Predictors of Transition to Frailty in Middle-Aged and Older People With HIV: A Prospective Cohort Study

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Background: People with HIV (PWH) have increased frailty risk at younger ages compared with the general population. Multimorbidity is associated with frailty, yet effects of specific comorbidities on transition to frailty in PWH are unknown.

Setting: Prospective study of 219 PWH age 45 years or older in the National NeuroAIDS Tissue Consortium.

Methods: Frailty status was categorized using Fried frailty phenotype criteria. Comorbidities [bone disease, cardiovascular disease, cerebrovascular disease, liver disease, renal disease, diabetes, chronic obstructive pulmonary disease (COPD), hypertension, obesity, cancers, neuropsychiatric conditions] were assessed from longitudinal data. Associations between baseline comorbidities and transition to frailty within 30 months were analyzed using Kaplan–Meier and Cox regression models. Grip strength was assessed using mixed-effects models.

Results: At baseline, the median age was 61 years, 73% were male 98% were on antiretroviral therapy, 29% had ≥3 comorbidities, 27% were robust, and 73% were pre-frail. Cerebrovascular disease, diabetes, and COPD were independent predictors of transition to frailty within 30 months in models adjusted for age, sex, and multimorbidity (≥3 additional comorbidities) [hazard ratios (95% confidence intervals) 2.52 (1.29 to 4.93), 2.31 (1.12 to 4.76), and 1.82 (0.95 to 3.48), respectively]. Furthermore, cerebrovascular disease, diabetes, COPD, or liver disease co-occurring with multimorbidity was associated with substantially increased frailty hazards compared with multimorbidity alone (hazard ratios 4.75–7.46). Cerebrovascular disease was associated with decreased baseline grip strength ($P = 0.0001$), whereas multimorbidity, diabetes, and COPD were associated with declining grip strength ($P < 0.10$).

Conclusions: In older PWH, cerebrovascular disease, diabetes, COPD, or liver disease co-occurring with multimorbidity is associated with substantially increased risk of becoming frail within 30 months. Interventions targeting these comorbidities may ameliorate frailty and age-related functional decline in PWH.

Key Words: frailty, HIV, multimorbidity, aging, diabetes, COPD

(*J Acquir Immune Defic Syndr* 2021;88:518–527)

Received for publication June 7, 2021; accepted August 31, 2021.

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Supported by NIH grants to D.G. (R01 DA040391 and R01 DA046203). S.S.M. was supported by K23 MH115812. NNTC sites were supported by NIMH and National Institute of Neurological Disorders and Stroke (NINDS) (grants U24MH100931, U24MH100930, U24MH100929, U24MH100928, and U24MH100925).

The authors have no conflicts of interest to disclose.

D.R.L. participated in study design, performed data assembly and statistical analysis, drafted the manuscript, and prepared tables and figures. S.S.M. participated in study design, analysis, interpretation, and drafting the manuscript and tables. V.M. participated in data assembly, analysis, and interpretation, preparation of tables, and manuscript editing. H.U. participated in study design, data analysis and interpretation, and manuscript editing. B.B.G., D.J.M., and E.J.S. participated in study design, acquisition of data, interpretation, and manuscript editing. S.M. participated in study design, acquisition of data, cohort selection, data analysis, interpretation, and manuscript editing. D.G. designed and supervised the study, coordinated assembly and organization of data, and participated in data analysis and interpretation, and drafting and editing the manuscript. All authors read, participated in editing the manuscript, and approved the final manuscript.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

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INTRODUCTION

Nearly 50% of people with HIV (PWH) in the United States are over age 50 years due to the success of contemporary antiretroviral therapy (ART). However, older PWH continue to face challenges in maintaining health span and physical function with aging. Frailty is more common in PWH compared with the general population, with prevalence between 5% and 20% depending on age and other characteristics of the study population[1–7] compared with 5%–10% of the general population over age 65 years.[8] The increased risk of frailty among PWH likely reflects a combination of factors more prevalent in this population, including comorbidities, coinfections, chronic inflammation, metabolic abnormalities, substance use, and early life stress.[1–4,7–11] HIV-related factors such as low $CD4^+$ T-cell counts, nonsuppressed viremia, and

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long-term exposure to some ART drugs can also increase the risk of becoming frail.[2,3,12,13] Understanding factors associated with progression to frailty is important for identifying those at greatest risk and developing interventions to improve quality of life in older PWH.

Frailty status is often assessed using the Fried frailty phenotype (FFP) based on the presence of 3 or more of 5 criteria: unintentional weight loss, exhaustion, weak grip strength, slow walking speed, and low physical activity.[4,14] Individuals are classified as pre-frail if only 1 or 2 criteria are met or robust if no criteria are met. Pre-frail status predicts progression to frailty, with pre-frail individuals having greater than 2-fold higher odds of progressing to frail within 3 years compared with robust individuals.[15] In the general population, predictors of progression to frailty include older age, female sex, obesity, multimorbidity, and some diseases such as chronic obstructive pulmonary disease (COPD), diabetes, stroke, coronary heart disease, and depression.[16] Some of these factors have been associated with frailty in PWH in cross-sectional studies, whereas other studies reported associations between frailty as the independent variable and comorbidities, multimorbidity, or mortality as the outcome.[1,4–7,17,18]

Comorbidities and multimorbidity are more prevalent in middle-aged and older PWH compared with the general population, yet few studies have evaluated comorbidities and other factors as predictors of transition to frailty in PWH.[1,19–21] Moreover, the extent to which aging in PWH is "accentuated" due to higher prevalence of comorbidities and functional decline at every age or "accelerated" due to onset of comorbidities and geriatric conditions at younger ages remains unclear.[9,22] We performed a prospective cohort study of 219 PWH older than 45 years enrolled in the National NeuroAIDS Tissue Consortium (NNTC) between 2014 and 2020 to evaluate specific comorbidities in the presence or absence of multimorbidity as predictors of transition to frailty within 30 months.

