox proportional hazards regression (MACS) were performed, controlled for education, income, cholesterol medication and hepatitis C virus serostatus, and among MWH and WWH, $CD4^+$ cell count/μl, antiretroviral therapy, and HIV viral load.

Results: There were 5554 participants (1265 HIV seronegative/1396 MWH; 768 seronegative/1924 WWH) included. Among men, high-risk FRS was associated with increased risk of incident frailty among seronegative [adjusted hazard ratio (aHR)) = 2.12, 95% confidence interval (CI):1.22–3.69] and MWH (aHR = 2.19, 95% CI: 1.33–3.61). Similar associations were seen with high-risk PCE and incident frailty among SN (aHR = 1.88, 95% CI: 1.48–2.39) and MWH (aHR = 1.59, 95% CI: 1.26–2.00). Among women, high-risk PCE was associated with frailty in SN [adjusted odds ratio (aOR) = 1.43, 95% CI: 1.02–2.00] and WWH (aOR = 1.36, 95% CI: 1.08–1.71); however, high-risk FRS was not (seronegative: aOR = 1.03, 95% CI: 0.30–3.49; WWH: aOR = 0.86, 95% CI: 0.23–3.20).

[a]Department of Epidemiology and Biostatistics, University at Albany, State University of New York, Rensselaer, New York, [b]Department of Infectious Diseases and Microbiology, University of Pittsburgh, Pittsburgh, Pennsylvania, [c]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, [d]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, California, [e]Department of Medicine, [f]Department of Epidemiology, Johns Hopkins Medical Institutions, Baltimore, Maryland, [g]Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, [h]Department of Psychiatry & Behavioral Sciences, Miller School of Medicine, University of Miami, Miami, Florida, [i]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina, [j]Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, [k]Cook County Health/Hektoen Institute of Medicine, Chicago, Illinois, [l]Department of Medicine, University of California, San Francisco, and Department of Veterans Affairs, San Francisco, California, [m]Department of Medicine, Georgetown University Medical Center, Washington, DC, [n]Department of Medicine, Albert Einstein College of Medicine, Bronx, and [o]Department of Neurology, State University of New York Downstate Health Sciences University, Brooklyn, New York, USA.

Correspondence to Mark H. Kuniholm, PhD, Department of Epidemiology & Biostatistics, University at Albany, State University of New York, GEC 137, One University Place, Rensselaer, NY 12144, USA.

Tel: +1 518 402 0397; fax: +1 518 402 0380; e-mail: mkuniholm@albany.edu
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Conclusion: Higher CVD risk was associated with increased frailty regardless of HIV serostatus among men and women. These findings may inform clinical practices of screening for frailty.

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Introduction

Frailty is characterized by physical weakness and a marked decline of physiologic reserve [1]. Higher prevalence of frailty has been reported among people with HIV (PWH) compared with adults without HIV infection in the United States [2–4], Europe [5], China [6], and Africa [7], suggesting that PWH worldwide are at increased risk for frailty. Risk factors common to cardiovascular disease (CVD) and frailty, such as older age, presence of comorbidities, smoking, physical inactivity, and poor nutrition exist, yet the relationship between CVD and frailty in PWH is not well established [8,9]. Cross-sectional research in the Multicenter AIDS Cohort Study (MACS) demonstrated that the Fried Frailty Phenotype (FFP) was associated with subclinical coronary atherosclerosis among HIV seronegative (SN) men but not among men living with HIV (MWH) [10]. Cross-sectional data in the Women's Interagency HIV Study (WIHS) showed that hypertension and cigarette smoking were associated with the FFP during middle age [3]. Some groups have suggested that frailty reflects the interaction between multiple morbidities and disability, and hence CVD contributes to frailty [11]. It may also be argued that frailty is a biologic syndrome distinct from either comorbidities or disability. Notably, in the Cardiovascular Health Study, 7% of those who were frail according to FFP criteria had no chronic diseases [1]. Among persons without HIV, prevalence of frailty – defined by the FFP, the Frailty Index [12] or other frailty measures – was greater in those with vs. without CVD [13–16]. Moreover, among persons without CVD, risk factors for CVD were associated with frailty [15,16].

CVD risk factors are used in clinical practice as part of CVD event risk prediction and to guide therapeutic decision making in adults, including PWH [17–23]. However, traditional CVD risk prediction tools underperform among PWH, and differ by sociodemographic and race/ethnicity factors [18,19,22]. The 2001 National Cholesterol Education Program Adult Treatment Program III (ATP-III) [24] and the 2013 American College of Cardiology/American Heart Association (ACC/AHA) [25] guidelines, with corresponding risk scores, have been widely used for primary prevention of CVD. These risk scores have important differences; however, as they were released a decade apart, there was an expansion of statin eligibility in the 2013 ACC/AHA guidelines compared with the 2001 ATP-III [26]. The ATP-III recommendations for primary prevention are based on the Framingham risk score (FRS) for coronary heart disease (CHD). The ATP-III FRS includes the components: sex, age, total cholesterol, high-density lipoprotein (HDL) cholesterol, smoking status, SBP and antihypertensive medication use [24]. The ACC/AHA recommendations are based on pooled cohort equations (PCE) for atherosclerotic cardiovascular disease (ASCVD) with components of race (white/African American) and diabetes, in addition to the components included in ATP-III FRS [25].

