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Evaluating the Sick Quitting Hypothesis for Frailty Status and Reducing Alcohol Use Among People With HIV in a Longitudinal Clinical Cohort Study

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Abstract

"Sick quitting," a phenomenon describing reductions in alcohol consumption following poor health, may explain observations that alcohol appears protective for frailty risk. We examined associations between frailty and reductions in drinking frequency among people with HIV (PWH). At six Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) sites between January 2012 and August 2021, we assessed whether frailty, measured through validated modified frailty phenotype, precedes reductions in drinking frequency. We associated time-updated frailty with quitting and reducing frequency of any drinking and heavy episodic drinking (HED), adjusted for demographic and clinical characteristics in Cox models. Among 5,654 PWH reporting drinking, 60% reported >monthly drinking and 18% reported ≥monthly HED. Over an average of 5.4 years, frail PWH had greater probabilities of quitting (HR: 1.56, 95% confidence interval [95% CI] [1.13–2.15]) and reducing (HR: 1.35, 95% CI [1.13–1.62]) drinking frequency, as well as reducing HED frequency (HR: 1.58, 95% CI [1.20–2.09]) versus robust PWH. Sick quitting likely confounds the association between alcohol use and frailty risk, requiring investigation for control.

Key words: alcohol, confounding, frailty, people with HIV, sick quitting

Frailty is a complex geriatric syndrome characterized by increased vulnerability to health stressors that can develop in conjunction with aging (Clegg et al., 2013; Fried et al., 2001). There are a variety of interventions used to manage and mitigate frailty progression, which are often focused on behavioral changes such as exercise and nutrition (Morley et al., 2013; Travers et al., 2019; Walston et al., 2018). People also may self-manage their health behaviors in light of changes, such as declines in health or frailty status (Perreira & Sloan, 2001). One

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http://dx.doi.org/10.1097/JNC.0000000000000441

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 or new diagnoses (Howell et al., 2021; Liang & Chikritzhs, 2013; Sarich et al., 2019). In fact, sick quitting has been proposed as an explanation for some uniquely paradoxical associations observed between alcohol and health outcomes (Fillmore et al., 2007).

Researchers have identified potential epidemiologic implications of naive approaches to estimating associations between alcohol and outcomes such as frailty, namely, unmeasured confounding related to sick quitting (Klatsky & Udaltsova, 2013; Liang & Chikritzhs, 2013; Zuccolo & Holmes, 2017). This explanation was developed based on evidence from multiple studies reporting observations that recent alcohol use, primarily when light drinking and occasionally when heavy drinking are involved, seems protective for frailty risk, similar to the observed cardioprotective properties of modest alcohol use (Jazbar et al., 2021; Kojima et al., 2018; Ortola et al., 2016; Roerecke, 2021; Seematter-Bagnoud et al., 2014). These studies have generally been limited to cross-sectional analyses or relatively short follow-up. Thus, it has been hypothesized that this is a spurious association due to the confounding by sick quitting (Jazbar et al., 2021; Kojima et al., 2018, 2019; Ortola et al., 2016; Seematter-Bagnoud et al., 2014). Few studies have estimated associations between alcohol use and frailty considering both recent and historical use; these studies found that recent alcohol use is protective, but long-term use is a risk factor for frailty development (Maffei et al., 2020; Strandberg et al., 2018). These findings underscore the potential for confounding by sick quitting to affect estimates of the effect of recent alcohol use. Ultimately, however, 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 was associated with reductions in alcohol use frequency (i.e., days drinking per month) in a large cohort of people with HIV (PWH), a population with high rates of both frailty and risky alcohol use (Crane et al., 2017; Duko et al., 2019). We hypothesized that being frail is associated with quitting and reducing drinking frequency, in alignment with the sick quitting hypothesis. 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 (Kitahata et al., 2008). CNICS is a longitudinal observational clinical cohort of PWH ages 18 years and older engaged in care at eight academic clinical sites across the United States, comprising a rich diverse population. PWH at six sites (Case Western Reserve University, Fenway Health, University of Alabama at Birmingham, University of California San Diego, University of North Carolina Chapel Hill, and University of Washington) with data on frailty and alcohol use were included in this study. The CNICS data include demographic characteristics, laboratory values, diagnoses, and medications that are all collected as part of routine care and extracted from the electronic medical record and other data sources. The CNICS repository also includes results of an assessment of patient-reported outcomes and measures (PROs). PWH complete the CNICS clinical assessment of PROs on tablets at the beginning of routine HIV care appointments approximately every 4–6 months. It includes standardized questions in domains such as HIV symptoms, substance use, and mental health and is available in English, Spanish, and Amharic (Fredericksen et al., 2012). Institutional review boards at each site approved CNICS protocols, and PWH provided written consent before joining CNICS. This study was conducted using deidentified data and therefore received a waiver of authorization requirement (UW: 27674-D).

