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Frailty and Pre-Frailty in a Contemporary Cohort of HIV-Infected Adults

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Abstract

Objectives—To determine the prevalence of pre-frailty among HIV-infected persons and associations with pre-frailty and frailty in this population.

Design, Setting and Participants—From a contemporary, prospective observational cohort of HIV-infected persons (SUN Study), we determined, using a cross-sectional analytic study design, the proportions of non-frail, pre-frail, and frail persons by the respective presence of 0, 1-2, and 3 of 5 established frailty criteria: unintentional weight loss, exhaustion, physical-inactivity, weak-grip and slow-walk. We evaluated associations with pre-frailty/frailty using multivariate analysis.

Results—Of 322 participants assessed (79% men, 58% white non-Hispanic, median age 47 years, 95% on combination antiretroviral therapy [cART], median CD4 + cell count 641 cells/mm³ and 93% HIV RNA < 400 copies/mL), 57% were non-frail, 38% pre-frail, and 5% frail. Age increased from non-frailty through frailty. Notably, however, half of pre-frail and frail participants were < 50 years, and of those, 42% and 100%, respectively, were long-term unemployed (versus 16% of non-frail counterparts). In multivariate analysis, pre-frail/frail participants were more likely to have Hepatitis C seropositivity (adjusted odds ratio [aOR] 3.24, 95% CI: 1.35-7.78), a history of AIDS-defining-illness (aOR 3.51, 95% CI: 1.82-6.76), greater

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depressive symptoms (aOR 1.16, 95% CI:1.09-1.23), higher D-dimer levels (aOR 2.94, 95% CI: 1.10-7.87), and were less likely to be white non-Hispanic (aOR 0.35, 95% CI: 0.20-0.61).

Conclusions—Pre-frailty and frailty are prevalent in the cART era and are associated with unemployment even among persons < 50 years. Pre-frailty appears to be an intermediate state in the spectrum from non-frailty through frailty and our characterization of pre-frailty/frailty suggests complex multifactorial associations.

Keywords

Pre-frailty; frailty; HIV; human immunodeficiency virus

Introduction

Frailty is a state of diminished reserve and increased vulnerability due to an accumulation of deficits in multiple physiological domains (1). It is characterized by weight loss, exhaustion, physical inactivity, reduced muscle strength, and slowed motor function but medical and psychosocial comorbidity are also evident (1-6).

Immunodeficiency is associated with HIV-related frailty (6-8), and to higher levels of markers of monocyte/macrophage and T-cell activation (9). The additional contributions of coagulopathy and endocrine dysfunction, as seen in age-related frailty (10, 11), remain to be elucidated.

Lastly, frailty among older HIV-uninfected persons is typically preceded by a subclinical pre-frail state that transitions to frailty once a threshold of physiological dysregulation is reached (3). However, the prevalence and significance of pre-frailty among HIV-infected populations is not well-described. We evaluated the prevalence of non-frailty, pre-frailty, and frailty among HIV-infected participants in the SUN Study (Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy) and examined associations of pre-frailty and frailty with multiple behavioral and clinical factors and biomarkers of inflammation.

Methods

Study Population

The SUN Study is a closed, prospective, observational cohort study funded by the Centers for Disease Control and Prevention (CDC) that monitored the clinical course of persons in the combination antiretroviral therapy (cART) era at seven HIV-specialty clinics in four US cities: St. Louis, MO; Providence, RI; Minneapolis, MN; and Denver, CO. Seven hundred HIV-infected participants were enrolled between March 1, 2004 and June 30, 2006. The study's design and methods have been described previously (12). Participants were generally healthy adults receiving routine outpatient care and were either treatment naïve, or had only received combination antiretroviral therapy (cART). Participant data were abstracted from medical charts and entered into an electronic database (Clinical Practice Analyst; Cerner Corporation, Vienna, VA) by trained staff.

Additional data were collected through biannual study visits and included comprehensive testing for sexually transmitted diseases (STD), and an audio computer-assisted interview about health-related information; tobacco, alcohol, and recreational drug use, assessment of depression (PRIME MD depression screener) and general function (Short Form 12 [SF-12]) (12)). The study protocol was approved and annually reviewed by the CDC and participating sites' institutional review boards.