METHODS

Study Design and Participants

Participants were from the NNTC, a longitudinal cohort composed of participants at 4 sites (Galveston, TX, Los Angeles, CA, New York, NY, and San Diego, CA). The NNTC has high rates of morbidity because criteria for entry include a significant neurological or medical condition; age 60 years or older was recently added as qualifying criterion.[4] Participants are assessed every 6 months and undergo standardized visits with formal assessments of neurobehavioral characteristics, medical and neurological conditions, neurocognitive function, virological and immunological parameters, frailty status, and other clinical and laboratory data at 6-month, 12-month, or 24-month intervals depending on participant's health status. All participants were enrolled with written informed consent, and Institutional Review Board approval was obtained at each site. Eligible participants were 219 PWH older than 45 years with ≥2 frailty assessments between 2014 and 2020 and non-frail (robust or pre-frail) at first frailty assessment. Sixty-four who were frail at first assessment and 10 who were non-frail at first and last assessments but frail at intervening assessments were excluded.

Covariate and Outcome Definitions

The primary outcome was binary frail status (frail vs. non-frail) within 30 months of baseline, defined using FFP.[4,14] Individuals with ≥3 criteria are classified as frail; non-frail individuals include those categorized as robust (0 criterion) or pre-frail (1–2 criteria). Slow walk speed and impaired grip strength criteria included participants unable to complete these assessments because of physical disability.[4] The following medical comorbidities were defined based on 1 or more diagnoses: bone disease (osteoarthritis, arthritis, osteoporosis, or fracture), cardiovascular disease (myocardial infarction, coronary artery disease, stents, bypass surgery, atherosclerosis, heart failure, or cardiomyopathy), cerebrovascular disease (stroke or cerebral small vessel white matter disease), COPD, and non-AIDS defining cancers. Additional medical comorbidities were defined as follows: diabetes, ≥2 visits with diabetes medication use or hemoglobin A1C (HbA1c) ≥6.5%; hypertension, ≥2 visits with antihypertensive medication use, or systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg; liver disease, ≥4 visits with a diagnosis of end-stage liver disease or ≥2 visits with a diagnosis of end-stage liver disease or cirrhosis, and Fibrosis 4 (FIB-4) score >1.9 within 2 years; renal disease, end-stage renal disease, stage 3–5 chronic kidney disease, use of dialysis, or ≥4 visits with estimated glomerular filtration rate <60 mL/min within 2 years; and class 2 or 3 obesity, body mass index (BMI) ≥35 kg/m^2. Medical diagnoses were based on participant examination, interview, medication use, and, when available, medical record review.[4] The neuropsychological test battery assessed 7 neurocognitive domains; global T scores were calculated as described.[23] Neuropsychiatric comorbidities included cognitive impairment (symptomatic HIV-associated neurocognitive disorder diagnosis of mild neurocognitive disorder or HIV-associated dementia[24]) and depressive symptoms (Beck Depression Inventory-II score ≥14). Diagnoses were included if documented at or before the baseline frailty assessment visit within the following time intervals: depressive symptoms, cognitive impairment, and obesity, ≤1 year; hypertension, ≤2 years; and all other diagnoses, ≤5 years.

Statistical Analysis

Cross-sectional associations between participant characteristics and baseline frailty status, COPD, diabetes, class 2 or 3 obesity, and cerebrovascular disease were evaluated using Fisher's exact tests or Wilcoxon rank sum tests for categorical or continuous variables, respectively. Kaplan–Meier and Cox regression analyses were used to assess associations between individual comorbidities or multimorbidity and transition to frailty; participants were followed up until the first assessment classified as frail, loss to follow-up, last assessment, or 30 months, whichever came first. Multimorbidity was assessed as a categorical variable

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for ≥4, 2–3, and 0–1 (reference) medical comorbidities in univariate and multivariable Cox models adjusted for age and sex. Each comorbidity was assessed in univariate and multivariable models adjusted for (1) baseline age and sex and (2) baseline age, sex, and multimorbidity (≥3 additional medical comorbidities). Cerebrovascular disease was a strong independent predictor of transition to frailty and, therefore, not included in multimorbidity variables when assessing individual comorbidities in Cox models. Additional univariate and age-adjusted and sex-adjusted multivariable Cox models were fit using factorial combinations between each individual comorbidity and multimorbidity defined as ≥3 additional medical comorbidities; similar models were fit using factorial combinations with ≥2 additional medical comorbidities to evaluate consistency of relationships.

Mixed-effects models were fit for $\log_2$-transformed continuous measures of 2 FFP components, grip strength and walk speed, as dependent variables combined with each comorbidity. Multivariable models tested group-by-time interactions between baseline comorbidity status and months in study and were adjusted for baseline age and sex. Separate models included adjustments for multimorbidity (≥3 additional medical comorbidities, excluding cerebrovascular disease); models for grip strength were additionally adjusted by BMI as a time-varying continuous variable. All models included a random intercept and slope for each participant. Main effects with $P < 0.05$ and group-by-time interactions with $P < 0.10$ were considered statistically significant. All statistical analyses were performed using R (version 4.0.3). For sensitivity analyses, cross-sectional comparisons, Cox models, and mixed-effects models were assessed in a cohort restricted to participants classified as pre-frail at baseline (n = 159).

RESULTS

Cohort and Frailty Characteristics

Of 219 eligible participants non-frail at baseline, 27% were robust and 73% were pre-frail (Table 1). The cohort was 73% male 34% White, 35% Black, and 28% Latinx; the median age and duration of HIV infection at baseline were 61 years [interquartile range (IQR), 54–67 years] and 25 years (IQR 19–30 years), respectively. Forty participants (18%) transitioned to frail status within 30 months of follow-up; the median number of assessments was similar between participants who remained non-frail vs. became frail (2.5 and 2.0, respectively; $P = 0.191$). Participants who became frail were more likely to be pre-frail than robust at baseline (92.5% vs. 68.2%, respectively; $P = 0.001$); 3 transitioned from robust to frail without intervening assessments categorized as pre-frail. Although mortality within 1 year of endpoint was more prevalent in participants who became frail vs. those who remained non-frail (15.0% vs. 1.1%, respectively; $P = 0.001$), there were no significant differences in other demographic, HIV-related, and clinical characteristics. Measures of cognitive function in participants who became frail were worse than in those who remained non-frail, including lower median global T-scores [44 (IQR 38–48) vs. 47 (IQR 41–52), respectively; $P = 0.007$], and fewer classified as neurocognitively normal based on HIV-associated neurocognitive disorder diagnosis (12.5% vs. 33.5%, $P = 0.002$). Severity of depressive symptoms did not differ by frailty outcomes. As expected, the median grip strength was lower ($P < 0.001$) and walk time was slower ($P = 0.001$) at baseline in participants who became frail vs. those who remained non-frail, whereas other FFP components (weight loss, exhaustion, and low physical activity) were not significantly different. Similar associations were observed in unadjusted analyses among 159 participants who were pre-frail at baseline (see Table, Supplemental Digital Content 1, http://links.lww.com/QAI/B726). Among participants with cerebrovascular disease, diabetes, COPD, or class 2 or 3 obesity at baseline (see Table, Supplemental Digital Content 2, http://links.lww.com/QAI/B726), diabetes and BMI >30 kg/m^2 were associated with female sex in unadjusted analyses ($P = 0.016$ and $P < 0.001$, respectively), whereas other demographic, HIV-related, and clinical characteristics were similar between participants with vs. without these comorbidities.