People with HIV who completed ≥2 PROs with alcohol and frailty measures between January 3, 2012, and August 23, 2021, were included in this study. Detailed information on how many PWH were eligible for this study can be found in Figure 1. Among 21,890 PWH who attended an HIV primary care visit within the study window, 15,355 began at least one PRO assessment, 8,608 completed at least two PROs, 5,944 reported any alcohol use at baseline, and 5,654 had complete information on all covariates. There were 3,419 PWH who reported active drinking, 2,948 who reported any heavy episodic drinking (HED), and 1,044 who reported active HED. PWH were followed from "baseline," defined as the first date on which they had self-reported complete information on alcohol use *and* frailty. PWH who reported not drinking at baseline were excluded based on their inability to further reduce alcohol consumption. Follow-up ended at the earliest date of (a) reduction in alcohol consumption (i.e., quitting/reducing drinking frequency) or (b)

censoring at the last clinical encounter within the observation period (including loss to follow-up or death).

Exposure: Frailty Status

Frailty was defined by a validated modified Fried frailty phenotype from the PRO assessment with four self-reported components: low physical activity, fatigue, poor mobility, and unintentional weight loss (Fried et al., 2001; Ruderman et al., 2023). Fried's original phenotype also includes a fifth component, grip strength, which CNICS did not capture; however, our modified phenotype has good validation properties compared with Fried phenotype (Ruderman et al., 2023). Each component was dichotomized, and the phenotype was scored from 0 to 4 (Ruderman et al., 2023). We considered frailty status with three 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, as in Fried phenotype (Fried et al., 2001; Ruderman et al., 2023). Frailty status was updated at each PRO assessment it was reported; otherwise,

