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Multimorbidity networks associated with frailty among middle-aged and older people with HIV

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Abstract:	Objective People with human immunodeficiency virus (HIV) (PWH) have increased prevalence of multimorbidity and frailty at younger ages compared to the general population. This study investigated individual and combinatorial effects of neuropsychiatric and medical comorbidities as predictors of frailty in PWH. Design Longitudinal observational cohort study. Methods 524 PWH over age 40 in the National NeuroAIDS Tissue Consortium were classified using the Fried Frailty Index. Twelve comorbidities were documented from longitudinal data and associations between individual and co-occurring comorbidities with frailty were assessed using weighted network and logistic regression analyses. Results

	At frailty assessment between 2015-2020, median age was 61 years, 76% were male, 94% were on ART, 49% had three or more comorbidities, 24% were frail, 52% were prefrail, and 24% were robust. Among 12 individual comorbidities, highest odds of frailty were in participants with depressive symptoms (adjusted odds ratio [aOR], 95% confidence interval [CI] 3.65 [2.35-5.72]), followed by bone disease and COPD (2.45 [1.28-4.63] and 2.13 [1.36-3.31], respectively). Among co-occurring comorbidities, highest odds of frailty were in participants having depressive symptoms with hypertension, diabetes, or obesity (aORs [95% CIs] 6.16 [3.16-12.16], 5.77 [2.56-13.06], 5.40 [2.67-10.98], respectively), cognitive impairment with diabetes or renal disease, (3.20 [1.58-6.43] and 3.09 [1.56-6.07], respectively), renal disease with cardiovascular disease (3.44 [1.62-7.30]), and diabetes with obesity (3.12 [1.60-6.07]). Conclusions Co-occurrence of depressive symptoms, cognitive impairment, renal disease, or diabetes with other medical conditions substantially increases odds of frailty in middle-aged and older PWH. Identifying and treating these comorbidities may help to reduce functional decline with aging in PWH.
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Dear Editor,

Please find the enclosed manuscript entitled "*Multimorbidity networks associated with frailty among middle aged and older people with HIV*" for consideration as an original article in *AIDS*.

In this prospective study of 524 HIV+ participants in the National NeuroAIDS Tissue Consortium, we use network-based approaches and regression models to identify combinatorial effects of comorbidities on odds of frailty in middle-aged and older people with HIV (PWH). Among co-occurring comorbidities, depressive symptoms, cognitive impairment, renal disease, or diabetes paired with other medical conditions were associated with substantially increased odds of frailty (3.1- to 6.2-fold increased odds). The findings are significant and will be of interest to readers of *AIDS* because they identify combinations of comorbidities that amplify odds of frailty with aging in PWH. Frailty and multimorbidity are more prevalent among PWH compared to the general population. While previous studies identified multimorbidity as a risk factor for frailty, to our knowledge this is the first report to evaluate combinatorial effects of neuropsychological and medical comorbidities on frailty in PWH.

All authors have seen and approved the manuscript as presented, and the data has not been previously published.

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Multimorbidity networks associated with frailty among middle aged and older people with HIV

Running title: Multimorbidity and frailty in HIV

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The authors declare that they have no competing interests.

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ABSTRACT

Objective: People with human immunodeficiency virus (HIV) (PWH) have increased prevalence of multimorbidity and frailty at younger ages compared to the general population. This study investigated individual and combinatorial effects of neuropsychiatric and medical comorbidities as predictors of frailty in PWH.

Design: Longitudinal observational cohort study.

Methods: 524 PWH over age 40 in the National NeuroAIDS Tissue Consortium were classified using the Fried Frailty Index. Twelve comorbidities were documented from longitudinal data and associations between individual and co-occurring comorbidities with frailty were assessed using weighted network and logistic regression analyses.

Results: At frailty assessment between 2015-2020, median age was 61 years, 76% were male, 94% were on ART, 49% had three or more comorbidities, 24% were frail, 52% were prefrail, and 24% were robust. Among 12 individual comorbidities, highest odds of frailty were in participants with depressive symptoms (adjusted odds ratio [aOR], 95% confidence interval [CI] 3.65 [2.35-5.72]), followed by bone disease and COPD (2.45 [1.28-4.63] and 2.13 [1.36-3.31], respectively). Among co-occurring comorbidities, highest odds of frailty were in participants having depressive symptoms with hypertension, diabetes, or obesity (aORs [95% CIs] 6.16 [3.16-12.16], 5.77 [2.56-13.06], 5.40 [2.67-10.98], respectively), cognitive impairment with diabetes or renal disease, (3.20 [1.58-6.43] and 3.09 [1.56-6.07], respectively), renal disease with cardiovascular disease (3.44 [1.62-7.30]), and diabetes with obesity (3.12 [1.60-6.07]).

Conclusions. Co-occurrence of depressive symptoms, cognitive impairment, renal disease, or diabetes with other medical conditions substantially increases odds of frailty in middle-aged and older PWH. Identifying and treating these comorbidities may help to reduce functional decline with aging in PWH.

KEYWORDS: HIV; frailty; aging; multimorbidity; depressive symptoms; neurocognitive impairment.

INTRODUCTION

Despite success of current antiretroviral therapy (ART), people with HIV (PWH) have an increased prevalence of age-associated comorbidities and frailty phenotypes occurring at younger ages compared to the general population [1-5]. Frailty is a clinical state characterized by physical decline and increased vulnerability to stressors [6]. Mechanisms underlying age-related frailty are poorly understood, but they appear to involve complex multifactorial etiologies and multisystem dysregulation. The increased prevalence of frailty among PWH may reflect multiple factors including comorbidities and co-infections, chronic immune activation, inflammation, oxidative stress, metabolic abnormalities, behavioral/lifestyle factors (*e.g.,* smoking, substance use), and early life stress/trauma [7-10]. HIV-related factors such as low CD4+ T cells, non-suppressed viremia, and long-term exposure to some ART drugs may also increase risk of frailty [3-5, 11]. Understanding mechanisms that impact emergence and progression of frailty in PWH is important for developing interventions to ameliorate frailty in older PWH.