Frailty assessment

Frailty assessments, using a well-validated and applied frailty appraisal as devised by Fried et al. (1), were incorporated into the SUN Study in June 2010 and prospectively conducted bi-annually thereafter. Only initial frailty assessment data from June 2010 to April 2011 were used for this analysis. The frailty assessment took a few minutes to perform by trained study coordinators. Non-frailty, pre-frailty, and frailty were defined by the presence of 0, 1-2, and 3 of 5 frailty criteria, respectively: unintentional weight loss, physical inactivity, exhaustion, weak grip strength, and slow walk, with modification to accommodate physical inactivity (Table 2).

Data and definitions

Data collected at the time of initial frailty assessment and retrospectively through study enrollment were used. Data at initial frailty assessment included, race/ethnicity (white non-Hispanic versus [vs.] all others), employment status (fulltime/part-time employed vs. unemployed), tobacco use (ever/current vs. never), and recent (past 30 days) alcohol use, as well as the number of days per month in which alcohol was consumed. Long-term unemployment and long-term alcohol use were defined as reports of unemployment and recent alcohol use at 75% of previous visits, respectively.

The variable for 'past depression score' was calculated as the median of all scores from PRIME MD at previous study visits. 'Current depression score' was the score from PRIME MD at initial frailty assessment. Similar assessments were made for statements of perceived general health and past health limitations to moderate activities using the SF-12 (12). 'Past physical inactivity' was present if the median response to past health limitations to moderate activities was "limited a lot".

HIV-related data included history of AIDS-defining opportunistic illnesses (ADI), and cART, CD4+ cell count and HIV viral load history. A plasma HIV RNA concentration of < 400 copies/mL defined viral suppression. Hepatitis C seropositivity defined hepatitis C infection, and detectable serum surface antigen defined active hepatitis B infection. A body mass index (BMI) ≥ 30 kg/m² defined obesity and a BMI < 18.5 kg/m² defined underweight. Chronic kidney disease was defined as a glomerular filtration rate (eGFR) < 60 ml/min/1.73m² calculated using Modification of Diet in Renal Disease (MDRD) formula. The Diabetes Research and Training Center Radioimmunoassay Core Laboratory (Washington University School of Medicine) used stored serum and plasma collected at study entry from all participants to assay select biomarker levels retrospectively. Serum and plasma used for these assays were iced, centrifuged, and stored at -70°C within 24 hours of collection until time of batched assay. We assayed for the following biomarkers: high sensitivity C-reactive

protein (hs-CRP), interleukin-1 (IL-1), IL-6, tumor necrosis factor- α (TNF- α), 25-hydroxyvitamin D, D-dimer, soluble CD-14, and lipoprotein A.

Statistical analysis

Univariate analyses—Descriptive statistics were used to compare characteristics between non-frail, pre-frail and frail groups. Associations between non-frailty, pre-frailty, and frailty were assessed using the chi-square test for categorical variables; a p-value of < 0.001 was considered significant using the Bonferroni correction. For normally distributed and non-normally distributed continuous variables, one-way analysis of variance and the Kruskal-Wallis tests were used, respectively; a p-value of < 0.05 was considered significant for these tests.

Multivariate analyses—Pre-frail and frail categories were collapsed into one outcome to evaluate factors independently associated with pre-frailty/frailty. Categorical variables were analyzed using chi square. For normally distributed and non-normally distributed continuous variables, student t-test and Mann-Whitney test were used, respectively. In order to generate odds ratios (OR) for each continuous variable, all were analyzed individually using logistic regression. Using clinically relevant cut-points, where possible, D-dimer was categorized by a cut-point of $> 0.34 \mu\text{g/mL}$ (13), hsCRP by a cut-point of $> 3.00 \text{ mg/L}$ (14) and 25 hydroxyvitamin D levels by a cut-point of $< 30 \text{ ng/mL}$ (15). The upper quartile levels of TNF- α , sCD14 and lipoprotein A were calculated for all persons and the respective values used as cut-points to calculate the OR categorized by upper quartile vs. the lower quartiles. Cut-points of 200 cells/mm^3 and 350 cells/mm^3 were used to categorize nadir and current CD4+ counts, respectively. All variables associated with pre-frailty/frailty at $p < 0.10$ in univariate analyses were initially included in a multivariate logistic regression model. Variables which were non-significant in the multivariable model ($p > 0.05$) were then eliminated and the model re-fit. The Hosmer-Lemeshow test was used to assess the model's calibration (goodness of fit). All analyses were performed using SPSS version 20.0 (Chicago, IL).