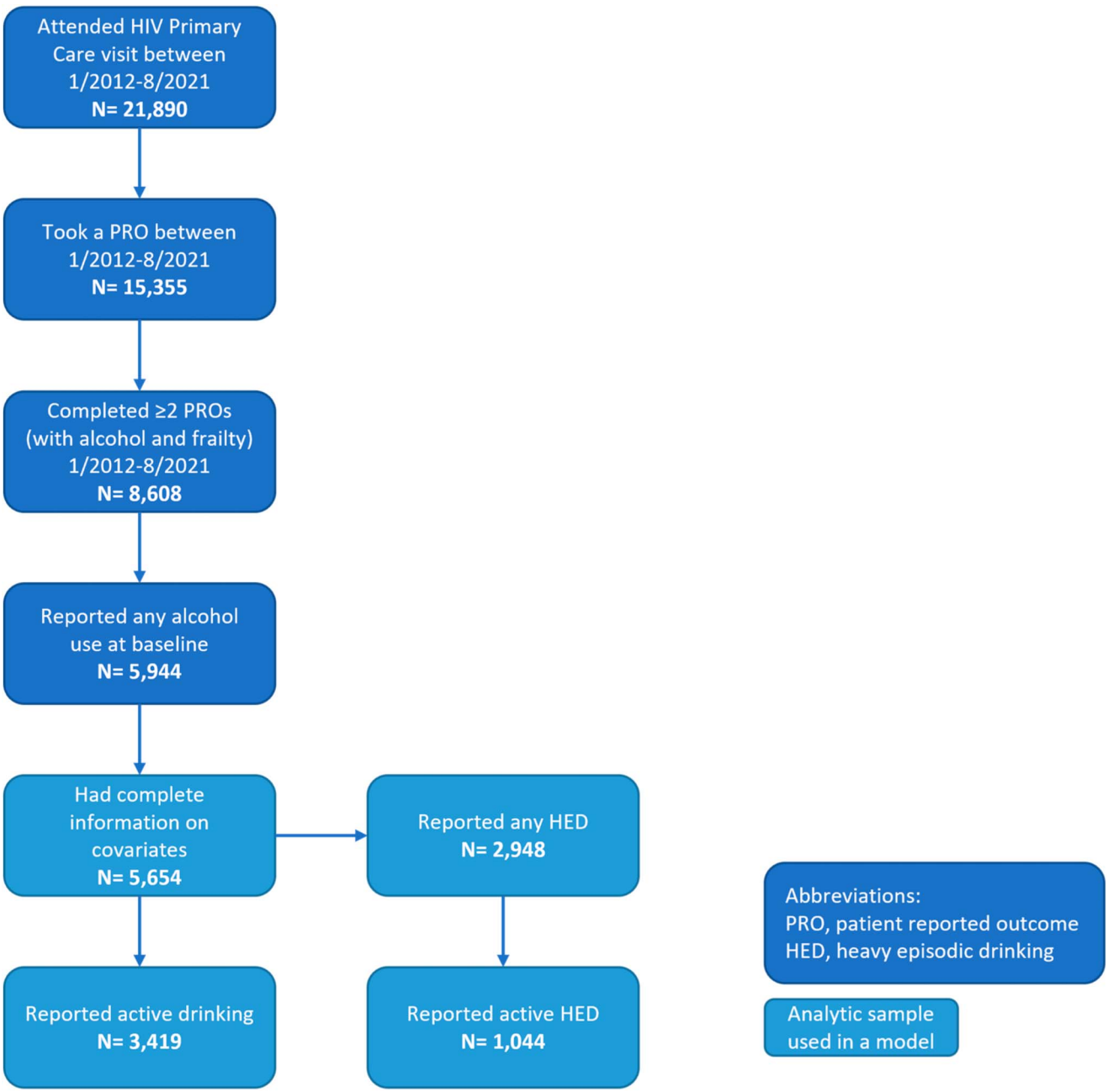

Figure 1. Eligibility of CNICS participants given inclusion criteria. CNICS = Centers for AIDS Research Network of Integrated Clinical Systems. This figure is available in color online www.janacnet.org.

status from the previously completed PRO was carried forward.

Outcome: Declines in Alcohol Use Frequency

Alcohol consumption was collected in the PROs using the Alcohol Use Disorders Identification Test Consumption (AUDIT-C) instrument (Bush et al., 1998). We considered frequency of drinking and heavy episodic (binge) drinking (HED; defined by ≥5 drinks for men or ≥4 drinks for women in one sitting) at each assessment based on the categorical response options on the AUDIT-C items. We defined rare/inactive drinking as report of "monthly or less" on item 1 and rare HED as report of "less than monthly" on item 3. We defined four shifts in consumption to measure changes in use frequency: (a) quitting alcohol use, (b) quitting HED, (c) reducing alcohol use frequency, and (d) reducing HED frequency. Quitting was defined as a shift from nonzero (at baseline) to zero days of consumption at a follow-up PRO assessment, whereas reductions were defined as any decrease from baseline consumption frequency (including quitting). We fit four separate models describing each of the changes in frequency of alcohol use or HED. PWH who increased their drinking frequency remained in the analytic cohort until their follow-up ended (i.e., a reduction or censoring at last encounter occurred).

Covariates

We included covariates that, based on the existing literature, may act as confounders for the effect of frailty on alcohol consumption. Demographic characteristics included age, sex assigned at birth, site, 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) co-infection (defined by any lifetime positive result from an HCV antibody, RNA, or genotype test), diabetes (any of the following criteria: (a) hemoglobin A1c ≥6.5; (b) use of a diabetes-specific medication, such as insulin; or (c) 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 (9-item patient health questionnaire score), time-varying CD4$^+$ T-cell count, and other substance use (Crane et al., 2006; Sterling et al., 2006). Other substance use included (a) smoking status and (b) a composite recreational drug use variable (including illicit opioids, methamphetamines, and cocaine/crack, collected through a modified World Health Organization Alcohol, Smoking and Substance Involvement Screening Test [ASSIST] instrument), both measured as never, former, or current use (Newcombe et al., 2005).

Statistical Analysis

We modeled the association between time-updated frailty status (not frail, prefrail, frail) and changes in alcohol use or HED frequency using four Cox proportional hazards models, one for each type of change in alcohol use defined above. Our findings represent the relative difference in the rate of quitting or reducing drinking frequency among PWH who were frail or prefrail compared with those who were not frail. We excluded PWH who reported rare use (monthly or less for any drinking and less than monthly for HED) because our aim was to estimate associations for "active" drinking, but these PWH were then included in a sensitivity analysis (described below). Each model was adjusted for age, sex, race/ethnicity, site, ART use, smoking status, illicit drug use, FIB-4, HCV co-infection, diabetes, treated hypertension, dyslipidemia, BMI, and time-updated depressive symptomology and CD4$^+$ T-cell count. Covariates were measured only at baseline unless specified as time updated (i.e., updated prospectively throughout engagement in CNICS).

We conducted two sensitivity analyses, including (a) subgrouping the cohort by baseline age (younger than 50 years vs. 50 years and older) to consider the tendency to reduce alcohol intake at older ages and (b) restricting to only PWH with rare baseline alcohol use to evaluate whether there is also a relationship between frailty and quitting drinking for PWH with rare use (i.e., if there may be a threshold of alcohol use frequency above which sick quitting occurs).