Comorbidities Predictive of Transition to Frailty

Comorbidity frequencies at baseline and their associations with becoming frail within 30 months in unadjusted and adjusted analyses are summarized in Table 2. High burden of comorbidities (≥4 medical comorbidities) was more common among participants who became frail (35%) compared with those who remained non-frail (9.5%) and was associated with increased transition to frailty in Kaplan–Meier analyses ($P < 0.0001$, log-rank test; Fig. 1). In Cox models adjusted for baseline age and sex, participants with ≥4 comorbidities had 5.52-fold increased hazard for frailty compared with those with 0–1 medical comorbidities [95% confidence interval (CI) 2.32 to 13.12; $P < 0.0001$]; participants with 2–3 medical comorbidities also had increased hazard for frailty compared with those with 0–1 medical comorbidities {adjusted hazard ratio (HR) 2.19 [1.0 to 4.8]; $P = 0.049$}. Cerebrovascular disease, diabetes, COPD, bone disease, and liver disease had the strongest associations with becoming frail within 30 months based on Kaplan–Meier analyses (all log-rank tests $P < 0.05$; Fig. 1) and Cox models adjusted for baseline age and sex [HR 3.02 (95% CI: 1.56 to 5.84), HR 2.69 (95% CI: 1.35 to 5.34), HR 1.97 (95% CI: 1.03 to 3.75), HR 2.76 (95% CI: 1.10 to 6.90), and HR 1.89 (95% CI: 1.00 to 3.57), respectively; Table 2]. In models with additional adjustment for multimorbidity, cerebrovascular disease and diabetes remained independent predictors of transition to frailty [HR 2.52 (95% CI: 1.29 to 4.93) and HR 2.31 (95% CI: 1.12 to 4.76), respectively], whereas estimates for COPD and liver disease trended toward statistical significance ($P < 0.10$).

In sensitivity analyses restricted to 159 participants classified as pre-frail at baseline, associations between cerebrovascular disease, diabetes, COPD, and liver disease and high risk of transition to frailty remained significant in Cox regression models (see Table, Supplemental Digital Content 3, http://links.lww.com/QAI/B726). Liver disease was notable in that the strength of its association with transition from pre-frail to frail in models adjusted for age, sex, and multimorbidity was comparable with those of estimates from models including all subjects [HR 1.89

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Table 1. Baseline Demographic and Clinical Characteristics According to Outcomes

Characteristic	Total (n = 219)	Remain non-frail (Robust or pre-frail) (n = 179)	Transition to frail within 30 mo (n = 40)	*P*
Demographics				
Length of follow-up (yr)	1.8 [1.1–2.1]	1.6 [1.0–2.1]	1.9 [1.1–2.0]	0.480
Age, yr	61.0 [54.1–67.0]	60.11 [54.0–67.0]	62.05 [56.2–67.7]	0.154
Male sex, n (%)	160 (73.1)	135 (75.4)	25 (62.5)	0.115
Race/ethnicity, n (%)				0.863
Black	76 (34.7)	62 (34.6)	14 (35.0)	
White	75 (34.2)	62 (34.6)	13 (32.5)	
Latinx/Other	68 (31.1)	55 (30.8)	13 (37.5)	
Education (yr)	13.0 [11.0–16.0]	13.0 [11.0–16.0]	13.0 [11.8–15.3]	0.924
Current smoking, n (%)	132 (60.3)	106 (59.2)	26 (65.0)	0.593
Current marijuana use, n (%)	73 (33.3)	61 (35.1)	12 (30.0)	0.672
Current or past IVDU, n (%)	46 (21.0)	37 (20.7)	9 (22.5)	0.831
HIV characteristics				
Estimated yr of HIV infection	24.5 [19.3–29.5]	24.4 [18.9–29.3]	26.5 [20.4–30.4]	0.151
$CD4^+$ T-cell count, cells/μL	500 [332–724]	499 [324–712]	578 [384–793]	0.259
$CD8^+$ T-cell count, cells/μL	835 [589–1149]	835 [591.50–1142]	823 [544–1268]	0.867
$CD4^+$ T-cell nadir, cells/μL	50 [11–190]	50 [9–192]	71 [13–150]	0.989
HIV viral load <200 copies/mL, n (%)	191 (89.7)	32 (84.2)	159 (90.9)	0.241
ART use, n (%)	214 (97.7)	39 (97.5)	175 (97.8)	1.000
NNRTI	52 (24.3)	42 (24.0)	10 (25.6)	0.838
PI	85 (39.7)	71 (40.6)	14 (35.9)	0.718
INSTI	139 (65.0)	112 (64.0)	27 (69.2)	0.583
Other clinical characteristics				
BMI, kg/m^2	26.4 [22.7–30.1]	26.1 [23.1–29.6]	28.2 [21.4–31.9]	0.377
BMI, $kg/m,^2$ n (%)				0.087
≤30	160 (74.1)	134 (76.1)	26 (65.0)	
>30–35	34 (15.7)	28 (15.9)	6 (15.0)	
>35	22 (10.2)	14 (8.0)	8 (20.0)	
Neutrophil–lymphocyte ratio	1.8 [1.2–2.4]	1.8 [1.2–2.4]	1.5 [1.2–2.1]	0.313
HbA1c ≥6.5%, n (%)	19 (9.9)	12 (7.7)	7 (18.9)	0.061
CKD-EPI eGFR <60 mL/min, n (%)	43 (22.5)	9 (26.5)	34 (21.7)	0.651
FIB-4 score	1.5 [1.1–2.1]	1.5 [1.1–2.0]	1.5 [1.2–2.5]	0.239
Positive HCV ab, n (%)	59 (26.9)	46 (25.7)	13 (32.5)	0.431
Death within 1 yr of endpoint, n (%)	8 (3.7)	2 (1.1)	6 (15.0)	**0.001**
Neuropsychiatric assessments				
HAND diagnosis, n (%)				**0.002**
ANI	18 (8.2)	18 (10.1)	0 (0.0)	
MND	58 (26.5)	46 (25.7)	12 (30.0)	
HAD	32 (14.6)	22 (12.3)	10 (25.0)	
NPI-O	45 (20.5)	32 (17.9)	13 (32.5)	
Neurocognitively normal	65 (29.7)	60 (33.5)	5 (12.5)	
Global cognitive T-score[1]	47 [41–52]	47 [41–52]	44 [38–48]	**0.007**
BDI-II score	6 [1–15]	6 [1–14]	8 [1–16]	0.506
Frailty assessments and multimorbidity				
No. of frailty assessments	2.0 [2.0–3.0]	2.5 [2.0–3.0]	2.0 [2.0–3.0]	0.191
Frailty status, n (%)				
Robust	60 (27.4)	57 (31.8)	3 (7.5)	**0.001**