Results

Overall, 346 SUN participants underwent a frailty assessment, however, 24 (7%) participants were excluded from analysis due to missing components of the assessment; all had no positive frailty criteria and exact frailty status could not be ascertained. Ten additional participants also had missing components of the assessment but had 1-2 frailty criteria present. This latter group was included for analysis of the pre-frail/frail group vs. the non-frail group and their characteristics are also presented below.

Therefore of 322 (93%) participants with sufficient data for study analysis; 79% were men, 58% were white non-Hispanic with median age 47 years, 24% had a history of ADI, current median CD4+ cell count was 641 cells/mm^3 , 95% were taking cART, and 93% were virologically suppressed (Table 1).

In total, 176 (57%) participants were non-frail and 146 (43%) had 1 frailty criteria present. Excluding the ten participants mentioned above; 121 (38%) participants were definitively

defined as pre-frail, and 15 (5%) as frail. Most participants were categorized as pre-frail by exhaustion (63%), then physical inactivity (29%). Most persons were categorized as frail by physical inactivity (100%), exhaustion (73%), and weak grip strength (73%) (Table 2). Of note, current depression scores were greater among participants who reported physical inactivity, median 8 (4-13) vs. no physical inactivity 3 (1-7), or exhaustion, median 7 (3-11) vs. no exhaustion 3 (1-6); both $p < 0.001$. Age increased from non-frailty through frailty (Table 1), although half of pre-frail (67/121) and frail (7/15) participants were < 50 years of age (Figure 1). Notably, 42% of pre-frail and 100% of frail participants < 50 years of age were long-term unemployed compared with 16% of non-frail ones. Findings were similar for current unemployment. Lastly, 53% of frail participants perceived their current general health to be either fair or poor compared with 26% of pre-frail and 6% of non-frail participants ($p < 0.001$). Furthermore, 47% of frail participants reported past physical inactivity compared with 7% of pre-frail and 1% of non-frail ones, ($p < 0.001$).

Compared with non-frail participants, pre-frail/frail participants had lower odds of being white non-Hispanic (aOR 0.35, 95%CI: 0.20-0.61), higher odds of hepatitis C seropositivity (aOR 3.24, 95% CI: 1.35-7.78), and higher odds of history of ADI (aOR 3.51, 95% CI: 1.82-6.76) (Table 3). Current depression scores were greater (aOR 1.16, 95% CI: 1.09-1.23) and D-dimer levels were higher (aOR 2.94, 95% CI: 1.10-7.87).

Current CD4+ cell counts and the proportion of participants with viral suppression were comparable between groups. A sub-analysis of participants ($n = 203$) with full viral suppression on cART, demonstrated similar associations excluding hepatitis C seropositivity (results not shown).

Discussion

Among our contemporary cohort of predominantly middle-aged participants with well-controlled HIV infection and high median CD4+ cell counts, we demonstrated a prevalence of frailty of 5%. This was comparable to the lower prevalence reported among similarly aged HIV-infected cohorts (6-8) and among HIV-uninfected persons in their 7th decade of life (1, 3-5, 7, 16). Our pre-frailty prevalence of 38% was comparable to estimates reported among older HIV-uninfected persons (28-51%) (4, 7). Furthermore, half of pre-frail and frail participants in our study were < 50 years of age, a concerning finding given the many comorbidities that affect HIV-infected persons as they age (17) and the higher mortality risk associated with pre-frailty/frailty as determined by the Veterans Aging Cohort (VACS) Index (18). Consistent with studies of the general population, our data also suggest that pre-frailty in the HIV population is an intermediary in the spectrum of progression from non-frailty to frailty (3, 5) and that it is a state more modestly associated with frailty-related factors such as medical and psychosocial comorbidity (6). In this cross-sectional analysis, several factors were associated with pre-frailty/frailty: high D-dimer, history of ADI, hepatitis C seropositivity, and greater current depression score. White non-Hispanic participants were less likely to be pre-frail/frail.

D-dimer, a marker of activation of the coagulation cascade has been associated with incident age-related frailty (19). A low-grade, chronic and systemic pro-inflammatory state

negatively impacts multiple organ systems (11) and is a hallmark of aging, age-related frailty, HIV disease, and increasingly, HIV-related frailty (9). Longitudinal analyses of changes in biomarker levels during progression to frailty would be necessary to further elucidate the role of chronic inflammation and activation of the coagulation cascade in the development of frailty.