For all models, we checked for violations of the proportional hazards assumption using Schoenfeld residuals and evaluated significance at the 95% confidence level (95% CI; i.e., $p < .05$ signifies a violation of proportional hazards; George et al., 2014). There were a few instances of violation of proportional hazards; however, we identified these to be due to a single site each time and attributed the violation to a transition in data collection procedures, which occurred at the end of the observation period. In sensitivity analyses excluding that site, the point estimates were preserved; therefore, we maintained the models with violations because they were representative and the violation was artifactual. Statistical significance for our models was also assessed at the

95% CI ($p < .05$). All analyses were performed using Stata version 17.0 (StataCorp, College Station, TX).

Results

We identified a cohort of 5,654 PWH who reported alcohol use at their first PRO assessment within the study period (2012–2021), with 3,419 (60%) reporting "active" drinking (i.e., multiple days per month), 2,948 (52%) reporting any HED, and 1,044 (18%) reporting at least monthly HED. The mean age at baseline was 44 years (median: 44 years, interquartile range [IQR]: 34–52 years, range: 19–81 years) and 679 PWH (12%) were assigned female at birth (Table 1). Half were non-Hispanic White, and 29% were non-Hispanic Black. At the end of follow-up (mean: 5.4 years, median: 5.2 years), the mean age was 49 (median: 50 years, IQR: 39–58 years), with 9% ages 65 years and older. Frail PWH (n = 604, 11%) were, on average, older, female, had greater comorbidity burden, and reported greater depressive symptomology and use of substances (except alcohol), compared with not frail and prefrail PWH (Table 1).

Among 5,654 PWH, one in four (n = 1,345, 24%) reported quitting any drinking over 25,654 person-years of follow-up, whereas half (n = 2,844, 50%) reported a reduction in drinking frequency over 20,019 person-years of follow-up. Among the 2,948 PWH who reported HED at baseline, half (n = 1,503, 51%) quit over 10,027 person-years of follow-up, and about two thirds (n = 1,913, 65%) reduced their HED frequency over 8,273 person-years of follow-up.

We found that frailty was associated with a greater probability of quitting and reducing frequency both of any drinking and of HED over follow-up (Table 2; Figure 2). In demographic-adjusted and comorbidity-adjusted analyses, being frail was associated with a 56% greater probability of quitting (95% CI [1.13–2.15]) and 35% greater probability of reducing (95% CI [1.13–1.62]) drinking frequency compared with being not frail. Similarly, being frail was associated with a 42% greater probability of quitting (95% CI [0.97–2.09]) and a 58% greater probability of reducing (95% CI [1.20–2.09]) frequency of HED. Our findings also suggested an association between prefrailty and decreasing consumption frequency; however, the results were generally not statistically significant (Table 2; Figure 2).

In sensitivity analyses stratified by age, we observed comparable estimates to the pooled analyses and did not observe evidence of effect measure modification by age category, although some subgroups were not well-powered and had confidence intervals that crossed the null value (Table 3). In sensitivity models including only PWH reporting rare drinking and HED frequency at baseline, we observed generally null associations, suggesting that PWH with rare drinking may not be subject to the same sick quitting patterns as more frequent drinking (Table 4).

Discussion

We found that frailty was associated with a greater probability of both quitting and reducing any drinking *and* HED frequency among PWH. Importantly, these findings were estimated in models adjusted for other health factors that may influence drinking behaviors (e.g., substance use, mental health, and comorbidities), suggesting that frailty may be an important motivator of consumption changes, supporting the sick quitting hypothesis, illustrated in Figure 3 (Skogen et al., 2009). Specifically, frail PWH were more than 50% more likely to report quitting any drinking and reducing HED frequency compared with 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 (Bilal et al., 2018). These findings have significant implications for longitudinal research on alcohol use and frailty regarding issues of confounding and considerations for measuring alcohol use correctly and comprehensively.

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 (Kyriacou & Lewis, 2016). We believe that poor health status increases the probability 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. Consequently, those who *do* drink seemingly have a lower probability of frailty; however, this is a confounded relationship (Kyriacou & Lewis, 2016). 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 (poor health) that also predicts the outcome (frailty; Joseph et al., 2014). Like other situations affected by confounding by indication, this type of bias poses a complex challenge for analysis, requiring methodological modifications and careful attention to measurement techniques (Joseph et al., 2014).