Frailty is a strong predictor of adverse health effects including multimorbidity, hospitalization, disability, and mortality among middle-aged and older PWH on suppressive ART [12-15]. The relationship between frailty and multimorbidity is bidirectional, as multimorbidity also predicts increased odds of frailty [1, 6, 16, 17]. Comorbidities associated with frailty among PWH include chronic obstructive pulmonary disease (COPD), cardiovascular, renal, and liver diseases, diabetes, depressive symptoms, and cognitive impairment [1, 13, 14, 17-20]. Particular combinations of comorbidities may act synergistically to amplify odds of frailty in PWH, and effects of specific comorbidities on frailty risk are impacted by gender, behavioral/lifestyle factors, and other characteristics of the population [17, 19, 20]. Thus, network-based approaches have the potential to uncover unexpected relationships between diseases, and highlight shared mechanisms or environmental factors not otherwise considered [21].

Multimorbidity is more prevalent in PWH compared to the general population and is a strong predictor of frailty in middle-aged and older PWH, yet little is known about combinatorial effects of comorbidities that amplify odds of frailty in this population. Here, we use network-based approaches to

evaluate individual and combinatorial comorbidities as predictors of frailty in 524 PWH over age 40 enrolled in the National NeuroAIDS Tissue Consortium. We also examine inter-relationships between depressive symptoms and medical diagnoses to understand how neuropsychiatric and medical conditions interact to impact frailty risk in PWH.

METHODS

Study design and participants

Participants were from the National NeuroAIDS Tissue Consortium (NNTC), a longitudinal cohort comprised of participants at four sites: Texas NeuroAIDS Research Center (Galveston, TX), National Neurological AIDS Bank (Los Angeles, CA), Manhattan HIV Brain Bank (New York, NY), and California NeuroAIDS Tissue Network (San Diego, CA). NNTC participants have high rates of morbidity because criteria for entry includes a qualifying neurological or significant medical condition; age 60 or older was recently added to the list of possible criteria for entry [17]. Participants undergo standardized visits with formal assessments of behavioral characteristics, medical and neurological conditions, medication use, virological and immunological parameters, and other clinical and laboratory data at 6- or 12-month intervals. All participants were enrolled with written informed consent, and Institutional Review Board approval was obtained at each site. Eligible participants were HIV-positive adults over age 40 with one or more frailty assessments between 2015 and 2020.

Covariate and outcome definitions

The primary outcome was the Fried Frailty Index, a standardized definition of frailty based on presence of unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity [17, 22] at last frailty assessment. Participants with $\geq$3 criteria are classified as frail, as pre-frail if 1-2 criteria, or robust if no criteria are met. The following comorbidities were defined based on one 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 or stroke; chronic obstructive pulmonary disease (COPD); non-AIDS defining cancers (any excluding basal or squamous skin carcinomas and benign tumors). Additional comorbidities were defined as follows: cognitive impairment, symptomatic HIV-associated neurocognitive disorder (HAND) diagnosis of mild neurocognitive disorder (MND) or HIV-associated dementia (HAD) [23]; depressive symptoms, Beck Depression Inventory-II (BDI) score ≥14; 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 two years; renal disease, end-stage renal disease, stage 3-5 chronic kidney disease, use of dialysis, or ≥4 visits with estimated glomerular filtration rate (eGFR) <60 mL/min within two years; obesity, body mass index (BMI) ≥30 kg/m^2. Diagnoses were included if documented at or prior to the last frailty assessment visit within the following time intervals: depressive symptoms, cognitive impairment, and obesity, within one year; hypertension, within two years; all other diagnoses, within five years.

Statistical analysis

Weighted networks were used to assess the prevalence and inter-relationships of individual and co-occurring comorbidities among frail, pre-frail, and robust participants at last frailty assessment [24]. Networks were visualized as undirected graphs between diagnoses (nodes), with edges representing pairwise co-occurrences of comorbidities. Node heights were proportional to comorbidity prevalence, edge thicknesses were proportional to the prevalence of co-occurring comorbidity pairs. Prevalence was calculated as the number of participants with each comorbidity or comorbidity pair divided by group size.

Logistic regression models were used to assess associations between each individual comorbidity or selected co-occurring comorbidities with binary frail outcome at last frailty assessment. Comorbidity pairs included all possible 2x2 factorial combinations between depressive symptoms, diabetes, hypertension, and renal disease and the set of remaining comorbidities (n=22 pairwise combinations). Combinations with <14 (~10%) frail subjects positive for both comorbidities were excluded from

analyses. Multinomial logistic regression models were fit for individual comorbidities using ternary frailty status (frail *vs.* robust and pre-frail *vs*. robust) as the outcome. All models were adjusted by age and gender.

RESULTS

Cohort and Frailty Characteristics

Demographic and clinical data for the 524 HIV+ participants stratified by frailty status at last assessment are shown in **Table 1**. The median age was 61 years (interquartile range [IQR], 55-68 years), 398 (76%) were men, 198 (38%) were white, and 176 (34%) were black. ART use and HIV plasma viral load (VL) <200 copies/mL were reported in 491 (94%) and 432 (91%) of participants, respectively; 366 (75%) were on integrase inhibitor-based regimens. The median duration of observation was 8.4 years (IQR, 3-14 years) and median number of frailty assessments per participant was 2 (IQR, 1-3 visits).

A total of 127 (24.2%), 270 (51.5%), and 127 (24.2%) participants were classified as frail, pre-frail, and robust, respectively. Groups were comparable with respect to median years of observation, number of frailty assessments, age, race, years of education, tobacco and intravenous drug use, BMI, and hepatitis C virus infection, but frail participants were more likely to be women (P=0.03) and less likely to have plasma VL <200 copies/ml (P<0.01). While immunological parameters such as CD4+ and CD8+ T cell counts and other clinical disease markers were similar between groups, depressive symptoms were more prevalent, global cognitive T scores were lower (P<0.0001, both), and eGFR <60 mL/min was more common (P=0.017) among frail compared with robust and pre-frail participants. A higher proportion of frail participants had three or more comorbidities or died within 12 months of last frailty assessment (P<0.0001, both).

Associations between individual comorbidities and frailty

The frequencies of twelve common comorbidities in PWH [1, 14, 17, 19, 20] are shown for participants by frailty status in **Table 2**. As expected, all comorbidities were more prevalent in frail compared to robust participants, and incrementally more prevalent compared to pre-frail participants.