Our finding that history of ADI was associated with prevalent pre-frailty/frailty is consistent with other studies (6-8). A history of ADI (clinical immunodeficiency) may confer an increased risk of developing pre-frailty or frailty when, additional physiological insults ultimately accumulate due to aging, sociodemographic factors, lifestyle behaviors, comorbidities, and/or ongoing chronic inflammation (20). Furthermore, the additive effect of the number of past ADI may also increase the risk of becoming pre-frail/frail (6). Future longitudinal studies on prevention of ADI to ameliorate risk for pre-frailty/frailty might underscore the importance of earlier HIV diagnosis, treatment, and retention in care (20, 21).

Consistent with findings in the Women's Interagency Health Study, wherein, Hispanic HIV-infected women had significantly weaker grip strength than women from other racial/ethnic groups (8), we demonstrated a higher pre-frailty/frailty prevalence among persons of non-white race/ethnicity. Older HIV-uninfected black and Hispanic adults have a higher frailty prevalence (5, 22) and over classification of racial/ethnic minorities as pre-frail or frail could occur since the standardized height and BMI in frailty assessment criteria fail to account for normal differences in the range of these values among different racial/ethnic groups (16). However, differences in other factors associated with racial/ethnic disparities, such as poverty, unemployment, health-care utilization, comorbidity, HIV testing, retention in HIV-related care and antiretroviral adherence (21, 23, 24), may have contributed to our findings.

Greater current depression scores have been consistently reported in numerous cross-sectional studies of age and HIV-related frailty (2, 4-6, 9). Depression may influence self-reporting of exhaustion and physical inactivity due to an overlap of symptoms with frailty. Furthermore, both depression and frailty are associated with racial/ethnic minorities, medical and psychosocial comorbidity, advanced HIV disease, hepatitis C co-infection and increased risk of death (24-27). However, depression can negatively impact motor function and contribute to disability (27) and depressive symptoms were strongly associated with incident frailty in older HIV-uninfected women in the Women's Health Initiative Study (5). Lastly, a study exploring the relationship between the constructs of depression (as defined by the Diagnostic Interview Schedule) and frailty showed that these are distinct but still overlapping syndromes (28). If one considers depression and frailty to be interrelated, then identification of depressive symptoms is imperative in the assessment of frailty state. Effective management of depression in the HIV-outpatient care setting is gaining prominence (29) and its impact on frailty states should be studied.

Hepatitis C seropositivity, a marker for a viral infection, that like HIV infection is associated with pro-inflammatory, psychiatric, psychosocial, and multisystem comorbidity (30-32), was also associated with frailty among HIV-infected men who have sex with men (33). Approximately a quarter of HIV-infected individuals in Europe and USA are Hepatitis C/HIV co-infected and at increased risk of cirrhosis, HIV-related disease, and overall

mortality (32). Persons with co-infection may be at increased risk for pre-frailty and frailty as well and effective treatment of this co-infection to prevent pre-frailty or frailty warrants consideration.

Our analysis present some limitations. The low prevalence of frailty in this cohort likely reduced our capacity to robustly test for and detect associations. We also did not collect data on disability. We combined the categories of pre-frail and frail in an effort to increase our statistical power. Some nuances may have been lost on subsequent analyses of this combined group; for readers' reference we presented the data in table 1 stratified by all three groups, with p-values calculated using alternative statistical analysis. Missing data may have further limited analysis. We obtained initial frailty assessment data up to six years after study enrollment and can only make inferences based on our retrospective examination of longitudinal data and biomarker results. Lastly, we analyzed data from a contemporary, predominantly male population and our findings may not be generalizable to other HIV-infected populations in the United States or elsewhere.

In conclusion, pre-frailty and frailty were prevalent in our cohort of HIV-infected adults receiving contemporary cART and was associated with unemployment, even among persons <50 years. Our analysis that included sociodemographic, clinical, and biomarker data corroborates the complex multifactorial associations with this syndrome. Furthermore, our data support the concept of pre-frailty as an intermediate state in the spectrum from non-frailty through frailty that may represent a population of persons most likely to benefit from prevention strategies as well as depression screening.