Our objective was to consider ATP-III FRS and ACC/AHA PCE risk scores in association with frailty, defined using the FFP, among men and women enrolled in the MACS and WIHS. Understanding these associations could be important as the FFP requires assessment of physical performance (grip strength and walking speed) and may be ascertained less often than CVD risk in clinical practice. Notably, this article is among the first to consider CVD risk profiles as a predictor of frailty among two large longitudinal cohorts of men and women living with or at risk for HIV who have been followed at 14 clinical sites across the United States.

Methods

Study populations

The MACS and WIHS (now known as the MACS/WIHS Combined Cohort Study [27]) were prospective multicenter cohorts of United States men and women living with or without HIV. Eligibility criteria, study protocols, and follow-up procedures for the MACS and WIHS have been previously described [28–32]. Briefly, MACS participants were recruited at 4 sites across 3 time periods starting in 1984, and WIHS participants were recruited at 10 sites over four time periods starting in 1994. Data for both cohorts were collected using structured in-person interviews and standardized physical and laboratory assessments, with study visits occurring every 6 months. As part of a detailed medication history, participants self-reported all prescribed medications consumed, even transiently, since their last study visit. Institutional review boards at the respective clinical

research centers approved the MACS and WIHS study protocols, and all participants provided written informed consent.

Participant selection and inclusion criteria

MACS and WIHS participant visits were selected for inclusion in these analyses if components of the FFP and ATP-III FRS were available at any baseline when measures were conducted among participants aged at least 20 years (Supplementary Figure 1, http://links.lww.com/QAD/C344). The ATP-III FRS is valid for adults age 20–79 years [24]. The subset of ATP-III participant visits where participants were aged 40–79 years were included in analyses of ACC/AHA PCE as that is the age group for which the ACC/AHA PCE is valid [25]. FFP characteristics in MACS were ascertained at all four MACS sites during 2004–2019. In contrast, frailty in WIHS was assessed at six sites at a single time point between 2005 and 2006 [3,33], in a sub-group of three of the six sites during 2012–2014, and then annually at nine sites during 2015–2019. All components of CVD risk scores were available across all study visits.

Outcome ascertainment: fried frailty phenotype

Participants were classified as frail if they exhibited three or more of five FFP characteristics: slow walking speed; weakness (reduced grip strength), and self-reported; physical exhaustion; low physical activity; and unintentional weight loss. Walking speed was measured using a 3 or 4 m timed gait test, and impaired walking speed was defined as at least 80th percentile of seronegative participants, as in prior studies [3,10,34]. Grip strength was measured using a dominant hand-held dynamometer with maximum force; reduced grip strength was mean grip strength (three trials) 20th percentile or less of seronegative participants. Physical exhaustion was defined as a 'Yes' response to: 'During the past four weeks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra effort)?' Low physical activity was a 'Yes' to 'Does your health now limit you in vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports?' Unintentional weight loss was a 'Yes' to: 'Since your last visit, have you had unintentional weight loss of at least 10 pounds?'

Predictor ascertainment: cardiovascular risk score calculations

For each participant, we calculated ATP-III FRS [24] and ACC/AHA PCE [25] cardiovascular risk scores using: age, race (black or African American vs. other race), hypertension treatment and smoking status (yes/no); and clinically measured SBP (mmHg), diabetes (fasting glucose $\geq$126 mg/dl or taking diabetes medication at the visit), and total and HDL cholesterol measured on a Roche Modular automated system (Roche Diagnostics Corporation, Indianapolis, Indiana, USA). For ATP-III FRS, 10-year risk of CHD was defined as high (>20%), moderate (10–20%), or low (<10%) [24]. Persons with ACC/AHA PCE at least 7.5% were considered at high 10-year risk of ASCVD whereas those with ACC/AHA PCE less than 7.5% were at low 10-year risk of ASCVD [25]. These definitions of risk are consistent with each respective guideline.

Covariates

A limited set of covariates was selected *a priori* for inclusion: education (<high school, high school, >high school), income (WIHS:$\leq$\$6000, \$6001–\$18 000, $\geq$\$18 001; MACS: $\leq$\$20 000, \$20 000–\$39 999, $\geq$\$40 000), cholesterol medication usage and hepatitis C virus (HCV) serostatus. HCV was selected as it affects cholesterol metabolism in seronegative [35] and PWH [36] and predicts CVD events in PWH [37]. A noninvasive measure of liver fibrosis (FIB-4) was also associated with frailty in WIHS [3] and HCV is associated with immune dysregulation in PWH [38,39], which could contribute to frailty. Among PWH-only, models also included $CD4^+$ T-cell count/μl, use of antiretroviral therapy, and HIV viral load below the lower limit of quantification (LLQ or suppressed HIV viral load). LLQs for WIHS were 80 (2004–2006) and 20 (2011–2019) copies/ml and for MACS were 50 (2004–2010) and 20 (2011–2019) copies/ml.