Hypertension (52%), depressive symptoms (45%), and cognitive impairment (44%) were the most frequent individual comorbidities among frail participants (**Table 2**). In logistic regression models adjusted for gender and age at last frailty assessment, depressive symptoms had the strongest association with frailty (adjusted odds ratio [aOR] 3.65 [95% confidence interval {CI} 2.35-5.72]; *P*<0.0001), followed by bone disease (aOR [95% CI] 2.45 [1.28-4.63]; *P*<0.001) and COPD (aOR [95% CI] 2.13 [1.36-3.31]; *P*<0.001). In multinomial logistic regression analyses modeling frail *vs.* robust and pre-frail *vs.* robust nominal outcomes, depressive symptoms had the strongest association with frail *vs*. robust status among all comorbidities tested (aOR [95% CI] 5.13 [2.77-9.50]; *P*<0.0001) (**Supplemental Digital Content 1**). Multinomial models also identified an association between cerebrovascular disease and pre-frail *vs.* robust status (aOR [95% CI] 2.60 [1.33-5.08]; *P*=0.005), and marginal associations between depressive symptoms, COPD, diabetes, and obesity and pre-frail *vs.* robust status (aORs [95% CIs] 1.61 [0.91-2.85], 1.75 [0.98-3.12], 1.89 [0.98-3.65], 1.64 [0.96-2.83], respectively).

Network analysis of comorbidities by frailty status

To assess differences in multimorbidity by frailty status, we used weighted networks visualizing the prevalence of individual comorbidities (represented by node height) and co-occurring comorbidities (represented by edge thickness) for participants with ≥2 comorbidities (n=398 participants) (**Figure 1A**). Most co-occurring comorbidities showed a stepwise prevalence increase between robust *vs.* pre-frail and pre-frail *vs.* frail participants. Depressive symptoms and cognitive impairment, hypertension and renal disease, and hypertension and cognitive impairment were the most common co-occurring comorbidities among frail participants. In a separate weighted network analysis by gender (**Figure 1B**), frail females had a higher prevalence of obesity, hypertension, COPD, diabetes, and most co-occurring comorbidities compared with frail males. While females were more likely to be black and have less years of education compared to males, most other clinical and demographic characteristics were not significantly different between male and female participants (**Supplemental Digital Content 2**).

Associations between co-occurring comorbidities and frailty

Among all participants, the most common co-occurring comorbidities in frail participants included cognitive impairment with depression and hypertension with renal disease (26% and 25%, respectively), followed by cognitive impairment with hypertension, depressive symptoms with hypertension, and hypertension with obesity (22% each) (**Figure 2**). Other co-morbidity pairs occurred at <20% prevalence. Comorbidities co-occurring with depressive symptoms showed the greatest increased prevalence difference in frail compared to pre-frail and robust participants, including depressive symptoms and cognitive impairment (in 26% frail, 12% pre-frail, 7% robust participants), hypertension (in 22% frail, 7% pre-frail, 4% robust participants), and obesity (in 17%, frail, 7% pre-frail, 2% robust participants).

To further assess associations between co-occurring comorbidities and frailty, we fit multivariable logistic regression models including full factorial variables for all pairwise combinations of selected comorbidities (**Figure 3A**) with hypertension, depression, renal disease, and diabetes. These comorbidities were selected based on their increased prevalence among co-occurring comorbidities in frail participants (**Figure 2**), and association with frailty in previous studies of PWH [1, 4, 11, 17-19, 25]. Co-occurring comorbidities associated with highest odds of frailty included depressive symptoms and hypertension (OR 6.16 [95% CI 3.16-12.16]; $P<0.0001$), depressive symptoms and diabetes (OR 5.77 [95% CI 2.56-13.06]; $P<0.0001$), and depressive symptoms and renal disease (OR 5.56 [95% CI 2.54-12.17]; $P<0.0001$) (**Figure 3B**). While these results were influenced by the strong association between depressive status and frailty (**Figure 3A**), other comorbidities showed marginal or non-significant associations with frailty when modeled individually, but were associated with significantly increased odds of frailty when modeled in co-occurring combinations. Among these combinations, renal and cardiovascular disease (OR 3.44 [95% CI 1.62-7.30]; $P=0.001$), diabetes and cognitive impairment (OR 3.20 [95% CI 1.58-6.43]; $P=0.001$), and diabetes and obesity (OR 3.12 [95% CI 1.60-6.07]; $P=0.001$) had the highest increased odds ratios compared to the individual comorbidities (**Figure 3B**). Model results for all co-occurring comorbidities tested are in **Supplemental Digital Content 3**.

DISCUSSION

In this prospective study of 524 middle aged and older PWH, we identified individual and co-occurring comorbidities associated with increased odds of frailty. Compared with previous studies of PWH using the Fried Frailty index, the prevalence of frailty was high (24%), despite high prevalence of ART use (94%) and suppressed VL (91%). Previous studies of PWH reported frailty prevalence between 5-15% [1, 4, 11, 18-20, 26], with lower prevalence typically reported in cohorts with younger participants [2, 14, 18], more males [1, 2], and fewer comorbidities per individual [4, 7, 14]. The high frailty prevalence in this study most likely reflects the older age and higher proportion with multiple comorbidities in the NNTC, which recruits individuals with serious medical and neurological conditions [17]. Consistent with previous studies, frailty prevalence was higher among females compared to males (31% *vs.* 22%) [4, 11, 17], and frail females had higher rates of hypertension, diabetes, and obesity [11, 17]. In contrast to some prior studies, we did not find a significant association between HIV-related parameters such as current or nadir CD4 count and frailty [2, 3, 11], nor between tobacco smoking, black race, or intravenous drug use and frailty [1, 4, 11, 20]. These different results may in part reflect the high prevalence and impact of comorbidities observed here compared to other studies of PWH [5, 27], particularly depressive symptoms, COPD, renal disease, and diabetes.

