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## CARDIOVASCULAR RISK SCORE ASSOCIATIONS WITH FRAILTY IN MEN AND WOMEN WITH OR AT RISK FOR HIV

Mark H. KUNIHOLM<sup>1</sup>, Elizabeth VÁSQUEZ<sup>1</sup>, Allison A. APPLETON<sup>1</sup>, Lawrence KINGSLEY<sup>2</sup>, Frank J. PALELLA<sup>3</sup>, Matthew BUDOFF<sup>4</sup>, Erin D. MICHOS<sup>5</sup>, Ervin FOX<sup>7</sup>, Deborah JONES<sup>8</sup>, Adaora A. ADIMORA<sup>9</sup>, Igbo OFOTOKUN<sup>10</sup>, Gypsyamber D'SOUZA<sup>6</sup>, Kathleen M. WEBER<sup>11</sup>, Phyllis C. TIEN<sup>12</sup>, Michael PLANKEY<sup>13</sup>, Anjali SHARMA<sup>14</sup>, Deborah R. GUSTAFSON<sup>15</sup>

<sup>1</sup>Department of Epidemiology and Biostatistics, University at Albany, State University of New York, Rensselaer, NY;

<sup>2</sup>Department of Infectious Diseases and Microbiology, University of Pittsburgh, Pittsburgh, PA;

<sup>3</sup>Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL;

<sup>4</sup>Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA;

<sup>5</sup>Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD;

<sup>6</sup>Department of Epidemiology, Johns Hopkins Medical Institutions, Baltimore, MD;

<sup>7</sup>Department of Medicine, University of Mississippi Medical Center, Jackson, MS;

<sup>8</sup>Department of Psychiatry & Behavioral Sciences, Miller School of Medicine, University of Miami, Miami, FL;

<sup>9</sup>Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC;

<sup>10</sup>Department of Medicine, Emory University School of Medicine, Atlanta, GA;

<sup>11</sup>Cook County Health/Hektoen Institute of Medicine, Chicago, IL;

<sup>12</sup>Department of Medicine, University of California, San Francisco, and Department of Veterans Affairs, San Francisco, CA;

<sup>13</sup>Department of Medicine, Georgetown University Medical Center, Washington, DC;

<sup>14</sup>Department of Medicine, Albert Einstein College of Medicine, Bronx, NY;

<sup>15</sup>Department of Neurology, State University of New York Downstate Health Sciences University, Brooklyn, NY

### Abstract

**CORRESPONDING AUTHOR:** Mark H. Kuniholm, PhD, Department of Epidemiology & Biostatistics, University at Albany, State University of New York, GEC 137, One University Place, Rensselaer, NY 12144. Phone: (518) 402-0397. Fax: (518) 402-0380. mkuniholm@albany.edu.

Author roles:

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**OBJECTIVE:** To understand the relationship between cardiovascular disease (CVD) risk and frailty among men (MLWH) and women living with HIV (WLWH), 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 2004–2019 and in WIHS from 2005–2006 and 2011–2019. FFP score  $\geq 3/5$  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 MLWH and WLWH, CD4 cell count/mL, antiretroviral therapy and HIV viral load.

**RESULTS:** There were 5,554 participants (1,265 HIV seronegative [SN]/1,396 MLWH; 768 SN/1,924 WLWH) included. Among men, high-risk FRS was associated with increased risk of incident frailty among SN (adjusted hazard ratio(aHR))=2.12, 95% CI:1.22–3.69) and MLWH (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 MLWH (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 WLWH (aOR=1.36, 95% CI:1.08–1.71); however high-risk FRS was not (SN:aOR=1.03, 95% CI:0.30–3.49; WLWH:aOR=0.86, 95% CI:0.23–3.20).

**CONCLUSIONS:** 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.

### Keywords

HIV; cardiovascular risk; frailty; men; women; cohort

## INTRODUCTION

Frailty is characterized by physical weakness and a marked decline of physiologic reserve. [1] Higher prevalence of frailty has been reported among people living with human immunodeficiency virus (PLWH) compared to adults without HIV infection in the United States(US),[2–4] Europe,[5] China,[6] and Africa,[7] suggesting that PLWH 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 PLWH 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 (MLWH).[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 co-morbidities 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 versus 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 PLWH.[17–23] However, traditional CVD risk prediction tools underperform among PLWH, 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, since they were released a decade apart, there was an expansion of statin eligibility in the 2013 ACC/AHA guidelines compared to 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, systolic blood pressure (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 because 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 paper 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 US.