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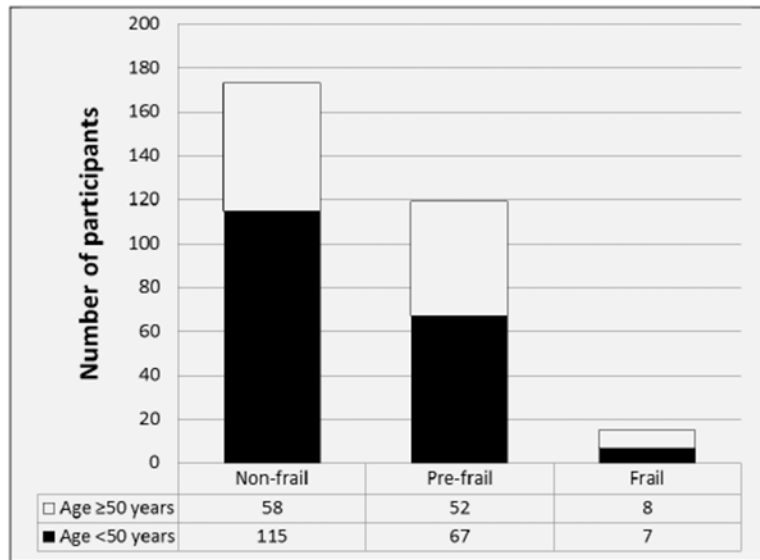


Figure 1. Non-frail, pre-frail* and frail SUN study participants by age
 *excluding 10 participants with 1-2 frailty criteria but missing additional data such that they could not be assigned pre-frailty or frailty status with certainty.

Table 1
Characteristics of SUN study participants by frailty status

Characteristic	Non-frail (n =176)	Pre-frail* (n =121)	Frail (n =15)	p-value
<i>Demographics and behaviors</i>				
Age, years \ddagger	46 (40-52)	48 (43-54)	53 (45-54)	0.03
Male sex	149 (85%)	86 (71%)	13 (87%)	0.01
Race				<0.001
White, non-Hispanic	119 (68%)	57 (47%)	6 (40%)	
Black, non-Hispanic	38 (22%)	47 (39%)	6 (40%)	
Hispanic	15 (9%)	13 (11%)	3 (20%)	
Other/unknown	4 (2%)	4 (3%)	0	
Current unemployment, n =311	48 (29%)	63 (52%)	13 (87%)	<0.001
Long-term unemployment, n =265	29 (19%)	44 (46%)	9 (82%)	<0.001
Current tobacco use	50 (29%)	53 (44%)	7 (47%)	0.02
Ever tobacco use	98 (57%)	78 (65%)	13 (87%)	0.03
Alcohol use last 30 days, n =311	123 (74%)	73 (60%)	5 (33%)	0.001
No. of days alcohol used per month \ddagger , n =311	3 (0-8)	2 (0-6)	0 (0-1)	0.006
Long-term alcohol use	137 (78%)	73 (60%)	5 (38%)	0.001
Past physical inactivity	2 (1%)	9 (7%)	7 (47%)	<0.001
<i>Perception of general health</i>				
Current response on study \ddagger , n =301	very good (excellent-good)	good (very good-good)	fair (good-fair)	<0.001
Excellent	42 (24%)	9 (7%)	0	
Good	29 (17%)	41 (34%)	5 (33%)	
Fair	8 (5%)	22 (20%)	5 (33%)	
Poor	1 (1%)	6 (6%)	3 (20%)	
Past responses on study \ddagger , n =309	very good (very good-good)	good (very good-good)	fair (good-fair)	<0.001
Excellent	37 (21%)	11 (9%)	0	
Very good	93 (53%)	33 (28%)	1 (7%)	
Good	35 (20%)	52 (43%)	3 (21%)	
Fair	9 (6%)	21 (18%)	10 (72%)	
Poor	1 (1%)	3 (3%)	0	
<i>Co-morbidities</i>				
Body mass index, kg/m ² \ddagger	26.9 (24.2-30.6)	26.1 (22.9-29.6)	26.1 (23.0-29.8)	0.32
Obese BMI	26%	22%	27%	0.91
Underweight BMI	1%	3%	4%	0.09
Hepatitis C seropositivity	10 (6%)	24 (20%)	5 (33%)	0.001
Active hepatitis B infection	6 (1%)	3 (3%)	2 (13%)	0.08
Current depression score \ddagger , n=306	3 (0-5)	6 (2-11)	8 (4-10)	<0.001
Past depression score \ddagger , n=255	3 (1-7)	5 (3-10)	7 (3-9)	<0.001
Hemoglobin, g/L \ddagger	15.1 (14.4-15.9)	14.3 (13.0-15.3)	14.6 (13.1-15.6)	<0.001