Statistical methods

Statistical analyses were stratified by cohort because of differences in participant sociodemographic characteristics beyond sex, as well as differences in MACS and WIHS protocols, including assessment of income using different thresholds and frequency of functional measures over time. We defined an index study visit for each participant as the first ascertainment of both ATP-III FRS and physical performance. Bivariate comparisons of continuous variables at the index visit (i.e. cross-sectional analyses) were analyzed using the Wilcoxon rank sum test and categorical variables using Fisher's exact test. In both MACS and WIHS, associations of cardiovascular risk scores as the predictors with frailty as the outcome, including both index and follow-up visits (i.e. longitudinal analyses) were estimated using repeated measures logistic regression models, with generalized estimating equations (GEE) with exchangeable covariance structures.

Among MACS participants only, associations of cardiovascular risk scores at the index visit with incident frailty among men who were not frail at the index visit were estimated using Kaplan–Meier curves, global log-rank tests and Cox proportional hazards regression models. These analyses were restricted to men with at least two follow-up visits after the index visit and the Cox models included time-updated covariate information. Proportional hazards assumptions were verified. We did not assess associations of cardiovascular risk with incident frailty in women because of gaps in physical performance

Table 1. Cardiovascular risk scores and their components in Multicenter AIDS Cohort Study men at the index visit.[a,b,c]

	HIV- ($n=1265$)			HIV+ ($n=1396$)		
	Not frail ($n=1187$)	Frail ($n=78$)	P^a	Not frail ($n=1270$)	Frail ($n=126$)	P^a
Cardiovascular risk scores [median (IQR)]						
ATP-III FRS (%)[b]	6 (2–10)	10 (5–16)	<0.001	4 (1–8)	6 (3–12)	<0.001
ACC/AHA PCE (%)[b,c]	6 (4–11)	10 (7–19)	<0.001	6 (3–9)	8 (4–14)	<0.001
Cardiovascular risk scores, strata						
ATP-III FRS (%)[b]			<0.001			0.001
Low risk (<10%)	813 (68%)	32 (41%)		983 (77%)	79 (63%)	
Moderate risk (10–20%)	344 (29%)	40 (51%)		259 (20%)	42 (33%)	
High risk (>20%)	30 (3%)	6 (8%)		28 (2%)	5 (4%)	
ACC/AHA PCE (%)[b,c]			<0.001			<0.001
Low risk (<7.5%)	539 (57%)	19 (29%)		568 (64%)	48 (46%)	
High risk (≥7.5%)	406 (43%)	46 (71%)		325 (36%)	56 (54%)	
Cardiovascular risk score components, median (IQR)						
Age	50 (42–57)	54 (45–58)	0.03	45 (38–51)	50 (44–55)	<0.001
Total cholesterol (mg/dl)	188 (165–216)	186 (160–220)	0.86	180 (153–208)	167 (147–187)	0.006
HDL cholesterol (mg/dl)	49 (41–58)	46 (39–55)	0.10	43 (36–53)	40 (35–50)	0.09
SBP (mmHg)	128 (118–137)	130 (121–140)	0.09	126 (117–134)	128 (115–138)	0.58
Cardiovascular risk score components, strata						
Race (black or African American)			0.02			0.55
No	929 (78%)	52 (67%)		848 (67%)	88 (70%)	
Yes	258 (22%)	26 (33%)		422 (33%)	38 (30%)	
Current smoker			0.003			0.03
No	888 (75%)	46 (59%)		830 (65%)	70 (56%)	
Yes	299 (25%)	32 (41%)		440 (35%)	56 (44%)	
Antihypertensive medication use	<0.001			<0.001		
No	923 (78%)	44 (56%)		1011 (80%)	75 (60%)	
Yes	264 (22%)	34 (44%)		259 (20%)	51 (40%)	
Diabetes			0.001			0.001
No	1105 (93%)	64 (82%)		1176 (93%)	105 (83%)	
Yes	82 (7%)	14 (18%)		94 (7%)	21 (17%)	

ACC/AHA PCE, American College of Cardiology/American Heart Association pooled cohort equations; ATP-III FRS, Adult Treatment Program III Framingham risk score; IQR, interquartile range; MACS, Multicenter AIDS Cohort Study.
[a]Comparisons of continuous variables by Wilcoxon rank sum and categorical variables by Fisher's exact test.
[b]ATP-III FRS and ACC/AHA PCE are in men 20–79 and 40–79 years of age, respectively.
[c]ACC/AHA PCE were available for 1010 (80%) HIV (−) and 997 (71%) HIV+ men at the index visit.

measures over time. SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA) was used for analyses.

Results

Cardiovascular risk scores in men by frailty status at the index visit

The ATP-III FRS and FFP were ascertained at at least one MACS visit among 1265 seronegative men and 1396 MWH. The median date of the index visit was 14 February 2006 (IQR: 29 October 2005–10 August 2006) for seronegative men and 20 March 2006 (IQR: 19 December 2005–24 May 2011) for MWH. The ACC/AHA PCE risk score was available for 1010 (80%) seronegative and 997 (71%) MWH at the index visit.

Prevalence of frailty was 6.1% in seronegative men and 9% in MWH at the index visit (Table 1). In both seronegative men and MWH, ATP-III FRS 10-year risk was higher in frail [median (IQR): 10% (5–16) and 6% (3–12), respectively] vs. nonfrail [median (IQR):6% (2–10) and 4% (1–8), respectively] men (both $P<0.001$; Table 1). Similarly, in seronegative men and MWH, ACC/AHA PCE 10-year risk was higher in frail [median (IQR)):10% (7–19%) and 8% (4–14%), respectively] vs. nonfrail (median (IQR): 6% (4–11%) and 6% (3–9%), respectively] men (both $P<0.001$). When considered by strata of 10-year risk, both higher ATP-III FRS and ACC/AHA PCE were associated with frailty in seronegative men and MWH (all $P<0.001$).

