Understanding Frailty among People Living with HIV in the United States

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Abstract

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In the recent era of HIV treatment, updated guidelines and antiretroviral therapy (ART) improvements have transformed HIV care into management of a chronic disease and people with HIV (PWH) are living longer and healthier lives as a result. Consequently, there has also been a rise in rates of aging-related conditions among this population, including frailty, a measure of physiologic reserve and vulnerability to health stressors. Frailty among PWH has been observed more often and at younger ages compared to non-HIV populations, leading to a need for accurate and efficient ascertainment integrated within HIV care as well as a better understanding of the risk factors and outcomes related to frailty.

The field of research on frailty among PWH is rapidly growing, both expanding our knowledge and introducing new questions. At the forefront is understanding methods to measure frailty in a fast, low-burden, and accurate way to collect frailty information on many PWH. One of the most commonly used measures of frailty, Fried's frailty phenotype, captures 5 functional status measures and classifies people as not frail, prefrail, or frail based on their results. Fried's phenotype is often modified to conform to data availability, however, modifications warrant careful evaluation of their impact on measurement of frailty. Additionally, evaluating relationships between frailty and commonly used substances, such as tobacco and alcohol, could elucidate complex interplays between patterns in substance use behaviors and physical health.

To answer these questions, we leveraged the Impact of Physical Activity Routines and Dietary Intake on the Longitudinal Symptom Experience of people living with HIV (PROSPER-HIV) study nested within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort to evaluate the validity of a self-reported modified frailty phenotype used widely within CNICS. We then utilized the rich, comprehensive follow-up data within CNICS to assess relationships between smoking and alcohol with frailty.

We found that the modified frailty phenotype developed and used within CNICS is a highly feasible and accurate measure of frailty, well-suited for ascertainment of frailty among PWH in clinical care and for application in epidemiologic studies. The modified phenotype classified PWH similarly to the gold standard comparator (i.e., Fried's phenotype), with Cohen's kappa values ranging from 0.64-0.75 depending on weighting scheme and receiver operator characteristics area under the curve values of 0.93 (95% CI: 0.91-0.96) for classifying PWH with frailty and 0.86 (0.83-0.89) for classifying prefrailty. Additionally, both definitions estimated comparable associations between frailty and having experienced a fall in the past year, highlighting the clinical relevance and utility of the CNICS modified frailty phenotype.

Furthermore, among 8,608 PWH, 60% reported former (29%) or current (31%) smoking. We found strong evidence of a relationship between smoking tobacco and incident frailty, with a 79% greater risk of frailty associated with current smoking (95% CI: 1.54-2.08) and 12% greater risk associated with every 5 pack-years of smoking (95% CI: 1.09-1.16). We also found an association between current and cumulative (i.e., pack-years), but not former, smoking on the risk of deterioration of frailty, suggesting an important potential for smoking cessation to mitigate frailty risk in this population.

Finally, in our investigation of the relationship between frailty status and alcohol consumption, we found that frailty is associated with a greater likelihood to quit and reduce drinking, including binge drinking. Among 8,174 PWH, most (69%) reported currently drinking alcohol, and 13% reported binge drinking at least monthly. We observed that frail PWH were 56% (95% CI: 1.14-2.14) and 33% (95% CI: 1.11-1.59) more likely to quit and reduce frequency of drinking, respectively, compared to not frail PWH. Additionally, frail PWH were 56% (95% CI: 1.19-2.04) more likely to reduce their frequency of binge drinking compared to not frail PWH. These findings are consistent with the sick quitting hypothesis, in which people may reduce alcohol consumption in response to declines in health status. In comparison to 20-35% lower risks of incident frailty associated with drinking (including former risky drinking), these findings highlight methodological concerns with estimating relationships between alcohol and frailty with observational data. Specifically, sick quitting may be confounding estimates for the risk of frailty associated with alcohol and future research should consider individual-level characteristics, such as health status, when evaluating this relationship.

Overall, these findings expand the field of aging research among PWH by describing and evaluating a widespread frailty phenotype as well as applying it to answer important questions regarding substance use and frailty in this population. We describe issues of bias that are present in the existing literature and present areas for future work addressing remaining unanswered questions on this topic.

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Dedication

To my mom and dad.

For being my biggest cheerleaders my whole life and supporting me endlessly in all I have endeavored. And for teaching me planning and time-management skills. This would not have been possible without you both.

Chapter 1: Introduction

Accelerated Aging Among People with HIV

People with HIV (PWH) are living longer and healthier lives in the current era of antiretroviral therapy (ART) treatment, such that by 2030, it is predicted that 73% of PWH will be aged 50 and older.[1] At the same time, PWH experience chronic immune activation and inflammation, which may lead to accelerated aging, characterized by biological mechanisms that elicit a faster presentation of aging-related conditions.[2] Consequently, there is a growing need to assess the presence and development of these aging-related conditions among PWH, including frailty, a clinical syndrome characterized by a state of increased vulnerability to health stressors and prediction of poor health outcomes including all-cause mortality.[3-6]

The mechanisms that drive accelerated aging and high rates of comorbidities among PWH may be unique compared to the general population. PWH face persistent and chronic immune activation, which leads to deterioration of the immune system and earlier presentation of immunosenescence, a clinical presentation of an aging immune system.[7,8] Immunosenescence is related to reduced vaccine efficacy, many non-HIV associated comorbidities, and heightened vulnerability to viral infections, which could be particularly harmful to PWH with compromised immune systems from HIV infection.[8,9] Impacts to the immune system include alterations in functional mechanisms and homeostasis of T-cell production/management and a persistent presentation of pro-inflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6.[7,8,10,11] The presence of many aging- and immune-related risk factors in tandem is referred to as “inflammaging” and has been correlated with frailty.[7,11-16]

In the presence of HIV, there is also chronic pressure on the immune system to produce T-cells, contributing to eventual immune exhaustion and premature aging (i.e., accelerated aging).[7,17] Even among PWH on ART (and virally suppressed), this immunosenescent phenotype is similar to that of older adults without HIV, highlighting the disparities in aging processes and the

importance of HIV and aging focused research.[7,12,14,18,19] A Multicenter AIDS Cohort Study (MACS) analysis identified elevated inflammatory markers among virally suppressed men with HIV, and C-reactive protein, which is regulated by IL-6, remained independently associated with frailty after adjustment for risk factors.[11] Additionally, the Strategies for Management of Anti-Retroviral Therapy (SMART) trial showed evidence of elevated immune factors, such as IL-6, predicting mortality and non-HIV related morbidity.[20] Other studies have shown that PWH have worse or declining physical functioning compared to individuals without HIV decades older.[21-24] Additionally, comorbidities and behaviors (e.g., substance use) that impact inflammation may further exacerbate immunosenescence.[25,26] The heightened long-lasting immune response to HIV and prevalence of aging-related comorbidities provide evidence of accelerated aging among PWH and highlight the need for additional studies investigating HIV and aging.[7,14,15,27,28] It is important to understand how to prolong healthy living, or healthspan, among PWH and the extent of the benefit from possible interventions targeted toward modifiable behaviors, such as cessation of harmful substance use.[29]

Frailty

Frailty is a syndrome that measures vulnerability to stressors, such as minor falls or fractures, that may lead to future morbidity or mortality.[30-32] It is generally used to evaluate non-disease-specific markers among aging adults as a metric of physical wellbeing.[3,31] Frailty is an independent predictor of mortality, with a dose-response relationship with increasing severity, and is often studied in the general population.[3-5]

Frailty can encompass a variety of individual measures and domains of health, leading to many different definitions in the literature and no clear gold standard. The lack of a universal definition makes it difficult to compare frailty across studies using different definitions but provides flexibility in how a study utilizes the available data to answer their research question with the

most appropriate and feasible measure.[33-36] For instance, some definitions focus entirely on physical health, while others include measures of mental health, cognition, and/or social support.[3,37,38] Moreover, certain measures seek to strictly define frailty as a distinct construct while others view it as a collection of factors largely related to overall health.[33] There are, however, consistencies in the fundamentals of frailty as a measure of health and aging, and a syndrome to be prioritized as an area to guide interventions and prolong healthy living.[30,31]

The most commonly used approaches to measuring frailty are phenotypes and accumulation of deficits (AOD) models.[3,33] Both approaches have notable strengths and weaknesses: frailty phenotypes aim to identify the physical presentation of frailty, which may be limited in scope, but present frailty as a distinct, independent construct. AOD approaches collect much more information but combine many concurrent conditions into a single index.[3,33,37,39,40]

There has been research investigating agreement between these various frailty measures in light of the many existing definitions. For example, a study within the English Longitudinal Study of Ageing assessed measurement agreement between 35 published frailty scores and found that different scales may classify different individuals as frail. The authors suggest that published cutoff values may behave differently among subgroups and ultimately recommend avoiding direct comparisons between different frailty scores.[33] These findings are consistent with another analysis within the Survey of Health, Ageing, and Retirement in Europe (SHARE) study that reviewed 262 frailty phenotypes and found that, while modifications are common in frailty research, there are ranges in frailty prevalence, agreement between phenotypes, and predicting mortality amongst the various definitions.[41] Additionally, phenotypes may be a more appropriate approach to measuring frailty among PWH compared to an AOD index due to the high prevalence of comorbidities among PWH, which could lead to collecting a comorbidity/symptom index rather than a physical frailty measurement.[42]

Fried and colleagues introduced a frailty phenotype developed in the Cardiovascular Health Study (CHS) that focused on five components of physical functioning among community-dwelling older adults.[3] It is now the most commonly used phenotype in frailty research (though not necessarily universally used), incorporating 5 components related to the physical presentation of frailty: fatigue/exhaustion, unintentional weight loss, slow gait speed, low physical activity, and poor grip strength.[3] Individuals who present 3 or more of these components are considered frail, while those who present 1-2 components are considered prefrail, and those with no components are not frail.[3] Of these 5 components, grip strength and gait speed have been used to independently predict frailty but can be more difficult to measure in a routine clinical care setting, as they require specific instruments and more time than other measures. As a result, they are often modified or excluded from frailty phenotypes.[43] Modified phenotypes can increase the feasibility of ascertaining frailty, but they also need to be thoroughly evaluated to understand if the accuracy and validity are retained in the modified measure. Ultimately, as PWH continue to age, there is a need for a validated, low-burden clinical assessment of frailty that aligns with the resources available in routine HIV clinical care settings, which we address in Chapter 2.

Frailty Among People with HIV

As mentioned above, frailty is among the indicators of aging that PWH face at relatively young ages due to accelerated aging and immunosenescence.[2,6] Frailty and HIV both independently predict mortality and together they can increase risk of death 7-fold, but relatively little is known about additional factors that contribute to frailty development or potential ways to mitigate frailty risk among PWH.[32,44]

Substance use, including smoking tobacco cigarettes and drinking alcohol, is very common among PWH and likely has a complicated association with the risk of frailty.[45] Much of the frailty

literature has focused on people without HIV or on cross-sectional associations, providing little evidence regarding these important long-term risk factors for frailty in this population.[4,5,46-48] For example, while current use may represent good health (i.e., that someone is able to access and utilize substances), heavy use may predict future frailty. Thus, substance use reduction could be an area of intervention for promoting long-term health among PWH, but we currently lack the evidence to fully understand this relationship.[47,48] Longitudinal research is warranted to better understand this association between substance use and frailty and elucidate possible interventions or treatment options for people at-risk of or experiencing frailty.

Smoking and Frailty

Our current understanding of the association between cigarette smoking and frailty is incomplete, particularly among PWH. There are gaps and inconsistencies in the literature regarding parameterization of smoking variables and the length of follow-up time considered. A study in the English Longitudinal Study of Ageing found that smoking predicts future frailty, but only dichotomized participants as current smokers or non-smokers.[48] Among PWH, there have been cross-sectional analyses associating smoking with frailty, but these studies lack the context of long-term follow-up.[49,50] Therefore, these studies provide some evidence that smoking increases the risk of frailty, however, less is known about the cumulative impact or how severity/intensity of smoking affects frailty progression.[51-53] These initial results coupled with hypotheses regarding the biological mechanisms illustrate a compelling relationship. The physiologic burden smoking applies to the immune system, such as increasing the production of inflammatory biomarkers and contributing to oxidative stress, adds to inflammaging and ultimately impacts frailty development.[54,55] In Chapter 3 we provide a comprehensive evaluation of smoking and frailty development among a large cohort of PWH.

Alcohol Use and Frailty

There are mixed and inconsistent findings in the literature on the association between alcohol use and frailty, ranging from harmful to null or even protective.[47,53,56-58] The prevalence of alcohol use (including risky use) is high among PWH, and as a modifiable risk factor, this important relationship warrants a better understanding.[59] Of note, there is a wide range of approaches to assessing alcohol use in research, and inconsistencies between measurements may be complicating the interpretations and comparisons of findings. For example, a limitation of some of the existing literature is that many studies evaluate recent or current alcohol use rather than a broader history of use, which can obfuscate the risk associated with drinking.[58]

The alcohol-frailty paradox, where alcohol use at times seems to be protective against frailty, but when studied over the life course high alcohol consumption is a risk factor for frailty, has been observed multiple times.[56,58] In a study within the English Longitudinal Study of Ageing, nondrinkers were at a higher risk of developing frailty until baseline health status was considered.[57] The attenuation impact of baseline health status possibly may be attributed to individuals who used to drink then stopped due to physical or mental health concerns, a phenomenon known as “sick quitting”.[60] This is consistent with other studies that considered historical alcohol use, such as the New Orleans Alcohol Use in HIV (NOAH) Study, which evaluated alcohol use and frailty among 365 PWH and demonstrated that lifetime alcohol use was associated with frailty, while current use was protective.[56] Additionally, the AGEhIV (n=598 PWH) cohort found that current alcohol use (including heavy daily use and binge use) was less common among frail individuals as well as inversely associated with mortality.[6] These authors hypothesized that participants with risky health behaviors had likely reduced or stopped using alcohol, consistent with sick quitting, or otherwise a process of tapering use in older ages may be occurring.[6,56] Ultimately, the current literature includes a range of conclusions and a better evaluation of drinking behaviors and patterns, including sick quitting, may further our

understanding of this complicated relationship. In Chapter 4 we evaluate the relationship between frailty status and reducing drinking frequency to address this question.

Contribution of this project

The many interconnected pathways and mechanisms involved in the development and progression of frailty among PWH underscore the need for an in-depth investigation of these longitudinal associations. This dissertation will fill important gaps in HIV and frailty literature through robust assessment of frailty ascertainment and modifiable behaviors in an understudied aging population.

The purpose of this dissertation is to better characterize frailty among PWH and contribute to the growing knowledge aimed at improving the length of healthspan of PWH.[29] Using rich data and advanced statistical methods, we aim to understand and highlight possible areas of intervention for modifiable behaviors or clinical care to promote long-term health in this population. Much of the current literature on frailty is conducted among the general population and the studies among PWH are small, cross-sectional, or limited in scope.[4-6,22,23,56,61-65] This dissertation will evaluate the validity of a modified frailty phenotype then will also investigate longitudinal associations between substance use behaviors and frailty in a large cohort of PWH. This cohort, the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), boasts geographic and demographic diversity as well as offering a rich data source including clinical diagnoses and medications, laboratory values, and mental health. Better ascertainment of frailty and understanding the impact of modifiable risk factors could improve management of frailty, as well as quality of life and healthspan of PWH.

Chapter 2: Validity Properties of a Self-reported Modified Frailty Phenotype among People with HIV in Clinical Care in the U.S.

Validity Properties of a Self-reported Modified Frailty Phenotype among People with HIV in Clinical Care in the U.S.

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Preface

This Chapter contains a manuscript accepted for publication in the *Journal of the Association of Nurses in AIDS Care* (JANAC).

In developing this Chapter, I led analyses and manuscript writing as well as harmonization of input from coauthors listed above. I compiled and reviewed literature on frailty phenotypes, modifications to phenotypes, and validation studies to identify prior successful approaches, highlight important problems, and construct the statistical plan. I designed the comprehensive analytic approach to incorporate critical components of PROSPER-HIV and CNICS data and served as a liaison between the two teams. I then executed the analysis plan and presented the findings to coauthors and senior collaborators to engage stakeholders and discuss methods, results, and sensitivity analyses. I developed a framework for the manuscript and drafted the initial version then incorporated coauthor comments from 25+ academic collaborators to develop a consensus draft for submission to *JANAC*. Upon receipt of Reviewer and Editor comments, I led the revision by drafting a response to comments, revising the manuscript, and incorporating requested additions to the analysis. I again collaborated with coauthors to incorporate suggestions and further edits to the paper and response to reviewers for resubmission. I also prepared an abstract of these findings, which has been accepted for presentation at the Conference on Retroviruses and Opportunistic Infections (CROI) 2023.

Abstract

Modifications to Fried's frailty phenotype (FFP) are common. We evaluated a self-reported modified frailty phenotype (Mod-FP) used among people with HIV (PWH). Among 522 PWH engaged in two longitudinal studies, we assessed validity of the 4-item Mod-FP compared to 5-item FFP. We compared the phenotypes via receiver operator characteristic (ROC) curves, agreement in classifying frailty, and criterion validity via association with having experienced falls. Mod-FP classified 8% of PWH as frail, while FFP classified 9%. The area under the ROC curve for Mod-FP classifying frailty was 0.93 (95% CI = 0.91 - 0.96). We observed kappa ranging from 0.64 (unweighted) to 0.75 (weighted) for categorizing frailty status. Both definitions found frailty associated with a greater odds of experiencing a fall; FFP estimated a slightly greater magnitude (i.e., OR) for the association than Mod-FP. The Mod-FP has good performance in measuring frailty among PWH and is reasonable to use when the gold standards of observed assessments (i.e., weakness and slowness) are not feasible.

Key words: Frailty phenotype, feasibility, HIV and aging, people with HIV, validity

Introduction

Frailty captures vulnerability to health stressors and is associated with mortality and other negative health outcomes, including falls and hospitalization, among aging adults.[31,66] Due to advancements in antiretroviral therapy, HIV has become a chronic condition and people with HIV (PWH), while living longer, are experiencing a growing burden of morbidity and aging-related conditions, including frailty.[2,67-70] Reliable, self-reported, low-burden frailty assessments may facilitate greater frailty ascertainment in HIV care and other clinical and research settings, which could enhance our understanding and promotion of successful aging among PWH.

Fried's frailty phenotype (FFP) is commonly used to measure frailty,[3,69,71] and includes 5 components of physical health and functional status including unintentional weight loss, low physical activity, exhaustion measured by self-report, and observed weakness, and slowness.[3] Fried and colleagues (2001) conducted many analyses evaluating the FFP, and the accumulation of their results support its validity among older adults. However, it can be difficult to collect components of FFP that require specialized equipment in busy or low-resourced care settings. Specifically, slowness (measured by gait speed test of a timed walk over a designated distance) and weakness (measured by grip strength with an instrument such as a dynamometer) require more time and resources to collect and may not be feasible in all clinical settings. As a result, several modified versions of the FFP have proposed substitutions replacing objectively assessed measures with self-report[41,72] or excluding the objectively assessed measures.[41,67] There is limited validation work among clinical care cohorts specifically evaluating modifications to FFP,[65,71,73] especially among PWH,[74-77] which is important to understand how measurement properties may be affected by modifications.