## METHODS

### Study Populations

The MACS and WIHS (now known as the MACS/WIHS Combined Cohort Study[27]) were prospective multi-center cohorts of US 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 4 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 six 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  $\geq 20$  years (Supplementary Figure 1). 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 since that is the age group for which the ACC/AHA PCE is valid.[25] FFP characteristics in MACS were ascertained at all 4 MACS sites during 2004–2019. In contrast, frailty in WIHS was assessed at 6 sites at a single time point between 2005–2006,[3, 33] in a sub-group of 3 of the 6 sites during 2012–2014, and then annually at 9 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: 1) slow walking speed, 2) weakness (reduced grip strength), and self-reported 3) physical exhaustion, 4) low physical activity and 5) unintentional weight loss. Walking speed was measured using a 3 or 4 meter timed gait test, and impaired walking speed was defined as  $\leq 80$ th percentile of SN 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 (3 trials)  $\leq 20$ th percentile of SN 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, IN). 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  $\geq 7.5\%$  were considered at high 10-year risk of ASCVD while those with ACC/AHA PCE  $<7.5\%$  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: \$6,000, \$6,001–\$18,000, \$18,001; MACS: \$20,000, \$20,000–\$39,999, \$40,000), cholesterol medication usage and hepatitis C virus (HCV) serostatus. HCV was selected because it affects cholesterol metabolism in SN[35] and PLWH[36] and predicts CVD events in PLWH. [37] A non-invasive measure of liver fibrosis (FIB-4) was also associated with frailty in WIHS[3] and HCV is associated with immune dysregulation in PLWH[38, 39] which could contribute to frailty. Among PLWH-only, models also included CD4 T cell count/mL, use of antiretroviral therapy (ART), 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 due to 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 ≥ 2 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 measures over time. SAS version 9.4 (SAS Institute Inc, Cary, NC) 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 1 MACS visit among 1,265 SN men and 1,396 men living with HIV (MLWH). The median date of the index visit was 02/14/2006 (IQR: 10/29/2005–08/10/2006) for SN men and 03/20/2006 (IQR: 12/19/2005–05/24/2011) for MLWH. The ACC/AHA PCE risk score was available for 1010 (80%) SN and 997 (71%) MLWH at the index visit.

Prevalence of frailty was 6.1% in SN men and 9.0% in MLWH at the index visit (Table 1). In both SN men and MLWH, ATP-III FRS 10-year risk was higher in frail (median (IQR): 10%(5–16) and 6%(3–12), respectively) vs. non-frail (median (IQR): 6%(2–10) and 4%(1–8), respectively) men (both  $P < 0.001$ –Table 1). Similarly, in SN men and MLWH, ACC/AHA PCE 10-year risk was higher in frail (median (IQR): 10%(7–19%) and 8%(4–14%), respectively) vs. non-frail (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 SN men and MLWH (all  $P < 0.001$ ).

CVD risk score components associated with frailty in both SN men and MLWH included age, smoking, antihypertensive medication use, and diabetes (all  $P < 0.05$ ). In addition, among SN men, those who were frail were more likely to be Black or African American, while frail MLWH 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 1 WIHS visit among 768 SN women and 1,924 WLWH. Of these, 60% ( $n = 460$ ) of SN women and 62% ( $n = 1,202$ ) of WLWH had an index visit from 04/04/2005–03/28/2006 with the remainder having an index visit from 01/09/2012–03/13/2019. ACC/AHA PCE were available for 487 (63%) SN and 1,416 (74%) WLWH at the index visit (because ACC/AHA PCE are only valid for persons  $\geq 40$  years of age).

Prevalence of frailty was 10.1% in SN women and 13.3% in WLWH at the index visit (Table 2). ATP-III FRS 10-year risk was higher in frail than non-frail WLWH (median (interquartile range (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 non-frail WLWH (median (IQR): 4%(2–9) vs 3%(1–6);  $P < 0.001$ ). Results for ACC/AHA PCE were similar for SN 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 WLWH and HIV SN 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 versus non-frail SN women ( $P = 0.03$ ) but not in WLWH ( $P = 0.28$ ).

### Repeated measures associations of cardiovascular risk scores with frailty in men

The 1,265 SN 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 1,396 MLWH at the index visit along with  $n = 46$  MLWH 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 SN men and MLWH, in unadjusted and adjusted analyses (all  $P < 0.001$ –Table 3). Odds ratios (ORs) for frailty were uniformly higher in SN men vs.