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Table 1. (*Continued*) Baseline Demographic and Clinical Characteristics According to Outcomes

Characteristic	Total (n = 219)	Remain non-frail (Robust or pre-frail) (n = 179)	Transition to frail within 30 mo (n = 40)	*P*
Pre-frail	159 (72.6)	122 (68.2)	37 (92.5)	
Grip strength (kg)	32.0 [25.0–38.2]	33.0 [26.0–39.0]	25.15 [21.0–29.8]	**<0.001**
Walk time (s)	4.0 [4.0–5.0]	4.0 [3.8–5.0]	5.0 [4.0–6.0]	**0.001**
Unintentional weight loss, n (%)	22 (10.0)	18 (10.1)	4 (10.0)	1.000
Exhaustion, n (%)	63 (28.8)	49 (27.4)	14 (35.0)	0.340
Low physical activity, n (%)	36 (16.4)	26 (14.5)	10 (25.0)	0.154
Fried frailty phenotype summary score	1.0 [0.0–2.0]	1.0 [0.0–1.0]	1.5 [1.0–2.0]	**<0.001**
No. of medical comorbidities	1.0 [1.0–3.0]	1.0 [0.5–2.0]	3.0 [1.0–4.0]	**<0.001**
3 or more medical comorbidities, n (%)	64 (29.2)	41 (22.9)	23 (57.5)	**<0.001**

All data are median [IQR] unless otherwise indicated. *P* values for 2 group comparisons by frailty status were calculated using the Fisher exact test for categorical variables or Wilcoxon rank sum test for continuous variables; bold font denotes $P < 0.05$. Medical comorbidities were defined as described in the "Methods" section.

1—Clinical ratings derived from neuropsychological tests as previously described.[23] T-scores correlate negatively with severity of neurocognitive impairment; values <40 signify impairment.

Ab, antibody; ANI, asymptomatic neurocognitive impairment; BDI, Beck Depression Inventory-II; CKD-EPI, chronic kidney disease epidemiology collaboration equation; eGFR, estimated glomerular filtration rate; FIB-4, Fibrosis-4; HbA1c, hemoglobin A1c; HAD, HIV-associated dementia; HAND, HIV-associated neurocognitive disorder; INSTIs, integrase inhibitors; IVDU, intravenous drug use; MND, mild neurocognitive disorder; NPI-O, neuropsychological impairment attributable to other causes; NNRTIs, nonnucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.

(95% CI: 0.97 to 3.66), pre-frail restricted cohort; HR 1.75 (95% CI: 0.92 to 3.32), all participants], whereas estimates for diabetes and COPD were not significant in similar models restricted to pre-frail participants.

To further evaluate associations between comorbidities and risk of transition to frailty in the context of multimorbidity, we fit additional multivariable Cox regression models using full factorial variables combining baseline comorbidity with multimorbidity status. Cerebrovascular disease remained the strongest predictor of transition to frailty, followed by diabetes, COPD, and liver disease (Fig. 2 and see Table, Supplemental Digital Content 4, http://links.lww.com/QAI/B726). Participants with cerebrovascular disease and multimorbidity (≥3 additional medical comorbidities) had a 7.46-fold increased hazard for becoming frail compared with subjects with <3 comorbidities (95% CI: 2.80 to 19.88), whereas those with cerebrovascular disease without multimorbidity or multimorbidity without cerebrovascular disease had 4.31-fold and 4.63-fold increased hazards, respectively (95% CIs 1.68 to 11.04 and 1.68 to 11.04, respectively). Cerebrovascular disease was a strong independent predictor of transition to frailty and, therefore, not included in multimorbidity variables when assessing other individual comorbidities. Similar independent additive associations were observed for diabetes, COPD, and liver disease co-occurring with multimorbidity (Fig. 2). Factorial combinations of diabetes, COPD, and liver disease with a less stringent multimorbidity definition (≥2 additional medical comorbidities) showed similar additive associations with frailty in adjusted models [HR 4.06 (95% CI: 1.69 to 9.74), HR 3.76 (95% CI: 1.62 to 8.72), and HR 2.81 (95% CI: 1.27 to 6.20), respectively] and in sensitivity analyses restricted to pre-frail participants (see Table, Supplemental Digital Content 4, http://links.lww.com/QAI/B726). By contrast, factorial combinations of hypertension and class 2 or 3 obesity with multimorbidity did not show additive increases in frailty risk compared with multimorbidity alone. These results suggest that cerebrovascular disease, diabetes, COPD, and liver disease were the strongest predictors of transition to frailty among comorbidities examined, and frailty risk was further augmented when these conditions co-occurred with multimorbidity.