Investigators within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a large U.S. based cohort of PWH,[78] developed a modified FFP (Mod-FP) based on 4

self-reported components: unintentional weight loss, low physical activity, fatigue, and poor mobility.[79] The Mod-FP is similar to other modified phenotypes used among PWH, with the use of self-reported components and exclusion of a weakness/grip strength measure which is not collected at routine appointments in CNICS.[67,73] Grip strength and gait speed have been observed as strong standalone predictors of frailty among the general aging population.[80,81] Thus, it is important to evaluate the impact of excluding or modifying these components for the Mod-FP, which has not been published for similar modified phenotypes among PWH.

The Impact of Physical Activity Routines and Dietary Intake on the Longitudinal Symptom Experience of people living with HIV (PROSPER-HIV) study is an ongoing study collecting in-depth measurements of physical activity and functional status among a subset of PWH in CNICS,[82] including grip strength and gait speed. Utilizing these measures from PROSPER-HIV in conjunction with the self-reported components from CNICS, we created an FFP with all 5 original components and used it as a gold standard comparator to evaluate the validity and reliability of the Mod-FP among PWH.

Methods

Study Setting and Participants

This study was conducted among PWH enrolled in the PROSPER-HIV study[82] nested within the CNICS cohort.[78] CNICS is a large, longitudinal cohort of adult PWH engaged in HIV care at 8 academic clinical sites across the U. S. PROSPER-HIV is an ongoing longitudinal nested study at 4 CNICS sites focused on understanding the impact of nutrition, exercise, and functional status on outcomes and symptoms in PWH. PROSPER-HIV administers assessments of physical activity and dietary intake[82] to complement comprehensive clinical information (e.g., laboratory values, medications, diagnoses) collected within CNICS.

Most PWH complete the CNICS patient reported outcomes (PRO) clinical assessment at the beginning of routine HIV primary care appointments.[83] The CNICS PRO assessment is a tablet-based questionnaire that includes various instruments covering clinically relevant health domains, such as symptoms (HIV Symptom Index[84]) and physical activity (Lipid Research Clinics Questionnaire[85]).

Eligibility criteria for PROSPER-HIV include PWH who are active CNICS participants with a completed PRO assessment within the past 12 months; prescribed antiretroviral therapy; have an undetectable HIV viral load (<200 copies/mL); not pregnant, breastfeeding, or planning to become pregnant; English-speaking; and have reliable access to a telephone. PWH (n=522) who completed their Year 1 PROSPER-HIV assessment were included in this study. The PROSPER-HIV enhanced assessments include physical function measures, including handgrip strength and gait speed, as well as self-reported falls (described below). Data from both the PROSPER-HIV assessment and CNICS PRO assessments were combined to evaluate the Mod-FP. Data were collected from January 2019 through September 2021. Institutional review boards at participating sites approved CNICS and PROSPER-HIV protocols (Protocol 27674-D at the University of Washington for CNICS and STUDY20180761 at Case Western Reserve University for PROSPER-HIV) and participants completed written informed consent prior to entry into CNICS and PROSPER-HIV.

It was preferred that PWH complete their first PROSPER-HIV assessment on the same day as their PRO assessment, however due to limitations in clinical space some assessments (n=200, 38%) occurred on different days, while the majority (n=322, 62%) occurred on the same day. We further assessed the difference in time between assessments among PWH who had a study visit before the COVID-19 pandemic compared to those who had a study visit during the pandemic. Overall, the mean time between assessments was 36 days (median=0, interquartile

range [IQR]=0,9) and 77% of PWH took both assessments within 30 days. Among PWH who had their first PROSPER-HIV visit before March 1, 2020 (indication of the start of the COVID-19 pandemic), the mean time between visits was 14 days (median=0, IQR=0,6), while among PWH who had their first visit after March 1, 2020, the mean time between visits was 101 days (median=0, IQR=0,66).

Instrumentation

Fatigue

Fatigue was collected via the single fatigue item on the HIV Symptom Index where PWH report symptom burden in the preceding 4 weeks with Likert scale response options, including “I do not have this symptom”, “I have this symptom and it doesn’t bother me”, “I have this symptom and it bothers me a little”, “I have this symptom and it bothers me”, “I have this symptom and it bothers me a lot”.[84] If PWH responded, “I have this symptom and it bothers me” or “I have this symptom and it bothers me a lot”, they were categorized as having the fatigue component.

Unintentional Weight Loss

Wasting and unintentional weight loss was also collected using a single self-reported item in the HIV Symptom Index.[84] With the same Likert scale response options as fatigue, PWH were categorized as having the unintentional weight loss component if they responded, “I have this symptom and it bothers me a little”, “I have this symptom and it bothers me”, or “I have this symptom and it bothers me a lot”. The dichotomization of PRO items based on Likert scales were decided based on clinical knowledge and empirical investigation of the distribution to ensure cut points were robust.

Low Physical Activity

Physical activity was collected with the 4-item Lipid Research Clinics questionnaire and categorized based on the original scoring scheme for physical activity level, which includes self-report of strenuous exercise and overall activity level.[85] We categorized PWH as having the low physical activity component if they were in the "very low active" classification, which means they reported not engaging in strenuous exercise *and* being less active than their peers (compared to people of the same age and sex).

Poor mobility

Mobility was assessed in the EuroQOL Health Related Quality of Life questionnaire (EQ-5D-3L), where PWH were asked to report using a single item how they are with doing activities today.[86] For mobility, the response options include "I have no problems in walking about", "I have some problems walking about", and "I am unable to walk". PWH were considered as having poor mobility if they reported either "I have some problems walking about" or "I am unable to walk".

Slowness

Slowness, captured via gait speed, was measured by 4-meter timed walk, repeated twice and the faster of the 2 trials was recorded as the result. PWH were considered to have slow gait speed if their walk time exceeded 5.0 seconds total (slower than 0.8 meters/second).[87,88]

Weakness

Weakness was captured by grip strength, measured via Jamar hand-held dynamometer (Sammons Preston, Rolyan, Bolingbrook, IL, USA), with 2 trials conducted using the self-reported dominant hand after noting historical hand injuries and surgeries. The maximum strength (measured in kg) of the attempts was recorded as the result. A global standard for frailty using hand grip strength has not been established. Per recommendations of the European

Working Group on Sarcopenia in Older People, PWH were considered to have low grip strength if their maximum strength was <16kg for women or <27kg for men.[88,89]

Phenotypes

We calculated two frailty phenotypes from our data (Figure 2.1). First, Mod-FP consisted of the 4 items collected within the PROs (i.e., fatigue, unintentional weight loss, low physical activity, and poor mobility). The Mod-FP was scored from 0-4 based on the presence of each component. Second, we used a combination of 3 PRO (i.e., fatigue, unintentional weight loss, and low physical activity) and 2 PROSPER-HIV functional status (i.e., grip strength and gait speed) items to create the FFP. FFP was scored from 0-5 based on present components. We categorized the phenotypes by not frail (0 components), prefrail (1-2 components), or frail (≥3 components), as in Fried's original definition.[3]

Falls

We analyzed cross-sectional associations between frailty and falls to further evaluate the Mod-FP. Frailty and falls are associated in the general population,[90] and there is limited but compelling evidence of this association among PWH.[69,91,92] We sought to leverage this association and compared the estimates between the Mod-FP and FFP to evaluate criterion validity of the Mod-FP. PWH self-reported the incidence and frequency of falls occurring in the past 12 months during their PROSPER-HIV visit assessment. Response options included "None", "1 fall", "2 falls", and "3 or more". We dichotomized PWH in two ways for having experienced falls in the past 12 months: 1) any fall (1, 2, or 3 falls vs. None) and 2) recurrent falls (2 or 3 falls vs. None, excluding PWH who self-reported exactly 1 fall). This question was added to the PROSPER-HIV assessment after study initiation, so falls data are only available for a portion (n=253) of PWH.

Statistical Analysis

We assessed criterion validity of the Mod-FP via Spearman correlation coefficient between the Mod-FP and FFP. For this comparison, a high correlation would suggest the two phenotype definitions are measuring a similar trait.[93,94] We also compared the subjective report of mobility (mobility PRO item) with the objective measure of gait speed to evaluate the degree of overlap between these two items we are substituting to represent the same general trait in the Mod-FP and FFP.

To assess the association of the Mod-FP with the FFP, we estimated receiver operator characteristic (ROC) curves. FFP was used as a gold standard measure with the 3-level categorization of not frail, prefrail, and frail. We evaluated the sensitivity, specificity, and classification of the Mod-FP at various cut-offs to determine the optimal points to categorize PWH as not frail, prefrail and frail. We repeated these analyses among subgroups of PWH by age (over 55 versus under 55 [55 years selected based on 54 being the median age], sex, and race [Black/White only, due to sample size]) to confirm the consistency of classification among subgroups and highlight the generalizability of the Mod-FP. We also conducted a sensitivity analysis among PWH based on whether their two visits were within or beyond 30 days apart to evaluate the impact of the time lag on classification of frailty and prefrailty. Using the identified cut points, we also categorized the Mod-FP into not frail, prefrail, and frail. We then evaluated the agreement of classifying PWH as not frail, prefrail, and frail between the two phenotypes with Cohen's kappa. We estimated unweighted and weighted (linear and quadratic) kappa.

Finally, we assessed construct validity via hypothesis testing of the Mod-FP by estimating the association between frailty at that study visit and the report of falls in the prior year (any and recurrent) with logistic regression.[93] We compared the estimated associations (i.e., odd ratios) between frailty and falls. We hypothesized that the Mod-FP would distinguish between PWH

who reported falls vs. no falls. Regression models were adjusted for age and sex assigned at birth. We also stratified by age (and only adjusted for sex in these models) to examine the validity within age strata for the 'any fall' models. The results for these models represent the odds ratio of experiencing a fall associated with each additional component on either phenotype. Statistical significance was evaluated at the 95% confidence level. All analyses were performed using Stata version 16.1 (StataCorp, College Station, TX).

Results

Among 522 PWH included in this study, the mean age was 52 years (median: 54 [Interquartile Range: 44-61]) and 112 (21%) were female (Table 2.1). Over half (268, 51%) self-reported Black race, while 217 (42%) self-reported White race. The prevalence of individual frailty components ranged from 12% for low grip strength to 25% for low physical activity (Table 2.1). Among the 253 PWH who responded to the falls question, 48 (19%) reported at least one fall and 22 (9%) reported recurrent falls in the past 12 months.

The Spearman correlation coefficient between the Mod-FP and FFP was 0.81 ($p<0.001$), suggesting good overlap in their measurement of frailty. We observed that PWH who reported mobility difficulty (i.e., presenting with the low mobility component) had slower average gait speed times than PWH reporting no mobility difficulty, with mean gait speed of 4.3 seconds vs. 3.8 seconds, respectively (Supplement Figure 2.1).

Sensitivity, specificity, and ROC area under the curve (AUC) are presented in Table 2.2. At a cut-point of 3 (i.e., where a Mod-FP score ≥3 was classified as frail), the Mod-FP had a sensitivity of 62%, specificity of 97%, and 94% of PWH correctly classified as frail or not frail based on their status in FFP. There was an AUC of 0.93 (95% CI = 0.91 - 0.96) for this analysis. In analyses stratified by age, sex, and race, we observed similar results, suggesting robust diagnostic accuracy persisting within the subgroups. We also evaluated the Mod-FP for

classification of prefrail PWH and observed a sensitivity of 77% and specificity of 92% at a cut-point of 1 and AUC of 0.86 (95% CI: 0.83-0.89) (Table 2.2). These results suggest the original cut-points used in the FFP (where a score of 0 is not frail, 1-2 is prefrail, and ≥3 is frail) are appropriate for the Mod-FP as well. In the sensitivity analysis based on time between visits (i.e., PROSPER-HIV and CNICS PRO assessments), we observed comparable ROC AUC values for frailty between the two groups (0.94 for PWH with visits within 30 days vs. 0.94 for beyond 30 days) and worse, but still acceptable, ROC AUC for prefrailty among the PWH with visits beyond 30 days (0.88 for PWH with visits within 30 days vs. 0.77 for beyond 30 days), suggesting the prefrailty stage in particular may be a dynamic state that fluctuates over time, especially since it can be defined with a single component (Supplement Table 2.1).

Using these cut-points for categorization of frailty stages, the Mod-FP categorized 43 (8%) PWH as frail and 209 (40%) as prefrail, while the FFP categorized 45 (9%) PWH as frail and 246 (47%) as prefrail (Table 2.3). Agreement between the frailty definitions, measured by Cohen's kappa, conferred substantial agreement (0.64 unweighted, 0.75 quadratic weighted) (Table 2.3). The unweighted observed agreement was 80%.

Finally, in logistic regression models summarizing associations with having experienced a fall, we observed significant associations between additional frailty components and falls, with smaller magnitude of point estimates for the Mod-FP (odds ratio [OR]: 1.36, 95% CI = 1.02 - 1.81, p=0.04) compared to the FFP (OR: 1.63, 95% CI = 1.22 - 2.18, p<0.01), though the confidence intervals overlapped (Figure 2.2, Table 2.4). In age-stratified analyses, these associations and trend persisted among PWH ≥55 years (Mod-FP: OR: 1.76, 95% CI = 1.15-2.68, p=0.01; FFP: OR: 2.07, 95% CI = 1.26-3.41, p<0.01) and were attenuated among PWH <55 years (Mod-FP: OR: 1.09, 95% CI = 0.72-1.63, p=0.69; FFP: OR: 1.41, 95% CI = 0.99-1.99, p=0.053) (Figure 2.2). We also estimated associations between frailty and recurrent falls and

observed similar results (Mod-FP: OR: 1.56, 95% CI = 1.07-2.28, p=0.02; FFP: OR: 1.76, 95% CI = 1.23-2.51, p<0.01) (Figure 2.2). We did not stratify these models due to the small number of recurrent falls.

Discussion

We evaluated the utility of Mod-FP compared to FFP in discriminating not frail, prefrail and frail PWH and observed good measurement properties, including excellent discrimination of frailty and substantial agreement with FFP in classifying PWH by their frailty status. Identical cut-points were used for categorization into the 3 levels often used to classify frailty stages (not frail, prefrail, frail) and Mod-FP produced comparable, albeit weaker, association estimates for the relationship between frailty and falls. Our results also support the utility of the observed functional status measures (i.e., grip strength and gait speed) as important components to collect when possible and when heightened sensitivity is required based on research questions and clinic resources since they add additional context beyond the self-reported components. Overall, the Mod-FP has excellent feasibility; it is low-burden and an easily collected self-report measure of frailty. Mod-FP can be systematically integrated and collected in most settings, with specific utility in HIV care settings and large research studies, given the increasing rates of frailty in this aging population, the impact of frailty on long-term outcomes, and growing interest in HIV and aging research specifically focused on frailty.

Mod-FP had excellent discrimination for not frail PWH (specificity of 97%) but had lower discrimination for frail PWH (sensitivity of 62%) at a cutoff of 3 components. While low sensitivity is less desirable, the sensitivity for detecting frailty at a cutoff of 2 components is higher (89%). Therefore, some frail PWH may be misclassified as prefrail but would likely remain within consideration for frailty interventions for slowing or managing the progression. For prefrailty diagnostics, the Mod-FP was also better at discriminating non-prefrail (specificity of 92%) than

prefrail (sensitivity of 77%) PWH at a cutoff of 1 component. These results are consistent with a study by Van der Elst *et al.* (2020) evaluating the substitution of the functional status measures with self-reported questions. Van der Elst and colleagues hypothesized that these differences in sensitivity and specificity may be an indicator of people overestimating their physical health/status in self-report compared to their performance-based assessment results, which may also be the case in our cohort.

Furthermore, our results suggest that cut-points for categorizing not frail, prefrail, and frail PWH could be the same as for the FFP, even though the Mod-FFP has one fewer component: not frail, score of 0; prefrail, score of 1-2; and frail, score of ≥3.[3] These classification values and cut points observed in the full cohort also performed well in stratified analyses in older/younger PWH, men/women, and Black/White PWH. This consistency is important to confirm, as future studies may focus on specific population subgroups for certain research questions. This is also a new approach that has not been done in other studies evaluating phenotype validity but is an important feature of the measure.[65,76,77]

We also observed very good agreement between the Mod-FP and FFP in this cohort: 8% and 9% of PWH were classified as frail, respectively, with observed agreement of 80%. The agreement between the phenotypes was substantial in all weighting schemes (Cohen's kappa ranged from 0.64 to 0.75). Our results were similar to the study by Van der Elst and colleagues (2020), though they included replacement questions for both weakness and slowness, while we replaced slowness and excluded weakness from the Mod-FP. We also confirmed that the substitution of gait speed with the mobility PRO is reasonable.

The prevalence of frailty among the 522 participants in this study was lower than in all of CNICS – 8% on the Mod-FP in this study vs. 13% as measured by the Mod-FP across the whole CNICS cohort.[79] This difference may be due to enrolling PWH who are less likely to have frailty

perhaps being more likely to volunteer to participate in the PROSPER-HIV study, which is focused on nutrition and physical activity assessments. This particular subset of PWH in CNICS may have better overall health. Also, all PROSPER-HIV participants must be prescribed ART and have an undetectable HIV viral load, which confers better health. Misrepresentations of health in self-report has been hypothesized as a reason for modified phenotypes misclassifying frail individuals (exemplified by the lower sensitivity values).[77] Our study sample, PWH in CNICS who were independently assessed at PROSPER-HIV visits and not selected for inclusion based on frailty status, highlights a strength of this analysis in the context of evaluating the Mod-FP.

Both the Mod-FP and FFP were associated with falls in the prior year, especially for recurrent falls, consistent with the general older adult population.[90] The observed association (i.e., higher odds of having experienced a fall associated with higher frailty scores) persisted in both phenotype definitions among older PWH when we stratified by age but was attenuated for younger PWH in the FFP and null for the Mod-FP. Overall, these results show similar estimation of associations for the definitions, however, the observed functional status measures provide additional important information especially for younger PWH, consistent with evidence from other studies.[95,96] Of note, this study was not designed to fully evaluate falls among PWH, but we did observe a higher risk of falls associated with higher frailty scores, warranting future studies evaluating the epidemiology of frailty and falls in this population, including risk factors, potential causes, and best strategies for prevention.

The attenuation of associations between frailty and falls among younger PWH requires some additional investigation. While PWH experience frailty at younger ages than the general population,[67-70] less is known about how well the commonly used instruments measure frailty among younger PWH. Our results align with this. Sensitivity and specificity were similar, and the AUC of the ROC was higher among younger PWH than older, suggesting the Mod-FP is

comparable to the FFP in identifying younger frail PWH. However, the lower magnitude of the point estimates in the falls analyses highlights the need for further investigation regarding the predictive ability of frailty phenotypes among younger PWH. Frailty assessment among younger adults is not often done in the general population and understanding the limitations of frailty measurement poses clinical importance among PWH. Ultimately, our study provides clear evidence as to the ability of the Mod-FP to identify frailty and prefrailty, which is an essential first step to manage and follow its progression in care.