Our findings suggest that depressive symptoms, and to a lesser extent neurocognitive impairment, are independent risk factors for frailty among middle aged and older PWH, particularly when they co-occur with medical comorbidities. Consistent with other contemporary cohort studies assessing frailty among PWH on ART [13, 15, 17, 19, 28], participants in this study with depressive symptoms or neurocognitive impairment had 3.6- and 1.7-fold increased odds of frailty in adjusted models, respectively. The prevalence of depressive disorders and frailty increase with aging, and longitudinal studies suggest reciprocal relationships between depression and frail phenotypes in people without HIV [29-32]. This study expands our current understanding of comorbidities associated with frailty using a network approach, and shows substantial combinatorial associations between depression or neurocognitive impairment and frailty when medical comorbidities are also present. For example, obesity

was prevalent among frail participants but was not associated with frailty in adjusted models. In contrast, network and regression analyses suggest that an obese participant with depressive symptoms has 5.4-fold increased odds of frailty, while the association with frailty was not significant for an obese participant without depressive symptoms; a similar combinatorial pattern was observed for hypertensive participants with depressive symptoms. Given that depressive disorders and age-related medical comorbidities are both associated with chronic inflammation and multisystem dysregulation, the amplifying effect of depressive symptoms combined with age-related diseases such as obesity, hypertension, renal disease, and diabetes may point towards shared frailty pathophysiology [33, 34]. Alternatively, it may reflect the impact of depressive symptoms on reporting frailty symptoms such as exhaustion or physical activity, or effort put forth in physical measures such as grip strength. As multimorbidity poses major challenges to quality of life and is a critical issue in HIV care, analyzing disease networks will help to identify key diseases and cumulative risk trends that influence frailty phenotypes in aging PWH.

Multimorbidity in frailty studies is typically assessed by counts of comorbid diagnoses, yet our findings suggest that some combinations of comorbidities have much stronger effects on frailty than others. In addition to depressive symptoms and neurocognitive impairment, individual comorbidities associated with frailty in adjusted logistic regression models included bone disease and COPD followed by cardiovascular and renal diseases, diabetes, and hypertension. Network analyses of co-occurring comorbidities showed increased prevalence of nearly all (96%) pairwise combinations in frail *vs.* pre-frail and pre-frail *vs.* robust individuals, with comparably high prevalence for pairwise combinations between depressive symptoms, cognitive impairment, renal disease, hypertension, diabetes, and obesity (21-26% prevalence in frail persons). Similarly, in adjusted logistic regression models, co-occurring comorbidities with depressive symptoms, including hypertension, diabetes, and renal disease, displayed the highest overall increased odds of frailty. Other co-occurring comorbidities showing increased associations with frailty compared to either individual comorbidity included renal and cardiovascular diseases, diabetes and cognitive impairment, and diabetes and obesity, suggesting these combinations interact synergistically. For example, participants with both renal and cardiovascular diseases had increased odds of frailty over

twice as high as participants with only one of these comorbidities. These findings highlight important inter-relationships between multisystem disease that includes neuropsychiatric conditions and occurrence or progression of frailty in PWH.

This study has limitations, including the possibility that results may be specific to PWH with serious neurological and medical conditions recruited for the NNTC. Accordingly, high rates of frailty and multimorbidity observed in this study may entail latent factors not present in less medically complex cohorts. While the cohort size was comparable to or larger than many previous studies of HIV and frailty phenotypes, small numbers of some diagnoses limited statistical power to detect associations between some co-occurring comorbidities and frailty and to characterize effects of more than two comorbidities. Additionally, we did not assess effects of some potential confounders such as race, tobacco smoking, substance use, and ART regimens in factorial models due to limited numbers of participants. While female gender was associated with increased frailty and associated comorbidities, there were too few females to allow evaluation of co-occurring comorbidities with factorial variables in adjusted models. We relied on depressive symptoms and did not use a formal diagnosis of a depressive disorder as a comorbidity, so some misclassification of depression is possible. Furthermore, depressive symptoms may have impacted reporting of Fried frailty index components, particularly exhaustion and physical activity. Epidemiological studies suggest PWH and depressive symptoms are at increased risk of all-cause mortality compared to people without depressive symptoms [35], while other studies demonstrated that depressive symptoms are independently associated with frailty in PWH [17, 28]. We focused on relationships between medical comorbidities and frailty and did not account for social and/or behavioral factors, which also play a critical role in frail phenotypes. Under-reporting of some comorbidities is likely, particularly bone disease, which was classified based on text mining of notes rather than systematic coding. Lastly, as this was a cross-sectional study, we cannot reach conclusions about causality. Future longitudinal prospective studies are needed to evaluate potential causal roles and interplay between multimorbid conditions identified here and subsequent progression to frailty.

Our study identifies multimorbidity patterns associated with substantially higher odds of frailty in older PWH. These patterns include comorbid depressive symptoms, cognitive impairment, renal disease, or diabetes co-occurring with other medical conditions. The care of older PWH is increasingly complex as HIV providers navigate age-related multimorbidity, polypharmacy, ART toxicity, and changes in pharmacokinetics in the setting of diminishing renal and liver function. While age-related frailty is a progression from robust to pre-frail to frail [32, 36], this progression has the potential to be reversible in a subset of individuals. As HIV clinics begin to adopt new care models that include geriatric principles, our findings suggest that approaches incorporating prevention and treatment of neuropsychological conditions, renal disease, and diabetes have significant potential to delay or ameliorate frailty in aging PWH [16, 37].

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Author contributions: DRL participated in study design, performed data assembly and statistical analysis, drafted the manuscript, and prepared tables and figures. SSM participated in study design, analysis, interpretation, and drafting the manuscript and tables. VM participated in data assembly, analysis, and interpretation, preparation of tables and figures, and manuscript editing. HU participated in study design, data analysis and interpretation, and manuscript editing. BBG, DJM, and EJS participated in study design, acquisition of data, interpretation, and manuscript editing. SM participated in study design, acquisition of data, cohort selection, data analysis, interpretation, and manuscript editing. DG 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.

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Table 1: Demographics and clinical characteristics by frailty stage at last assessment.