Multimorbidity, COPD, and Diabetes Are Associated With Declining Grip Strength

Among the frailty criteria, weak grip and slow walk speed had the strongest associations with transition to frailty within 30 months in Table 1. Furthermore, longitudinal patterns of individual frailty criteria showed that weak grip was the component most closely associated with transition to frailty (see Supplemental Digital Content 5, http://links.lww.com/QAI/B727 and Fig. 3A), consistent with evidence linking weakening grip to sarcopenia,[25] a central feature of physical frailty. We therefore assessed longitudinal associations between comorbidities and continuous measures of grip strength and walk speed. All participants had ≥1 grip strength assessment during 30 months of follow-up (522 person-visits), whereas walk speed was measured for 195 participants able to complete the assessment (422 person-visits). In analyses of participants with ≥2 grip strength assessments (n = 199), participants who became frail within 30 months had lower median grip strength at endpoint compared with that at baseline ($P = 0.0089$, paired Wilcoxon test; Fig. 3B). Compared with participants who remained non-frail, those transitioning to frailty with multimorbidity (≥3 medical comorbidities), diabetes, or COPD showed significant declines in grip strength between baseline and endpoint ($P = 0.0089$, $P = 0.040$, and $P = 0.0045$, respectively; Fig. 3B). By contrast, participants with cerebrovascular disease who became frail had overall lower grip strength compared with participants who remained non-frail, but no significant decline between baseline and endpoint ($P = 0.13$). Multimorbidity, diabetes, and COPD were associated with faster rate of decline in grip strength during 30 months of

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TABLE 2. Associations Between Comorbidities and Transition to Frailty Within 30 Months

			Unadjusted Cox Models		Multivariable Cox Models			
					Model 1: Age-Adjusted and Sex-Adjusted Models		Model 2: Age-Adjusted, Sex-Adjusted, and Multimorbidity-Adjusted Models[1]	
	Remain Non-frail, n (%)	Become Frail, n (%)	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Total subjects	**179 (81.7)**	**40 (18.3)**						
Multimorbidity								
0–1 medical comorbidities	99 (55.3)	11 (27.5)	Ref.	—	Ref.	—	—	—
2–3 medical comorbidities	63 (35.2)	15 (37.5)	**2.24 (1.02 to 4.88)**	**0.0432**	**2.19 (1.00 to 4.80)**	**0.0491**	—	—
≥4 medical comorbidities	17 (9.5)	14 (35.0)	**6.24 (2.80 to 13.90)**	**<0.0001**	**5.52 (2.32 to 13.12)**	**0.0001**	—	—
Medical comorbidities								
Cerebrovascular disease	28 (15.6)	14 (35.0)	**3.17 (1.64 to 6.11)**	**0.0006**	**3.02 (1.56 to 5.84)**	**0.0010**	**2.52 (1.29 to 4.93)**	**0.0069**
Diabetes	25 (14.0)	14 (35.0)	**3.10 (1.61 to 5.96)**	**0.0007**	**2.69 (1.35 to 5.34)**	**0.0047**	**2.31 (1.12 to 4.76)**	**0.023**
COPD	35 (19.6)	16 (40.0)	**2.18 (1.16 to 4.12)**	**0.0162**	**1.97 (1.03 to 3.75)**	**0.0396**	1.82 (0.95 to 3.48)	0.072
Liver disease	67 (37.4)	20 (50.0)	**2.02 (1.08 to 3.76)**	**0.0279**	1.89 (1.00 to 3.57)	0.0517	1.75 (0.92 to 3.32)	0.087
Bone disease	8 (4.5)	6 (15.0)	**3.19 (1.33 to 7.64)**	**0.0091**	**2.76 (1.10 to 6.90)**	**0.0302**	1.90 (0.75 to 4.82)	0.179
Hypertension	68 (38.0)	23 (57.5)	**2.08 (1.11 to 3.90)**	**0.0226**	1.77 (0.91 to 3.45)	0.0925	1.51 (0.76 to 3.03)	0.243
Non-AIDS defining cancers	23 (12.8)	7 (17.5)	1.72 (0.76 to 3.90)	0.194	1.58 (0.70 to 3.60)	0.274	1.51 (0.66 to 3.43)	0.330
Class 2 or 3 obesity[2]	14 (7.8)	8 (20.0)	**2.32 (1.07 to 5.05)**	**0.0337**	1.90 (0.75 to 4.83)	0.178	1.35 (0.52 to 3.48)	0.538
Renal disease	35 (19.6)	10 (25.0)	1.46 (0.71 to 2.99)	0.299	1.45 (0.71 to 2.96)	0.314	1.23 (0.59 to 2.53)	0.581
Cardiovascular disease	18 (10.1)	6 (15.0)	1.16 (0.49 to 2.78)	0.731	1.14 (0.47 to 2.75)	0.765	1.00 (0.42 to 2.41)	1.000
Neuropsychiatric comorbidities								
Cognitive impairment	68 (38.0)	22 (55.0)	1.69 (0.90 to 3.15)	0.100	1.65 (0.88 to 3.09)	0.1149	1.31 (0.69 to 2.49)	0.403
Depressive symptoms	45 (25.1)	13 (32.5)	1.20 (0.62 to 2.32)	0.594	1.28 (0.66 to 2.51)	0.4652	1.34 (0.68 to 2.61)	0.398

Medical comorbidities, cognitive impairment, and depressive symptoms were defined as described in the methods. Models are ordered by increasing *P* value for comorbidities in age-adjusted, sex-adjusted, and multimorbidity-adjusted models. Bold denotes $P < 0.05$.

1 – ≥3 additional medical comorbidities (excluding cerebrovascular disease).

2 - BMI >35 kg/m^2.

follow-up in adjusted mixed-effects models (group-by-time interactions $P < 0.10$; Fig. 3C and see Table, Supplemental Digital Content 6, http://links.lww.com/QAI/B726). By contrast, cerebrovascular disease was associated with lower grip strength at baseline ($P < 0.0001$), but no significant interaction with time. Associations between diabetes or COPD and decline in grip strength were observed in separate models additionally adjusted for multimorbidity and in sensitivity analyses restricted to 159 pre-frail participants, whereas other comorbidities showed no associations with reduced or declining grip strength (see Table, Supplemental Digital Content 6, http://links.lww.com/QAI/B726).

In models with walk speed as the dependent variable, COPD and cerebrovascular disease were associated with slower walk times at baseline in models adjusted for baseline age, sex, and multimorbidity (ß = 0.114, $P = 0.049$, and ß = 0.117, $P = 0.059$, respectively; see Table, Supplemental Digital Content 7, http://links.lww.com/QAI/B726), but no comorbidity or multimorbidity variables were associated with a significant group-by-time interaction. Thus, whereas diabetes and COPD were associated with significant decline in grip strength over 30 months of follow-up, cerebrovascular disease was associated with lower grip strength and slower walk time at baseline, but no significant interaction with time.

