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Lifetime Alcohol Use Among Persons Living with HIV Is Associated with Frailty

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Abstract

BACKGROUND—The average lifespan of persons living with HIV (PLWH) on antiretroviral therapy approximates the general population. However, PLWH are susceptible to early aging and frailty. Behaviors such as alcohol consumption may contribute to frailty among PLWH.

OBJECTIVE—To determine the relationships between recent and lifetime alcohol use and frailty among PLWH.

DESIGN—Cross-sectional, prospective cohort study of in-care PLWH (n=365) participating in the New Orleans Alcohol Use in HIV Study.

METHODS—Recent alcohol exposure was measured by the 30-day alcohol timeline follow-back (TLFB) assessment and by whole-blood-spot phosphatidylethanol (PEth) quantitation. Lifetime alcohol exposure (LAE) was estimated by a modified lifetime drinking history instrument. Frailty was assessed by a 58-item deficit index (DI58) and the phenotypic frailty index (PFI). The Veterans Aging Cohort Study Risk Index 2.0 was calculated.

RESULTS—Using generalized linear regression, LAE was positively associated with the DI58 [95% CI: (0.001, 0.006)] and PFI severity [95% CI: (0.004, 0.023)] after adjustment for age and other factors. Conversely, recent alcohol exposure was negatively associated with the DI58 [TLFB 95% CI: (−0.126, −0.034), PEth: (−0.163, −0.058)] and PFI severity [TLFB 95% CI: (−0.404, −0.015), PEth: (−0.406, 0.034)]. The VACS was not associated with alcohol use. Median per-decade alcohol exposure peaked in the second decade and tapered with aging thereafter. Increasing LAE and decreasing TLFB were co-associated with a specific subset of health deficits.

CONCLUSION—Lifetime alcohol use is positively associated with frailty among PLWH. Specific health deficits may discourage alcohol consumption in some PLWH.

Keywords

Frailty; HIV; Alcohol; Aging; Deficits

Introduction

Combination anti-retroviral therapy (cART) has markedly reduced the mortality of HIV infection. The prolonged life span of persons living with HIV (PLWH) has revealed a tendency for an earlier onset of geriatric comorbidities^{1–4}. Precocious aging significantly reduces health-related quality-of-life and increases the risk for poor HIV-related outcomes⁵. Factors contributing to frailty among PLWH may be leveraged to delay comorbidity development.

Modifiable factors such as alcohol use are thought to accelerate aging in the general population⁶ and may contribute to frailty among PLWH on cART. Alcohol use is prevalent in 50–66% of PLWH^{7–10}. Nearly 27% of PLWH consume potentially hazardous quantities of alcohol^{9,10}. An estimated 12–14% of PLWH may meet the criteria for an alcohol use disorder⁸. Interestingly, PLWH with a history of alcohol-related health complications are at an increased risk for hospitalization¹¹. Moreover, PLWH who consume alcohol are at a higher risk to suffer physiologic injury¹². Frailty presents challenges to effective healthcare delivery¹³, and PLWH who become frail may be at increased risk for multimorbidity, polypharmacy, and subsequent cART nonadherence¹⁴.

Frailty is operationally defined as a state of vulnerability for health decline¹⁵. Two indices of frailty, the phenotypic frailty index¹⁶ (PFI) and the deficit index (DI), an assessment of “biological age¹⁷”, are widely utilized for their ability to stratify risk for aging-related adverse events independently of chronological age^{17–21}. Additionally, the Veterans Aging Cohort Study (VACS) Risk Index, a prognostic, PLWH mortality index, stratifies 5-year risk for all-cause mortality²². The VACS index also correlates with risk for other aging-related complications such as fragility fractures²³, functional dependence²⁴, and neurocognitive decline²⁵.

The relationship between alcohol use and frailty among PLWH has been incompletely explored. Lifetime alcohol consumption is infrequently considered in studies of alcohol-associated frailty and mortality. In studies on frailty^{6,26–28}, recent/near-recent alcohol exposure or current use rate has been assessed extensively. However, these lack

consideration of one's broader alcohol use history²⁹, which may influence alcohol intake later in life through a sick-quitter effect^{30,31} and lead to an inference that alcohol protects from frailty.