Characteristic	Total (n=524)	Robust (n=127)	Pre-frail (n=270)	Frail (n=127)	*P* value
Years of observation	8.4 [3.3, 14.3]	9.1 [4.1, 14.3]	8.3 [3.2, 14.1]	8.2 [3.2, 14.4]	0.671
Demographics					
Age, years	61.1 [54.9, 68]	62.4 [54.6, 68.6]	60.6 [54.7, 66.8]	63 [55.2, 69.6]	0.053
Male gender, n (%)	398 (76.0)	106 (83.5)	204 (75.6)	88 (69.3)	**0.030**
Race/Ethnicity, n (%)					0.414
Black	176 (33.6)	43 (33.9)	93 (34.4)	40 (31.5)	
White	198 (37.8)	54 (42.5)	97 (35.9)	47 (37.0)	
Latinx	137 (26.1)	29 (22.8)	74 (27.4)	34 (26.8)	
Education (years)	13 [11, 14.7]	13 [11, 16]	13 [11, 14]	13 [11, 14]	0.824
Current smokers, n (%)	294 (56.1)	68 (53.5)	152 (56.3)	74 (58.3)	0.747
Current or past IVDU, n (%)	110 (21.0)	25 (19.7)	56 (20.7)	29 (22.8)	0.818
HIV characteristics					
Estimated duration of HIV infection (years)	26.1 [20.1, 31.2]	24.9 [19.4, 31]	26.3 [20.5, 31.3]	27.5 [21.1, 31.4]	0.357
CD4+ T-cell count, cells/μl	507 [328, 710]	483 [356, 694]	508 [323, 705]	554 [342, 764]	0.608
CD8+ T-cell count, cells/μl	791[566, 1134]	746 [555, 1077]	794 [558, 1132]	826 [604, 1169]	0.463
CD4+ T-cell nadir, cells/μl	59 [13, 198]	53 [14, 200]	53 [8, 190]	71 [17, 170]	0.629
Plasma HIV viral load <200 copies/mL, n (%)	432 (90.6)	111 (96.5)	225 (90.7)	96 (84.2)	**0.006**
Using ART regimen at visit, n (%)	491 (93.7)	121 (95.3)	256 (94.8)	114 (89.8)	0.109
NNRTI	103 (21.0)	26 (21.5)	47 (18.4)	30 (26.3)	0.219
PI	168 (34.2)	39 (32.2)	91 (35.5)	38 (33.3)	0.798
INSTI	366 (74.5)	88 (72.7)	194 (75.8)	84 (73.7)	0.794
Other clinical characteristics					
Body mass index (kg/m^2)	26.2 [22.7, 30.4]	25.9 [23.8, 28.7]	26.3 [22.5, 30.7]	26.8 [22.1, 32.3]	0.752
Neutrophil-Lymphocyte Ratio	1.73 [1.23, 2.43]	1.62 [1.32, 2.26]	1.74 [1.18, 2.44]	1.73 [1.25, 2.53]	0.774
HbA1c ≥6.5%, n (%)	66 (14.6)	9 (8.6)	38 (16.0)	19 (17.4)	0.128
CKD-EPI eGFR <60 mL/min, n (%)	107 (25.1)	21 (20.6)	49 (22.3)	37 (35.6)	**0.017**
FIB-4 score >3.25, n (%)	36 (8.5)	10 (9.5)	14 (6.4)	12 (11.8)	0.246
Positive HCV Ab, n (%)	133 (25.4)	30 (23.6)	65 (24.1)	38 (29.9)	0.400
Death within 12 months, n (%)	30 (5.7)	1 (0.8)	10 (3.7)	19 (15.0)	**<0.0001**
Neuropsychological Assessments					
Cognitive diagnosis, n (%)					**<0.001**
ANI	64 (12.6)	19 (15.3)	33 (12.6)	12 (9.8)	
MND	107 (21.0)	30 (24.2)	52 (19.8)	25 (20.3)	
HAD	73 (14.3)	6 (4.8)	36 (13.7)	31 (25.2)	
NPI-O	95 (18.7)	17 (13.7)	47 (17.9)	31 (25.2)	
Neurocognitively normal	165 (32.4)	51 (41.1)	91 (34.7)	23 (18.7)	
Global cognitive T score	46 [40, 51]	47 [42, 53]	46 [40, 51]	41 [35, 47]	**<0.0001**
BDI score	8 [3, 15]	4 [1, 9]	7 [3, 13]	13 [6, 21]	**<0.0001**
Frailty assessments					
Number of assessments	2 [1, 3]	2 [1, 3]	2 [1, 3]	2 [1, 3]	0.606
Walk time (sec)	4.9 [4, 5.9]	4 [3.4, 5]	4.7 [4, 5.1]	6.5 [5.2, 7.7]	**<0.0001**
Grip strength (kg)	29 [22, 35.1]	35 [31.5, 40]	28 [23, 35]	21.5 [16, 27]	**<0.0001**
Number of comorbidities					
Three or more comorbidities, n (%)	256 (48.9)	42 (33.1)	124 (45.9)	90 (70.9)	**<0.0001**
Number of comorbidities	2 [1, 4]	2 [1, 3]	2 [1, 4]	3 [2, 5]	**<0.001**

All data are median [interquartile range] unless otherwise indicated. *P* values for three group comparisons between frailty stages were calculated using chi-square test for categorical variables or ANOVA for continuous variables; bold font denotes $P < 0.05$.

Abbreviations: Ab, Antibody; ANI, asymptomatic neurocognitive impairment; ART, antiretroviral therapy; 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; INSTI, integrase inhibitors; IVDU, intravenous drug use; MND, mild neurocognitive disorder; NPI-O, neuropsychological impairment attributable to other causes; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

Table 2: Associations between comorbidities and odds of frailty.

	Number of Cases (%)			Unadjusted Model		Multivariable Model[α]	
Comorbidity	**Robust (n=127)**	**Pre-frail (n=270)**	**Frail (n=127)**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Depressive symptoms	19 (15.0)	61 (22.6)	57 (44.9)	3.23 (2.10-4.95)	<0.0001	3.65 (2.35-5.72)	<0.0001
Bone disease	6 (4.7)	19 (7.0)	20 (15.7)	2.78 (1.47-5.19)	0.001	2.45 (1.28-4.63)	0.006
COPD	18 (14.2)	61 (22.6)	46 (36.2)	2.29 (1.47-3.54)	<0.001	2.13 (1.36-3.31)	<0.001
Cardiovascular disease	10 (7.9)	31 (11.5)	24 (18.9)	2.02 (1.16-3.48)	0.012	1.86 (1.05-3.23)	0.029
Diabetes	13 (10.2)	49 (18.1)	34 (26.8)	1.98 (1.22-3.17)	0.005	1.86 (1.14-3.00)	0.012
Renal disease	24 (18.9)	60 (22.2)	43 (33.9)	1.91 (1.22-2.95)	0.004	1.79 (1.14-2.78,)	0.010
Cognitive impairment	36 (28.3)	88 (32.6)	56 (44.1)	1.74 (1.15-2.61)	0.008	1.69 (1.11-2.55)	0.013
Hypertension	52 (40.9)	102 (37.8)	66 (52.0)	1.71 (1.14-2.56)	0.009	1.53 (1.01-2.32)	0.044
Obesity	22 (17.3)	74 (27.4)	41 (32.3)	1.49 (0.96-2.31)	0.072	1.47 (0.93-2.31)	0.095
Non-AIDS defining cancer	17 (13.4)	35 (13.0)	23 (18.1)	1.47 (0.84-2.49)	0.162	1.40 (0.80-2.38)	0.228
Liver disease	24 (18.9)	70 (25.9)	36 (28.3)	1.28 (0.81-1.99)	0.29	1.27 (0.80-1.99)	0.301
Cerebrovascular disease	15 (11.8)	71 (26.3)	34 (26.8)	1.32 (0.83-2.08)	0.234	1.25 (0.78-1.98)	0.339