Our results support the use of the Mod-FP within CNICS; however, it is important to highlight that evaluating the validity of a new measure is a lengthy process involving a large body of research with considerations of different settings and subgroups that the measure may be used among.[97] Further, the 'validity' of a measure should be viewed as a dynamic property that can fluctuate along a spectrum (not an 'all or nothing' property) and is the sum of its components, including but not limited to the forms of validity evidence presented here, rather than a conclusion from a single analysis.[93,97] In this study we collected and analyzed evidence to understand some of these properties in the setting of PWH engaged in clinical care in the US. We evaluated the performance of the Mod-FP specifically in subgroups to gain a more comprehensive view of these properties. Overall, evaluating the validity of a measure should be an ongoing process, including updating data and results, when possible, to continue accumulating evidence for these measurement properties.[97]

Strengths of this study include the demographic diversity and size of the cohort, which allowed for stratification and subgroup analyses. Our results are also consistent with other studies that evaluated modifications to the FFP with substitutions and/or exclusions of components, and we were able to expand this work to include the subgroup analyses among PWH.[77,95]

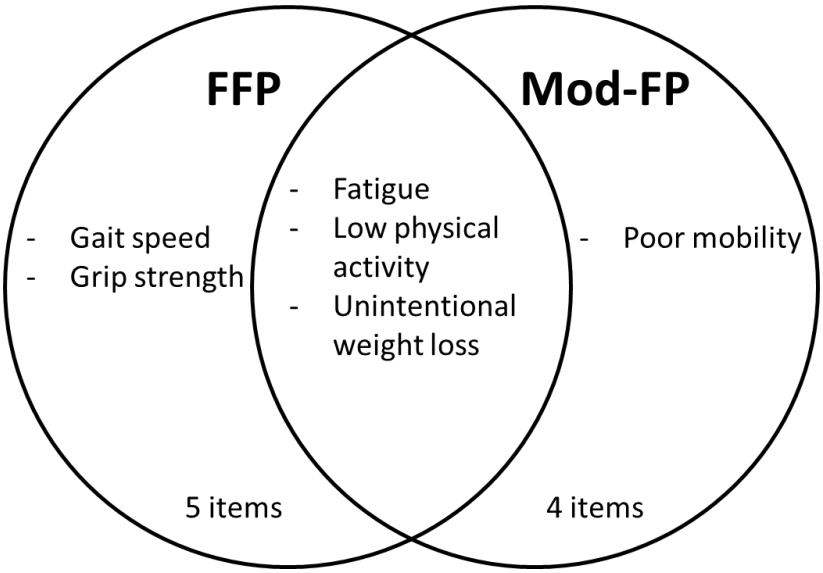
Notable limitations include limited generalizability due to self-selection into the PROSPER-HIV study. The prevalence of frailty in the PROSPER-HIV cohort was slightly lower than in the overall CNICS cohort, so participants in PROSPER-HIV may be healthier than the larger CNICS cohort. Additionally, we were limited by sample size to robustly assess recurrent falls within different strata; however, future work aims to thoroughly evaluate the epidemiology and risk factors for the relationship between frailty and falls among PWH. Furthermore, the cross-sectional design of this study limits our interpretation of causality or directionality of these associations. The cross-sectional nature also precluded any analyses of the progression of frailty, which could highlight further questions regarding differences in frailty measurements over time and could vary in age strata due to differential likelihood of transitions (both deterioration and recovery) in frailty associated with age.[98] Finally, there was a gap for some PWH between the dates of completing their 2 frailty assessments, particularly among those whose PROSPER-HIV visit occurred during the COVID-19 pandemic; however, most PWH (77%) completed both within 30 days. We assessed this time lag in sensitivity analyses and observed generally comparable ROC values (0.94 vs. 0.94 for frailty and 0.88 vs. 0.77 for prefrailty, Supplement Table 2.1), and the results suggest that prefrailty is a dynamic state.

Conclusion

The Mod-FP has good measurement properties for frailty with highly feasible (e.g., low-burden, fast, and does not require care provider administration) and widespread collection throughout CNICS that could be applied in other time or resource-constrained settings among PWH as well. Nevertheless, validity properties should be reassessed in other settings. We found frailty stages for the Mod-FP (not frail, prefrail, frail) should be defined as in FFP. Finally, functional status measures (e.g., grip strength and gait speed) provide valuable additional information when available.

Tables and Figures

Figure 2.1. Components included in each frailty phenotype definition. Fried's frailty phenotype (FFP) includes 5 components, with 3 overlapping with the modified frailty phenotype (Mod-FP), which includes 4 components in total.



Abbreviations: FFP: Fried's Frailty Phenotype; Mod-FP: Modified Fried Phenotype

Table 2.1. Descriptive statistics of the analytic cohort (N=522)

Variable	N (%) unless noted
Male	410 (79)
Female	112 (21)
Age, mean (SD)	52 (11)
Age, median (IQR)	54 (44-61)
Under 55	276 (53)
55 and older	246 (47)
Race/ethnicity	
Black	268 (51)
Hispanic	26 (5)
Other	11 (2)
White	217 (42)
Frailty components	
Unintentional weight loss	78 (15)
Exhaustion/fatigue	110 (21)
Low physical activity	129 (25)
Poor mobility	111 (21)
Walk time	85 (16)
Grip strength	65 (12)

Abbreviations: IQR: interquartile range; SD: standard deviation

Table 2.2. Receiver operator characteristics (ROC) results for the classification of prefrailty and frailty on the Mod-FP compared to the FFP.

Sample	ROC AUC (95% CI)	Cut point (Mod-FP score)	Sensitivity	Specificity	Correctly classified
Everyone	0.934 (0.905-0.963)	≥1	100%	57%	60%
		≥2	89%	83%	84%
		≥3	**62%**	**97%**	**94%**
		≥4	27%	100%	94%
PWH under 55	0.962 (0.935-0.990)	≥1	100%	56%	60%
		≥2	96%	84%	85%
		≥3	**69%**	**99%**	**96%**
		≥4	31%	100%	93%
PWH 55 & older	0.898 (0.843-0.954)	≥1	100%	58%	61%
		≥2	79%	82%	82%
		≥3	**54%**	**95%**	**91%**
		≥4	21%	100%	94%
Men	0.929 (0.894-0.963)	≥1	100%	59%	62%
		≥2	85%	85%	85%
		≥3	**59%**	**97%**	**94%**
		≥4	18%	100%	93%
Women	0.959 (0.918-0.999)	≥1	100%	48%	53%
		≥2	100%	76%	79%
		≥3	**73%**	**96%**	**94%**
		≥4	55%	100%	96%
Black PWH	0.943 (0.906-0.981)	≥1	100%	58%	62%
		≥2	91%	83%	84%
		≥3	**61%**	**98%**	**95%**
		≥4	35%	100%	94%
White PWH	0.920 (0.867-0.972)	≥1	100%	55%	59%
		≥2	84%	83%	83%
		≥3	**63%**	**96%**	**93%**
		≥4	16%	100%	93%
Everyone – prefrail classification	0.858 (0.828-0.888)	**≥1**	**77%**	**92%**	**84%**
		≥2	33%	100%	65%
		≥3	6%	100%	52%

Abbreviations: AUC: area under curve; FFP: Fried's Frailty Phenotype; Mod-FP: Modified Fried Phenotype; PWH, people with HIV

Table 2.3. Categorization (n [%]) and agreement of classification of frailty stages by Mod-FP and FFP

Categorization into frailty stages				
	FFP – not frail	**FFP – prefrail**	**FFP – frail**	**Total**
Mod-FP – not frail	213 (92)	57 (23)	0 (0)	270
Mod-FP – prefrail	18 (8)	174 (71)	17 (38)	209
Mod-FP – frail	0 (0)	15 (6)	28 (62)	43
Total	231	246	45	522
Agreement between Mod-FP and FFP				
Weighting Scheme	**Agreement**	**Expected Agreement**	**κ**	**Interpretation**
Unweighted	79.5%	42.5%	0.64	Substantial
Weighted linear	89.8%	67.2%	0.69	Substantial
Weighted quadratic	94.9%	79.5%	0.75	Substantial

Abbreviations: FFP: Fried's Frailty Phenotype; Mod-FP: Modified Fried Phenotype
Not frail (0 components), prefrail (1-2 components), frail (≥3 components)

Table 2.4. Comparison of logistic regression estimated associations between frailty measures (Mod-FP or FFP) and falls

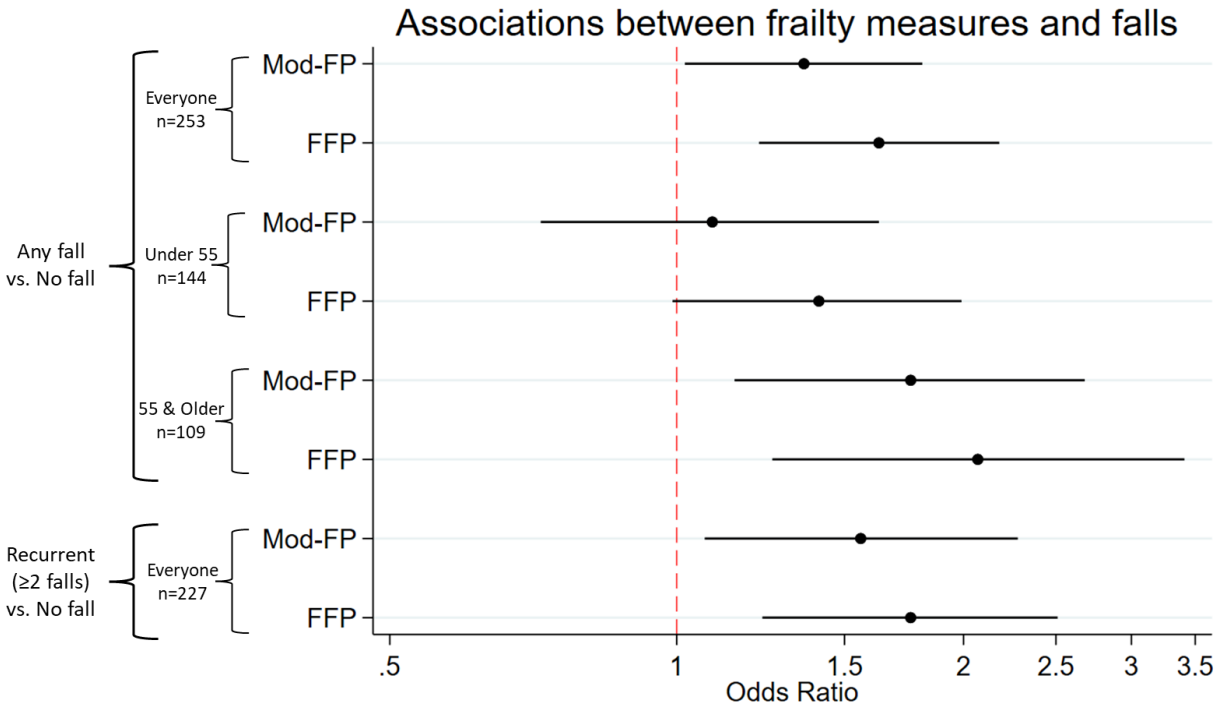
	Fall vs. No fall	Recurrent (≥2 falls) vs. No fall
Phenotype	**OR (95% CI), p-value**	**OR (95% CI), p-value**
Everyone [a], n=253		
Mod-FP Score	1.36 (1.02, 1.81), 0.04	1.56 (1.07, 2.28), 0.02
FFP Score	1.63 (1.22, 2.18), <0.01	1.76 (1.23, 2.51), <0.01
Under 55 [b], n=144		
Mod-FP Score	1.09 (0.72, 1.63), 0.69	
FFP Score	1.41 (0.99, 1.99), 0.053	
55 & Older [b], n=109		
Mod-FP Score	1.76 (1.15, 2.68), 0.01	
FFP Score	2.07 (1.26, 3.41), <0.01	

Abbreviations: 95% CI: 95% confidence interval; FFP: Fried's Frailty Phenotype; Mod-FP: Modified Fried Phenotype; OR: odds ratio

[a] Adjusted for age and birth sex

[b] Adjusted for birth sex

Figure 2.2. Forest plot comparison of logistic regression estimated associations between frailty measures and falls. We used logistic regression to estimate the association between frailty and self-reported falls in the past 12 months. Falls were dichotomized as any vs. none and recurrent vs. none. We found both phenotype definitions to be associated with any fall and recurrent falls, with stronger associations with the FFP. We stratified the model for any fall by age (at 55 years) and observed stronger associations among older people with HIV (PWH), while the associations were attenuated among younger PWH.



Abbreviations: FFP: Fried's Frailty Phenotype; Mod-FP: Modified Fried Phenotype

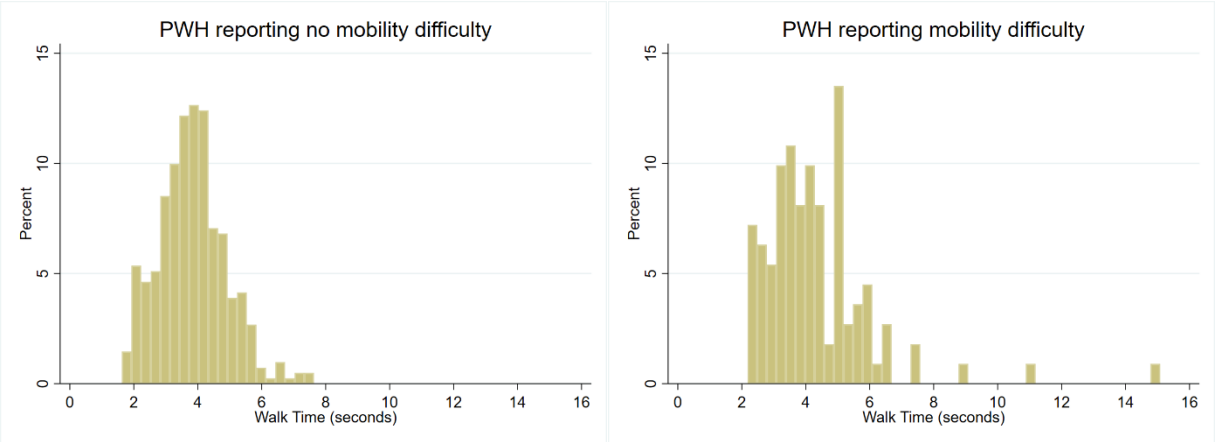
Supplement Content

Table S2.1. Receiver operator characteristics (ROC) results for the classification of prefrailty and frailty on the Mod-FP compared to the FFP, based on time between visits (within 30 days and beyond 30 days).

Sample	ROC AUC (95% CI)	Cut point (Mod-FP score)	Sensitivity	Specificity	Correctly classified
Visits within 30 days – Frail classification	0.935 (0.899-0.971)	≥1	100%	54%	58%
		≥2	90%	82%	83%
		≥3	**63%**	**97%**	**95%**
		≥4	27%	100%	95%
Visits within 30 days – Prefrail classification	0.883 (0.852-0.914)	**≥1**	**82%**	**92%**	**87%**
		≥2	35%	100%	66%
		≥3	6%	100%	52%
Visits beyond 30 days – Frail classification	0.936 (0.887-0.985)	≥1	100%	64%	69%
		≥2	87%	86%	86%
		≥3	**60%**	**96%**	**92%**
		≥4	27%	100%	91%
Visits beyond 30 days – Prefrail classification	0.770 (0.697-0.844)	**≥1**	**60%**	**92%**	**75%**
		≥2	27%	100%	62%
		≥3	7%	100%	51%

Abbreviations: AUC: area under curve; FFP: Fried's Frailty Phenotype; Mod-FP: Modified Fried Phenotype; PWH, people with HIV

Figure S2.1. Histograms of walk time (gait speed) among people with HIV (PWH) without vs. with mobility difficulty. We graphed histograms of walk time (measured in seconds) based on self-reported mobility. Mobility was dichotomized between PWH reporting mobility difficulty and PWH reporting no mobility difficulty. Walk times among PWH reporting mobility difficulty were skewed towards being slower than times among PWH reporting no difficulty.



Chapter 3: Tobacco Smoking and Pack-years are Associated with Frailty among People with HIV

Tobacco Smoking and Pack-years are Associated with Frailty among People with HIV

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Preface

This Chapter contains a manuscript prepared for submission (currently under review) to the *Journal of Acquired Immune Deficiency Syndrome* (JAIDS).

In developing this Chapter, I conceptualized the research question and analysis plan then executed the analyses and led manuscript writing as well as incorporation of coauthor feedback to the text. I reviewed the literature to understand existing studies, gaps in evidence, and identify key areas of scientific and clinical interest to focus the statistical and methodological approach (e.g., age- and sex-specific subgroup modeling and interaction analyses). I built the dataset from the CNICS data repository files and analyzed all iterations of the models, including many sensitivity models and data checks, then presented the findings and led discussions regarding modeling choices and methodology to ensure detailed and in-depth knowledge of the results by collaborators. I drafted the initial version of the manuscript and harmonized coauthor comments to develop a consensus draft for submission to *JAIDS*. I also successfully created and delivered an oral presentation of these findings to leaders in the field at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE 2022), from August 24-28, 2022, in Copenhagen, Denmark.

Abstract

Background

Tobacco smoking increases frailty risk among the general population and is common among people with HIV (PWH), who experience higher rates of frailty at earlier ages than the general population.

Methods

We identified 8,608 PWH across 6 Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites who completed ≥2 patient-reported outcome assessments, including a frailty phenotype measuring unintentional weight loss, poor mobility, fatigue, and inactivity, scored 0-4. Smoking was measured as baseline pack-years and time-updated never, former, or current use with cigarettes/day. We used Cox models to associate smoking with risk of incident frailty (score ≥3) and deterioration (frailty score increase by ≥2 points), adjusted for demographics, antiviral medication, and time-updated CD4 count.

Results

Mean follow-up of PWH was 5.3 years (median: 5.0), the mean age at baseline was 45 years, 15% were female, and 52% were non-White. At baseline, 60% reported current (31%) or former (29%) smoking. Current (HR: 1.79; 95%CI: 1.54-2.08) and former (HR: 1.31; 95%CI: 1.12-1.53) smoking were associated with higher frailty risk, as was higher pack-years (HR: 1.12; 95%CI: 1.09-1.16). Current smoking (among younger PWH) and pack-years, but not former smoking, were associated with higher risk of deterioration.

Conclusion

Among PWH, smoking status and duration are associated with incident and worsening frailty.

Key words: Frailty, Tobacco Smoking, People with HIV, HIV and aging

Introduction

Smoking is common among people with HIV (PWH);[99,100] an estimated 42% of PWH engaged in care in the US smoke compared to 21% of the US adult population.[101] Additionally, smoking is a risk factor for many chronic diseases and mortality[54,100,102] yet remains understudied in the context of aging with HIV.[100,103,104] As PWH experience healthier aging due to advancements in HIV treatment, the focus of care is shifting to aging-related disease, functional decline, and frailty, a measure of physiologic reserve and vulnerability to health stressors.[31,105] Frailty is observed more often[32,106,107] and at younger ages[67,68,108] among PWH and is often attributed to chronic inflammation from HIV infection leading to immune system exhaustion.[2,17,106,108,109] Similarly, smoking increases the production of pro-inflammatory cytokines and contributes to stress and declines in the immune system.[54,55,110] Together, smoking and HIV could negatively impact aging of PWH, but published evidence thoroughly investigating this association is scarce.