MLWH. The odds of frailty associated with high risk (7.5%) ACC/AHA PCE were  $OR=1.98(95\%CI:1.68,2.34;P<0.001)$  in SN men and  $OR=1.44(95\%CI:1.26,1.64;P<0.001)$  in MLWH. There was significant interaction by HIV serostatus for the association of ACC/AHA PCE high risk ( $P_{Interaction}=0.003$ ) with frailty in adjusted analyses. In contrast, there was no interaction by HIV serostatus for the associations of ATP-III FRS moderate ( $P_{Interaction}=0.15$ ) and high ( $P_{Interaction}=0.46$ ) risk strata with frailty in adjusted analyses.

### Repeated measures associations of cardiovascular risk scores with frailty in women

The 768 SN women had a median of 2(IQR:1–3) visits during follow-up with ascertainment of ATP-III FRS and FFP at 1,718 visits. The 1,924 WLWH had a median of 2(IQR:1–3) visits during follow-up with ascertainment of ATP-III FRS and FFP at 4,546 visits.

As continuous measures, ATP-III FRS and ACC/AHA PCE risk scores were associated with frailty among SN women and WLWH in unadjusted analyses. Continuous ATP-III FRS and ACC/AHA PCE risk scores remained associated with frailty in adjusted analyses in WLWH and SN, 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 SN women or WLWH in either unadjusted or adjusted analyses (Table 4). In contrast, high (7.5%) risk ACC/AHA PCE was associated with frailty in both SN women and WLWH, in unadjusted and adjusted analyses – adjusted ORs were  $1.43(95\%CI:1.02,2.00;P=0.04)$  for SN women and  $1.36(95\%CI:1.08,1.71;P=0.01)$  for WLWH.

### Cardiovascular risk score associations with incident frailty in men

The 1,072 SN men without frailty at the index visit and with 2 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 1,119 MLWH without frailty at the index visit and with 2 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 SN men and MLWH by ATP-III FRS and ACC/AHA PCE risk strata are shown in Figure 1, panels A-D. Incident frailty differed by ATP-III FRS and ACC/AHA PCE risk strata in SN men and MLWH using global log-rank tests (Figure 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). ATP-III FRS and ACC/AHA PCE risk strata were also associated with incident frailty among these groups in unadjusted analyses (Supplementary Table 1). In adjusted analyses, moderate risk ATP-III FRS (10–20%) status at index visit was associated with incident frailty in SN men (hazard ratio (HR)= $2.09,95\%CI:1.65, 2.64;P<0.001$ ) but not among MLWH (HR= $1.28,95\%CI:1.00,1.63;P=0.05$ ). High risk (>20%) ATP-III FRS status was associated with incident frailty in both SN men (HR= $2.12,95\%CI:1.22,3.69;P=0.008$ ) and MLWH (HR= $2.19,95\%CI:1.33,3.61;P=0.002$ ) in adjusted analysis. Similarly, high risk (7.5%) ACC/AHA PCE status at index visit was associated with incident frailty in SN men (HR= $1.88,95\%CI:1.48,2.39;P<0.001$ ) and MLWH (HR= $1.59,95\%CI:1.26,2.00;P<0.001$ ) in adjusted analyses (Supplementary Table 1). While unadjusted and adjusted HRs for

incident frailty were sometimes higher in SN men compared to MLWH, 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 PLWH and SN 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 because frailty is common in middle-aged populations of PLWH like MACS and WIHS in the US, and among some middle-aged PLWH living in low- and middle-income countries.[7]