DISCUSSION

In this prospective study of middle-aged and older PWH, we identified comorbidities predictive of transition to frailty while controlling for multimorbidity, and assessed associations between comorbidities and longitudinal trajectories of FFP components grip strength and walk speed. Previous prospective[1,19–21] and cross-sectional studies[2,3,5,12,26] of PWH reported prefrailty and frailty prevalence of 18%–52% and 5%–15%, respectively, which is lower than 56% prefrailty and 18% frailty prevalence at endpoint observed in this study. Twenty-nine percent of participants in this study had multimorbidity with ≥3 comorbidities at baseline, reflecting composition of the NNTC,[4] compared with multimorbidity estimates as low as 8% in some previous studies.[20] Consistent with previous cross-sectional studies,[1,4,18,20,21,26–29] multimorbidity was associated with increased risk of becoming frail. Participants with ≥4 and 2–3 comorbidities had 5.5-fold and 2.2-fold increased frailty hazards, respectively, compared with participants with ≤1 comorbidity. Among comorbidities tested in Cox models adjusted for baseline age, sex, and multimorbidity, cerebrovascular disease, diabetes, COPD, bone disease, and liver disease were top predictors of transition to frailty within 30 months. Furthermore, cerebrovascular disease, diabetes, COPD, and liver disease were top predictors of transition to

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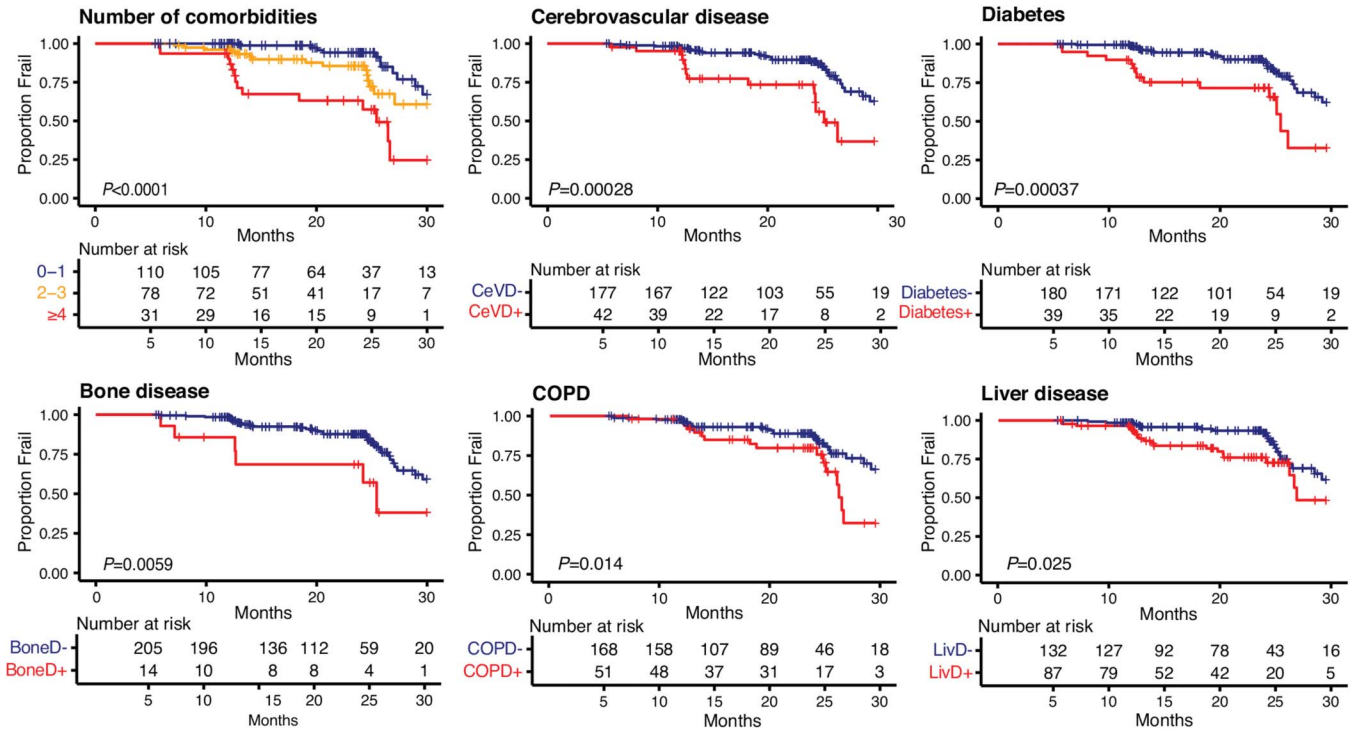

Figure 1. Kaplan–Meier curves of transition to frailty within 30 months for 219 HIV+ participants, stratified by multimorbidity or individual comorbidities. Multimorbidity and individual comorbidities were defined as described in the "Methods" section. *P* value, log-rank test. CeVD, cerebrovascular disease; BoneD, bone disease; LivD, liver disease.

frailty in adjusted models of factorial combinations of individual comorbidities with multimorbidity. In contrast with some cross-sectional studies, cognitive impairment or depressive symptoms[4,6,18,30,31] and HIV-related parameters including CD4 count and nadir[2,5,12] were not significant predictors of transition to frailty in this study, likely reflecting high prevalence of viral suppression <200 copies/mL (90%) and ART use (98%).

Previous studies in the general population reported an association between cerebrovascular disease and frailty, including recent meta-analyses that estimated a 2-fold to 4-fold increased odds of frailty among persons with a history of stroke in cross-sectional studies.[16,32] Previous studies have not reported an association between cerebrovascular disease and frailty in PWH,[4] or merged cerebrovascular disease with other cardiovascular disease.[21,26,33] Cerebrovascular disease, particularly stroke, typically entails physical impairments likely to affect several FFP components. Previous stroke was reported for all but one participant with cerebrovascular disease in this study, and participants with cerebrovascular disease had lower median grip strength at baseline compared with participants without cerebrovascular disease ($P < 0.001$). In longitudinal mixed-effects models, cerebrovascular disease was associated with lower grip strength and slower walk time at baseline with no significant group-by-time interactions, indicating these FFP components did not significantly change by cerebrovascular disease status during follow-up. By contrast, diabetes and COPD were associated with more rapid decline in grip strength ($P < 0.10$). These results suggest that cerebrovascular disease in PWH, particularly when combined with multimorbidity, abruptly accentuates transition to frailty by physical impairments associated with an acute cerebrovascular disease event, whereas chronic conditions such as diabetes and COPD affect transition to frailty through an accelerated physical decline manifested gradually over time.