In populations without HIV, smoking predicts worsening frailty,[5,48,111,112] but the relationship may differ by sex and age.[104,113,114] One study reported evidence of an association between smoking and frailty among men but not women,[113] while another found an association between smoking and frailty among men and women younger than 60, but nonsignificant associations among those 60 and older.[114] Whether these trends persist for PWH is unknown, but observed disparities in risky behaviors, frailty, and survival between men and women with HIV suggest possible differences.[104] The primary hypothesis linking smoking and frailty is that increased inflammation and physiologic stress caused by smoking contributes to immune system exhaustion, ultimately leading to frailty.[55,111,115-117] Specifically, reactive oxygen and nitrogen species caused by smoking induce a heightened inflammatory state and cellular senescence earlier than in the absence of smoking.[115] This cumulative oxidative stress is theorized to

contribute to aging via loss of organ function over time and can lead to an increase in aging-related conditions.[115-118]

The combination of smoking- and HIV-induced chronic inflammation is concerning as both can contribute to 'inflammaging', a theory connecting inflammation to accelerated aging, characterized by earlier presentation of frailty and other aging-related conditions.[16,115,119,120] Among PWH, there is evidence that smoking-associated DNA methylation (a biomarker used to evaluate biological and chronological age[119]) was linked with frailty and mortality,[121] and smoking has been associated with higher levels of inflammatory markers.[110] In addition, cross-sectional studies have found evidence of a direct association between smoking and frailty.[49,50] Most of these studies have been limited by cross-sectional design,[49,50,53,114] small sample size for subgroups,[52,121,122] only measuring smoking by status of use,[5,48,49,111,113,122] or excluding PWH.[5,48,53,111-114,123] In order to close existing gaps in knowledge, we conducted a longitudinal study to comprehensively evaluate associations between smoking and frailty among a large, diverse population of PWH, with particular focus on age and sex.

Methods

Setting and Participants

This study was conducted within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. CNICS is an ongoing study including PWH aged 18 years and older in care at 8 academic clinical sites in the US.[124] Six sites with relevant data were included in this study. The CNICS data repository integrates and harmonizes clinical data including laboratory values, diagnoses, and medications, as well as demographic information and patient reported outcome measures (PROs). The CNICS clinical PRO assessment is completed every ~6 months at routine clinic visits with electronic tablets and consists of validated survey instruments

such as the HIV Symptom Index and substance use measures, and is offered in English, Spanish, and Amharic.[83]

PWH who completed at least 2 clinical PRO assessments between 1/2012-8/2021 were included in this study. Baseline was the date of the first completed PRO assessment within the study period including tobacco and frailty measures. For time-to-event models, follow-up ended at the earliest date of 1) event occurrence or 2) last visit in CNICS within the observation period (including departure from CNICS or death). In some analyses we allowed follow-up time to include up to the last visit within the observation period rather than censoring at frailty incidence to allow for observation of frailty recovery. Time was measured as years since baseline. Institutional review boards at each site approved CNICS protocols and all participants completed informed consent prior to entry into CNICS.

Smoking

Smoking was collected in the PRO assessment. Time-varying smoking status was measured as never, former, or current use with intensity of smoking (the number of cigarettes smoked per day) among those reporting current use. Cigarettes smoked per day was centered at 10 per day so when status of use and intensity are modeled together, the interpretation for currently smoking represents someone who currently smokes 10 cigarettes per day. Pack-years smoking was assessed at baseline for ever-smokers.

Frailty

Frailty was defined using a modified version of Fried's frailty phenotype,[3] an approach that has been used in prior HIV studies.[67,73,125] We defined frailty by scoring PWH from 0-4 based on their PRO responses using 4 of the 5 components of Fried's phenotype: fatigue, low physical activity, poor mobility, and unintentional weight loss. The fifth component of Fried's phenotype,

weakness, was not collected. Each component was dichotomized as present or absent then combined into a single score (Table S3.1). We defined 2 frailty events: 1) incident frailty (score ≥3) and 2) deterioration (increase of ≥2 points compared to baseline score), which were modeled separately (i.e., someone could experience both incident frailty and deterioration).

Covariates

Demographic information (e.g., age, birth sex, and race/ethnicity [Black, White, Hispanic, or Other]) is collected at initial CNICS visit. Additional covariates included baseline self-report of antiretroviral therapy (ART) use (yes/no) and time-updated CD4 cell count as a measure of immune status. We also collected baseline alcohol (measured by Alcohol Use Disorders Identification Test Consumption [AUDIT-C])[126] and recreational drug use (illicit opioids, methamphetamines, cocaine/crack, and marijuana measured by a modified World Health Organization Alcohol, Smoking and Substance Involvement Screening Test [ASSIST] instrument).[127]

Statistical Analysis

We used Cox proportional hazards models to estimate the association between tobacco smoking and incident frailty, with the exposures of interest being 1) time-updated smoking status plus intensity of use (cigarettes smoked per day) and 2) baseline pack-years. These models were adjusted for demographic characteristics, ART use, and time-updated CD4 count. We stratified these models into 4 groups defined by sex and baseline age (cutoff at 50, as is common in frailty studies among PWH[2,65]) to evaluate sex- and age-specific associations and understand whether differences observed in studies among the general population persist among PWH.[113,114] We conducted multiple sensitivity analyses, including assessing for interactions with smoking by age and sex (see Methods S3.1 in Supplementary Appendix) and

adjusting for baseline alcohol and drug use. We repeated the main models to estimate the associations between smoking and deterioration of frailty. This analysis was intended to supplement the main models and represent significant change in frailty status even if it does not reach the frail stage (i.e., transition from 0 to 2). PWH with baseline frailty scores ≥3 were excluded from all Cox models (both for incident frailty and deterioration). Proportional hazards for each model were tested using Schoenfeld residuals and in the case of violations, we stratified on the variable(s) of concern.[128,129] Collinearity between smoking measures was checked and the variance inflation factors were low, below 1.3.[130]

We used linear mixed models (LMMs) to assess associations between smoking and frailty. LMMs utilize all available data (all baseline frailty scores) and allow for observation of increasing and decreasing frailty score without indicating a specific event/censoring as in Cox models.[131] We considered frailty as a continuous score and log-transformed (after adding 0.5 to each score to avoid undefined transformation) scores to fit a linear distribution. Therefore, we modeled log-transformed frailty scores as a linear function using LMMs with random intercepts and slopes for individuals, adjusting for demographic characteristics, ART use, site, time since baseline, and time-updated CD4 count. We exponentiated coefficients to represent the multiplicative increase in frailty score associated with each smoking exposure. We used separate models to estimate associations with 1) time-updated smoking status plus intensity of use and 2) baseline pack-years for each subgroup. Analyses were performed using Stata version 17.0 (StataCorp, College Station, TX, USA).

Results

Among 8,608 PWH, 924 (11%) were frail at the end of follow-up with mean follow-up of 5.3 years (median: 5.0). The mean age at baseline was 45 years (median: 46) and 15% were female, while almost half (48%) were non-Hispanic White and 31% were non-Hispanic Black

(Table 3.1). Sixty percent of PWH reported either former (29%) or current (31%) smoking at baseline (Table 3.1). Among all subgroups, more PWH who smoked (former or current) were frail (Figure 3.1). Follow-up time was similar across the subgroups and baseline median frailty score was 1 for all groups. Among PWH with a frailty score of 0-2 at baseline, the incidence rate of frailty was 27 per 1,000 person-years; the incidence rate was lower among men (26 per 1,000 person-years) than women (38 per 1,000 person-years).

Smoking status and cumulative burden of smoking (i.e., pack-years) were associated with both clinically and statistically significantly higher risks of incident frailty (Table 3.2). Among all participants, former smoking was associated with a 31% higher risk of incident frailty (95% confidence interval [CI]: 1.12-1.53) and current smoking was associated with a 79% higher risk (95%CI: 1.54-2.08). In a separate model, we observed a 12% greater risk of frailty for every 5 pack-years of smoking (95%CI: 1.09-1.16) (Table 3.2). When stratified into subgroups, we observed generally similar associations, although with some loss of precision likely due to smaller sample sizes. Among women under 50, we observed a dose-response association with cigarettes per day, where every 10 additional cigarettes smoked was associated with a 47% higher risk of incident frailty (95%CI: 1.07-2.02). We evaluated interactions with smoking by sex and age and did not find evidence of effect measure modification (Tables S3.2-S3.4).

In sensitivity analyses adjusting for baseline alcohol use, we observed similar associations (Table S3.5). When we adjusted for recreational drug use, there was some attenuation of the associations, but interpretations generally remained consistent with the main models (Table S3.6). There was concern regarding small sample size, discussed in Results S3.1.

We estimated the association between smoking status and deterioration stratified by age due to violation of proportional hazards. Among PWH <50, current smoking was associated with a 40% higher risk of deterioration compared to never smoking (95%CI: 1.17-1.68), as well as a 17%

higher risk associated with smoking an additional 10 cigarettes per day (95%CI: 1.01-1.37) (Table 3.3). We did not observe these associations among PWH ≥50. Among all ages, there was no greater risk of deterioration associated with former smoking. Among all PWH, every 5 pack-years smoking was associated with a 6% higher risk of deterioration (95%CI: 1.02-1.09) (Table 3.3). Subgroup results are presented in Table S3.7 and Results S3.2.

In LMMs, all measures of smoking were associated with increasing frailty scores over follow-up (Table 3.4, discussed in Results S3.3). Current smoking was associated with a 1.15-times higher frailty score over the study period (95%CI: 1.10-1.21) (Table 3.4). Intensity of smoking (cigarettes per day) was associated with frailty here, which was not in the Cox models, likely due to an increase in statistical power in LMMs compared to survival models. The subgroup results were similar to the pooled results, with some fluctuations in estimates and precision but consistent interpretations (Table S3.8).

Discussion

We found strong evidence of a higher risk of frailty associated with tobacco smoking in a large, diverse cohort of PWH in the US. Former and current smoking were associated with 31% and 79% higher risks of incident frailty, respectively. Moreover, every 5 pack-years smoking was associated with a 12% higher risk of frailty. Furthermore, in analyses estimating the risk of deterioration, we found that current smoking among PWH <50 years old and more pack-years of smoking (among all ages) were associated with higher risk of deterioration. Former smoking, however, was not associated with a higher risk of deterioration, suggesting smoking cessation could reduce the risk of worsening frailty. This study expands upon the limited literature on this topic by including subgroup analyses (i.e., age, sex), multiple measures of smoking (i.e., status, intensity, and pack-years), and significant follow-up (average >5 years). In addition, we

evaluated these relationships in multiple models to understand both incidence and deterioration of frailty, as well as changes in score over time to account for improvement.

We focused analyses on subgroups by age and sex due to possible important differences regarding both exposure to smoking (e.g., patterns/severity of use) as well as physiologic pathways of frailty development. Further, subgrouping is useful to understand which groups may benefit most from certain interventions.[132] Our approach was similar to that of DeClercq *et al.*[114] except we dichotomized age at 50 years (vs. 60) based on the relevance of PWH experiencing frailty at younger ages.[67,108] We observed some variability in estimates between subgroups but overall did not find evidence of effect measure modification by age or sex. Our results consistently suggest that smoking is associated with a higher risk of frailty among all subgroups and support the notion that smoking cessation is beneficial for healthy aging among PWH. We did, however, find that women, particularly young women with regard to smoking intensity, may experience the worst frailty outcomes associated with smoking, possibly due to biological differences from sex or age, or from differential behaviors that otherwise increase the risk of frailty.

There is a phenomenon observed in aging research in which women survive longer than men but experience a greater burden of disease throughout their life, referred to as the male-female health survival paradox or mortality-morbidity paradox.[133] One study evaluating this paradox among Danish, Japanese, and US adults found greater handgrip strength (the fifth component of Fried's frailty phenotype although not collected in CNICS) but lower survival among men compared to women.[134] Differences in immune response, with women having more active immune systems than men, has been among the hypothesized mechanisms for this paradox.[135,136] While this may pose some benefit for survival, immune exhaustion is a common metric of frailty and greater lifelong immune activation may predispose women to immune

exhaustion, thus frailty.[137] We did not study mortality in this analysis, although our findings that women experienced more frailty (incidence rates of 38 vs. 26 per 1,000 person-years) align with the evidence that women experience greater morbidity than men.

Women with HIV often face the intersection of substance abuse and violence in addition to HIV, which negatively influence risk behaviors (e.g., polysubstance use and medication adherence) leading to poor health.[138] A study within the Women's Interagency HIV Study (WIHS) observed that women who smoked were more likely to report using other drugs, such as cocaine or heroin, than women who did not smoke.[139] They found that 48% of women who smoked reported current recreational drug use, compared to 27% of former smokers and 9% of never smokers.[139] Further, polysubstance use may increase severity of use of the individual substances (such as the number of cigarettes smoked per day).[140] It is likely that drug use also impacts frailty based on associations with inflammation, other aging-related outcomes, and mortality, despite the paucity of evidence regarding the direct link.[104,141] We suspect there may be some effect of other risky behaviors that are common among women who smoke tobacco in our results. To address these concerns, we adjusted for recreational drug use in sensitivity models, the results of which align with this hypothesis, via attenuation of smoking associations. A thorough evaluation of these behaviors is warranted in a study designed to answer these questions with sufficient statistical power to assess individual drugs as well as subgroups since we faced sample size limitations (discussed in Results S3.1).

Our results among age strata were consistent with data indicating younger adults experience a slightly greater risk of frailty associated with smoking than older adults.[114] In conjunction with the evidence of earlier presentations of frailty among PWH,[67,107,108] these findings highlight the importance of measuring frailty in younger, as well as older, PWH. One possibility for the discrepancy between age strata could be related to surviving to baseline without frailty, where

some of the older PWH who smoked already died or become frail, thus are not included in analyses. A study within the ART Cohort Collaboration (ART-CC) reported the large burden smoking has on PWH and found that PWH on ART may lose more years of life to smoking than to HIV infection.[100] We observed that a greater proportion of older PWH were excluded from our analyses due to already being frail at baseline (see Figure 3.1), supporting the possibility that PWH who remained not frail (and included in our analyses) may be more resilient. Overall, these results warrant the consideration of the lifespan approach,[142] including increased attention to younger PWH with risky behaviors that may lead to frailty that could be managed to prevent severe frailty or death.

Our analysis evaluating the risk of deterioration of frailty offers an alternative perspective on the progression of frailty by considering baseline frailty status and modeling a standard change in score. Notably, we observed that former smoking was not associated with a risk of deterioration, while there was some risk associated with cumulative burden and currently smoking among younger PWH. A meta-analysis evaluating smoking and frailty among the general population found no difference between the risk of frailty among former and never smokers and concluded that cessation may reduce frailty risk.[51] Our results are less conclusive, given the observation of cumulative associations between smoking and deterioration risk, but the lack of association between former smoking and deterioration suggests there may be cases where cessation helps mitigate the risk of frailty progression. In addition, the differences in associations between age strata support the notion that older PWH who had not already experienced a deterioration in physical health, and thus were included in these analyses, may have been more resilient for some reason and maintained their health status.

We hypothesize that the mechanism between smoking and frailty is largely affected by long-term cumulative effects of smoking, including inflammation, as well as the presence of other

comorbidities, but may be mitigated through quitting followed by some degree of reduction in levels of inflammatory markers[110,143] and risks of comorbidities.[144,145] Among PWH in the Strategies for Management of Antiretroviral Therapy (SMART) trial, current smoking was found to contribute to 25% of cardiovascular disease, 31% of non-AIDS cancer, and 24% to overall mortality.[145] Additionally, an analysis within the Data collection on Adverse Events of Anti-HIV Drugs (D:A:D) study found risks of cardiovascular disease to further decrease as time since quitting smoking increased.[144] Whether this trend persists for frailty risk is currently unknown, but our results and the existing literature nonetheless suggest benefit of smoking reductions or cessation on frailty risk.[110] While we measured frailty via phenotype, which differentiates it clinically from other diseases and disability, the accumulation of deficits model of capturing frailty relies on enumerating present comorbidities,[37] directly linking these conditions to frailty.[112] Even though we do not take this approach or adjust for comorbidities, the presence of comorbidities likely influences the presence and degree of frailty (measured by phenotype) as well through deterioration of physiologic reserve and polypharmacy contributing to declines in overall health.[3,5,125]

CNICS boasts geographic and demographic diversity among a large cohort of PWH, allowing for subgroup analyses by sex and age. Additionally, we had sufficient follow-up to observe changes in frailty status over time, while many prior studies have conducted cross-sectional analyses. We also included multiple ways of measuring of smoking. Similarly, we considered multiple approaches to quantify changes in frailty, by incidence of becoming frail, a deterioration of frailty score, and changes in score.

Our study has an important focus on PWH engaged in HIV care in the US, but results may not be generalizable to other populations. We focused on tobacco cigarette smoking, thus did not capture other smoking behaviors such as cigars or vaping. We focused analyses on evaluating

the association of interest among subgroups, however, that resulted in small sample sizes for some groups. This particularly impacted sensitivity analysis models that were unable to produce estimates due to violations of positivity. Similarly, we were unable to differentiate between individual recreational drugs while preserving power, so we used a composite variable. Our frailty phenotype is self-reported and, while validated, includes 4 of the 5 original components included in Fried's frailty phenotype (missing weakness). There may be unmeasured confounding of this relationship, as we did not have data on socioeconomic status, which may increase the likelihood of smoking as well as frailty.[111,146] Additionally, we did not have enough participants to incorporate transgender status, which could be associated with hormone use and affect frailty risk.[135]

Conclusion

We found strong evidence of a higher risk of frailty associated with smoking among PWH. Both current and former smoking were associated with a greater risk of frailty, as well as cumulative burden (i.e., pack-years). We also provide evidence of a higher risk of deterioration of frailty associated with current and cumulative smoking, but not former smoking, suggesting benefit of cessation. Future studies to advance our understanding of this relationship and investigate the role of cessation should evaluate inflammatory biomarkers, recreational drug use, transitions in frailty, measure time since quitting smoking, and continue to consider sex and age subgroups.