Considering these findings, we hypothesized that lifetime alcohol exposure among PLWH is positively associated with frailty and that a history of lifetime use alters the association between recent use and frailty. We further hypothesized in *post-hoc* analyses that the median alcohol use rate varies over the life-course due, in part, to alcohol sick-quitting. In high-dimensional analyses, we attributed alcohol sick-quitting to a cluster of frailty-associated deficits that may discourage alcohol use.

Methods

Participant Recruitment

All human subject data presented in this work were collected in the baseline sample (n=365) of the New Orleans Alcohol Use in HIV (NOAH) prospective, longitudinal study. A detailed cohort description and recruitment strategy have been published³². Briefly, all participants are HIV-infected and in-care at the HIV Outpatient Clinic at the University Medical Center in New Orleans, Louisiana, USA. Participants with potentially hazardous alcohol consumption, as defined by an Alcohol Use Disorder Identification Test score >8, were oversampled (n=130/365).

Enrollment inclusion criteria were documented HIV+ status and age ≥ 18 years old. Exclusion criteria were 1) an acute infectious illness in past 3-months, 2) pregnancy, or 3) alcohol detected by breathalyzer testing at the study visit. Excluded participants were permitted to enroll after resolution of exclusion criteria.

The study was approved by the LSU Health Sciences Center-New Orleans Institutional Review Board. All participants provided written informed consent.

Alcohol and Other Substance Use Assessments

Lifetime Alcohol Exposure—Lifetime alcohol exposure (LAE) was estimated for all participants using a modified version of the Lifetime Drinking History instrument³³. Total-drinks lifetime alcohol exposure was calculated by taking the sum of the product of self-reported quantity and frequency of alcoholic drinks on a per-decade basis. Total-grams of alcohol exposure was calculated by taking the product of total drinks consumed and 13.6 grams ethanol per drink. Current age and age of initiation of regular drinking were used to truncate the present and initial exposure decades, respectively, into partial exposure decades.

Recent Alcohol Exposure—Alcohol use in the last 30 days was estimated by the 30-day Alcohol Timeline Follow back (TLFB) calendar structured interview³⁴. Participants were provided physical volume cues and chronicled their intake over the 30-days preceding their time of visit using a calendar aid. Total-grams alcohol consumed were calculated from each beverage volume and alcohol concentration.

Phosphatidylethanol Measurement—Dried blood spots were made by pipetting 50–60 μL of whole blood samples onto standardized blood-spot cards, which were then shipped for phosphatidylethanol (PEth) 16:0/18:1 concentration measurement by the United States Drug Testing Laboratories (Des Plaines, Illinois, USA). The PEth values for four subjects who had non-zero values below the limit of quantitation ($<8 \text{ ng}/\mu\text{L}$) were set to 0 $\text{ng}/\mu\text{L}$.

Smoke Tobacco—Current tobacco smoking status and pack-years exposure were calculated from self-reported daily consumption and years of use estimates.

Other Substance Use—Days in the past month and years of injection or oral analgesic, barbiturate, sedative, amphetamine, crack-cocaine, hallucinogen, inhalant, and cannabis use were collected using the Addiction Severity Index questionnaire³⁵.

Frailty Indices

Deficit Index—A 58-item deficit index (DI58) based on the accumulated deficits model¹⁷ was constructed from self-report and abstracted electronic medical record data (Supplemental Digital Content 1). The DI58 was constructed according to published procedures³⁶. All recorded deficits known to be positively associated in prevalence with aging were initially selected. Within these, AIDS-defining deficits were removed to maintain generalizability of the DI58 between HIV-uninfected and -infected populations. Sex-specific deficits were removed to equalize the deficit count between males and females. No deficits exhibited 100% prevalence in the cohort. This resulted in the 58 items of the DI58, exceeding the minimum recommended value of 30–40³⁶. All deficits were equally weighted. Binary deficits were scored either 0 or 1. Deficits with multi-level responses were graded evenly between 0 and 1. The sum of a participant's binary and graded deficit scores divided by 58 yielded their final DI58 score.