Comorbidities were defined as described in the Methods and ordered by adjusted odds ratios in the multivariable models. Multivariable models were adjusted for age and gender. Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

FIGURE LEGENDS

Figure 1. Multimorbidity networks by frailty status and gender. Network diagrams illustrating the prevalence of single and pairwise co-occurrences of comorbidities among (**A**) all participants separated by frailty status, and (**B**) frail participants separated by gender. Node heights are proportional to comorbidity prevalence, and edge thicknesses are proportional to prevalence of co-occurring comorbidity pairs. Comorbidities were defined as described in the Methods. Bone disease and non-AIDS defining cancers had <3% prevalence for most combinations and therefore excluded from networks.
Abbreviations: COPD, chronic obstructive pulmonary disease.

Figure 2. Prevalence of individual and co-occurring comorbidities by frailty status. Bar plots of participants with the indicated individual comorbidity (left panel) or co-occurring comorbidities (right panel). Percentages (top of bars) show proportions of subjects with each comorbidity or comorbidity pair among robust, pre-frail, and frail participants. Prevalence of comorbidities in combination with bone disease, non-AIDS defining cancers, COPD, and cerebrovascular disease was low and therefore excluded.
Abbreviations: COPD, chronic obstructive pulmonary disease.

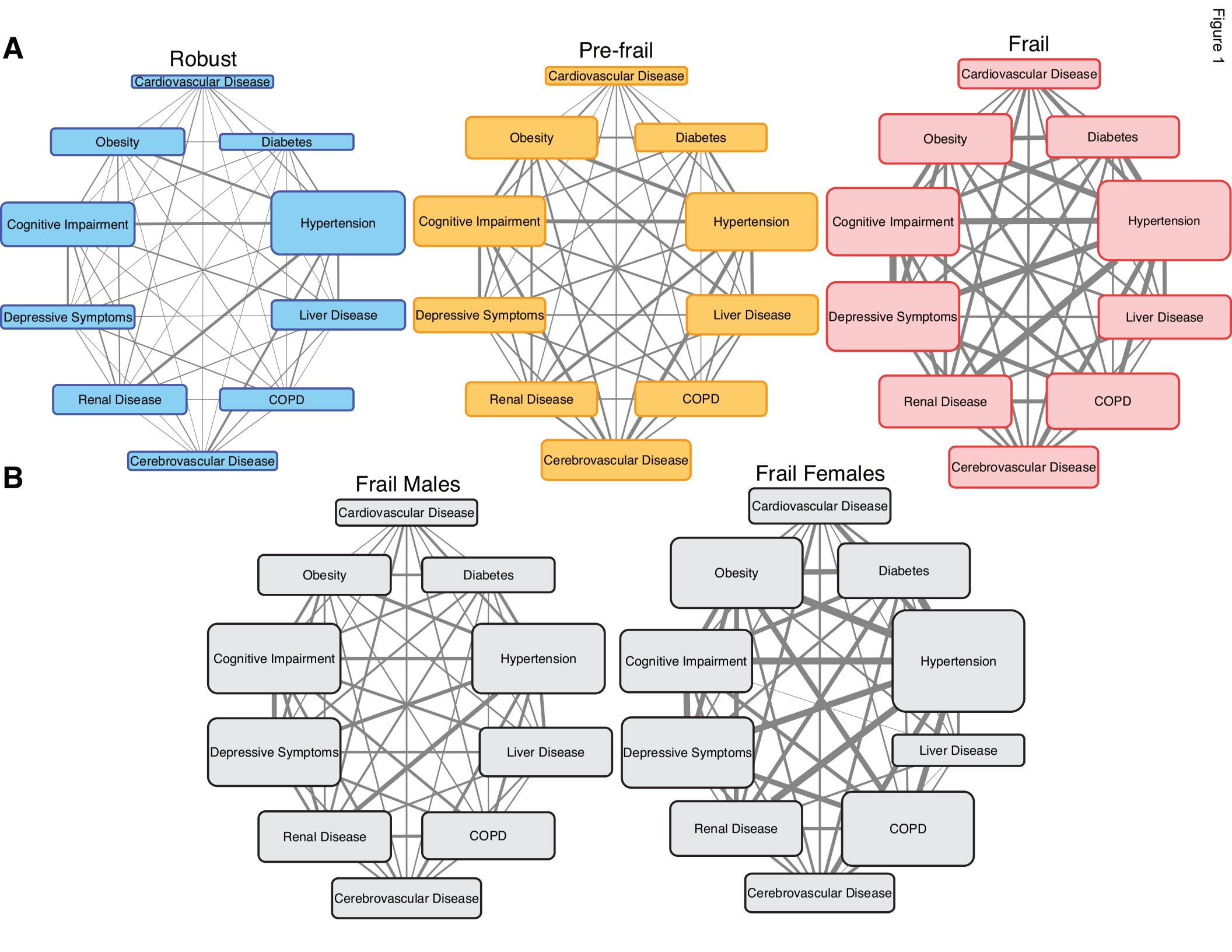
Figure 3. Individual and co-occurring comorbidities associated with frailty in logistic regression analyses. Forest plots illustrating (**A**) models of individual comorbidities and (**B**) models with pairwise factorial combinations of comorbidities with depressive symptoms, renal disease, and diabetes showing strongest associations with frailty. Points show odds ratio of frail vs. non-frail status, bars show 95% confidence intervals, point shape denotes *P* value significance level. The prevalence of most comorbidity combinations with bone disease, non-AIDS defining cancers, COPD, and cerebrovascular disease was low (<10%) and therefore not modeled. All models were adjusted for age at frailty assessment visit and gender. Results for all models of co-occurring comorbidities are in **Supplemental Digital Content 3**.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Supplemental Digital Content

Supplemental Digital Content 1 (Table). Comorbidities associated with frailty in multinomial logistic regression analyses.