Tables and Figures

Table 3.1. Baseline characteristics of PWH by sex and age subgroup in CNICS, 2012-2021

Characteristic	All	Men		Women	
		<50 years	≥50 years	<50 years	≥50 years
N (%)	8608	4687 (54)	2647 (31)	769 (9)	505 (6)
Age [a] (years)	45 (11)	38 (8)	57 (6)	39 (7)	57 (6)
Race/ethnicity					
Black	2643 (31)	1264 (27)	623 (24)	424 (55)	332 (66)
Hispanic	1410 (16)	947 (20)	313 (12)	111 (14)	39 (8)
White	4104 (48)	2160 (46)	1618 (61)	205 (27)	121 (24)
Other	451 (5)	316 (7)	93 (4)	29 (4)	13 (3)
Smoking					
Never	3493 (41)	1826 (39)	1046 (40)	388 (50)	233 (46)
Former	2478 (29)	1296 (28)	916 (35)	143 (19)	123 (24)
Current	2637 (31)	1565 (33)	685 (26)	238 (31)	149 (30)
Per day [a,b]	12 (8)	12 (8)	13 (9)	11 (8)	12 (9)
Pack-years [a,c]	9 (9)	7 (8)	12 (11)	7 (7)	10 (9)
CD4 cell count (cells/mm^3)					
≥500	4896 (57)	2559 (55)	1523 (58)	484 (63)	330 (65)
350-499	1619 (19)	894 (19)	500 (19)	136 (18)	89 (18)
<350	2093 (24)	1234 (26)	624 (24)	149 (19)	86 (17)
ART Use	7519 (88)	3964 (85)	2441 (92)	663 (86)	451 (89)
Frailty Score					
Mean (SD)	1.0 (1.1)	0.9 (1.1)	1.1 (1.2)	1.1 (1.1)	1.2 (1.2)
Median (IQR)	1 (0-2)	1 (0-1)	1 (0-2)	1 (0-2)	1 (0-2)
Follow-up yrs					
Mean (SD)	5.3 (2.7)	5.3 (2.7)	5.3 (2.7)	5.2 (2.5)	5.2 (2.5)
Median	5.0	5.2	5.0	4.6	4.5

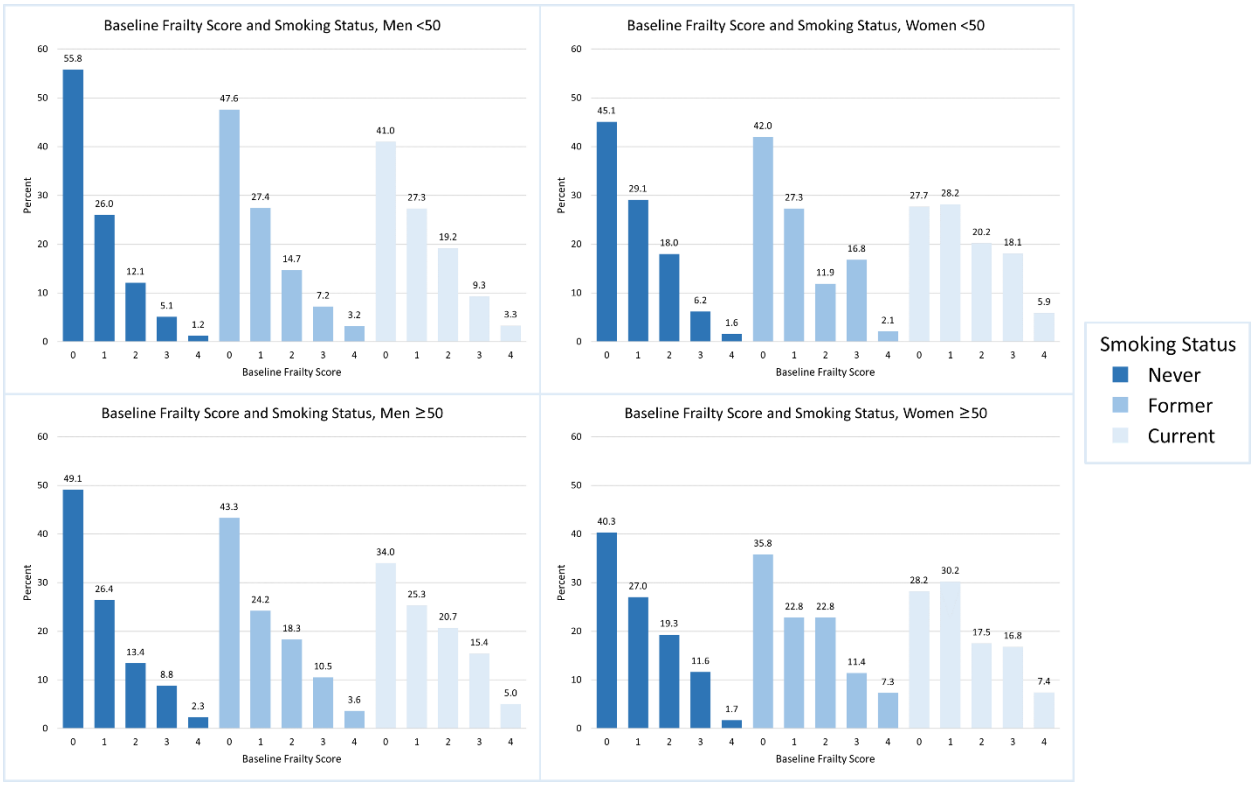
Abbreviations: antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; interquartile range, IQR; people with HIV, PWH; standard deviation, SD

[a] Mean (SD)

[b] Among current smokers

[c] Among ever-smokers

Figure 3.1. Distribution of baseline frailty score by baseline smoking status among people with HIV (PWH) by sex and age subgroup in CNICS, 2012-2021. We graphed the proportion of PWH by their baseline frailty score and baseline smoking status, stratified by the 4 subgroups of interest by age and sex. PWH who reported never smoking had a greater proportion of lower frailty scores than PWH reporting former or current smoking. Additionally, older and female PWH had a greater proportion of higher frailty scores compared to their younger and male counterparts.



Abbreviations: Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; people with HIV, PWH

Table 3.2. Associations between time-updated tobacco cigarette smoking and smoking intensity and baseline pack-years and incident frailty (score ≥3) among PWH in CNICS, stratified by age and sex

Cohort	Variable	Hazard Ratio (95% CI)	p-value	Proportional hazards
Everyone [a] n=7,494	Former Smoking	1.31 (1.12-1.53)	<0.01	0.17
	Current Smoking	1.79 (1.54-2.08)	<0.001	
	+ 10 cigarettes/day [b]	1.05 (0.93-1.19)	0.43	
Everyone [a] n=7,438	Pack-years (per 5)	1.12 (1.09-1.16)	<0.001	0.38
Men <50 [c] n=4,205	Former Smoking	1.49 (1.17-1.89)	<0.01	0.18
	Current Smoking	2.02 (1.61-2.52)	<0.001	
	+ 10 cigarettes/day [b]	1.03 (0.86-1.23)	0.78	
Men <50 [c] n=4,157	Pack-years (per 5)	1.13 (1.07-1.20)	<0.001	0.14
Men ≥50 [c] n=2,237	Former Smoking	1.26 (0.98-1.61)	0.07	0.59
	Current Smoking	1.53 (1.16-2.03)	<0.01	
	+ 10 cigarettes/day [b]	0.97 (0.76-1.23)	0.80	
Men ≥50 [c] n=2,197	Pack-years (per 5)	1.10 (1.05-1.16)	<0.001	0.62
Women <50 [c] n=643	Former Smoking	1.15 (0.67-1.98)	0.60	0.73
	Current Smoking	1.72 (1.11-2.65)	0.02	
	+ 10 cigarettes/day [b]	1.47 (1.07-2.02)	0.02	
Women <50 [c] n=639	Pack-years (per 5)	1.18 (1.05-1.34)	0.01	0.75
Women ≥50 [c] n=409	Former Smoking	0.86 (0.45-1.64)	0.65	0.52
	Current Smoking	1.89 (1.13-3.13)	0.01	
	+ 10 cigarettes/day [b]	0.98 (0.62-1.52)	0.91	
Women ≥50 [c] n=404	Pack-years (per 5)	1.11 (0.99-1.25)	0.08	0.51

Abbreviations: antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; people with HIV, PWH

[a] Adjusted for sex, age, race/ethnicity, ART use, and time updated CD4 count

[b] Cigarettes/day centered at 10

[c] Adjusted for age, race/ethnicity, ART use, and time updated CD4 count

Table 3.3. Associations between time-updated tobacco cigarette smoking and smoking intensity and baseline pack-years and increasing frailty at least 2 points (deterioration) among PWH in CNICS

Cohort	Variable	Hazard Ratio (95% CI)	p-value	Proportional hazards
Everyone [a] n=7,526	Former Smoking	1.05 (0.90-1.21)	0.54	
	Current Smoking	1.30 (1.12-1.50)	<0.001	0.01
	+ 10 cigarettes/day [b]	1.10 (0.97-1.24)	0.15	
Everyone [a] n=7,429	Pack-years (per 5)	1.06 (1.02-1.09)	<0.01	0.07
PWH <50 [a] n=4,860	Former Smoking	1.10 (0.91-1.34)	0.32	
	Current Smoking	1.40 (1.17-1.68)	<0.001	0.12
	+ 10 cigarettes/day [b]	1.17 (1.01-1.37)	0.04	
PWH ≥50 [a] n=2,666	Former Smoking	0.98 (0.79-1.22)	0.88	
	Current Smoking	1.15 (0.90-1.46)	0.26	0.08
	+ 10 cigarettes/day [b]	0.97 (0.78-1.22)	0.82	

Abbreviations: antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; people with HIV, PWH

[a] Adjusted for sex, age, race/ethnicity, ART use, and time updated CD4 count

[b] Cigarettes/day centered at 10

Table 3.4. Estimated frailty change associated with time-updated tobacco cigarette smoking, smoking intensity, and baseline pack-years among PWH in CNICS

	Variable	Relative Risk (95% CI) [c]	p-value
Everyone [a] n=8,565	Former Smoking	1.09 (1.05-1.13)	<0.001
	Current Smoking	1.15 (1.10-1.21)	<0.001
	+ 10 cigarettes/day [b]	1.03 (1.01-1.06)	0.02
Everyone [a] n=8,464	Pack-years (per 5)	1.07 (1.05-1.08)	<0.001

Abbreviations: antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; people with HIV, PWH

[a] Adjusted for sex, age, race/ethnicity, ART use, CNICS site, time in study, and time updated CD4 count

[b] Cigarettes/day centered at 10

[c] Exponentiated log-linear coefficients, representing the multiplicative increase in frailty score associated with exposure, i.e., relative risk

Supplement Content

Methods S3.1. Interactions with smoking by sex and baseline age

To evaluate for effect measure modification, we conducted additional analyses evaluating for interactions between smoking status, intensity, and duration with age (dichotomized at 50 years) and sex. Since we were interested in specific subgroups by age *and* sex, we did not include interaction terms for age and sex in the same model. Rather, we stratified by the other variable when evaluating one of them. For example, we stratified by sex to evaluate the interaction between smoking status and age. This yielded estimates for the interaction between smoking status and age among only men and only women, retaining the interpretations for specific subgroups as in the main analysis. Similarly, to estimate interactions with sex, we stratified by age (at 50 years). We estimated interactions for smoking status for former smoking and current smoking separately to improve interpretability of the effect estimates. Therefore, to evaluate the interaction between smoking status (former or current) with age and sex, we ran 8 models: 1) Age interaction with former smoking among men, 2) Age interaction with current smoking among men, 3) Age interaction with former smoking among women, 4) Age interaction with current smoking among women, 5) Sex interaction with former smoking among PWH <50, 6) Sex interaction with current smoking among PWH <50, 7) Sex interaction with former smoking among PWH ≥50, and 8) Sex interaction with current smoking among PWH ≥50. We ran 4 models for each of smoking intensity (cigarettes/day) and duration (pack-years), including 1) Age interaction among men, 2) Age interaction among women, 3) Sex interaction among PWH <50, and 4) Sex interaction among PWH ≥50. Models stratified by sex were adjusted for age, race/ethnicity, ART use, and time updated CD4 count. All other models were additionally adjusted for sex. These results are presented in Tables S3.2-S3.4. We did not find evidence of effect measure modification for age or sex in these analyses.

Results S3.1. Positivity violation among women under 50 in sensitivity analyses for recreational drug use

Due to an unlikely complete loss of the association between current smoking and frailty (a change from 1.72 [95% CI: 1.11-2.65] from Table 3.2 to 0.99 [95% CI: 0.60-1.63] from Table S3.6), hinting at instability of a model, we tabulated smoking status and recreational drug use status for the subgroup of women under 50 years old, a similar approach to Messer and colleagues (Table S3.9).[147] We found that individual table cells contained very small sample sizes: 29 women who reported never smoking cigarettes and currently using recreational drugs and also 29 women who reported former cigarette use and never using recreational drugs (Table S3.9). Further, among women who became frail during follow-up (i.e., experienced an event for this survival model), cells reached single digits and even 0 for women who reported former cigarette use and never using recreational drugs (Table S3.9).

These values show a clear violation of positivity occurring within this subgroup, via random chance due to the multi-leveled variables of interest (both substance use status variables were categorized as never, former, or current resulting in 9 individual cells of the table).[148] While positivity is not an explicit assumption of our statistical approach, as it is for, say, marginal structural models, violations still pose a threat to the integrity of the model.[147-149] Specifically, these models are inferring and extrapolating data for cells where no data exists, a process referred to as “off-support”.[147] While some amount of small cell size can be acceptable for inference, the present situation is likely too dire, with many cells at or approaching 0. We used the subgroup of women under 50 for this investigation, however, we believe the same to occur for the group of women over 50 since both suffer from small sample size. We suggest taking the simple “restrict the sample” approach and interpreting only the results from the subgroups of men for this specific sensitivity analysis.[148,150] Ultimately, our main analyses remain unharmed

by this violation, and these findings highlight the need for careful consideration of future analyses that incorporate multiple substance use variables.

Results S3.2. Log-log plots for evaluating proportional hazards violations for men <50 deterioration analyses

We used log-log plots to further evaluate the violations of the proportional hazards assumption in deterioration analyses among men <50 (Table S3.7, Figure S3.1-S3.2). In the plot for smoking status (Figure S3.1), we observed no crossing over of the survival curve for PWH reporting never or current smoking, however, there was some crossing with the former smoking curve. We suspect this may be occurring due to the dynamic nature of frailty risk associated with formerly smoking (i.e., quitting). Specifically, there may be a relationship between time since quitting and subsequent risk of frailty in which recently following quitting, there is a high risk of frailty (evident in Figure S3.1 where the former smoking survival curve shows the worst survival early during follow-up) then as time progresses, there is recovery back to risk levels comparable with never smokers. This relationship has not been thoroughly investigated but is consistent with evidence that quitting smoking reduces the risk of other comorbidities, and as time since quitting increases, the risk of comorbidities decreases.[144] In this situation, we suggest regarding the hazard ratio (HR) for former smoking with caution and focusing on the estimate for current smoking, which does not experience such violations of assumptions in the model.

We also evaluated the log-log plot for pack-years (Figure S3.2). Since pack-years is a continuous variable, we dichotomized PWH as any vs. none for the figure. In this case, we did not observe any crossing over of survival curves, rather the curves are not parallel (an indicator of proportional hazards), which is what we suspect led to failing this test. As a result, we caution that this HR should be interpreted as the average HR over the time period, rather than an instantaneous HR as is generally used.

Results S3.3. Log-linear results for frailty development using linear mixed models

In analyses using linear mixed models (LMMs), we log-transformed frailty scores to evaluate the linear associations because of the suggestive logarithmic form of frailty scores among the cohort (see Figure 3.1 for distribution). For this transformation, we added 0.5 to each score (since the scoring started at 0, which would be undefined in log transformations) and used a base 2 log because we did not want to over transform the data to a point where they did not meaningfully represent the frailty scale. Importantly, LMMs allow for recovery and consider the flexibility of frailty scores in modeling and in this approach after exponentiating model coefficients, we are able to interpret the output as relative risks, comparable to the hazard ratios from the Cox models. Our results from the LMMs are consistent with the results from Cox models providing further evidence as to the relationship between smoking and frailty progression (Table 3.4, S3.8). This is particularly notable given the dynamic nature of frailty allowed in LMMs. These results are driven by increasing scores (i.e., worsening frailty) and suggest minimal recovery in this cohort, highlighting the importance of smoking intervention, including reductions and/or cessation of use.

Table S3.1. Components of the modified frailty phenotype for the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort

Frailty Component	PRO Item(s)	Presence (=1)	Absence (=0)
Fatigue: "During the past 4 weeks, have you experienced any symptoms of fatigue or loss of energy?"	HIV Symptom Inventory	"I have this symptom and it… bothers me," or "…bothers me a lot"	"I have this symptom and it… does not bother me" or "…bothers me a little" or "I do not have this symptom"
Weight Loss: "During the past 4 weeks, have you ever experienced any problems with weight loss or wasting?"	HIV Symptom Inventory	"I have this symptom and it… bothers me a little," "…bothers me," or "…bothers me a lot"	"I have this symptom and it does not bother me" or "I do not have this symptom"
Low Mobility: "Have you had any problems with mobility today?"	EQ-5D	"Some" or "Extreme"	"None"
Low Physical Activity: Based on Lipid Research Clinics Physical Activity Scale [a]	Physical Activity	Very low active	Low active, Moderately active, High active

Abbreviations: EQ-5D: EuroQol-5D; PRO: Patient Reported Outcomes and Measures
[a] from Ainsworth BE, Jacobs, DR, & Leon SE; 1992; PMID: 8423761.

Table S3.2. Associations between time-updated tobacco cigarette smoking and incident frailty (score ≥3) among PWH in CNICS, assessing age and sex interactions with smoking status [does not include cig/day], interaction terms bolded

Cohort	Variable	Hazard Ratio (95% CI)	p-value	Proportional hazards
Everyone [a] n=7,525	Former Smoking	1.31 (1.12-1.53)	<0.01	0.23
	Current Smoking	1.80 (1.55-2.10)	<0.001	
Men [b] n=5,278	Former Smoking	1.30 (1.03-1.64)	0.03	0.45
	Former*<50	**1.09 (0.81-1.45)**	0.57	
Men [b] n=5,273	Current Smoking	1.57 (1.23-2.00)	<0.001	0.21
	Current*<50	**1.30 (0.98-1.73)**	0.07	
Women [b] n=872	Former Smoking	0.74 (0.40-1.38)	0.35	0.06
	Former*<50	**1.78 (0.82-3.86)**	0.14	
Women [b] n=943	Current Smoking	1.70 (1.09-2.65)	0.02	0.62
	Current*<50	**1.16 (0.68-1.98)**	0.59	
PWH <50 [b] n=3,900	Former Smoking	1.50 (1.18-1.90)	<0.01	0.70
	Former*Female	**0.80 (0.46-1.41)**	0.44	
PWH <50 [b] n=4,146	Current Smoking	2.03 (1.63-2.53)	<0.001	0.63
	Current*Female	**0.90 (0.57-1.43)**	0.65	
PWH ≥50 [b] n=2,250	Former Smoking	1.27 (0.99-1.63)	0.06	0.57
	Former*Female	**0.63 (0.32-1.25)**	0.19	
PWH ≥50 [b] n=2,070	Current Smoking	1.54 (1.17-2.02)	<0.01	0.44
	Current*Female	**1.23 (0.70-2.15)**	0.47	

Abbreviations: antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; people with HIV, PWH

[a] Adjusted for sex, age, race/ethnicity, ART use, and time updated CD4 count

[b] Adjusted for age, race/ethnicity, ART use, and time updated CD4 count

Table S3.3. Associations between time-updated tobacco smoking intensity and incident frailty (score ≥3) among PWH in CNICS, assessing age and sex interactions with smoking intensity (cig/day), interaction terms bolded

Cohort	Variable	Hazard Ratio (95% CI)	p-value	Proportional hazards
Everyone [a] n=7,522	Cigarettes/day (per 10)	1.27 (1.18-1.38)	<0.001	0.45
Men [b] n=5,269	Cigarettes/day (per 10)	1.18 (1.03-1.36)	0.02	0.18
	Cigarettes/day*<50	**1.17 (0.98-1.38)**	0.07	
Women [b] n=941	Cigarettes/day (per 10)	1.25 (0.94-1.65)	0.12	0.62
	Cigarettes/day*<50	**1.30 (0.93-1.80)**	0.12	
PWH <50 [b] n=4,140	Cigarettes/day (per 10)	1.35 (1.20-1.52)	<0.001	0.57
	Cigarettes/day*female	**1.19 (0.93-1.53)**	0.16	
PWH ≥50 [b] n=2,070	Cigarettes/day (per 10)	1.19 (1.03-1.38)	0.02	0.42
	Cigarettes/day*female	**1.07 (0.78-1.47)**	0.68	

Abbreviations: antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; people with HIV, PWH

[a] Adjusted for sex, age, race/ethnicity, ART use, and time updated CD4 count

[b] Adjusted for age, race/ethnicity, ART use, and time updated CD4 count

Table S3.4. Associations between baseline pack-years and incident frailty (score ≥3) among PWH in CNICS, assessing age and sex interactions with pack-years, interaction terms bolded