Diabetes remains a leading cause of death[34] and is a major cause of disability due to associated complications, including neuropathy, myopathy, and sarcopenia. Prevalence estimates of diabetes in PWH are up to 20%, compared with 14.6% in the general population,[35] and diabetes is associated with increased risk of transition to pre-frail or frail status in PWH[20] and people without HIV.[36–38] In this study, diabetes was a strong predictor of increased transition to frailty and decline in grip strength, and diabetes co-occurring with multimorbidity was associated with 2.5-fold increased hazards of becoming frail compared with diabetes alone. Female sex and obesity were associated with diabetes, and a higher proportion of women progressed to frailty, consistent with a previous study.[26] These findings are cause for concern given recent data on weight gain after ART initiation, particularly among newer integrase inhibitors, in women with HIV.[39] Although the pathophysiology of frailty is multifactorial,[38,40] decreased insulin sensitivity can result in muscle catabolism, loss of strength, and sarcopenia and thereby contribute to physical frailty. Increased prevalence of diabetes in PWH and its association with obesity, multimorbidity, and frailty suggests importance of this condition as an intervention target for maintaining health span and physical function with aging.

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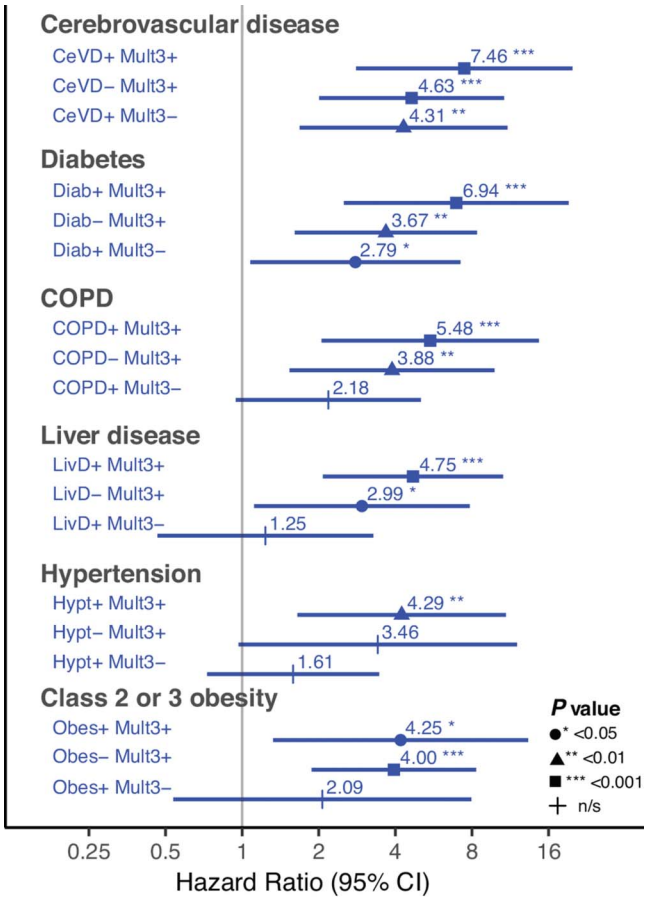

Figure 2. Associations between comorbidities in the presence or absence of multimorbidity and risk of transition to frailty within 30 months. Forest plots showing HRs from Cox regression models assessing factorial combinations of individual comorbidities with multimorbidity (≥3 additional medical comorbidities, excluding cerebrovascular disease). All models were adjusted for baseline age and sex. CeVD, cerebrovascular disease; Diab, diabetes; Hypt, hypertension; LivD, liver disease; Mult3, multimorbidity; Obes, obesity.

COPD is associated with frailty in the general population[41,42] and in PWH.[1,4,43,44] PWH have substantially higher rates of COPD than the general population, reflecting high rates of smoking in combination with HIV-related factors.[45,46] Among participants in this study, 24% had COPD, of whom 91% was current or former smokers. Previous studies reported greater rates of general physical exhaustion, weakness, or shortness of breath reported in frail persons with COPD,[42,43] consistent with higher rates of the FFP component "low physical activity" at baseline and declining grip strength over 30 months of follow-up among participants with COPD observed in this study. We did not detect an association between renal disease and transition to frailty, in contrast to some studies,[26,43] and liver disease was associated with increased frailty risk that did not reach statistical significance in Cox models adjusted for age, sex, and multimorbidity ($P < 0.10$). Previous studies in PWH also reported marginal associations between liver disease and frailty,[28,44,47,48] although one study reported an association for severe nonalcoholic fatty liver disease with fibrosis.[48] However, participants in our study with liver disease and co-occurring multimorbidity had 1.6-fold increased hazards of transition to frailty compared with multimorbid participants without liver disease. Cox models restricted to pre-frail participants showed slightly higher association between liver disease and transition to frailty compared with estimates including pre-frail and robust participants. These results suggest that liver disease may be a more important factor affecting progression to frailty among pre-frail or multimorbid PWH.

Limitations of this study include the possibility that results may be specific to PWH with serious neurological and medical conditions recruited for the NNTC. The high rates of pre-frailty frailty, and multimorbidity we observed may therefore involve latent factors absent from less medically complex cohorts. We did not include people without HIV in the study because these data were not available in NNTC. Small numbers of some comorbidities limited statistical power to detect associations with frailty in adjusted models. The small number of robust participants who became frail precluded adjusting for baseline pre-frailty in models; however, we performed sensitivity analyses restricted to pre-frail participants to mitigate this concern. Although female participants had higher prevalence of frailty and some comorbidities, including diabetes and obesity, there were too few female individuals to adequately assess associations with sex. Walk time tests were not administered for 24 participants using a wheelchair, walker, or cane, so strength of associations between comorbidities and walk time may be underestimated. Underreporting of some comorbidities, particularly bone disease, is likely due to using text notes rather than systematic coding for classifying these diagnoses by the NNTC. Likewise, COPD may be underreported or misreported due to lack of available pulmonary function test data. Finally, most participants had only 2 frailty assessments within 30 months of follow-up. Therefore, we could not distinguish transient vs. stable frailty classifications and did not have sufficient statistical power to assess incident comorbidities diagnosed after first frailty assessment or other frailty state transitions.[20,21,49] Additional longitudinal studies of frailty in less medically complex PWH are needed to evaluate comorbidities and other factors affecting long-term frailty outcomes and to identify potential interventions associated with frailty reversal or recovery.