Supplemental Digital Content 2 (Table). Demographics and clinical characteristics by gender and frailty status at last assessment.

Supplemental Digital Content 3 (Table). Comorbidity combinations associated with frailty in multivariable logistic regression analyses.


A
Robust
Cardiovascular Disease
Obesity
Diabetes
Cognitive Impairment
Hypertension
Depressive Symptoms
Liver Disease
Renal Disease
COPD
Cerebrovascular Disease
Pre-frail
Cardiovascular Disease
Obesity
Diabetes
Cognitive Impairment
Hypertension
Depressive Symptoms
Liver Disease
Renal Disease
COPD
Cerebrovascular Disease
Frail
Cardiovascular Disease
Obesity
Diabetes
Cognitive Impairment
Hypertension
Depressive Symptoms
Liver Disease
Renal Disease
COPD
Cerebrovascular Disease
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Frail Males
Cardiovascular Disease
Obesity
Diabetes
Cognitive Impairment
Hypertension
Depressive Symptoms
Liver Disease
Renal Disease
COPD
Cerebrovascular Disease
Frail Females
Cardiovascular Disease
Obesity
Diabetes
Cognitive Impairment
Hypertension
Depressive Symptoms
Liver Disease
Renal Disease
COPD
Cerebrovascular Disease

Figure 1

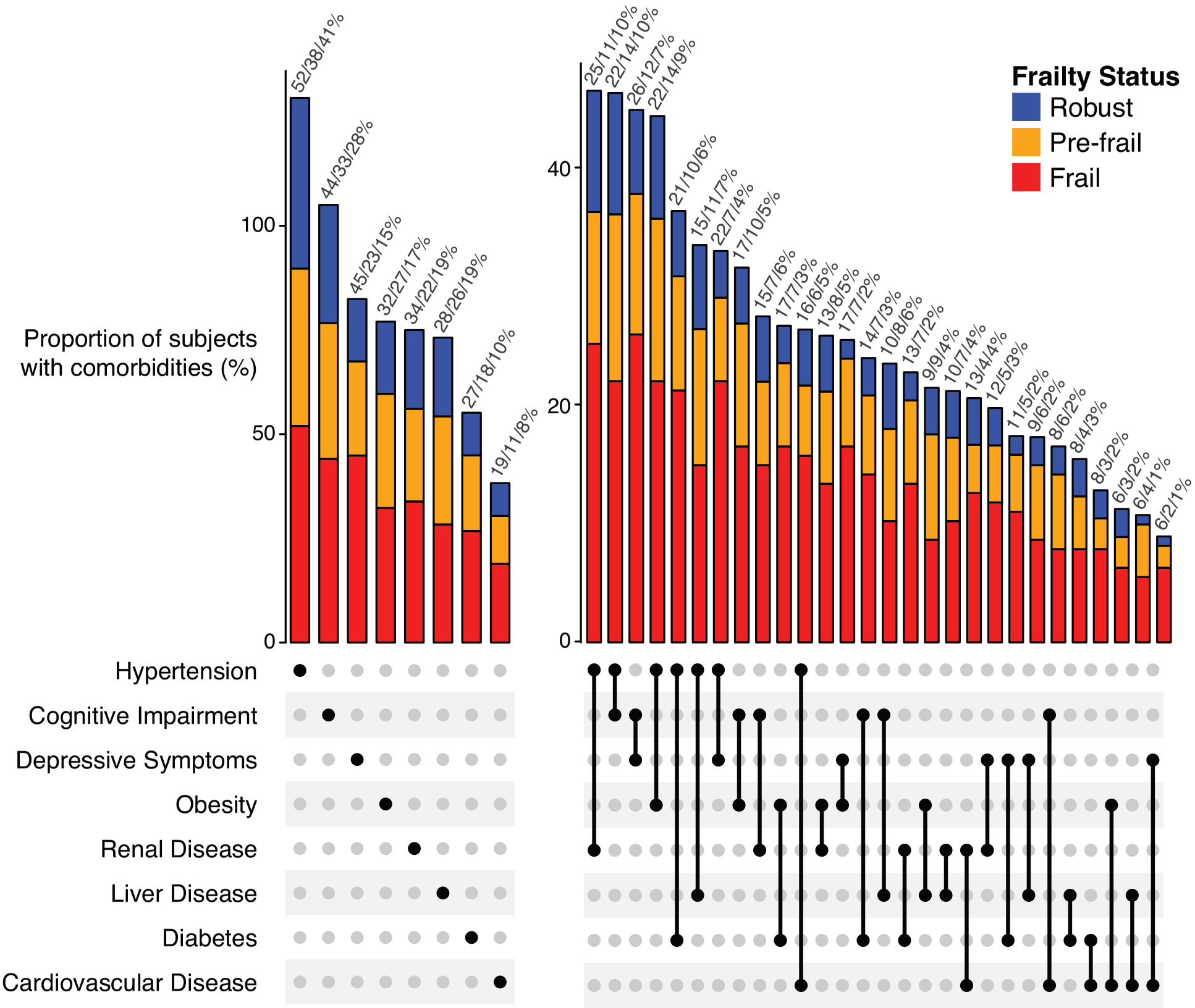
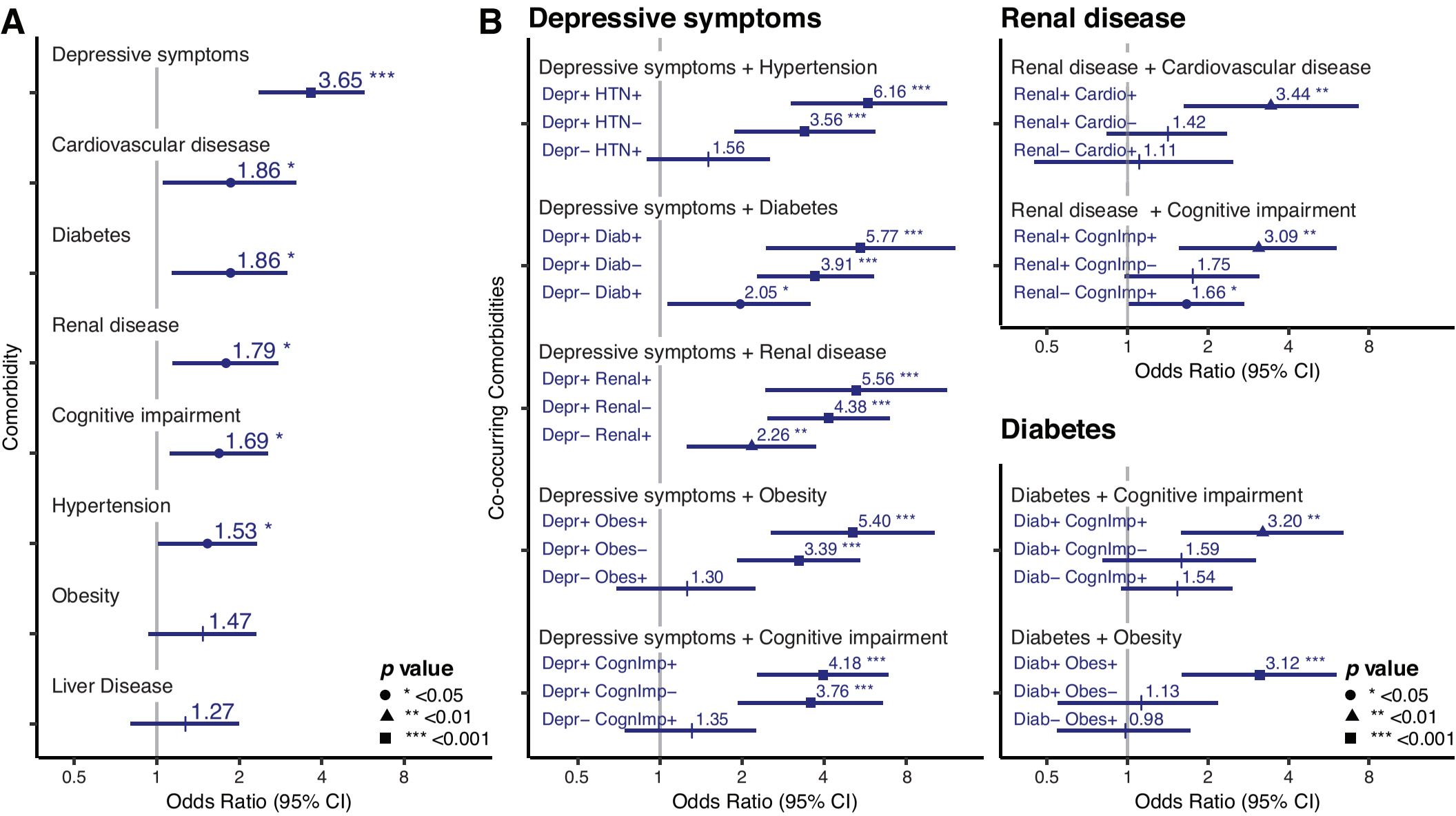