Cohort	Variable	Hazard Ratio (95% CI)	p-value	Proportional hazards
Everyone [a] n=7,425	Pack-years (per 5)	1.12 (1.09-1.16)	<0.001	0.33
Men [b] n=5,238	Pack-years (per 5)	1.11 (1.03-1.18)	<0.01	0.21
	Pack-years*<50	**1.06 (0.98-1.16)**	0.14	
Women [b] n=936	Pack-years (per 5)	1.13 (0.99-1.28)	0.06	0.68
	Pack-years*<50	**1.11 (0.95-1.31)**	0.19	
PWH <50 [b] n=4,119	Pack-years (per 5)	1.15 (1.08-1.23)	<0.001	0.69
	Pack-years*female	**1.08 (0.95-1.24)**	0.24	
PWH ≥50 [b] n=2,055	Pack-years (per 5)	1.11 (1.04-1.20)	<0.01	0.31
	Pack-years*female	**1.03 (0.89-1.19)**	0.71	

Abbreviations: antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; people with HIV, PWH

[a] Adjusted for sex, age, race/ethnicity, ART use, and time updated CD4 count

[b] Adjusted for age, race/ethnicity, ART use, and time updated CD4 count

Table S3.5. Associations between time-updated tobacco cigarette smoking and smoking intensity and baseline pack-years and incident frailty (score ≥3) among PWH in CNICS, adjusting for any baseline alcohol use

Cohort	Variable	Hazard Ratio (95% CI)	p-value	Proportional hazards
Everyone [a] n=7,465	Former Smoking	1.31 (1.12-1.54)	<0.01	0.06
	Current Smoking	1.80 (1.54-2.09)	<0.001	
	+ 10 cigarettes/day [b]	1.03 (0.91-1.17)	0.60	
Everyone [a] n=7,373	Pack-years (per 5)	1.12 (1.08-1.15)	<0.001	0.12
Men <50 [c] n=4,186	Former Smoking	1.47 (1.16-1.86)	<0.01	0.19
	Current Smoking	1.99 (1.59-2.49)	<0.001	
	+ 10 cigarettes/day [b]	1.01 (0.84-1.21)	0.94	
Men <50 [c] n=4,141	Pack-years (per 5)	1.12 (1.06-1.19)	<0.001	0.13
Men ≥50 [c] n=2,224	Former Smoking	1.28 (0.99-1.64)	0.053	0.15
	Current Smoking	1.55 (1.17-2.05)	<0.01	
	+ 10 cigarettes/day [b]	0.96 (0.75-1.22)	0.73	
Men ≥50 [c] n=2,186	Pack-years (per 5)	1.10 (1.05-1.15)	<0.001	0.12
Women <50 [c] n=645	Former Smoking	1.21 (0.70-2.08)	0.50	0.67
	Current Smoking	1.72 (1.11-2.65)	0.02	
	+ 10 cigarettes/day [b]	1.46 (1.06-2.00)	0.02	
Women <50 [c] n=641	Pack-years (per 5)	1.20 (1.06-1.35)	<0.01	0.69
Women ≥50 [c] n=410	Former Smoking	0.85 (0.45-1.62)	0.62	0.36
	Current Smoking	1.86 (1.12-3.08)	0.02	
	+ 10 cigarettes/day [b]	0.97 (0.62-1.52)	0.91	
Women ≥50 [c] n=405	Pack-years (per 5)	1.11 (0.99-1.24)	0.08	0.33

Abbreviations: antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; people with HIV, PWH

[a] Adjusted for sex, age, race/ethnicity, ART use, and time updated CD4 count

[b] Cigarettes/day centered at 10

[c] Adjusted for age, race/ethnicity, ART use, and time updated CD4 count

Table S3.6. Associations between time-updated tobacco cigarette smoking and smoking intensity and baseline pack-years and incident frailty (score ≥3) among PWH in CNICS, adjusting for recreational drug use

Cohort	Variable	Hazard Ratio (95% CI)	p-value	Proportional hazards
Everyone [a] n=7,348	Former Smoking	1.22 (1.03-1.43)	0.02	
	Current Smoking	1.62 (1.38-1.90)	<0.001	0.29
	+ 10 cigarettes/day [b]	1.05 (0.93-1.19)	0.42	
Everyone [a] n=7,259	Pack-years (per 5)	1.10 (1.07-1.14)	<0.001	0.50
Men <50 [c] n=4,135	Former Smoking	1.41 (1.10-1.81)	0.01	
	Current Smoking	1.87 (1.48-2.37)	<0.001	0.32
	+ 10 cigarettes/day [b]	1.04 (0.87-1.24)	0.68	
Men <50 [c] n=4,089	Pack-years (per 5)	1.11 (1.05-1.17)	<0.001	0.23
Men ≥50 [c] n=2,174	Former Smoking	1.26 (0.97-1.64)	0.08	
	Current Smoking	1.46 (1.09-1.95)	0.01	0.77
	+ 10 cigarettes/day [b]	0.99 (0.77-1.25)	0.91	
Men ≥50 [c] n=2,140	Pack-years (per 5)	1.10 (1.05-1.16)	<0.001	0.77
Women <50 [c] n=641	Former Smoking	0.71 (0.40-1.28)	0.25	
	Current Smoking	0.99 (0.60-1.63)	0.98	0.77
	+ 10 cigarettes/day [b]	1.41 (1.01-1.95)	0.04	
Women <50 [c] n=637	Pack-years (per 5)	1.07 (0.93-1.23)	0.37	0.84
Women ≥50 [c] n=398	Former Smoking	0.67 (0.34-1.32)	0.24	
	Current Smoking	1.62 (0.94-2.79)	0.08	0.24
	+ 10 cigarettes/day [b]	0.95 (0.61-1.49)	0.83	
Women ≥50 [c] n=393	Pack-years (per 5)	1.08 (0.95-1.22)	0.24	0.20

Abbreviations: antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; people with HIV, PWH

[a] Adjusted for sex, age, race/ethnicity, ART use, and time updated CD4 count

[b] Cigarettes/day centered at 10

[c] Adjusted for age, race/ethnicity, ART use, and time updated CD4 count

Table S3.7. Associations between time-updated tobacco cigarette smoking and smoking intensity and baseline pack-years and increasing frailty at least 2 points (deterioration) among PWH in CNICS, stratified by age and sex

Cohort	Variable	Hazard Ratio (95% CI)	p-value	Proportional hazards
Everyone [a] n=7,526	Former Smoking	1.05 (0.90-1.21)	0.54	
	Current Smoking	1.30 (1.12-1.50)	<0.001	0.01
	+ 10 cigarettes/day [b]	1.10 (0.97-1.24)	0.15	
Everyone [a] n=7,429	Pack-years (per 5)	1.06 (1.02-1.09)	<0.01	0.07
Men <50 [c] n=4,211	Former Smoking	1.07 (0.86-1.32)	0.55	
	Current Smoking	1.36 (1.11-1.66)	<0.01	0.05 [d]
	+ 10 cigarettes/day [b]	1.14 (0.96-1.34)	0.13	
Men <50 [c] n=4,163	Pack-years (per 5)	1.07 (1.01-1.13)	0.02	0.03 [d]
Men ≥50 [c] n=2,253	Former Smoking	0.99 (0.78-1.25)	0.91	
	Current Smoking	1.15 (0.88-1.51)	0.30	0.15
	+ 10 cigarettes/day [b]	1.00 (0.78-1.27)	0.97	
Men ≥50 [c] n=2,213	Pack-years (per 5)	1.04 (0.99-1.10)	0.09	0.15
Women <50 [c] n=649	Former Smoking	1.37 (0.81-2.33)	0.24	
	Current Smoking	1.64 (1.04-2.56)	0.03	0.69
	+ 10 cigarettes/day [b]	1.34 (0.95-1.90)	0.10	
Women <50 [c] n=645	Pack-years (per 5)	1.17 (1.03-1.33)	0.02	0.61
Women ≥50 [c] n=413	Former Smoking	0.95 (0.52-1.75)	0.88	
	Current Smoking	1.07 (0.62-1.88)	0.80	0.32
	+ 10 cigarettes/day [b]	0.91 (0.50-1.67)	0.77	
Women ≥50 [c] n=408	Pack-years (per 5)	0.99 (0.86-1.14)	0.86	0.14

Abbreviations: antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; people with HIV, PWH

[a] Adjusted for sex, age, race/ethnicity, ART use, and time updated CD4 count

[b] Cigarettes/day centered at 10

[c] Adjusted for age, race/ethnicity, ART use, and time updated CD4 count

[d] See Results S2 for further information

Table S3.8. Estimated ratio of the amount of frailty change associated with time-updated tobacco cigarette smoking, smoking intensity, and baseline pack-years among PWH in CNICS, stratified by age and sex

	Variable	Relative Risk (95% CI) [d]	p-value
Everyone [a] n=8,565	Former Smoking	1.09 (1.05-1.13)	<0.001
	Current Smoking	1.15 (1.10-1.21)	<0.001
	+ 10 cigarettes/day [b]	1.03 (1.01-1.06)	0.02
Everyone [a] n=8,464	Pack-years (per 5)	1.07 (1.05-1.08)	<0.001
Men <50 [c] n=4,659	Former Smoking	1.08 (1.03-1.14)	<0.01
	Current Smoking	1.16 (1.09-1.24)	<0.001
	+ 10 cigarettes/day [b]	1.05 (1.02-1.09)	0.01
Men <50 [c] n=4,611	Pack-years (per 5)	1.10 (1.07-1.12)	<0.001
Men ≥50 [c] n=2,639	Former Smoking	1.09 (1.02-1.17)	0.01
	Current Smoking	1.12 (1.03-1.22)	0.01
	+ 10 cigarettes/day [b]	1.01 (0.96-1.05)	0.84
Men ≥50 [c] n=2,599	Pack-years (per 5)	1.05 (1.03-1.07)	<0.001
Women <50 [c] n=763	Former Smoking	1.14 (0.99-1.30)	0.051
	Current Smoking	1.29 (1.11-1.51)	<0.01
	+ 10 cigarettes/day [b]	1.05 (0.94-1.17)	0.4
Women <50 [c] n=757	Pack-years (per 5)	1.04 (0.99-1.09)	0.10
Women ≥50 [c] n=504	Former Smoking	1.07 (0.94-1.20)	0.30
	Current Smoking	1.04 (0.89-1.22)	0.59
	+ 10 cigarettes/day [b]	0.99 (0.91-1.09)	0.90
Women ≥50 [c] n=497	Pack-years (per 5)	1.01 (0.97-1.05)	0.53

Abbreviations: antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; people with HIV, PWH

[a] Adjusted for sex, age, race/ethnicity, ART use, CNICS site, time in study, and time updated CD4 count

[b] Cigarettes/day centered at 10

[c] Adjusted for age, race/ethnicity, ART use, CNICS site, time in study, and time updated CD4 count

[d] Exponentiated log-linear coefficients, representing the multiplicative increase in frailty score associated with exposure, i.e., relative risk

Table 3.9. Smoking status and recreational drug use among women under 50 and among women under 50 who became frail, cells display n (%)

Drug use status	All women <50 Smoking status			
	Never	**Former**	**Current**	**Total**
Never	274 (82)	29 (9)	32 (10)	335
Former	52 (33)	49 (31)	59 (37)	160
Current	29 (19)	37 (24)	86 (57)	152
Total	355 (55)	115 (18)	177 (27)	647

Drug use status	Women <50 who became frail Smoking status			
	Never	**Former**	**Current**	**Total**
Never	33 (92)	0 (0)	3 (8)	36
Former	14 (37)	8 (21)	16 (42)	38
Current	5 (14)	9 (24)	23 (62)	37
Total	52 (47)	17 (15)	42 (38)	111

Drug use includes *any* of the following: marijuana, cocaine/crack, illicit opioids, and methamphetamine

Figure S3.1. Log-log plot of survival by smoking status

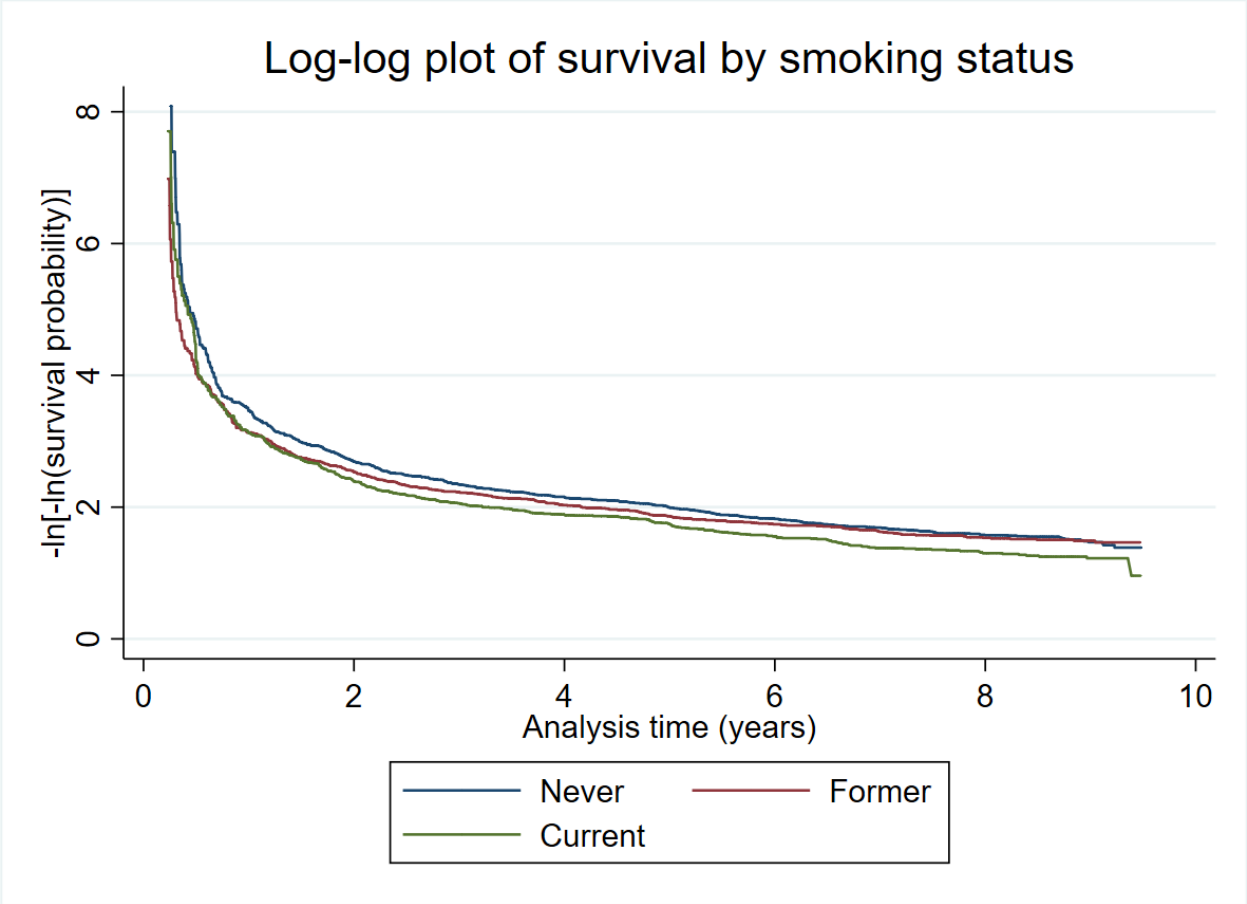
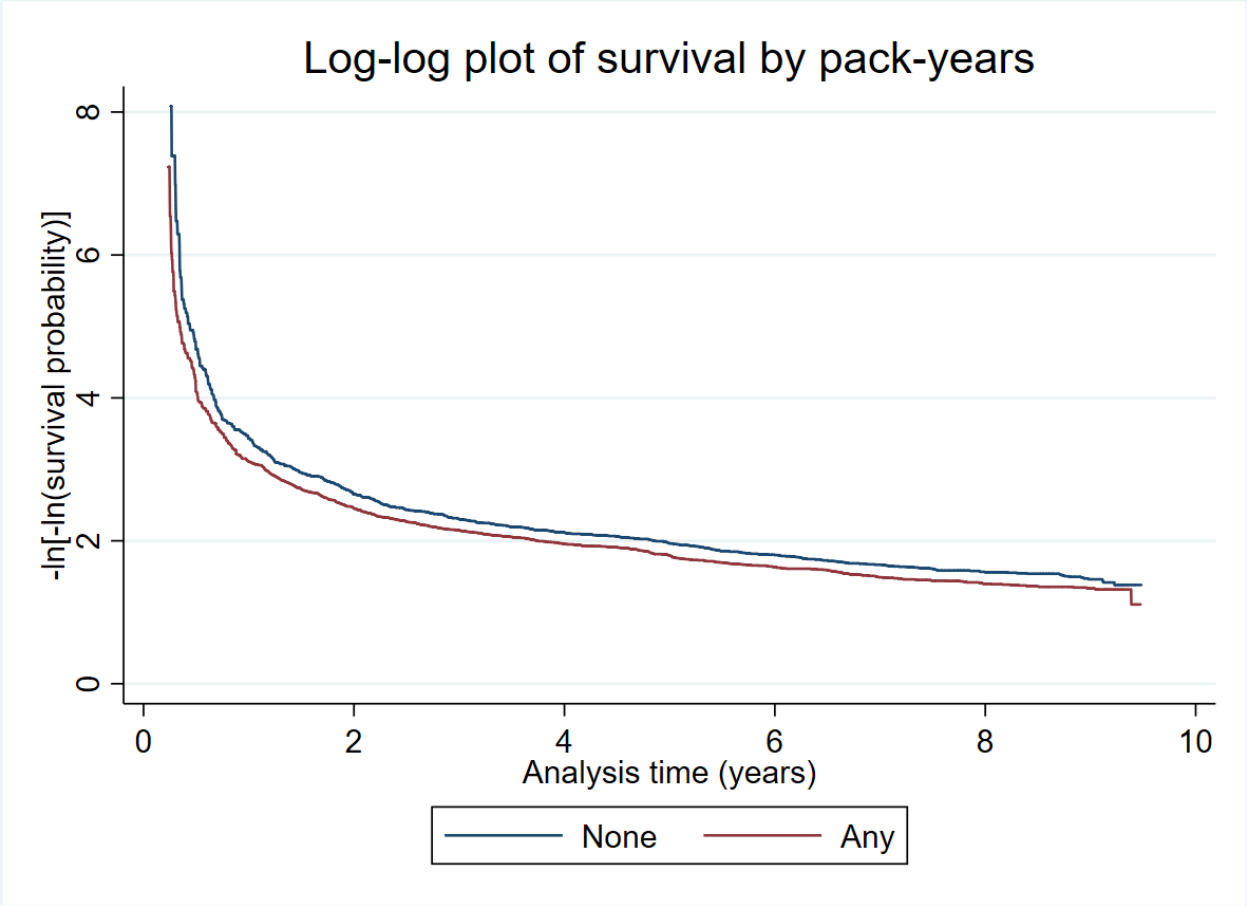


Figure S3.2. Log-log plot of survival by pack-years (any vs. none)



Chapter 4: Evaluating the Sick Quitting Hypothesis for Frailty Status and Reducing Alcohol use among People with HIV

Evaluating the Sick Quitting Hypothesis for Frailty Status and Reducing Alcohol use among People with HIV

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Word count: text: 3428, abstract: 296, 6 tables, 1 figure

Preface

In developing this Chapter, I designed the analysis plan and executed the analyses as well as a robust set of sensitivity analyses and data checks. I drafted the manuscript and developed a consensus among the coauthors listed above as to the merits of the text. I critically reviewed the literature on this complex relationship to understand prior findings and existing questions and led meetings with senior collaborators to develop approaches to overcoming the methodological obstacles and create an analytic plan capable of dealing with the challenges inherent to research combining alcohol and chronic diseases, focusing on considerations for frailty in particular. I built the dataset from individual files within the CNICS data repository then executed the statistical analysis plan while ensuring that results underwent a thorough stakeholder review. I drafted the initial version of the manuscript then actively revised it to incorporate and harmonize coauthor comments.