CVD risk score components associated with frailty in both seronegative men and MWH included age, smoking, antihypertensive medication use, and diabetes (all $P<0.05$). In addition, among seronegative men, those who were frail were more likely to be black or African American, whereas frail MWH had lower total cholesterol ($P=0.006$).

Cardiovascular risk scores in women by frailty status at the index visit

The ATP-III FRS and FFP were ascertained at at least one WIHS visit among 768 seronegative women and 1924 WWH. Of these, 60% ($n=460$) of seronegative women and 62% ($n=1202$) of WWH had an index visit from 04 April 2005 to 28 March 2006 with the remainder

Table 2. Cardiovascular risk scores and their components in Women's Interagency HIV Study women at the index visit.[a,b,c]

	HIV(−) ($n=768$)			HIV+ ($n=1924$)		
	Not frail ($n=690$)	Frail ($n=78$)	P^a	Not frail ($n=1668$)	Frail ($n=256$)	P^a
Cardiovascular risk scores, median (IQR)						
ATP-III FRS (%)[b]	1 (0–2)	2 ((1–4)	<0.001	1 (0–2)	1 (0–3)	<0.001
ACC/AHA PCE (%)[b,c]	3 (1–8)	5 (2–11)	0.011	3 (1–6)	4 (2–9)	<0.001
Cardiovascular risk scores, strata						
ATP-III FRS (%)[b]			0.83			0.06
Low risk (<10%)	671 (97%)	76 (95%)		1634 (98%)	245 (96%)	
Moderate risk (10–20%)	13 (2%)	1 (1%)		31 (2%)	11 (4%)	
High risk (>20%)	6 (1%)	1 (1%)		3 (0%)	0	
ACC/AHA PCE, %[b,c]			0.006			<0.001
Low risk (<7.5%)	307 (73%)	39 (57%)		956 (80%)	156 (70%)	
High risk (≥7.5%)	111 (27%)	30 (43%)		236 (20%)	68 (30%)	
Cardiovascular risk score components, median (IQR)						
Age	42 (33–50)	48 (42–53)	<0.001	44 (38–51)	48 (43–54)	<0.001
Total cholesterol (mg/dl)	177 (154–203)	187 (161–208)	0.25	178 (152–203)	171 (145–201)	0.08
HDL cholesterol (mg/dl)	53 (44–64)	54 (42–69)	0.69	48 (39–61)	47 (37–62)	0.27
SBP (mmHg)	118 (109–132)	123 (112–139)	0.03	117 (107–131)	119 (106–135)	0.28
Cardiovascular risk score components, strata						
Race (black or African American)			0.15			0.67
No	193 (28%)	28 (36%)		553 (33%)	81 (32%)	
Yes	497 (72%)	50 (64%)		1115 (67%)	175 (68%)	
Current smoker			0.02			<0.001
No	351 (51%)	29 (37%)		979 (59%)	118 (46%)	
Yes	339 (49%)	49 (63%)		689 (41%)	138 (54%)	
Antihypertensive medication use	<0.001			<0.001		
No	531 (77%)	38 (49%)		1187 (71%)	131 (51%)	
Yes	159 (23%)	40 (51%)		481 (29%)	125 (49%)	
Diabetes			<0.001			0.002
No	579 (84%)	46 (59%)		1413 (85%)	196 (77%)	
Yes	111 (16%)	32 (41%)		255 (15%)	60 (23%)	

ACC/AHA PCE, American College of Cardiology/American Heart Association pooled cohort equations; ATP-III FRS, Adult Treatment Program III Framingham risk score; IQR, interquartile range; WIHS, Women's Interagency HIV Study.
[a]Comparisons of continuous variables by Wilcoxon rank sum and categorical variables by Fisher's exact test.
[b]ATP-III FRS and ACC/AHA PCE are in women 20–79 and 40–79 years of age, respectively.
[c]ACC/AHA PCE were available for 487 (63%) HIV(−) and 1416 (74%) HIV+ women at the index visit.

having an index visit from 09 January 2012 to 13 March 2019. ACC/AHA PCE were available for 487(63%) seronegative and 1416 (74%) WWH at the index visit (as ACC/AHA PCE are only valid for persons ≥40 years of age).

Prevalence of frailty was 10.1% in seronegative women and 13.3% in WWH at the index visit (Table 2). ATP-III FRS 10-year risk was higher in frail than nonfrail WWH [median (IQR):1% (1–3) vs. 1% (0–2); $P<0.001$; Table 2]. Results for ATP-III FRS were similar for SN women (2% (1–4) vs. 1% (0–2); $P<0.001$). ACC/AHA PCE 10-year risk was also higher in frail than nonfrail WWH [median (IQR)): 4% (2–9) vs. 3% (1–6); $P<0.001$). Results for ACC/AHA PCE were similar for seronegative women [median (IQR):5% (2–11) vs. 3% (1–8); $P=0.01$]. However, when considered by strata of 10-year risk, ACC/AHA PCE and not the ATP-III FRS was associated with frailty status in WWH and HIV seronegative women (Table 2).