Phenotypic Frailty—Phenotypic Frailty Index (PFI) classification was based on the Fried *et. al.* frailty criteria¹⁶. Involuntary weight loss (not due to diet or exercise) in the past year was assessed by self-report with a threshold of >10 pounds lost. Participants scoring less than or equal to 50 on the Short-Form-36 energy/fatigue sub-score³⁷ were positive for the exhaustion criterion. Physical activity in kcals/week was assessed by the International Physical Activity Questionnaire³⁸ (IPAQ). Handgrip strength was assessed by the mean of 3 hand-grip strength trials using a JAMAR hang-grip dynamometer (Patterson Medical, Bolingbrook, Illinois, USA). Frail hand-grip strength cutoffs were stratified by body mass index and sex as prescribed¹⁶. Subject 4-meter walk time was stratified by sex and height as previously defined¹⁶ using cutoffs prorated to 4 meters (13.123 feet) from 15 feet. Participants with 3 or more positive criteria were classified as frail, 2 or 1 as pre-frail, and 0 as non-frail.

Veterans Aging Cohort Study Risk Index 2.0

Previous work on mortality among PLWH participating in the Veterans Aging Cohort Study (VACS) has led to the development of the VACS 2.0²². VACS 2.0 scores were calculated as prescribed²².

HIV Viral load & CD4+ T-Cell Counts

Whole-blood samples were collected by phlebotomy into BD Vacutainer EDTA-coated tubes (Becton-Dickinson, Franklin Lakes, NJ, USA). HIV viral titers and CD4+ T-cell counts were measured by the University Medical Center-New Orleans Clinical Laboratory.

Statistical Analysis

Multiple Linear Regression Modeling—All analyses were performed within the R statistical environment. Generalized linear models were specified based on outcome variable type and apparent distribution. Continuous predictors were mean-centered. Gamma family regression with a logarithmic link function was performed by the *glm* function in R where the DI58 or VACS 2.0 were specified as outcome variables. All PFI-based analyses utilized ordinal logistic regression via the *polr* function. Profile 95% confidence intervals (CI) were calculated from *glm* and *polr* analyses via *confint* in R.

Generalized Additive Models of Location, Scale, and Shape³⁹ were utilized for zero-inflated multiple linear regression. A zero-adjusted Gamma family distribution was specified for recent alcohol use in these models as specified in the text. Wald 95% CI were calculated from these models.

Constrained Principle Components (Redundancy) Analysis—A constrained principle component analysis (PCA) was performed on the DI58 items to identify clusters of health deficits associated with alcohol use.

In this analysis, also known as a redundancy analysis^{40–42}, PCA was performed on an $n \times p$ table of p deficits where each table element is the fitted prevalence of a deficit for an individual participant based on multiple linear regression between the deficit and a set of explanatory variables⁴¹. The PCA is thus “constrained” on the variation in reported deficits consistent with linear changes in explanatory variables⁴¹.

Deficits with zero prevalence ($n=6/58$) in NOAH were omitted from analysis. Redundancy analysis was performed using the *rda* function within the *vegan*⁴² package in R. Ordination of deficit clusters and explanatory variables was performed by the *plot.rda* function within *vegan* in R. Significant clustering of deficit prevalence according to explanatory variables was inferred by permutational analysis of variance⁴¹ using the *anova.cca* function in *vegan* in R.

Primary Outcomes and Exposures and Complete Data—The co-primary outcome variables of this study were the DI58 score, PFI classification severity, and the VACS 2.0 score. Alcohol usage was the primary exposure of interest. In zero-inflated models, recent alcohol use was specified as the outcome variable. Only subjects with complete data were analyzed in this study. Out of 365, the percent of subjects with missing data ranged from 3–9%.

Base and Extended Co-variate Models—In the base model, LAE and TLFB or LAE and PEth were tested as co-variables for association with primary outcome variables after adjusting for the demographic variables age, sex, and African-American race, body-mass-

index (BMI), and the HIV-related variables CD4+ T-cell immunodeficiency (CD4<350 cells/mm³), detectable HIV viral load (>20 copies/mL), and documented Hepatitis C co-infection.

In extended models, the potentially confounding exposures smoke tobacco pack-years, current active smoking, total years of substance use, and total days of substance use in the past 30 days were added to the base model to account for the coincidence of these exposures with alcohol use and their potential influence on frailty.

Effect Displays and Visualizations—Effect displays^{43,44} were plotted to illustrate the independent associations measured between exposures and outcomes adjusted for co-variables within the *glm* and *polr* regression functions. The effect display calculations were made in either the *effects* package or *base R*, plotted in *ggplot2*, and then compared to equivalent plots made in *effects* for consistency.