Table 1. Baseline Demographic and Clinical Characteristics of PWH Who Reported Alcohol Use in CNICS by Frailty Status, 2012–2021, *n* (%) Unless Noted

Variable	Everyone	Not Frail	Prefrail	Frail
n (%)	5,654	2,698 (48)	2,352 (42)	604 (11)
Age, mean (*SD*)	44 (11)	43 (11)	44 (11)	46 (10)
Female	679 (12)	249 (9)	319 (14)	111 (18)
Race/ethnicity				
Non-Hispanic White	2,836 (50)	1,318 (49)	1,189 (51)	329 (54)
Non-Hispanic Black	1,647 (29)	810 (30)	683 (29)	154 (26)
Hispanic	876 (15)	425 (16)	356 (15)	95 (16)
Other	295 (5)	145 (5)	124 (5)	26 (4)
Alcohol use frequency				
Active	3,419 (60)	1,699 (63)	1,395 (59)	325 (54)
Inactive/rare	2,235 (40)	999 (37)	957 (41)	279 (46)
HED frequency				
Active	1,044 (18)	489 (18)	441 (19)	114 (19)
Inactive/rare	4,610 (82)	2,209 (82)	1,911 (81)	490 (81)
Depression				
PHQ-9 ≥10	1,194 (21)	130 (5)	659 (28)	405 (67)
PHQ-9, mean (*SD*)	5.6 (6.0)	2.6 (3.5)	7.1 (5.9)	12.9 (6.3)
Smoking status				
Never	2,214 (39)	1,189 (44)	860 (37)	165 (27)
Former	1,663 (29)	793 (29)	691 (29)	179 (30)
Current	1,777 (31)	716 (27)	801 (34)	260 (43)
Recreational drug use[a]				
Never	2,712 (48)	1,484 (55)	1,029 (44)	199 (33)
Former	2,034 (36)	889 (33)	879 (37)	266 (44)
Current	908 (16)	325 (12)	444 (19)	139 (23)
$CD4^+$ T-cell count (cells/mm^3), mean (*SD*)	589 (309)	591 (295)	601 (316)	535 (338)
ART use	4,922 (87)	2,385 (88)	2,036 (87)	501 (83)
FIB-4 stage				
0–1	4,539 (80)	2,229 (83)	1,879 (80)	431 (71)
2–3	989 (17)	423 (16)	419 (18)	147 (24)
4–6	126 (2)	46 (2)	54 (2)	26 (4)
HCV co-infection	532 (9)	180 (7)	248 (11)	104 (17)
Diabetes	435 (8)	162 (6)	188 (8)	85 (14)

(*continued on next page*)

Table 1. (*continued*)				
Variable	**Everyone**	**Not Frail**	**Prefrail**	**Frail**
Treated hypertension	1,379 (24)	601 (22)	583 (25)	195 (32)
Dyslipidemia (statin use)	1,059 (19)	444 (16)	473 (20)	142 (24)
Follow-up years				
Mean (*SD*)	5.4 (2.7)	5.4 (2.7)	5.4 (2.7)	5.5 (2.7)
Median (IQR)	5.2 (3.1–8.0)	5.0 (3.1–7.9)	5.3 (3.1–8.1)	5.5 (3.2–8.3)

Note. ART = antiretroviral therapy; CNICS = Centers for AIDS Research Network of Integrated Clinical Systems; FIB-4 = fibrosis score; HCV = hepatitis C virus; HED = heavy episodic drinking; IQR = interquartile range; PHQ-9 = 9-item Patient Health Questionnaire; PWH = people with HIV.
[a] Recreational drug use includes cocaine/crack, methamphetamine, and illicit opioid use.

In addition, our sensitivity analysis suggests that this association may apply specifically to PWH with frequent (i.e., more than monthly) drinking and that rare drinking may not be subject to the same mechanism (Table 4). This observation is suggestive of a threshold effect in which sick quitting is primarily occurring among PWH with more frequent or severe alcohol use. However, for HED, there was some evidence of a higher probability of quitting associated with being frail (HR: 1.13, 95% CI [0.89–1.44]) among PWH reporting rare HED, although the confidence interval crossed the null. This finding is anecdotally aligned with the hypothesis that PWH may be inclined to reduce more "severe" drinking behaviors (e.g., HED, very high frequency) when they become frail but warrants further investigation.