Some components of ATP-III FRS and ACC/AHA PCE differed by frailty status at the index visit. Women who were frail were older, more likely to smoke, use antihypertensive medication and be diabetic than women who were not frail, regardless of HIV serostatus (all $P<0.05$); no differences were observed by frailty status in total and HDL cholesterol. SBP was higher among frail vs. nonfrail seronegative women ($P=0.03$) but not in WWH ($P=0.28$).

Repeated measures associations of cardiovascular risk scores with frailty in men

The 1265 seronegative men had a median of 15 (IQR: 5–22) visits during follow-up with ascertainment of ATP-III FRS and FFP at 17 349 visits. The 1396 MWH at the index visit along with $n=46$ MWH who seroconverted during follow-up, had a median of 11(IQR: 5–20) visits with ascertainment of ATP-III FRS and FFP at 17 771 visits.

As both continuous measures and by risk strata, ATP-III FRS and ACC/AHA PCE were associated with frailty in both seronegative men and MWH, in unadjusted and adjusted analyses(all $P<0.001$; Table 3). Odds ratios (ORs) for frailty were uniformly higher in seronegative men vs. MWH. The odds of frailty associated with high risk (≥7.5%) ACC/AHA PCE were OR = 1.98 (95%

Table 3. Repeated measures logistic regression of cardiovascular risk scores with frailty in Multicenter AIDS Cohort Study men.[a,b,c]

	HIV(−) ($n = 17\,349$ study visits; 1518 frail visits)			HIV+ ($n = 17\,771$ study visits, 2138 frail visits)		
	OR	95% CI	P^a	OR	95% CI	P^a
Cardiovascular risk scores, continuous						
ATP-III FRS (%) (unadjusted)	1.05	1.04–1.06	<0.001	1.04	1.03–1.05	<0.001
ATP-III FRS (%) (adjusted)	1.05	1.04–1.06	<0.001	1.04	1.03–1.05	<0.001
ACC/AHA PCE (%) (unadjusted)	1.04	1.04–1.05	<0.001	1.03	1.03–1.04	<0.001
ACC/AHA PCE (%) (adjusted)	1.04	1.03–1.05	<0.001	1.03	1.02–1.04	<0.001
Cardiovascular risk scores, strata						
ATP-III FRS (%)						
Low risk (<10%)	Ref			Ref		
Moderate risk (10–20%) (unadjusted)	1.53	1.35–1.75	<0.001	1.30	1.15–1.47	<0.001
Moderate risk (10–20%) (adjusted)	1.54	1.34–1.77	<0.001	1.29	1.14–1.47	<0.001
High risk (>20%) (unadjusted)	2.33	1.75–3.10	<0.001	2.00	1.58–2.53	<0.001
High risk (>20%) (adjusted)	2.31	1.74–3.07	<0.001	2.03	1.60–2.58	<0.001
ACC/AHA PCE (%)						
Low risk (<7.5%)	Ref			Ref		
High risk (≥7.5%) (unadjusted)	2.02	1.74–2.34	<0.001	1.44	1.27–1.63	<0.001
High risk (≥7.5%) (adjusted)[d]	1.98	1.68–2.34	<0.001	1.44	1.26–1.64	<0.001

ACC/AHA PCE, American College of Cardiology/American Heart Association pooled cohort equations; ATP-III FRS, Adult Treatment Program III Framingham risk score; CI, confidence interval; MACS, Multicenter AIDS Cohort Study; OR, odds ratio.
[a]Adjusted analyses include as covariates: education, income, cholesterol medication use, HCV serostatus, and in HIV+ participants, $CD4^+$ cell count, ART therapy and suppressed HIV viral load.
[b]ATP-III FRS and ACC/AHA PCE are in men 20–79 and 40–79 years of age, respectively.
[c]ACC/AHA PCE were available for 15 681 (90%) HIV- and 15 394 (87%) HIV+ study visits.
[d]$P_{\text{Interaction}} = 0.003$ by HIV serostatus.

CI: 1.68–2.34; $P < 0.001$) in seronegative men and OR = 1.44 (95% CI: 1.26–1.64; $P < 0.001$) in MWH. There was significant interaction by HIV serostatus for the association of ACC/AHA PCE high risk ($P_{\text{Interaction}} = 0.003$) with frailty in adjusted analyses. In contrast, there was no interaction by HIV serostatus for the associations of ATP-III FRS moderate ($P_{\text{Interaction}} = 0.15$) and high ($P_{\text{Interaction}} = 0.46$) risk strata with frailty in adjusted analyses.

Repeated measures associations of cardiovascular risk scores with frailty in women

The 768 seronegative women had a median of 2 (IQR: 1–3) visits during follow-up with ascertainment of ATP-III FRS and FFP at 1718 visits. The 1924 WWH had a median of 2 (IQR: 1–3) visits during follow-up with ascertainment of ATP-III FRS and FFP at 4546 visits.