CONCLUSIONS

Our study identifies increased risk of becoming frail among older PWH on ART with cerebrovascular disease, diabetes, COPD, and liver disease, particularly in the context of multimorbidity. Multimorbidity was highly prevalent and a strong predictor of transition to frailty within 30 months, suggesting prevention of multimorbidity is likely to be critical for preventing frailty.[50] Our findings suggest that including specific comorbidities and multimorbidity in screening tools, perhaps combined with other indices,[51] may improve risk stratification for preventive interventions. Our findings also provide insight into specific comorbidities that could be associated with "accentuated" vs. "accelerated" aging

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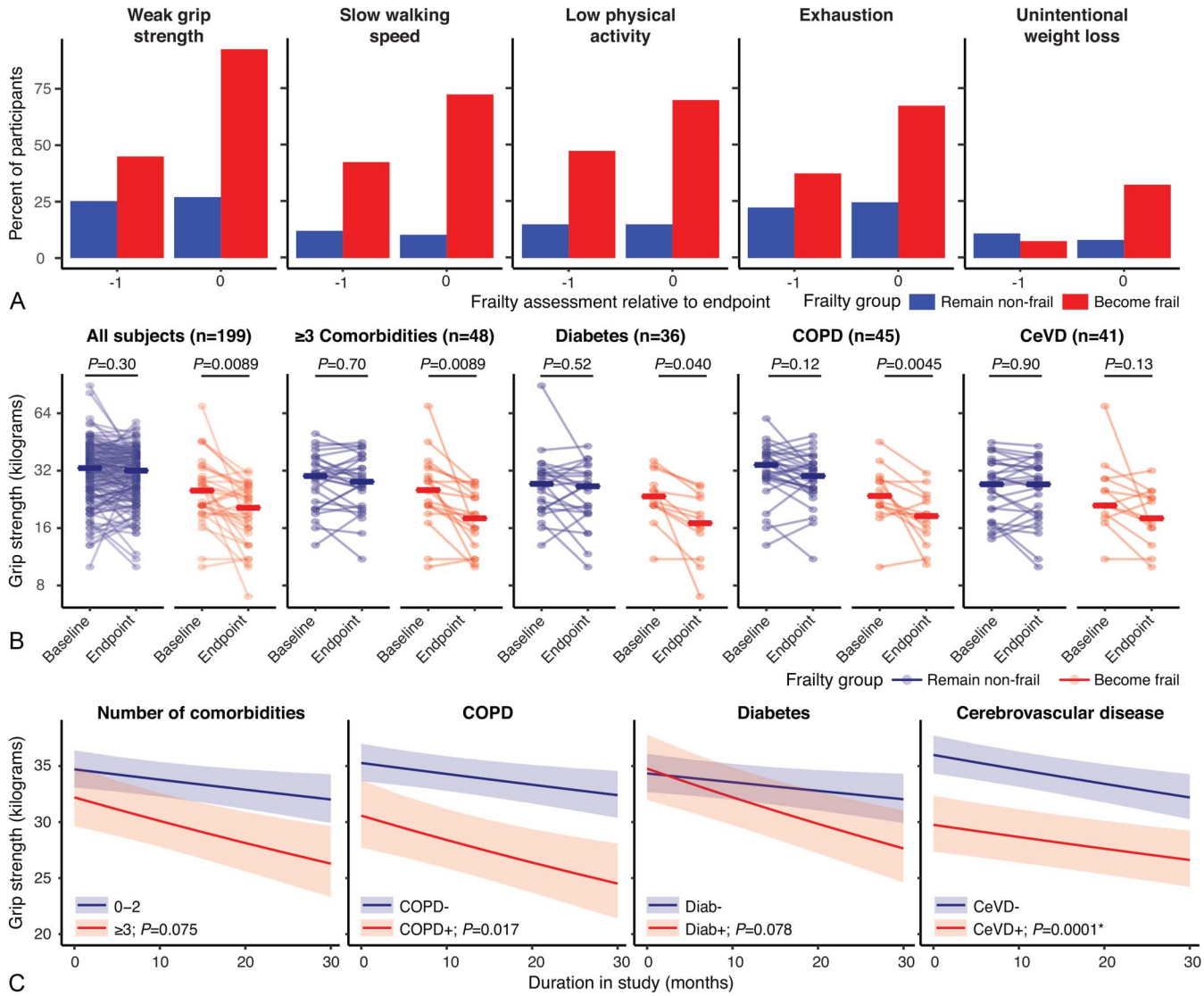

Figure 3. Longitudinal associations between Fried frailty criteria, comorbidities, and transition to frailty within 30 months. (A) Bar plots showing change in frequency of participants positive for each component of Fried frailty criteria at last 2 assessments before endpoint by frailty group. Endpoint was defined as the first visit classified as frail or last assessment for those who remained non-frail. (B) Paired plots illustrating baseline vs. endpoint grip strength for participants with paired data by frailty group and co-morbidities. Horizontal bars denote median values. *P* value, Wilcoxon rank sum test. (C) Predicted values (marginal effects) of grip strength for the indicated comorbidities from mixed-effects models adjusted by baseline age and sex. *P* values, group-by-time interaction estimates except * from ß at intercept for cerebrovascular disease. Grip strength values were $\log_2$-transformed for comparisons and models and back-transformed to original units for display. CeVD, cerebrovascular disease; Diab, diabetes.

phenotypes in the context of treated HIV.[22] Cerebrovascular disease can increase the burden of physical impairment (ie, reduced grip strength, slow walk time), but impairment resulting from an acute event does not necessarily worsen year-to-year, whereas diabetes and COPD seem to augment risk of transition to frailty at younger than expected ages, in addition to accelerating the rate of physical decline.[52] Frailty is conceptualized as a state of decreased physical resilience in the setting of deficits in multiple organ systems, but transitions can occur in either direction, and interventions that include sustained physical activity may ameliorate frailty and risk of morbidity.[7] Incorporating frailty assessment of older PWH in HIV clinics could be useful not only for risk stratification but also for projecting health care resource utilization and implementing timely interventions.

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