Float Points and P-value Significance Threshold—Float point decimals between 0.000 and 0.001 were truncated at <.001. All multiple linear regression coefficient p-values were calculated by the likelihood ratio test. P-values <.050 were considered significant in all analyses.

Results

Cohort Characteristics and Frailty Statistics

The NOAH Study cohort is composed predominantly of middle-aged African American men who are virally suppressed and not critically CD4+ T-cell immunodeficient, likely due to a high cART adherence rate (Table 1). Each alcohol and smoke tobacco variable was statistically significantly greater in males over females ($p<.050$, Table 1). Median BMI and DI58 were significantly higher in females over males (BMI: $p<.001$, DI58: $p=0.009$; Table 1).

Chronological age significantly positively correlated with the DI58 (Spearman $\rho=0.354$, $p<.001$) and the VACS 2.0 (Spearman $\rho=0.291$, $p<.001$, data not shown). Chronological age was not significantly associated with phenotypic frailty index (PFI) severity (Kruskal-Wallis chi-squared=0.751, $p=0.687$, data not shown).

The DI58 positively associated with PFI severity (Kruskal-Wallis chi-squared=86.292, $p<.001$) and the VACS (Spearman $\rho=0.270$, $p<.001$, data not shown). The VACS was not associated with PFI severity (Kruskal-Wallis chi-squared=0.870, $p=0.647$, data not shown).

Lifetime Alcohol Exposure Is Positively Associated with Frailty

Lifetime alcohol exposure (LAE) rank-percentile was positively associated with DI58 score and PFI severity in the base [DI58 CI: (0.002, 0.006); PFI CI: (0.004, 0.022)] and extended [DI58 CI: (0.001, 0.006); PFI CI: (0.004, 0.023)] co-variate models adjusting for recent alcohol exposure as measured by log₁₀ 30-day Alcohol Timeline Follow-back (TLFB) total-grams alcohol exposure (Table 2; Supplemental Figures, Supplemental Digital Content 2A

& 3-left column). Adjustment for $\log_{10}$ whole-blood phosphatidylethanol (PEth) concentration in place of TLFB yielded identical findings (Table 2).

Recent Alcohol Exposure Is Inversely Associated with Frailty

Participant TLFB was significantly negatively associated with the DI58 in the base [CI: (−0.117, −0.027)] and extended [CI: (−0.126, −0.034)] co-variate models (Table 2; Supplemental Digital Content 2B). Modeling PEth in place of TLFB yielded identical findings (Table 2).

Participant TLFB was significantly negatively associated with PFI frailty severity in the base [CI: (−0.374, −0.003)] and extended [CI: (−0.404, −0.015)] model (Table 2; Supplemental Digital Content 3-right column). Participant PEth was not significantly associated with PFI severity in any model (Table 2).

Interestingly, 26% and 36% of participants abstained from recent alcohol use (TLFB=0g or PEth=0ng/mL). In zero-inflated multiple linear regressions, the DI58 was positively associated with recent alcohol abstinence in base [TLFB=0g CI: (1.558, 7.824); PEth=0ng/mL CI: (3.592, 10.057)] and extended [TLFB=0g CI: (1.960, 8.534); PEth=0ng/mL CI: (3.755, 10.365)] co-variate models (Supplemental Table & Figure, Supplemental Digital Content 4). Participant PFI severity was also positively associated with recent alcohol abstinence in base [TLFB=0g CI: (0.055, 1.240)] and extended [TLFB=0g CI: (0.142, 1.386)] co-variate models although statistical significance was not observed by PEth. Notably, in the zero-inflated models the association between the DI58 or PFI and recent alcohol use was abolished when recent alcohol abstinence was separately modeled.

Lifetime and Recent Alcohol Exposure Are Not Associated with the VACS Risk Index 2.0

The VACS 2.0 was not significantly associated with LAE, TLFB, or PEth in the base and extended models omitted for co-variables (age, BMI, race, sex, CD4+ immunodeficiency, detectable HIV viral load, and HCV co-infection) already utilized within the index itself (Table 2).

Alcohol Use Rate Decreases throughout Adulthood

Stratification of retrospective lifetime alcohol exposure on a per decade basis suggests that the rate of alcohol consumption was a parabolic function of chronological age in NOAH. Generally, self-reported, 10-year alcohol exposure rate peaked in the second decade and fell gradually throughout middle and advanced age (Figure 1).