This Chapter has not yet been submitted for publication, but I will circulate the manuscript to all coauthors and incorporate suggestions and edits to develop a consensus draft for submission to the selected journal.

Abstract

Background

Previous studies have reported paradoxical relationships between alcohol use and frailty, including among people with HIV (PWH). Individuals may reduce alcohol consumption in response to poor health, a behavior pattern known as sick quitting, and the degree to which frailty may be associated with subsequent changes in alcohol use has important epidemiologic relevance. We examined this relationship among PWH.

Methods

At 6 sites within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort, we assessed whether self-reported frailty precedes reductions in drinking. PWH with at least 2 patient reported outcome assessments for alcohol use (measured by AUDIT-C) and frailty (measured by modified Fried phenotype) between 1/2012-8/2021 were included. We used adjusted Cox models to estimate the association between time-updated frailty status (not frail, prefrail, frail) and quitting and reducing frequency of any alcohol use and binge drinking.

Results

Among 8,174 PWH, average age at baseline was 45 years (median: 46), 15% were female, and almost half (48%) were non-Hispanic White, while 31% were non-Hispanic Black. At baseline, most (69%) PWH reported alcohol use, with 18% reporting hazardous use and 13% reporting at least monthly binge drinking. Over an average of 5.3 years of follow-up, we found that frail PWH were 56% (95%CI: 1.14-2.14) more likely to quit drinking and 56% (95%CI: 1.19-2.04) more likely to reduce binge drinking compared to not frail PWH.

Conclusion

The association between frailty and subsequent reductions in alcohol use and binge drinking is suggestive of sick quitting. Sick quitting likely acts as a source of confounding in the association between alcohol use and risk of frailty, requiring further investigation for methods of control. Furthermore, a better understanding of the impact of sick quitting on health is warranted to elucidate whether reductions in alcohol use offer health benefits.

Key words: Alcohol; Frailty; People with HIV; sick quitting; confounding

Introduction

Frailty is a complex physical condition characterized by increased vulnerability to health stressors that develops in conjunction with aging.[3,105] Frailty, similar to some other health states (e.g., pain, mental health), can be measured via self-report, given components such as fatigue, as opposed to being determined by laboratory tests or imaging as for many comorbidities.[151] Consequently, changes in frailty status may be overtly experienced by individuals. A variety of interventions are used to manage and mitigate frailty, generally focused on behavioral changes such as exercise and nutrition.[31,152,153] Evidence also exists highlighting self-management approaches in light of changes (i.e., declines) in health status.[154] One important example of this self-management is changing alcohol use behaviors, referred to as 'sick quitting', when individuals reduce drinking in response to poor health.[155-160] Sick quitting has garnered attention in methodological research to identify issues and solutions related to understanding the uniquely paradoxical associations between alcohol and health outcomes.[157-159,161-163]

The literature on alcohol and frailty consists of numerous studies presenting associations suggesting alcohol use (primarily for light drinking and occasionally for heavy drinking) is protective for frailty risk.[47,164-166] Modest alcohol use may have cardioprotective effects, however it has been hypothesized that unmeasured confounding related to sick quitting may be present and leading to spurious associations in relation to frailty risk.[47,57,164-167] These studies have generally been limited to cross-sectional analyses or relatively short follow-up, likely contributing to the findings and subsequent discussion. Few studies have estimated associations between alcohol use and frailty with consideration of both recent and historical use; these results highlight a paradox in which recent use is protective but long-term use is a risk factor for frailty development.[56,58] There remains a gap in our understanding regarding the extent to which frailty status may motivate sick quitting and subsequent approaches to manage this complex issue.

To better understand this relationship, we sought to evaluate whether frailty status is associated with changes in alcohol use frequency in a large cohort of people with HIV (PWH), a population with high rates of both frailty and risky alcohol use.[59,168] This longitudinal cohort of PWH includes rich data on frailty, substance use, and other comorbidities, allowing for the optimal setting to carefully measure sick quitting while controlling for the presence of other conditions.

Methods

Study Setting and Participants

This study took place within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort.[78] CNICS is a longitudinal observational cohort of PWH aged 18 and older engaged in care at 8 academic clinical sites across the US, comprising a rich, diverse population. Six sites with relevant data (e.g., frailty and alcohol use data) were included in this study. The CNICS data repository integrates comprehensive data including demographic characteristics, laboratory values, diagnoses, medications, and patient reported outcomes and measures (PROs). PROs are collected in electronic health questionnaires that PWH complete at the beginning of routine HIV care appointments and include domains such as symptoms, substance use, and mental health, and are offered in English, Spanish, and Amharic.[83] Institutional Review Boards at each site approve CNICS protocols.

PWH who completed ≥2 PROs with alcohol and frailty measures between 1/2012 to 8/2021 were included in this study, with baseline being the first date of complete information on alcohol use *and* frailty. Follow-up ended at the earliest date of 1) reduction in alcohol consumption (i.e., quitting/reducing drinking frequency) or 2) last visit within the observation period (including departure from CNICS or death).

Frailty

Frailty was defined by a validated modified Fried frailty phenotype with 4 self-reported components: physical activity, fatigue, mobility, and unintentional weight loss.[3] Fried's phenotype also includes a 5th component, grip strength, which CNICS does not capture. Each component was dichotomized, and the phenotype was scored from 0-4. We considered frailty status with 3 levels: frail if PWH presented with ≥3 components, prefrail if they presented with 1-2 components, and not frail if they presented with 0 components.

Alcohol

Alcohol consumption was collected in the PROs using the Alcohol Use Disorders Identification Test Consumption (AUDIT-C) instrument.[169] We considered frequency of drinking and binge drinking (defined by ≥5 drinks in one sitting) based on the categorical response options on the AUDIT-C items. We defined rare/inactive drinking as report of 'Monthly (e.g., Special occasions/Rare)' on question 1 and rare binge drinking as report of 'Less than monthly' on question 3. We then parameterized 4 shifts in consumption to measure changes in use frequency: 1) quitting any use, 2) quitting binge use, 3) reducing any use, and 4) reducing binge use. Quitting was defined as a shift from nonzero (at baseline) to zero days of consumption, while reductions were defined as any decrease from baseline consumption frequency (including quitting).

We also captured probable prior alcohol use disorder (AUD) defined by either a diagnosis of AUD in electronic health record or self-report of attending alcohol treatment or Alcoholics Anonymous.[170] The AUDIT-C is also scored on a scale ranging 0 to 12, which we used to categorize PWH into 4 levels for their alcohol use status: 1) no current use (AUDIT-C score of 0), 2) no current use with an AUD (score of 0), 3) current non-hazardous use (score <4 for women/<5 for men), and 4) current hazardous use (score ≥4 for women/≥5 for men).[126]

Covariates

We included covariates that, based on the existing literature, may act as confounders in the association between frailty and alcohol consumption. Demographic characteristics included age, sex assigned at birth, and race/ethnicity. Clinical factors included antiretroviral therapy (ART) use (yes/no), liver function (measured by fibrosis-4 [FIB-4] stage), hepatitis C virus (HCV) coinfection (defined by any lifetime positive result from an HCV antibody, RNA, or genotype test), diabetes (any of the following criteria: 1) hemoglobin A1c ≥6.5; 2) use of a diabetes-specific medication, such as insulin; or 3) use of a diabetes-related medication not exclusively used to treat diabetes [e.g., biguanides] in the setting of also having a diabetes diagnosis), treated hypertension, dyslipidemia (defined as lipid abnormalities severe enough to require lipid-lowering medications, e.g., statin use), body mass index (BMI) category (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, ≥30.0 kg/m^2), time-varying depression (PHQ-9 score), and time-varying CD4 cell count.[171,172] Other substance use included smoking status and recreational drug use (including illicit opioids, methamphetamines, cocaine/crack, and marijuana collected via a modified World Health Organization Alcohol, Smoking and Substance Involvement Screening Test [ASSIST] instrument), measured as never, former, or current use.[173]

Statistical Analysis

We modeled the association between time-updated frailty status (not frail, prefrail, frail) and changes in alcohol use frequency using 4 Cox proportional hazards models, one for each type of change in alcohol use defined above. PWH could contribute to multiple models. PWH who reported not drinking at baseline (i.e., AUDIT-C score of 0) were excluded from these models based on their inability to further reduce alcohol consumption. We also excluded PWH who reported rare use (Monthly or less for any drinking and less than monthly for binge drinking) because our goal was to estimate associations for ‘active’ drinking, but these PWH were then

included in sensitivity analyses (described below). Each model was adjusted for age, sex, race/ethnicity, ART use, smoking status, recreational drug use, FIB-4 stage, HCV coinfection, diabetes, treated hypertension, dyslipidemia, BMI, and time-updated depressive symptomology and CD4 count. We assessed models for violations of proportional hazards using Schoenfeld residuals and evaluated significance at the 95% confidence level (i.e., $p<0.05$ signifies a violation of proportional hazards).[128,129]

We conducted multiple sensitivity analyses, including assessing frailty at baseline (rather than time-updated) to evaluate the extended impact of frailty status on drinking behaviors, stratifying the cohort by baseline age (under 50 vs. 50 and older), and incorporating PWH with any baseline alcohol use.

We also estimated the association between time-updated alcohol use status and incident frailty to confirm the findings of other studies, that alcohol use appears protective for frailty. For these models, incident frailty was defined by a frailty phenotype score of ≥3 and frail PWH at baseline were excluded. Alcohol use was parameterized by the 4-level alcohol use status variable defined above (categories of: no current use without AUD, no current use with AUD, current non-hazardous use, and current hazardous use). We separately considered binge drinking, dichotomized at a frequency of monthly or more vs. less than monthly. We estimated these associations using Cox models adjusted for age, sex, race/ethnicity, ART use, smoking status, and time-updated depressive symptomology and CD4 count. We evaluated for proportional hazards using Schoenfeld residuals. We again stratified by age (at 50) in sensitivity models. All analyses were performed using Stata version 17.0 (StataCorp, College Station, TX, USA).

Results

Among the 8,174 PWH included in our analytic cohort, the mean age at baseline was 45 years (median: 46, interquartile range: 36-53) and 1,225 (15%) PWH were female (Table 4.1). Almost

half (48%) were non-Hispanic White and 31% were non-Hispanic Black. Average follow-up time was 5.3 years (median: 5.1) (Table 4.1). Most (69%) PWH reported drinking at baseline (51% non-hazardous, 18% hazardous), while 8% reported no current use with prior AUD. Frail PWH were, on average, older, female, had greater comorbidity burden, and reported greater depressive symptomology and use of substances (except alcohol) compared to not frail and prefrail PWH (Table 4.1). A lower proportion of PWH who reported drinking at baseline (AUDIT-C>0) were prefrail (42%) and frail (11%), compared to PWH who did not drink (45% prefrail, 15% frail).

We found that frailty was associated with a greater likelihood of quitting and reducing frequency both of any drinking and of binge drinking (Table 4.2). Being frail was associated with a 56% greater likelihood of quitting (95% confidence interval [95%CI]: 1.14-2.14) and 33% greater likelihood of reducing (95%CI: 1.11-1.59) drinking frequency. Similarly, being frail was associated with a 41% greater likelihood of quitting (95%CI: 0.98-2.05) and 56% greater likelihood of reducing (95%CI: 1.19-2.04) frequency of binge drinking. Our findings also suggested an association between prefrailty and lowering consumption frequency, however, the confidence intervals for these estimates crossed the null, and thus were not statistically significant (Table 4.2).

In sensitivity analyses, we observed stronger point estimates when considering frailty at baseline instead of time-updated, supporting a consistent relationship between deteriorating health status and reducing drinking behaviors over time (Table 4.3). In analyses stratified by age we observed comparable estimates to the pooled analyses and did not observe evidence of effect measure modification by age (Table 4.4). In sensitivity models including PWH with *any* baseline drinking and binge drinking, we observed attenuated but generally robust relationships (Table 4.5).

In models evaluating the reverse association, we observed strong protective associations of drinking (and former risky drinking) on frailty risk (Table 4.6). For example, current hazardous drinking was associated with a 30% lower risk of incident frailty compared to not drinking (HR: 0.70, 95%CI: 0.56-0.87). We did not observe significant associations between binge drinking and frailty risk. We observed similar associations in age-stratified analyses (Table 4.6).

Discussion

We found that frailty was associated with a greater likelihood of both quitting and reducing drinking and binge drinking frequency among PWH. Importantly, these findings were estimated in models adjusted for other health factors that may influence drinking behaviors (e.g., substance use and comorbidities), suggesting that frailty may be an important motivator of behavior change, supporting the sick quitting hypothesis. Specifically, frail PWH were over 50% more likely to report quitting any drinking and reducing binge drinking frequency compared to not frail PWH. We also observed similar associations in age-stratified models, highlighting a consistent relationship among different age groups, despite possible predispositions to reduce alcohol intake at older ages.[156,174,175] These findings have significant implications for research on alcohol use and frailty regarding issues of confounding and considerations for measuring alcohol use correctly and comprehensively.

This study builds on the important work on improving alcohol use research by expanding our understanding of the epidemiology between drinking and health status and providing evidence supporting the sick quitting hypothesis among PWH. Prior work has focused on appropriately defining alcohol use categories, such as separating former drinking from lifetime abstaining and correctly classifying people with alcohol use disorders.[60,159,161,162] Our findings highlight how alcohol use and patterns in behavior are complex and may be indicated or motivated by changing health, such as frailty status. Future work should aim to better identify motives for

quitting alcohol, such as with qualitative research, or focus on fluctuations in use over time, including increases *and* decreases. All these research efforts aid in robustly measuring and evaluating alcohol use as well as highlighting remaining issues and potential sources of bias, which we expand upon in this study.

Our findings suggest the presence of a strong form of confounding (that is similar to confounding by indication, which is often observed in pharmacoepidemiology studies) as a source of bias in analyses estimating the association between alcohol use and frailty (with alcohol as the exposure).[176] We believe that poor health status increases the likelihood for both quitting drinking and being frail. As a result, there is a distorted, spurious association that appears to suggest that alcohol use is protective against frailty due to the people with poor health who are less likely to drink also being more likely to be sick/frail, illustrated in Figure 4.1. Consequently, those who *do* drink seemingly have a lower likelihood of frailty, however this is a confounded relationship.[176] This situation resembles confounding by indication, where bias arises from the underlying reasons for 'treatment' or exposure, in this case, not drinking, that are being driven by a factor that also predicts the outcome (i.e., frailty).[177] Like confounding by indication, this type of bias poses a complex challenge for analyses, requiring modifications and careful attention to our measurement techniques.[177,178]

One approach that investigators have used to study this relationship with minimal concern of confounding by sick quitting has been collecting data on long-term or historical alcohol use. This tactic shifts the relationship between alcohol use and frailty to exclude concerns related to recent alcohol use. Some studies have used this method to compare recent and long-term alcohol use in side-by-side analyses. For instance, an analysis within the Helsinki Businessmen Study (HBS) over 30 years of follow-up found that heavy alcohol consumption during midlife was associated with greater odds of frailty and prefrailty at old age, but zero consumption at old

age was associated with frailty.[58] Another study among 365 PWH in the New Orleans Alcohol Use in HIV (NOAH) study found that lifetime alcohol exposure was associated with greater frailty, while the inverse was observed for recent alcohol consumption.[56] These studies provide useful comparisons of the different approaches to measuring alcohol and underscore the implications of measuring recent use, specifically, that sick quitting may be a confounding factor in these models. This literature underscores a central issue, that there is an association between alcohol use and increased frailty risk over the life course, but in certain situations the interplay between health status and alcohol consumption patterns can distort the true relationship. There also remains a need to expand upon the results from the NOAH study with a larger, more diverse cohort of PWH to confirm these important findings in another setting.

We also investigated the relationship between alcohol use and frailty in CNICS (over an average of 5 years of follow-up) and our findings further support the importance of considering individual-level characteristics that may have an influence on behaviors. We were able to leverage the AUD data within CNICS, which allowed us to distinguish between no current use with and without an AUD and current use (non-hazardous and hazardous). We found that non-hazardous drinking was associated with a lower risk of frailty compared to not drinking, which itself is not surprising given the plethora of studies suggesting that light or moderate drinking may offer protection to poor health outcomes.[47,165,167] However, this model also suggested that hazardous drinking was slightly more protective than non-hazardous use and, furthermore, not drinking in the setting of having a prior AUD was even more protective (Table 4.6). The observations that hazardous drinking and having an AUD offer protection against frailty are contradictory to many known frameworks and existing evidence on this association (e.g., the U- or J-shaped curves for alcohol and health outcomes, which describe light or moderate use as protective and heavy use and no use as risky).[158,167] Therefore, we believe these findings suggest that there are underlying differences between the individuals who are drinking and not

drinking that are leading to confounded estimates (e.g., sick quitting). It is not surprising that there is a complicated relationship between alcohol use and frailty, and our collective findings in this study highlight both the extent to which poor health may motivate behavior change and the misrepresentation of effects when factors related to certain behaviors are not considered.

Moreover, our modeling approach was designed to answer a specific question, which addresses how current frailty status (i.e., time-updated throughout the study period) is associated with subsequent changes in alcohol consumption frequency, considered as a singular, incident occurrence. Therefore, we defined changes in consumption as an absorbing state (i.e., a censoring event in a survival model) to understand if frailty status may act as an indicator or trigger for changes in alcohol use, and these results provide evidence suggesting as much. This focus exists within a wider scope of similarly important questions on this topic. Understanding whether changes in alcohol use are persistent or, if not, whether there is a way to predict recurrent changes and how those patterns occur in relation to health status is warranted. Similarly, including a focus on transitions between frailty states may help elucidate the mechanisms occurring in this relationship.

This study utilized a large, diverse cohort of PWH engaged in care to extend the field of alcohol research and encourage better and more comprehensive understanding of sick quitting. We were uniquely able to answer this question by leveraging rich data, including robust measurement of both frailty status and alcohol consumption over time as well as controlling for comorbidities and behaviors to carefully estimate associations. Further, we were able to define prior drinking and AUDs and differentiate between overall drinking and binge drinking to comprehensively evaluate alcohol use behaviors.