Characteristic	Non-frail (n =176)	Pre-frail* (n =121)	Frail (n =15)	p-value
Creatinine, mg/dL [†]	1.0 (0.9-1.1)	0.9 (0.8-1.1)	1.0 (0.9-1.4)	<0.001
eGFR <60mL/min/1.73m ² , n =258	3%	4%	30%	<0.001
Current STD, n=312	14 (8%)	4 (3%)	0 (0%)	0.13
Ever STD, n =266	56 (32%)	28 (29%)	0 (0%)	0.02
<i>HIV-related factors</i>				
Time since HIV diagnosis, years [†]	9.4 (6.7-12.8)	11.8 (8.1-14.4)	10.4 (7.4-12.1)	0.03
History of ADI	26 (15%)	38 (31%)	8 (53%)	< 0.001
Current cART	166 (94%)	112 (96%)	15 (100%)	0.58
Total time on cART, years [†]	7.5 (5.6-10.2)	8.2 (5.9-10.8)	6.8 (5.9-9.7)	0.7
<i>CD4+ cell count, cells/mm³[†]</i>				
Nadir	209 (100-295)	149 (45-257)	154 (70-175)	0.04
Current	649 (470-813)	619 (418-795)	641 (460-943)	0.87
Viral suppression, n =203	121 (94%)	66 (99%)	8 (89%)	0.13
<i>Biomarkers, median (IQR)</i>				
hs-CRP, mg/L	1.6 (0.8-3.3)	2.0 (0.9-4.2)	3.5 (0.9-7.6)	0.91
TNF- α , pg/mL, n=285	13.0 (10.3-18.9)	13.7 (11.2-24.4)	15.1 (10.1-339.0)	< 0.001
IL-6, pg/mL, n=288	2.9 (2.0-5.0)	3.0 (2.0-6.5)	9.2 (2.1-4641.5)	< 0.001
D-dimer, μ g/L	0.11 (0.04-0.23)	0.14 (0.06-0.27)	0.20 (0.10-0.45)	0.001
sCD14, ng/mL [‡]	1136.5 \pm 24.0	1233.6 \pm 33.8	1326.7 \pm 91.5	0.06
Lipoprotein A, mg/mL	10.0 (4.0-30.0)	17.0 (6.0-45.0)	13.0 (6.0-33.0)	0.1
25-hydroxy vitamin D, ng/mL [‡]	25.4 \pm 0.9	21.4 \pm 1.1	21.8 \pm 3.5	0.07

Comparison of all three groups.

* Excluding 10 persons who had 1-2 frailty criteria but could not be definitely assigned pre-frailty or frailty status due to missing values at the defining variables.

[†] median, (interquartile range, IQR),

[‡] mean \pm standard error. ADI, AIDS-defining illness; cART, combination antiretroviral therapy; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; sCD14, soluble CD14; STD, sexually transmitted diseases; TNF- α , tumor necrosis factor- α .

Table 2
Prevalence of individual frailty criteria among SUN study participants with complete data available

Frailty criteria	Pre-frail* (n=121)	Frail (n=15)
Unintentional weight loss <i>More than 10 pounds or 5% of weight loss occurred during the last year.</i>	13 (11%)	1 (7%)
Physical inactivity <i>Participants answering "3" when asked whether their health limits vigorous activities (eg running, lifting heavy objects, participating in strenuous sports (1 = not at all, 2 = a little, or 3 = a lot).</i>	35 (29%)	15 (100%)
Exhaustion <i>Participants answering 2 or 3 to either one of two statements – How often in the last week have you felt that: (a) everything you did was an effort or (b) I could not 'get going'. 0 = rarely (< 1 day), 1 = some of the time (1-2 days), 2 = occasionally (3-4 days) or 3 = most of the time (5-7 days)</i>	76 (63%)	11 (73%)
Weak grip strength <i>Strength, kg, median (IQR)</i>	9 (7%) 36 (29-44)	11 (73%) 29 (23-39)
<i>Cut-points according to BMI:</i> <i>M: 24 kg/m² 29 kg; 24.1-26.0 kg/m² 30 kg; 26.1-28.0 kg/m² 30 kg; >28 kg/m² 32 kg.</i> <i>W: <23 kg/m²<17 kg; 23.1-26.0 kg/m² <17.3 kg; 26.1-29.0 kg/m² <18 kg; >29 kg/m²<21 kg.</i>		
Slow walking speed (n=121) <i>Time, seconds, median (IQR)</i>	20 (17%) 4 (3-5)	7 (54%) 8 (4-9)
<i>Cut-points according to height:</i> <i>M: 173 cm 7 sec; >173 cm 6 sec.</i> <i>W: 159 cm 7 sec; >159 cm 6 sec.</i>		