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 whether frailty status may act as an indicator or trigger for changes in alcohol use, and these

Table 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, versus Not Frail	Alcohol Change	*n* in Model	HR (95% CI)	Estimate *p*-Value	Proportional Hazards *p*-Value[c]
Prefrail	Quit drinking	3,419	1.24 (1.00–1.52)	.047	.02
Frail			1.56 (1.13–2.15)	.01	
Prefrail	Quit HED	1,044	1.14 (0.90–1.44)	.28	.19
Frail			1.42 (0.97–2.09)	.07	
Prefrail	Reduce drinking	3,419	1.05 (0.95–1.17)	.32	<.01
Frail			1.35 (1.13–1.62)	<.01	
Prefrail	Reduce HED	1,044	1.14 (0.96–1.34)	.13	.33

Note. 95% CI = 95% confidence interval; ART = antiretroviral therapy; BMI = body mass index; CNICS = Centers for AIDS Research Network of Integrated Clinical Systems; FIB-4 = fibrosis-4; HCV = hepatitis C virus; HED = heavy episodic drinking; HR = hazard ratio; PHQ-9 = 9-item Patient Health Questionnaire; PWH = people with HIV.
[a] Adjusted for age, sex, race/ethnicity, site, ART use, smoking status, illicit drug use, FIB-4 stage, HCV co-infection, diabetes, treated hypertension, statin use, BMI category, time-updated depression (PHQ-9 score), and time-updated $CD4^+$ T-cell count.
[b] Active drinking defined as reporting any alcohol consumption frequency of greater than monthly or HED frequency of monthly or greater.
[c] Tested using Schoenfeld residuals.

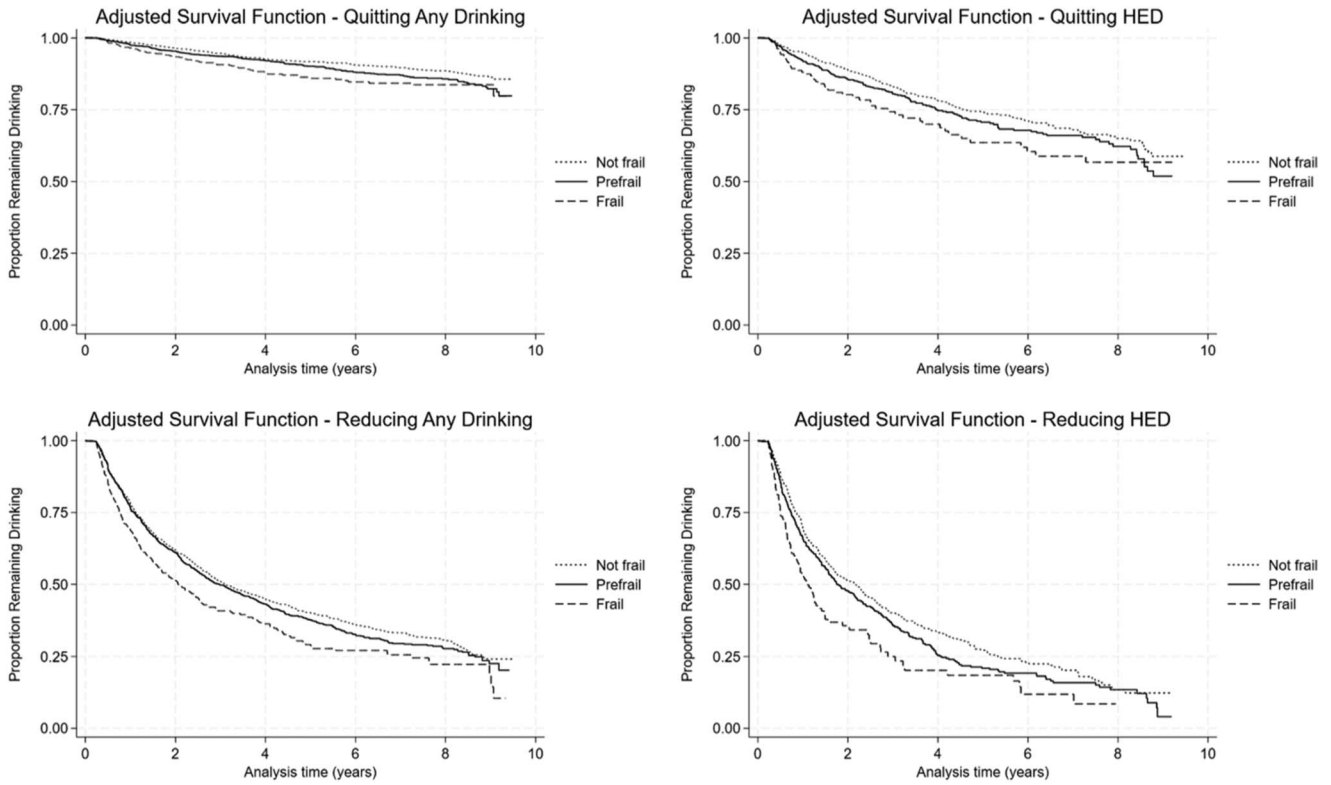

Figure 2. Adjusted survival functions for each alcohol use reduction outcome: quitting any drinking, quitting heavy episodic drinking (HED), reducing any drinking frequency, and reducing HED frequency.