As continuous measures, ATP-III FRS and ACC/AHA PCE risk scores were associated with frailty among seronegative women and WWH in unadjusted analyses. Continuous ATP-III FRS and ACC/AHA PCE risk scores remained associated with frailty in adjusted analyses in WWH and seronegatives, respectively (both $P < 0.05$; Table 4). However, moderate (10–20%) and high (>20%) risk strata of ATP-III FRS were not statistically associated with frailty in seronegative women or WWH in either unadjusted or adjusted analyses (Table 4). In contrast, high (≥7.5%) risk ACC/AHA PCE was associated with frailty in both seronegative women and WWH, in unadjusted and adjusted analyses – adjusted ORs were 1.43 (95% CI: 1.02–2.00; $P = 0.04$) for seronegative women and 1.36 (95% CI: 1.08–1.71; $P = 0.01$) for WWH.

Cardiovascular risk score associations with incident frailty in men

The 1072 seronegative men without frailty at the index visit and with at least two follow-up visits after the index visit had a median follow-up time of 9.9 years (IQR: 4.5–12.8), with incident frailty in 318. The 1119 MWH without frailty at the index visit and with at least two follow-up visits after the index visit had a median follow-up time of 6.5 years (IQR: 3.5–12.2), with incident frailty in 391. Kaplan–Meier curves of frailty-free survival in seronegative men and MWH by ATP-III FRS and ACC/AHA PCE risk strata are shown in Fig. 1, panels a–d. Incident frailty differed by ATP-III FRS and ACC/AHA PCE risk strata in seronegative men and MWH using global log-rank tests (Fig. 1).

As continuous measures, ATP-III FRS and ACC/AHA PCE at the index visit were associated with incident frailty among both HIV serostatus groups, in unadjusted and adjusted analyses (all $P < 0.001$, Supplementary Table 1, http://links.lww.com/QAD/C344). ATP-III FRS and ACC/AHA PCE risk strata were also associated with incident frailty among these groups in unadjusted analyses (Supplementary Table 1, http://links.lww.com/QAD/C344). In adjusted analyses, moderate risk ATP-III FRS (10–20%) status at index visit was associated with incident frailty in seronegative men (hazard ratio = 2.09, 95% CI: 1.65–2.64; $P < 0.001$) but not among MWH (hazard ratio = 1.28, 95% CI: 1.00–1.63; $P = 0.05$)). High risk

Table 4. Repeated measures logistic regression of cardiovascular risk scores with frailty in Women's Interagency HIV Study women.[a,b,c]

	HIV- ($n = 1718$ study visits, 185 frail visits)			HIV+ ($n = 4546$ study visits, 494 frail visits)		
	OR	95% CI	P^a	OR	95% CI	P^a
Cardiovascular risk scores, continuous						
ATP-III FRS (%) (unadjusted)	1.06	1.02–1.10	0.003	1.05	1.02–1.08	<0.001
ATP-III FRS (%) (adjusted)	1.02	0.98–1.07	0.32	1.04	1.01–1.07	0.009
ACC/AHA PCE (%) (unadjusted)	1.03	1.02–1.04	<0.001	1.02	1.01–1.03	<0.001
ACC/AHA PCE (%) (adjusted)	1.02	1.00–1.03	0.01	1.01	1.00–1.02	0.07
Cardiovascular risk scores, strata						
ATP-III FRS (%)						
Low risk (<10%)	Ref			Ref		
Moderate risk (10–20%) (unadjusted)	1.19	0.46–3.05	0.72	1.23	0.76–2.00	0.40
Moderate risk (10–20%) (adjusted)	0.83	0.33–2.09	0.69	1.11	0.68–1.81	0.67
High risk (>20%) (unadjusted)	1.65	0.48–5.62	0.42	0.78	0.19–3.24	0.73
High risk (>20%)(adjusted)	1.03	0.30–3.49	0.96	0.86	0.23–3.20	0.82
ACC/AHA PCE (%)						
Low risk (<7.5%)	Ref			Ref		
High risk (≥7.5%) (unadjusted)	1.77	1.29–2.43	<0.001	1.52	1.22–1.90	<0.001
High risk (≥7.5%) (adjusted)	1.43	1.02–2.00	0. 04	1.36	1.08–1.71	0.01

ACC/AHA PCE, American College of Cardiology/American Heart Association pooled cohort equations; ATP-III FRS, Adult Treatment Program III Framingham risk score; CI, confidence interval; OR, odds ratio; WIHS, Women's Interagency HIV Study.
[a]Adjusted analyses include as covariates: education, income, cholesterol medication use, HCV serostatus, and in HIV+ participants, $CD4^+$ cell count, ART therapy and suppressed HIV viral load.
[b]ATP-III FRS and ACC/AHA PCE are in women 20–79 and 40–79 years of age, respectively.
[c]ACC/AHA PCE were available for 1432 (83%) HIV(−) and 4029 (89%) HIV+ study visits.

(>20%) ATP-III FRS status was associated with incident frailty in both seronegative men (hazard ratio = 2.12, 95% CI: 1.22–3.69; $P = 0.008$) and MWH (hazard ratio = 2.19, 95% CI: 1.33–3.61; $P = 0.002$) in adjusted analysis. Similarly, high-risk (≥7.5%) ACC/AHA PCE status at index visit was associated with incident frailty in seronegative men (hazard ratio = 1.88, 95% CI: 1.48–2.39; $P < 0.001$) and MWH (hazard ratio = 1.59, 95% CI: 1.26–2.00; $P < 0.001$) in adjusted analyses (Supplementary Table 1, http://links.lww.com/QAD/C344). Although unadjusted and adjusted hazard ratios for incident frailty were sometimes higher in seronegative men compared with MWH, there was no interaction by HIV serostatus for associations of moderate and high-risk ATP-III FRS($P_{\text{Interaction}} = 0.17$ and 0.37, respectively) or high-risk ACC/AHA PCE($P_{\text{Interaction}} = 0.68$) in adjusted analyses.