Grip strength was determined from the average of three measurements of the dominant hand using a dynamometer (1). Walking was measured at usual pace over a 15-foot track (average of 2 trials) (1).

* Excluding 10 persons who had 1-2 frailty criteria but could not be definitely assigned pre-frailty or frailty status due to missing values at the defining variables. M, men; W, women

Table 3
Factors independently associated with pre-frail/frail versus non-frail status among SUN study participants

Characteristics	Non-frail (n=176)	Pre-frail/frail* (n=146)	Univariate analysis		Multivariate analysis	
			OR	95%CI	Pre-frail/frail versus non-frail p-value	Pre-frail/frail versus non-frail 95%CI
<i>Demographics and behaviors</i>						
Age, years [†]	46 (40-52)	48 (44-54)	1.04	1.01-1.06	0.01	
Male sex	149 (85%)	104 (71%)	0.45	0.26-0.77	0.003	
White, non-Hispanic race	119 (68%)	66 (45%)	0.4	0.25-0.62	<0.001	
Current unemployment, n=311	48 (29%)	85 (59%)	3.48	2.18-5.58	<0.001	
Long-term unemployment, n=265	29 (19%)	58 (52%)	4.59	2.65-7.95	<0.001	
Current tobacco use, n=313	50 (28%)	67 (48%)	2.26	1.41-3.60	0.001	
Ever tobacco use, n=313	98 (52%)	98 (70%)	1.79	1.12-2.86	0.02	
Alcohol use last 30 days, n=297	123 (74%)	80 (55%)	0.43	0.27-0.69	<0.001	
Alcohol use per month, days [†]	3 (0-8)	1 (0-1)	0.95	0.92-0.99	0.001	
Long-term alcohol use, n=314	137 (78%)	83 (60%)	0.41	0.25-0.67	<0.001	
Past inactivity	1 (1%)	17 (12%)	23.2	3.04-175.9	<0.001	
<i>Perception of general health</i>						
Current response on study [†] , n=311	very good (excellent-good)	Good	2.71	2.04-3.60	<0.001	
Excellent	42 (24%)	10 (7%)				(very good-fair)
Very good	86 (49%)	44 (31%)				
Good	29 (17%)	51 (35&percent;)				
Fair	8 (5%)	29 (20%)				
Poor	1 (1%)	11 (8%)				
Past responses on study [†] , n =318	very good (very good-good)	Good (very good-fair)	2.6	1.95-3.46	<0.001	
Excellent	37 (21%)	11 (8%)				
Very good	93 (53%)	37 (25%)				
Good	35 (20%)	58 (40%)				
Fair	9 (6%)	34 (26%)				
Poor	1 (1%)	4 (3%)				