ATP-III FRS risk scores were low (medians:1%–2%) at the index visit among women regardless of HIV serostatus. 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 (medians:3%–5%) than those of ATP-III FRS at the WIHS index visit. However, in a sample comprised of predominantly male Dutch PLWH, ATP-III FRS risk scores were higher than ACC/AHA PCE risk scores,[18] while among MACS SN 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 SN men as compared to MLWH, similar to data from a MACS study in which FFP was associated with subclinical coronary atherosclerosis among SN men but not MLWH.[10] One hypothesis to explain these observations is that a greater proportion of the variance in frailty is explained by CVD in SN men. HIV infection, including in MLWH 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 six month follow-up, multi-site representation across the US, and inclusion of control groups of both women and men living without HIV. These strengths notwithstanding, limitations should be considered in interpreting 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/body mass index, 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 to FFP based on average grip and walk speed and comparisons by HIV serostatus, as in this investigation and prior studies.[3, 10, 34] Second, while 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, 7.5% 10-year ASCVD risk is considered high risk in the 2013 guideline but 7.5% to <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 PLWH and SN 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 deficits models may be well-suited to screening patients in intensive care units.[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 out-patients. [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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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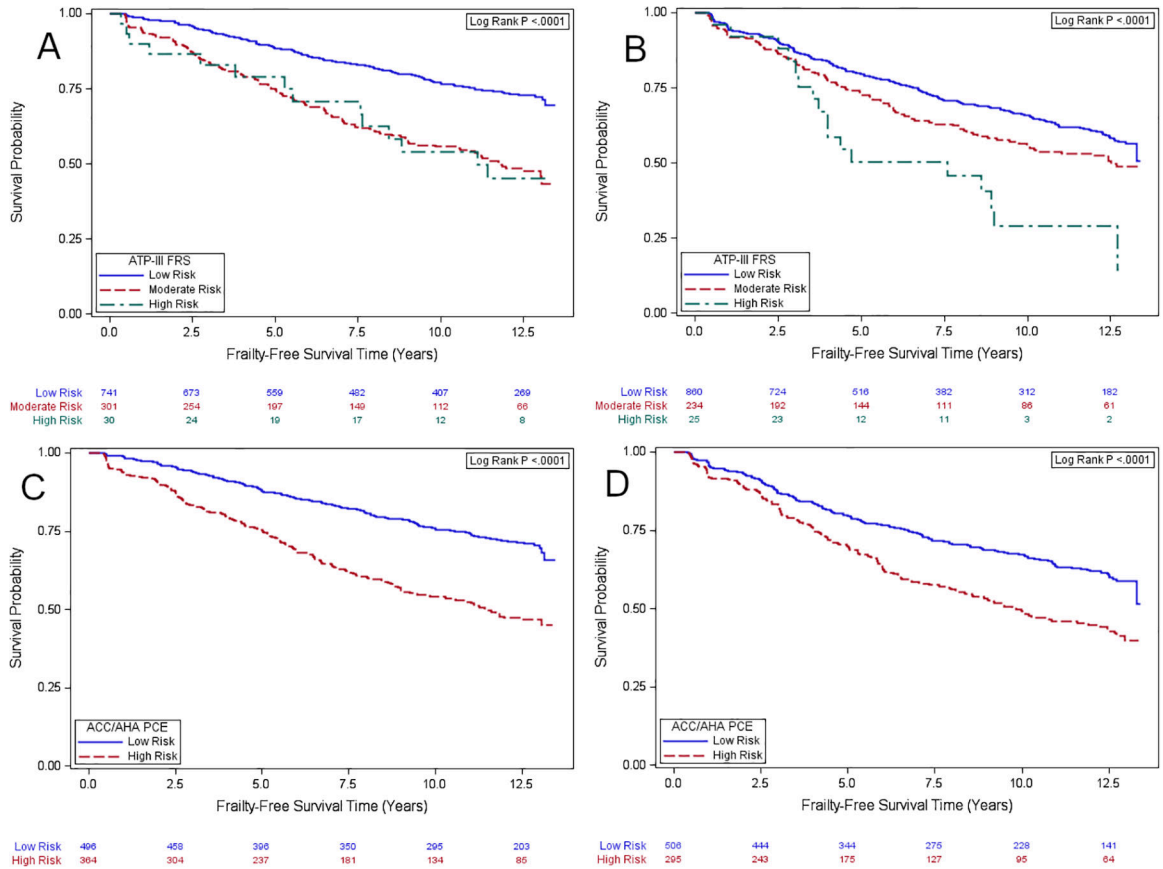
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**Figure 1.** Kaplan-Meier curves for frailty-free survival: (A) HIV(-) men by ATP-III FRS risk; (B) HIV(+) men by ATP-III FRS risk; (C) HIV(-) men by ACC/AHA PCE risk; (D) HIV(+) men by ACC/AHA PCE risk. For ATP-III FRS, individuals with >20% estimated risk of CHD within 10 years are high risk; persons with 10–20% risk are moderate risk, and persons with <10% risk are low risk. Individuals with ACC/AHA PCE  $\geq 7.5\%$  have high 10-year risk of ASCVD while those with ACC/AHA PCE <7.5% have low 10-year risk of ASCVD