Discussion

Associations of individual CVD risk factors including hypertension, diabetes, smoking, and abdominal obesity have been observed with prevalent and/or incident frailty in middle-aged and older PWH and seronegative adults [3,16,34,40–42]. Few studies, however, have considered CVD risk scores as used in clinical practice in relation to frailty [43]. We observed that high 10-year CVD risk as defined by 2013 ACC/AHA guidelines was positively associated with frailty among both men and women regardless of HIV serostatus. In contrast, high CHD risk as defined by 2001 ATP-III guidelines was positively associated with frailty among men only. These findings are important as frailty is common in middle-aged populations of PWH like MACS and WIHS in the United States, and among some middle-aged PWH living in low-income and middle-income countries [7].

ATP-III FRS risk scores were low (median: 1– 2%) at the index visit among women regardless of HIV serotatus. Age is included not only as a component of the ATP-III FRS risk score equations but also serves as a modifier of the contribution of smoking and total cholesterol [24]. It is possible that the relatively young age of WIHS women with and without frailty (median ages: 42–48 years) contributed to these low FRS risk scores. Age is included differently in ACC/AHA PCE risk score calculations [25], as PCE predicts both CHD and stroke. This could explain why ACC/AHA PCE risk scores were higher (median: 3–5%) than those of ATP-III FRS at the WIHS index visit. However, in a sample constituted of predominantly male Dutch PWH, ATP-III FRS risk scores were higher than ACC/AHA PCE risk scores [18], whereas among MACS seronegative men, the two algorithms yielded similar CVD risk. Another difference between ATP-III FRS and ACC/AHA PCE is inclusion of African American race in ACC/AHA PCE equations – WIHS women are mostly African American whereas MACS includes majority white men.

Associations of ATP-III FRS and ACC/AHA PCE risk scores with frailty were stronger among the seronegative men as compared with MWH, similar to data from a