Characteristics	Non-frail (n=176)	Pre-frail/frail* (n=146)	Univariate analysis		Multivariate analysis	
			Pre-frail/frail versus non-frail	p-value	Pre-frail/frail versus non-frail	p-value
<i>Co-morbidities</i>						
Body mass index, kg/m ² †	26.9 (24.2-30.6)	26.2 (23.0-29.9)	0.99	0.96-1.02	0.18	
Obese BMI	26%	25%	0.94	0.56-1.56	0.81	
Underweight BMI	1%	4%	6.35	0.73-55.0	0.09	
Hepatitis C seropositivity	10 (6%)	33 (23%)	4.85	2.30-10.23	<0.001	3.24 1.35-7.78 0.008
Active hepatitis B infection	6 (3%)	5 (3%)	1.01	0.30-3.37	0.99	1.16 1.09-1.23 <0.001
Current depression score †, n=306	3 (0-5)	7 (3-11)	1.17	1.11-1.23	<0.001	
Past depression score †, n=255	3 (1-7)	6 (3-10)	1.13	1.06-1.19	<0.001	
Hemoglobin, g/L †	15.1 (14.4-15.9)	14.3 (13.0-15.3)	0.72	0.62-0.84	<0.001	
Creatinine, mg/dL †	0.98 (0.86-1.07)	0.92 (0.80-1.11)	0.75	0.30-1.92	0.65	
eGFR < 60mL/min/1.73m ² , n=258	3%	8%	3.07	0.90-10.5	0.06	
Current STD, n=312	14 (8%)	4 (3%)	0.31	0.10-0.95	0.03	
Ever STD, n=266	56 (37%)	29 (25%)	0.56	0.33-0.96	0.04	
<i>HIV-related factors</i>						
Time since HIV diagnosis, years †	9.4 (6.7-12.8)	11.4 (8.2-14.4)	1.06	1.02-1.11	0.001	
History of ADI	26 (15%)	51 (35%)	3.1	1.81-5.30	<0.001	3.51 1.82-6.76 <0.001
Current cART	166 (94%)	140 (96&percent;)	1.41	0.50-3.96	0.52	
Total time on cART, years †	7.5 (5.6-10.2)	8.1 (5.9-10.5)	1.03	0.96-1.10	0.49	
Nadir CD4+ cell count, cells/mm ³ †,§	209 (100-295)	149 (46-250)	1.2	1.10-1.40	0.002	
<200 cells/mm ³	85 (49%)	96 (66%)	2.06	1.31-3.23	0.002	
Current CD4+ cell count, cells/mm ³ †	649 (470-813)	619 (418-794)	1	0.99-1.00	0.25	
350 cells/mm ³	152 (88%)	114 (84%)	0.71	0.37-1.39	0.32	
Viral suppression, n=215	122 (91%)	78 (96%)	2.56	0.70-9.35	0.14	
<i>Biomarkers</i>						
D-dimer, µg/L †	0.11 (0.04-0.23)	0.14 (0.07-0.28)	3.21	1.40-7.37	0.02	2.94 1.10-7.87 0.03
D-dimer >0.34 µg/L	19 (11%)	33 (23%)	2.46	1.33-4.56	0.003	
hs-CRP, mg/L †	1.6 (0.8-3.3)	1.9 (0.9-4.4)	1.01	0.98-1.04	0.08	

Characteristics	Non-frail (n=176)	Pre-frail/frail* (n=146)	Univariate analysis		Multivariate analysis	
			Pre-frail/frail versus non-frail	p-value	Pre-frail/frail versus non-frail	p-value
hs-CRP >3.00 mg/L	48 (27%)	55 (38%)	OR 1.62	1.01-2.59	OR 1.62	0.05
TNF- α , pg/mL [‡] //, n=298	13.0 (10.3-18.9)	13.9 (11.2-25.1)	OR 1.02	1.00-1.04	OR 1.02	0.02
TNF- α >20.5 pg/mL	31 (19%)	42 (30%)	OR 1.79	1.05-3.05	OR 1.79	0.03
sCD14, ng/mL [‡] //	1136.5 \pm 24.0	1249.7 \pm 30.0	OR 1.01	1.00-1.02	OR 1.01	0.003
sCD14 >1361 ng/mL	30 (17%)	50 (34%)	OR 2.54	1.51-4.27	OR 2.54	<0.001
Lipoprotein A [‡] //	10.0 (4.0-30.0)	19.0 (6.3-45.8)	OR 1.1	1.01-1.18	OR 1.1	0.01
Lipoprotein A >38.8 mg/mL	34 (20%)	45 (31%)	OR 1.85	1.10-3.09	OR 1.85	0.02
25-hydroxyvitamin D, ng/mL [‡]	25.4 \pm 0.9	22.7 \pm 1.0	OR 0.98	0.96-1.00	OR 0.98	0.04
25-hydroxyvitamin D <30 ng/mL	121 (70%)	112(77%)	OR 1.49	0.90-2.46	OR 1.49	0.12

* including all participants with at least 1 frailty criterion;

[‡] median (IQR);

[‡] mean \pm standard error;

[§] per 100 cells/mm³ decrease in CD4+ cells;

// per 10 unit increase. ADI, AIDS-defining illness; cART, combination antiretroviral therapy; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; sCD14, soluble CD14; STD, sexually transmitted diseases; TNF- α , tumor necrosis factor- α .