**Table 1.**Cardiovascular risk scores and their components in MACS men at the index visit<sup>a,b,c</sup>

	HIV- (n=1,265)		<i>P</i> <sup>a</sup>	HIV+ (n=1,396)		<i>P</i> <sup>a</sup>
	Not frail (n=1187)	Frail (n=78)		Not frail (n=1270)	Frail (n=126)	
Cardiovascular risk scores, median (IQR)						
ATP-III FRS, % <sup>b</sup>	6 (2–10)	10 (5–16)	<0.001	4 (1–8)	6 (3–12)	<0.001
ACC/AHA PCE, % <sup>b,c</sup>	6 (4–11)	10 (7–19)	<0.001	6 (3–9)	8 (4–14)	<0.001
Cardiovascular risk scores, strata						
ATP-III FRS, % <sup>b</sup>			<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, % <sup>b,c</sup>			<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; HIV: human immunodeficiency virus; IQR: interquartile range; MACS: Multicenter AIDS Cohort Study; SBP: systolic blood pressure

<sup>a</sup>Comparisons of continuous variables by Wilcoxon rank sum and categorical variables by Fisher's exact test

<sup>b</sup>ATP-III FRS and ACC/AHA PCE are in men 20–79 and 40–79 years of age, respectively

<sup>c</sup>ACC/AHA PCE were available for 1010 (80%) HIV- and 997 (71%) HIV+ men at the index visit

**Table 2.**Cardiovascular risk scores and their components in WIHS women at the index visit <sup>a,b,c</sup>

	HIV- (n=768)		<i>p</i> <sup>a</sup>	HIV+ (n=1924)		<i>p</i> <sup>a</sup>
	Not frail (n=690)	Frail (n=78)		Not frail (n=1668)	Frail (n=256)	
Cardiovascular risk scores, median (IQR)						
ATP-III FRS, % <sup>b</sup>	1 (0–2)	2 (1–4)	<0.001	1 (0–2)	1 (0–3)	<0.001
ACC/AHA PCE, % <sup>b,c</sup>	3 (1–8)	5 (2–11)	0.011	3 (1–6)	4 (2–9)	<0.001
Cardiovascular risk scores, strata						
ATP-III FRS, % <sup>b</sup>			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, % <sup>b,c</sup>			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; HIV: human immunodeficiency virus; IQR: interquartile range; SBP: systolic blood pressure; WIHS: Women's Interagency HIV Study

<sup>a</sup>Comparisons of continuous variables by Wilcoxon rank sum and categorical variables by Fisher's exact test

<sup>b</sup>ATP-III FRS and ACC/AHA PCE are in women 20–79 and 40–79 years of age, respectively

<sup>c</sup>ACC/AHA PCE were available for 487 (63%) HIV- and 1,416 (74%) HIV+ women at the index visit



**Table 3.**Repeated measures logistic regression of cardiovascular risk scores with frailty in MACS men <sup>a,b,c</sup>

	HIV- (n=17,349 study visits; 1,518 frail visits)			HIV+ (n=17,771 study visits, 2,138 frail visits)		
	OR	95% CI	<i>P</i> <sup>a</sup>	OR	95% CI	<i>P</i> <sup>a</sup>
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) <sup>d</sup>	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; HIV: human immunodeficiency virus; MACS: Multicenter AIDS Cohort Study; OR: odds ratio;

<sup>a</sup>Adjusted analyses include as covariates: education, income, cholesterol medication use, HCV serostatus, and in HIV+ participants, CD4 count, ART therapy and suppressed HIV viral load

<sup>b</sup>ATP-III FRS and ACC/AHA PCE are in men 20–79 and 40–79 years of age, respectively

<sup>c</sup>ACC/AHA PCE were available for 15,681 (90%) HIV- and 15,394 (87%) HIV+ study visits

<sup>d</sup>*P*<sub>Interaction</sub> = 0.003 by HIV serostatus

**Table 4.**Repeated measures logistic regression of cardiovascular risk scores with frailty in WIHS women <sup>a,b,c</sup>

	HIV- (n=1,718 study visits, 185 frail visits)			HIV+ (n=4,546 study visits, 494 frail visits)		
	OR	95% CI	<i>P</i> <sup>a</sup>	OR	95% CI	<i>P</i> <sup>a</sup>
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; HIV: human immunodeficiency virus; OR: odds ratio; WIHS: Women's Interagency HIV Study

<sup>a</sup> Adjusted analyses include as covariates: education, income, cholesterol medication use, HCV serostatus, and in HIV+ participants, CD4 count, ART therapy and suppressed HIV viral load

<sup>b</sup> ATP-III FRS and ACC/AHA PCE are in women 20–79 and 40–79 years of age, respectively

<sup>c</sup> ACC/AHA PCE were available for 1,432 (83%) HIV- and 4,029 (89%) HIV+ study visits