Our study also has limitations, including the lack of granularity in our data to observe measures such as drinks per day or exact number of days of use. We are also unable to discern lifetime

abstaining from former drinking without an AUD, which has been highlighted previously as an issue in alcohol research.[161,162] Similarly, while our AUD definition is a combination of self-report and diagnosis, it is possible that we do not have information for everyone who may qualify as having an AUD (defined by diagnosis and self-report). However, our main analyses only include PWH reporting drinking at baseline, so we are not too concerned about this with regard to our findings, although these issues highlight the importance of precise data for studies on alcohol use. We also do not have data on alcohol type, which has been suggested as an important factor regarding health impacts.[159,164] In addition, due to the observational nature of the study, there may be unmeasured confounders on the association, including socioeconomic status or factors such as household life that may impact drinking behaviors and frailty.[154,179]

Conclusion

We observed an association among PWH between frailty status and reporting reductions in alcohol consumption frequency, including binge drinking. These findings are consistent with the sick quitting hypothesis, in which health status influences alcohol consumption, and illustrate a potential source of bias in studies of the association between alcohol use and frailty. Our results answer an important scientific question and also inform additional novel areas for research. We only observed 'incident' reductions in alcohol consumption, but it is important to understand whether these are transient or persistent changes in use. It is well-known that drinking patterns are complex and can fluctuate within individuals over the life course.[161] Longer-term studies may be better suited to answer these questions as well as considering transitions in frailty states over time, which may be an important factor as suggested by our sensitivity analysis using baseline frailty stage. Additionally, qualitative research may provide important context regarding reasons for quitting or reducing use and allow stronger inferences as to why PWH may be changing their behaviors related to their health status. Finally, it is still important to better understand the long-term impact of alcohol use on frailty risk among PWH and further work is

warranted, with the considerations we outline here, to study this relationship. Overall, our findings provide insight into the mechanism and epidemiology between alcohol consumption and health status, underscoring their relationship and highlighting that they are inextricably linked, requiring further investigation.

Tables and Figures

Table 4.1. Baseline demographic and clinical characteristics of PWH in CNICS by frailty status, 2012-2021, n (%) unless noted

Variable	Everyone	Not Frail	Prefrail	Frail
N (%)	8174	3728 (46)	3480 (43)	966 (12)
Age, mean (SD)	45 (11)	44 (11)	45 (11)	48 (10)
Female	1225 (15)	470 (13)	559 (16)	196 (20)
Race/ethnicity				
Black	2526 (31)	1209 (32)	1067 (31)	250 (26)
Hispanic	1311 (16)	620 (17)	526 (15)	165 (17)
White	3917 (48)	1703 (46)	1706 (49)	508 (53)
Other	420 (5)	196 (5)	181 (5)	43 (4)
Alcohol use status				
None	1883 (23)	794 (21)	834 (24)	255 (26)
None + prior AUD	623 (8)	231 (6)	283 (8)	109 (11)
Non-hazardous	4189 (51)	2021 (54)	1724 (50)	444 (46)
Hazardous	1479 (18)	682 (18)	639 (18)	158 (16)
Binge ≥monthly	1046 (13)	492 (13)	441 (13)	113 (12)
Depression				
PHQ-9 ≥10	1766 (22)	179 (5)	955 (27)	632 (65)
PHQ-9, mean (SD)	5.6 (6.0)	2.5 (3.5)	6.9 (5.9)	12.8 (6.4)
Smoking status				
Never	3300 (40)	1711 (46)	1314 (38)	275 (28)
Former	2325 (28)	1057 (28)	984 (28)	284 (29)
Current	2549 (31)	960 (26)	1182 (34)	407 (42)
Recreational Drug Use				
Never	2234 (27)	1199 (32)	864 (25)	171 (18)
Former	2770 (34)	1242 (33)	1172 (34)	356 (37)
Current	3170 (39)	1287 (35)	1444 (41)	439 (45)
CD4 cell count, mean (SD)	590 (317)	592 (300)	600 (325)	543 (346)
ART Use	7186 (88)	3330 (89)	3029 (87)	827 (86)
FIB-4 Stage				
0-1	6423 (79)	3020 (81)	2725 (78)	678 (70)
2-3	1546 (19)	643 (17)	659 (19)	244 (25)
4-6	205 (3)	65 (2)	96 (3)	44 (5)
HCV Coinfection	956 (12)	322 (9)	444 (13)	190 (20)
Diabetes	830 (10)	301 (8)	376 (11)	153 (16)
Treated Hypertension	2188 (27)	908 (24)	959 (28)	321 (33)
Dyslipidemia (Statin Use)	1745 (21)	708 (19)	792 (23)	245 (25)
Follow-up Years				
Mean (SD)	5.3 (2.7)	5.3 (2.7)	5.3 (2.7)	5.4 (2.7)
Median	5.1	5.0	5.1	5.6

Abbreviations: 9-item patient health questionnaire, PHQ-9; alcohol use disorder, AUD; antiretroviral therapy, ART; Centers for AIDS Research Network of Integrated Clinical Systems, CNICS; fibrosis score, FIB-4; hepatitis C virus, HCV; interquartile range, IQR; people with HIV, PWH; standard deviation, SD

Alcohol use status definition: None: AUDIT-C score 0, None + prior AUD: AUDIT-C score 0 *and* report of attending AA, receiving treatment for alcohol abuse, or alcohol abuse diagnosis, Non-hazardous: AUDIT-C score 0-4 for men or 0-3 for women, Hazardous: AUDIT-C score ≥5 for men or ≥4 for women

Table 4.2. Associations[a] between time-updated frailty and quitting or reducing alcohol use among PWH reporting active drinking[b] in CNICS, 2012-2021

Frailty stage, vs. not frail	Alcohol change	n	HR (95% CI)	Estimate p-value	Proportional Hazards p-value[c]
Prefrail	Quit drinking	3486	1.22 (0.99-1.50)	0.06	0.23
Frail			1.56 (1.14-2.14)	0.01	
Prefrail	Quit binge drinking	1071	1.15 (0.92-1.44)	0.23	0.33
Frail			1.41 (0.98-2.05)	0.07	
Prefrail	Reduce drinking	3480	1.04 (0.94-1.17)	0.40	0.25
Frail			1.33 (1.11-1.59)	<0.01	
Prefrail	Reduce binge drinking	1068	1.13 (0.96-1.33)	0.13	0.51
Frail			1.56 (1.19-2.04)	<0.01	

Abbreviations: 95% CI: 95% confidence interval, HR: hazard ratio

[a] Adjusted for age, sex, race/ethnicity, ART use, smoking status, recreational drug use, FIB-4 stage, HCV coinfection, diabetes, treated hypertension, statin use, BMI category, time-updated depression (PHQ-9 score), and time-updated CD4 cell count

[b] Active drinking defined as reporting any alcohol consumption frequency of greater than monthly or binge drinking frequency of monthly or greater

[c] Tested using Schoenfeld residuals

Table 4.3. Associations[a] between baseline frailty status and quitting or reducing alcohol use among PWH reporting active drinking[b] in CNICS, 2012-2021

Frailty stage, vs. not frail	Alcohol change	n	HR (95% CI)	Estimate p-value	Proportional Hazards p-value[c]
Prefrail	Quit drinking	3486	1.30 (1.06-1.59)	0.01	0.30
Frail			1.73 (1.29-2.31)	<0.001	
Prefrail	Quit binge drinking	1071	1.19 (0.95-1.49)	0.13	0.52
Frail			1.96 (1.38-2.78)	<0.001	
Prefrail	Reduce drinking	3480	1.08 (0.98-1.19)	0.14	0.23
Frail			1.18 (0.99-1.40)	0.06	
Prefrail	Reduce binge drinking	1068	1.20 (1.03-1.41)	0.02	0.61
Frail			1.78 (1.36-2.32)	<0.001	

Abbreviations: 95% CI: 95% confidence interval, HR: hazard ratio

[a] Adjusted for age, sex, race/ethnicity, ART use, smoking status, recreational drug use, FIB-4 stage, HCV coinfection, diabetes, treated hypertension, statin use, BMI category, time-updated depression (PHQ-9 score), and time-updated CD4 cell count

[b] Active drinking defined as reporting any alcohol consumption frequency of greater than monthly or binge drinking frequency of monthly or greater

[c] Tested using Schoenfeld residuals

Table 4.4. Associations[a] between time-updated frailty status and quitting or reducing alcohol use among PWH reporting active drinking[b] in CNICS, stratified by age, 2012-2021

Age strata	Frailty stage, vs. not frail	Alcohol change	n	HR (95% CI)	Estimate p-value	Proportional Hazards p-value[c]
<50	Prefrail	Quit drinking	2352	1.20 (0.94-1.53)	0.15	0.33
	Frail			1.50 (1.00-2.23)	0.048	
≥50	Prefrail	Quit drinking	1134	1.27 (0.87-1.86)	0.21	0.35
	Frail			1.64 (0.96-2.79)	0.07	
<50	Prefrail	Quit binge drinking	814	1.11 (0.85-1.45)	0.44	0.17
	Frail			1.45 (0.92-2.28)	0.11	
≥50	Prefrail	Quit binge drinking	257	1.42 (0.89-1.26)	0.14	0.08
	Frail			1.48 (0.74-2.97)	0.27	
<50	Prefrail	Reduce drinking	2346	1.07 (0.95-1.21)	0.27	0.87
	Frail			1.42 (1.13-1.78)	<0.01	
≥50	Prefrail	Reduce drinking	1134	1.01 (0.84-1.21)	0.94	0.30
	Frail			1.22 (0.91-1.64)	0.18	
<50	Prefrail	Reduce binge drinking	812	1.09 (0.90-1.30)	0.38	0.80
	Frail			1.49 (1.08-2.07)	0.02	
≥50	Prefrail	Reduce binge drinking	256	1.31 (0.92-1.88)	0.13	0.78
	Frail			1.70 (0.98-2.97)	0.06	

Abbreviations: 95% CI: 95% confidence interval, HR: hazard ratio

[a] Adjusted for age, sex, race/ethnicity, ART use, smoking status, recreational drug use, FIB-4 stage, HCV coinfection, diabetes, treated hypertension, statin use, BMI category, time-updated depression (PHQ-9 score), and time-updated CD4 cell count

[b] Active drinking defined as reporting any alcohol consumption frequency of greater than monthly or binge drinking frequency of monthly or greater

[c] Tested using Schoenfeld residuals

Table 4.5. Associations[a] between time-updated frailty status and quitting or reducing alcohol use among PWH with any baseline drinking frequency in CNICS, 2012-2021

Frailty stage, vs. not frail	Alcohol change	n	HR (95% CI)	Estimate p-value	Proportional Hazards p-value[b]
Prefrail	Quit drinking	5757	1.11 (0.98-1.26)	0.10	0.53
Frail			1.29 (1.06-1.57)	0.01	
Prefrail	Quit binge drinking	3006	1.10 (0.98-1.24)	0.11	0.42
Frail			1.27 (1.04-1.55)	0.02	
Prefrail	Reduce drinking	5751	1.02 (0.94-1.11)	0.61	0.41
Frail			1.12 (0.97-1.29)	0.14	
Prefrail	Reduce binge drinking	3003	1.07 (0.97-1.19)	0.19	0.42
Frail			1.25 (1.05-1.48)	0.01	

Abbreviations: 95% CI: 95% confidence interval, HR: hazard ratio

[a] Adjusted for age, sex, race/ethnicity, ART use, smoking status, recreational drug use, FIB-4 stage, HCV coinfection, diabetes, treated hypertension, statin use, BMI category, time-updated depression (PHQ-9 score), and time-updated CD4 cell count

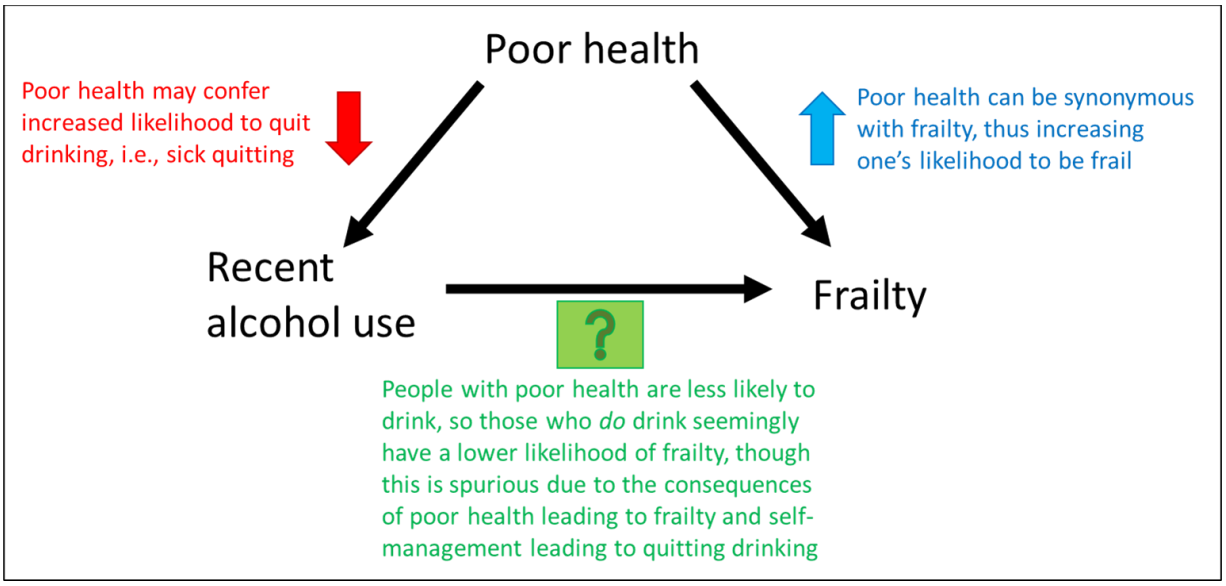
[b] Tested using Schoenfeld residuals

Table 4.6. Associations[a] between alcohol use and incident frailty among PWH in CNICS, 2012-2021

Strata	Alcohol use	n	HR (95% CI)	Estimate p-value	Proportional Hazards p-value[b]
All	Alcohol use level (vs. None)	7089			0.72
	None with AUD		0.65 (0.49-0.86)	<0.01	
	Current non-hazardous		0.81 (0.69-0.96)	0.01	
	Current hazardous		0.70 (0.56-0.87)	<0.01	
	Binge (monthly or more)	7089	0.87 (0.70-1.08)	0.21	0.74
<50	Alcohol use level (vs. None)	4601			0.65
	None with AUD		0.63 (0.43-0.92)	0.02	
	Current non-hazardous		0.87 (0.70-1.09)	0.22	
	Current hazardous		0.73 (0.55-0.96)	0.03	
	Binge (monthly or more)	4601	0.85 (0.65-1.10)	0.22	0.55
≥50	Alcohol use level (vs. None)	2488			0.86
	None with AUD		0.68 (0.45-1.02)	0.06	
	Current non-hazardous		0.75 (0.59-0.95)	0.02	
	Current hazardous		0.67 (0.47-0.95)	0.02	
	Binge (monthly or more)	2488	0.90 (0.62-1.31)	0.60	0.91

Abbreviations: 95% CI: 95% confidence interval, AUD: alcohol use disorder, HR: hazard ratio
[a] Adjusted for age, sex, race/ethnicity, ART use, smoking status, time-updated depression (PHQ-9 score), and time-updated CD4 cell count
[b] Tested using Schoenfeld residuals

Figure 4.1. Confounding structure of poor health in the association between recent alcohol use and frailty. Poor health likely decreases the likelihood of drinking alcohol and also increases the likelihood of being frail. When this confounding is not accounted for, there is a spurious association in which alcohol appears protective for frailty.



Chapter 5: Conclusion

In its entirety, this dissertation expands the field of HIV and aging research and clinical understanding by defining and validating a self-reported measure of frailty among PWH (Chapter 2), then applying the phenotype to better understand relationships between frailty and commonly used substances, including tobacco (Chapter 3) and alcohol (Chapter 4). These are important questions with significant impact on a growing field and have notable clinical and scientific relevance, as well as suggesting tangible points for investigating intervention strategies for modifiable behaviors. Prior frailty and substance use research has been focused on the general population, among relatively small cohorts of PWH, or limited to cross-sectional associations, while we were able to use longitudinal modeling approaches among a large, diverse cohort.[6,15,49,50,53,56,63,122,180] We also expanded on prior work by including multiple measures of smoking (e.g., pack-years and cigarettes per day) and alcohol (e.g., prior AUD and binge drinking) to cover a wider range of behaviors.

Our validation study utilized in-depth physical functioning data from the PROSPER-HIV study nested within CNICS to evaluate various validity measures of our self-reported frailty phenotype. Our findings support the validity of the self-reported phenotype as a tool to measure frailty in busy clinical settings and for large-scale studies. Furthermore, our results provide evidence as to the additional information for frailty that the objective physical function measures (e.g., grip strength and gait speed) offer when they are available. This study focused on the classical approach to defining and measuring frailty as a phenotype (introduced by Fried and colleagues), in which each component is dichotomized as present or absent and weighted equally in the summation for total frailty score.[3] Frailty phenotype scores (and potentially frailty indexes as well) may benefit from more nuanced scoring approaches, such as with item response theory (IRT). IRT is a method in which the psychometric properties of instruments or tests are evaluated and then transformed into a new scoring scheme that allows for unequal weighting among components and includes all levels of potential response options (rather than using

binary dichotomization for components).[181-183] Future work may employ IRT approaches to help elucidate differences between components, such as whether the presence of specific individual components confers a greater likelihood of frailty compared to others, and thus, should be weighted differently in scoring. Further, IRT may be applied to both populations with and without HIV to better understand differences in defining frailty among certain groups, since the phenotypes developed among the general population have been applied to PWH without this investigation. Additionally, we observed that frailty was better at estimating associations with falls among older PWH compared to younger, suggesting that continued investigation into frailty among younger individuals is warranted. IRT could potentially highlight differential impact of the components between the age strata.

Our study into the association between smoking and frailty expands on many existing findings by combining multiple measures of smoking into a single study, as well as confirming results of prior analyses and hypotheses regarding the negative impact of smoking on health outcomes.[51-53] We also included multiple parameterizations of frailty to better encapsulate and represent the dynamic nature of frailty states, which allowed us to identify a potential role of smoking cessation as a factor in mitigating frailty progression. A focused investigation into the impacts of quitting smoking would offer important tangible results for implementation into care and intervention tactics. Moving forward, measuring and incorporating time since quitting smoking could offer insight into the actuality and magnitude of this observation. This has been an important area of research for other health outcomes, with evidence showing that as time since quitting increases, the risk of poor outcomes decreases.[144] Whether this trend persists for frailty is an important question to consider and answer and should be a focus of future research.

Finally, our study on the relationship between frailty and alcohol use provides important context and nuance for understanding this complex epidemiologic question. Our results suggest that

frailty is a strong indicator and potential motivator of reducing alcohol use frequency, including binge drinking. We encourage including individual-level characteristics that may influence drinking behaviors in models to better estimate these relationships and ultimately allow for improved measurement of the association between alcohol use and frailty. There are many ways to expand on our findings. From an epidemiological perspective, a better understanding of the transitions in both measures (i.e., worsening and improving frailty *and* quitting and relapsing with alcohol) poses significant impact into applying these findings to care of PWH. From a methods perspective, investigation into techniques to address the confounding by sick quitting we observed would aid in managing data limitations and offer statistical solutions. For example, research into developing a polygenic risk score for predicting alcohol use/abuse among PWH and then implementing Mendelian randomization, or genetic instrumental variable analysis (GIVA), into observational research to develop causal interpretation in these studies could serve as to a method to reduce bias and improve inferences.[184] For these questions, and many more, the work presented here is a step to illuminating the complex interplay between frailty and alcohol consumption.

Overall, our findings are unique in their scope and generalizability to PWH engaged in care in the United States and elucidate aspects of frailty development and progression that may impact care practices and future research. We focused on mechanisms related to modifiable behaviors, which can aid in improving care and healthy aging for PWH. This dissertation suggests many subsequent novel research questions to further our understanding and identify interventions with high clinical impact.

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