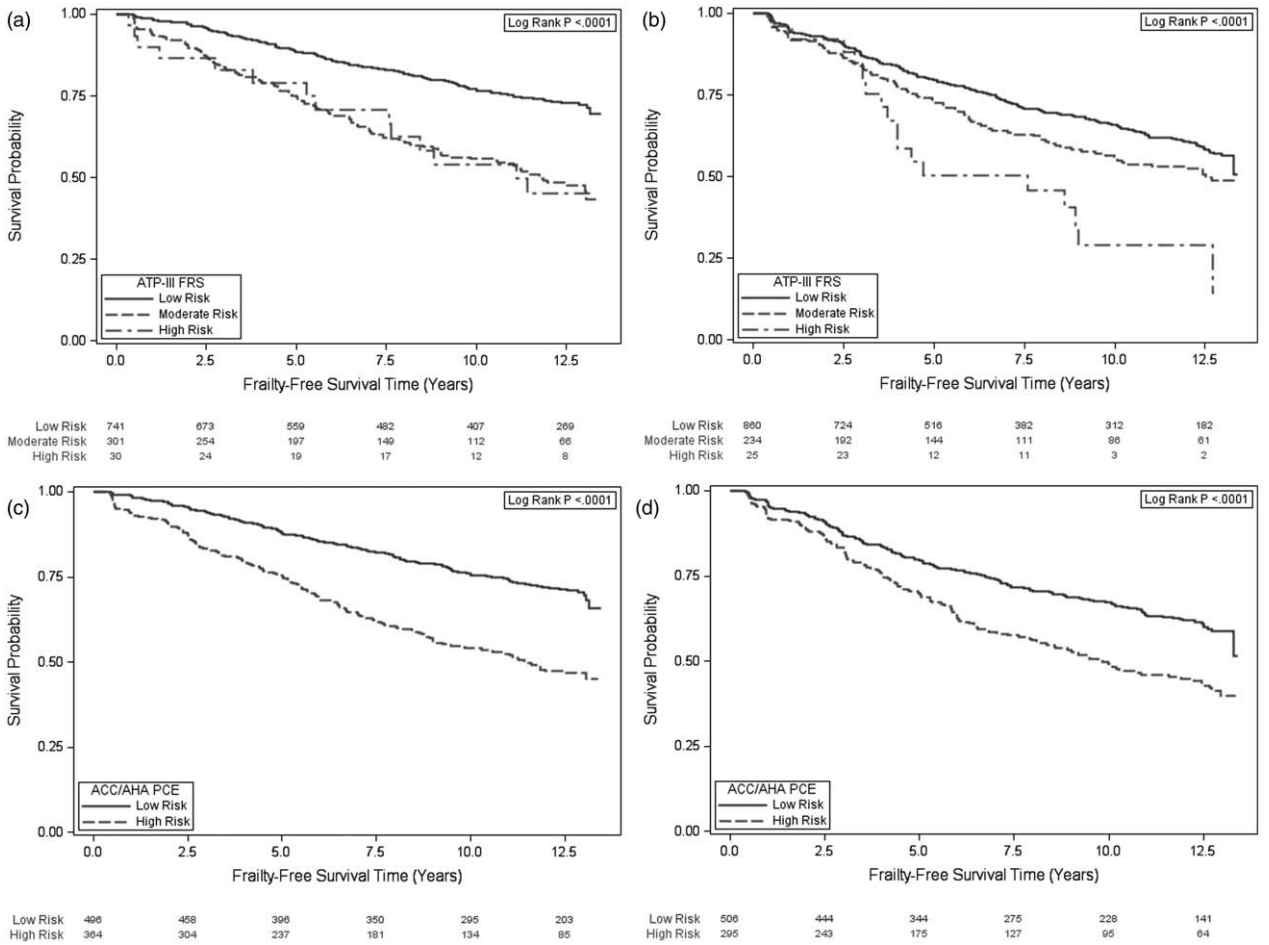

Fig. 1. Kaplan–Meier curves for frailty-free survival. (a) HIV(−) men by ATP-III FRS risk; (b) HIV(+) men by ATP-III FRS risk; (c) HIV(−) men by ACC/AHA PCE risk; (d) HIV(+) men by ACC/AHA PCE risk. For ATP-III FRS, individuals with more than 20% estimated risk of CHD within 10 years are high risk; persons with 10–20% risk are moderate risk, and persons with less than 10% risk are low risk. Individuals with ACC/AHA PCE at least 7.5% have high 10-year risk of ASCVD whereas those with ACC/AHA PCE less than 7.5% have low 10-year risk of ASCVD. ACC/AHA, American College of Cardiology/American Heart Association; CHD, coronary heart disease; FRS, Framingham risk score; PCE, pooled cohort equations.

MACS study in which FFP was associated with subclinical coronary atherosclerosis among seronegative men but not MWH [10]. One hypothesis to explain these observations is that a greater proportion of the variance in frailty is explained by CVD in seronegative men. HIV infection, including in MWH who consume ART with 100% adherence, may be associated with immune activation and systemic inflammation [44,45], which may also contribute to frailty, but to a lesser extent than CVD. Regardless, our findings are consistent with the concept that CVD contributes to frailty [11]. For example, among participants in the AIDS Clinical Trials Group A5322 HIV Infection, Aging, Immune Function Long-Term Observational Study, frailty at baseline was associated with incident CVD with incidence rate ratio of 3.83 (95% CI: 1.59–9.23) over a median of 4.0 years of follow-up [46].

This study has a number of strengths including clinically standardized frailty measurements and CVD risk factors, every 6-month follow-up, multisite representation across the United States, and inclusion of control groups of both women and men living without HIV. These strengths notwithstanding, limitations should be considered in interpretating our findings. First, there is no consensus on a single definition of frailty. The FFP reflects a physical phenotype whereas other measures are based on accumulation of deficits or other frameworks [47,48]. Moreover, optimal cut-points and algorithms to define 'weakness' (e.g. grip/BMI, grip/body weight) and 'slowness' (e.g. walking speed/body height) in relation to the frailty outcome are an area of active investigation [49,50]. Different methods to define the FFP components might lead to different findings as compared with FFP based on average grip and walk speed and comparisons by HIV serostatus, as in this investigation and prior studies [3,10,34]. Second, although ATP-III FRS and 2013 ACC/AHA PCE have been widely used in clinical practice, they represent two of several validated CVD risk

scores (e.g. FRS ASCVD [51], 2019 ACC/AHA PCE [52], Systematic Coronary Risk Evaluation(SCORE) [53], and Data collection on Adverse Effects of Anti-HIV Drugs Study (D:A:D) [54]). Different CVD risk equations may have different associations with frailty as for CVD events [22,23] and subclinical CVD [20], which can vary by race/ethnicity [19]. Notably, the 2019 ACC/AHA guideline uses the same PCE as the 2013 ACC/AHA guideline. However, at least 7.5% 10-year ASCVD risk is considered high risk in the 2013 guideline but at least 7.5 to less than 20% is considered intermediate risk in the 2019 guideline, and HIV infection is considered a risk-enhancing factor that would favor initiation of statin therapy particularly in borderline (5 to <7.5%) and intermediate-risk groups [52]. Finally, our study of frailty did not exclude participants who might have been excluded in a study of cardiovascular endpoints – those with self-reported CVD (myocardial infarction or heart attack, revascularization or angioplasty, transient ischemic attack/stroke, angina or hospitalization for heart condition).

In conclusion, these data suggest that CVD risk prediction tools may be valuable in clinical practice to identify PWH and seronegative adults who may benefit from frailty phenotyping to reduce consequences of frailty onset including falls, hospitalization, disability, and mortality. Unfortunately, one of the reasons that frailty is not assessed more often clinically is lack of consensus around a single reliable metric. Frailty screening under accumulation of deficit models may be well suited to screening patients in ICUs [55]. For example, 234 568 critically ill patients were screened under a single protocol [56]. Protocols for physical frailty assessment have included hospitalized patients as well as community-dwelling participants, those living in long-term care/assisted living facilities and outpatients [57]. It may be that optimal frailty screening strategies will differ according to the population to be screened. Ultimately implementation science strategies are needed to assess if, how and when CVD risk assessment should be part of best practices for frailty identification and intervention in diverse settings among men and women with or at risk for HIV.

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Conflicts of interest

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