Frailty Status
Robust
Pre-frail
Frail
Proportion of subjects with comorbidities (%)
0
50
100
0
20
40
52/38/41%
44/33/28%
45/23/15%
32/27/17%
34/22/19%
28/26/19%
27/18/10%
19/11/8%
25/11/10%
22/14/10%
26/12/7%
22/14/9%
21/10/6%
15/11/7%
22/7/4%
17/10/5%
15/7/6%
17/7/3%
16/6/5%
13/8/5%
17/7/2%
14/7/3%
10/8/6%
13/7/2%
9/9/4%
10/7/4%
13/4/4%
12/5/3%
11/5/2%
9/6/2%
8/6/2%
8/4/3%
8/3/2%
6/3/2%
6/4/1%
6/2/1%
Hypertension
Cognitive Impairment
Depressive Symptoms
Obesity
Renal Disease
Liver Disease
Diabetes
Cardiovascular Disease

Figure 2


A
Depressive symptoms
3.65 ***
Cardiovascular disesase
1.86 *
Diabetes
1.86 *
Renal disease
1.79 *
Cognitive impairment
1.69 *
Hypertension
1.53 *
Obesity
1.47
Liver Disease
1.27
Comorbidity
p value
* <0.05
** <0.01
*** <0.001
0.5
1
2
4
8
Odds Ratio (95% CI)
B
Depressive symptoms
Co-occurring Comorbidities
Depressive symptoms + Hypertension
Depr+ HTN+
6.16 ***
Depr+ HTN−
3.56 ***
Depr− HTN+
1.56
Depressive symptoms + Diabetes
Depr+ Diab+
5.77 ***
Depr+ Diab−
3.91 ***
Depr− Diab+
2.05 *
Depressive symptoms + Renal disease
Depr+ Renal+
5.56 ***
Depr+ Renal−
4.38 ***
Depr− Renal+
2.26 **
Depressive symptoms + Obesity
Depr+ Obes+
5.40 ***
Depr+ Obes−
3.39 ***
Depr− Obes+
1.30
Depressive symptoms + Cognitive impairment
Depr+ CognImp+
4.18 ***
Depr+ CognImp−
3.76 ***
Depr− CognImp+
1.35
0.5
1
2
4
8
Odds Ratio (95% CI)
Renal disease
Renal disease + Cardiovascular disease
Renal+ Cardio+
3.44 **
Renal+ Cardio−
1.42
Renal− Cardio+
1.11
Renal disease + Cognitive impairment
Renal+ CognImp+
3.09 **
Renal+ CognImp−
1.75
Renal− CognImp+
1.66 *
0.5
1
2
4
8
Odds Ratio (95% CI)
Diabetes
Diabetes + Cognitive impairment
Diab+ CognImp+
3.20 **
Diab+ CognImp−
1.59
Diab− CognImp+
1.54
Diabetes + Obesity
Diab+ Obes+
3.12 ***
Diab+ Obes−
1.13
Diab− Obes+
0.98
p value
* <0.05
** <0.01
*** <0.001
0.5
1
2
4
8
Odds Ratio (95% CI)