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.

In addition, the question remains regarding the reverse association between alcohol use and risk of developing frailty, illustrated by the dotted line in Figure 3, which poses significant clinical importance in promoting healthy aging among PWH and to date has often been reported in potentially confounded analyses (Jazbar et al., 2021; Kojima et al., 2018, 2019; Ortola et al., 2016; Seematter-Bagnoud et al., 2014). One approach that investigators have used to study this relationship has been to collect data on long-term or historical alcohol use and use the historical measures as a comparator to recent use in side-by-side analyses. For instance, an analysis within the Helsinki Businessmen Study 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 (Strandberg et al., 2018). 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, whereas the inverse was observed for recent alcohol consumption (Maffei et al., 2020). 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 an individual's health status and alcohol consumption patterns can distort the true relationship, and this dynamic needs to be considered. There also remains a need to expand upon the results from the NOAH study with a larger and more diverse cohort of PWH.

These findings have clinical implications beyond research as well. Early identification of frailty is crucial in efforts for recovery or mitigation of its impacts and nurses are among the first health care providers to conduct this early identification. Routine client-centered assessment of all substance use, including current and past alcohol use, should continue to be prioritized in both primary and acute care nursing. Furthermore, gaining an understanding of motivations for behavioral changes, such as reducing alcohol use, could help inform health care providers of subtle changes in health status that may be difficult to otherwise identify. Therefore, connecting these behavioral changes with other clinical information and characteristics of PWH could aid in

Table 3. 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, versus Not Frail	Alcohol Change	*n* in Model	HR (95% CI)	Estimate *p*-Value	Proportional Hazards *p*-Value[c]
<50	Prefrail	Quit drinking	2,311	1.24 (0.97–1.59)	.09	.22
	Frail			1.50 (0.99–2.26)	.052	
≥50	Prefrail	Quit drinking	1,108	1.21 (0.82–1.78)	.34	.14
	Frail			1.56 (0.91–2.69)	.11	
<50	Prefrail	Quit HED	796	1.13 (0.86–1.49)	.37	.21
	Frail			1.58 (0.99–2.52)	.053	
≥50	Prefrail	Quit HED	248	1.45 (0.88–2.40)	.15	.08
	Frail			1.28 (0.61–2.66)	.51	
<50	Prefrail	Reduce drinking	2,311	1.10 (0.97–1.24)	.12	.16
	Frail			1.49 (1.18–1.87)	<.01	
≥50	Prefrail	Reduce drinking	1,108	0.98 (0.81–1.18)	.82	.20
	Frail			1.18 (0.88–1.59)	.27	
<50	Prefrail	Reduce HED	796	1.11 (0.92–1.33)	.29	.87
	Frail			1.62 (1.16–2.26)	<.01	
≥50	Prefrail	Reduce HED	248	1.22 (0.84–1.76)	.31	.44
	Frail			1.45 (0.81–2.61)	.21	

Note. 95% CI = 95% confidence interval; ART = antiretroviral therapy; BMI = body mass index; CNICS = Centers for AIDS Research Network of Integrated Clinical Systems; FIB-4 = fibrosis-4; HCV = hepatitis C virus; HED = heavy episodic drinking; HR = hazard ratio; PHQ-9 = 9-item Patient Health Questionnaire; PWH = people with HIV.

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

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

[c] Tested using Schoenfeld residuals.

implementing the most appropriate nursing interventions to manage their conditions potentially earlier than without knowing about the patterns of sick quitting. Ultimately, a consideration of the larger picture, including new and changing behaviors of PWH, in addition to any general nursing assessments of health may promote earlier identification of worsening frailty, at the time when reversal is more possible.

This study used a large diverse cohort of PWH engaged in care, extending the field of alcohol research, helping to provide a better and more comprehensive understanding of sick quitting. We were uniquely able to investigate 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.

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. As such, our indication for reductions in use was based on categorical response options, which was our best approach with the available data. Also, this study was conducted among PWH reporting drinking, so the characteristics of the cohort are specific to this group (e.g., younger age, greater proportion of men) and may not reflect all PWH in care. Similarly, we are unable (precluded by sample size) to effectively subgroup by sex or race/ethnicity to evaluate interactions by these important characteristics. In addition, due to the observational nature of the study, there may be unmeasured confounders of the association, including socioeconomic status, that may impact drinking behaviors and frailty (Dawson et al., 2012).

Table 4. Associations[a] Between Time-Updated Frailty Status and Quitting Alcohol Use Among PWH With Rare Baseline Drinking Frequency in CNICS, 2012–2021

Frailty Stage, versus Not Frail	Alcohol Change	*n* in Model	HR (95% CI)	Estimate *p*-Value	Proportional Hazards *p*-Value[b]
Prefrail	Quit drinking	2,235	0.99 (0.84–1.16)	.86	.24
Frail			0.98 (0.76–1.27)	.89	
Prefrail	Quit HED	1,904	1.06 (0.92–1.22)	.42	<.01
Frail			1.13 (0.89–1.44)	.30	

Note. 95% CI = 95% confidence interval; ART = antiretroviral therapy; BMI = body mass index; CNICS = Centers for AIDS Research Network of Integrated Clinical Systems; FIB-4 = fibrosis-4; HCV = hepatitis C virus; HED = heavy episodic drinking; HR = hazard ratio; PHQ-9 = 9-item Patient Health Questionnaire; PWH = people with HIV.

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

[b] Tested using Schoenfeld residuals.

Because we used a simple last observation carried forward approach, there is some potential for misclassification of the exposure, although we do not expect significant bias because both the exposure and outcome were collected through PROs. Finally, we did not have data on dietary intake or day-to-day exercise patterns, which may be similarly important factors or indicators in frailty management and should be considered in future work (Travers et al., 2019; Walston et al., 2018).

Conclusion

We observed an association among PWH between being frail and reporting reductions in alcohol consumption and HED frequency. 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 (Fillmore et al., 2007). Longer-term studies may be better suited to answer these questions as well as considering transitions in frailty states over time. In addition, 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. 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.

Availability of Data, Code, and Materials

Data may be available upon request to the corresponding author.

Figure 3. Confounding structure of poor health in the association between frailty and alcohol use.

Author Contributions

All authors meet the four criteria for authorship as identified by the International Committee of Medical Journal Editors (ICMJE); all authors have contributed to the conception and design of the study, drafted or have been involved in revising this manuscript, reviewed the final version of this manuscript before submission, and agree to be accountable for all aspects of the work. Using the CRediT taxonomy, the contribution of each author is as follows: Conceptualization & Methodology: S. A. Ruderman, J. A. C. Delaney, A. R. Webel, A. L. Fitzpatrick, M. C. Odden; Data curation: A. L. Willig, K. H. Mayer, M. Greene, M. McCaul, M. S. Saag, M. M. Kitahata, H. M. Crane; Formal Analysis: S. A. Ruderman; Funding acquisition: H. M. Crane, G. Chander, M. S. Saag, M. M. Kitahata, J. J. Eron; Supervision: J. A. C. Delaney, A. R. Webel, A. L. Fitzpatrick, M. C. Odden, H. M. Crane; Writing—original draft: S. A. Ruderman; Writing—revising: J. A. C. Delaney, A. R. Webel, A. L. Fitzpatrick, M. C. Odden, A. L. Willig, H. M. Crane, L. N. Drumright, R. M. Nance, B. M. Whitney, L. S. Mixson, A. W. Hahn, J. Ma, S. Eltonsy, G. Chander, E. Cachay, S. B. Kritchevsky, S. Austad, A. Landay, B. Lau, C. Lesko, S. Napravnik.

Disclosures

H. M. Crane has served as an advisory for a study for ViiV and Gilead, and E. Cachay has served on an advisory board for Teratechnologies. All other coauthors report no real or perceived vested interests that relate to this article that could be construed as a conflict of interest. As with all peer-reviewed manuscripts published in JANAC, this article was reviewed by two impartial reviewers in a double-blind review process. The JANAC Editor-in-Chief (Relf) handled the review process for the paper, and the Deputy Editor (Webel) had no access to the paper in her role as editor.

Acknowledgments

The authors acknowledge all CNICS participants and study personnel for their essential contributions to this work. This study was supported by the National Institute of Alcohol and Alcoholism (AA020793, Recipient: H. M. Crane; AA029544, Recipient: G. Chander), the National Institute of Allergy and Infectious Diseases (CNICS AI067039, Recipient: M. S. Saag; UW CFAR AI027757, Recipient: M. M. Kitahata; UNC CFAR AI050410, Recipient: J. J. Eron, and UAB CFAR AI027767, Recipient: M. S. Saag), and the National Institute of Aging (AG067069, Recipient: H. M. Crane).

Key Considerations

- We observed evidence that frailty is associated with reporting reductions in alcohol consumption and heavy episodic drinking frequency among people with HIV.
- Sick quitting is a behavior pattern in which individuals reduce drinking in response to poor health or new diagnoses.
- Sick quitting likely acts as a source of confounding in the association between alcohol use and risk of frailty, therefore, observations of protective effects of alcohol on frailty risk may be biased by this confounding.

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