At the time of study visit, the NOAH cohort's chronological age ranged from 20 to 71, suggesting that on average a process of alcohol use rate tapering had occurred with increasing chronological age. The number of participants who decreased their 10-year alcohol exposure between the prior and current exposure decades exceeded that of subjects that increased their consumption (Wilcoxon signed-rank test $V=9,546.5$, $p<.001$).

Interaction between Recent and Lifetime Alcohol Exposure

The rate at which recent alcohol exposure inversely associated with deficit accumulation was modified in participants with a history of lifetime alcohol exposure. Participant DI58 was positively associated with the LAE x TLFB interaction term [base CI: ($<.001$, 0.003); extended CI: ($<.001$, 0.003); Table 2] where increasing LAE mitigated the rise in DI58 with decreasing TLFB (Figure 2). Modeling PEth in place of TLFB yielded similar although marginally significant findings [base CI: ($>-.001$, 0.003), extended CI: ($>-.001$, 0.003); Table 2]. Altogether, maximal frailty was observed among recent alcohol abstainers with the highest LAE (Figure 2).

Increasing Lifetime Alcohol Exposure and Decreasing Recent Exposure Cluster Similar Deficits

Tapering of the association between TLFB and the DI58 score due to LAE suggests that TLFB and LAE are co-associated with a similar set of frailty deficits. The 58 deficits comprising the DI58 were subjected to a constrained principle components (redundancy) analysis to investigate this *post-hoc* hypothesis. Both LAE and TLFB were significantly associated with the overall variation in reported deficits (LAE: $F=2.627$, $p=.002$; TLFB: $F=2.167$, $p=.006$; Figure 3A). Substance use, smoking, and CD4 immunodeficiency co-variables were not significantly associated with deficit clustering and were removed to simplify the ordination within a pruned co-variate model.

Increasing LAE and decreasing TLFB co-associated with a similar set of reported “Symptom” deficits (Figure 3B). These were comprised of self-reported “Appetite loss,” “Memory loss,” “Difficulty Swallowing,” “Dyspnea,” “Muscle Weakness,” “Involuntary weight loss,” “Fatigue,” and “Constipation” (Supplemental Figure, Supplemental Digital Content 5).

Interestingly, removal of the “Symptom” deficits [CI: (-0.001 , 0.002)] but not the “Activities of Daily Living” [CI: ($<.001$, 0.003)] or “Medical Diagnosis” [CI: (0.001 , 0.003)] deficits from the DI58 was sufficient to eliminate the significant LAE x TLFB interaction effect on the DI58 in the pruned model (Figure 3C). Moreover, an 8-item DI comprised of the LAE/TLFB co-associated deficits was significantly, positively associated with the LAE x TLFB interaction term [CI: ($<.001$, 0.003)] in the pruned model (Supplemental Figure, Supplemental Digital Content 7).

Discussion

PLWH are at risk for precocious aging and frailty due, in part, to aging-accelerating factors related to HIV infection. In this study we tested the association between alcohol consumption and frailty among a cohort of in-care PLWH living in New Orleans, LA, USA. We found that lifetime alcohol use was positively associated with biological age and phenotypic frailty after controlling for chronological age. Similar to previous reports in PLWH¹², no J-shaped relationship was observed between lifetime alcohol use and frailty.

In contrast to lifetime alcohol use, recent use was inversely associated with biological age and frail or pre-frail PFI classification due primarily to alcohol abstention with increasing

biological age and frailty rather than a continuous negative gradient. We utilized both self-report and an endogenous biomarker measured in whole blood to assess recent alcohol use. TLFB and PEth were highly correlated in NOAH, consistent with other published studies on PLWH^{45,46}. Discordance between these measures is likely due to uncontrolled exogenous and endogenous factors⁴⁷.

In the NOAH cohort, the observed decay in mean alcohol use rate over adulthood suggests a process of alcohol use tapering as participants chronologically age. Similar alcohol use de-escalation with aging has been previously reported among PLWH^{9,10} and the general population⁴⁸. In the NOAH cohort, chronological age strongly, positively correlated with biological age, implicating frailty and “sick-quitting^{30,31}” in the mitigation of alcohol consumption rates among PLWH.

Although paradoxical, the differential associations between lifetime use, recent use, and frailty are not contradictory. Recent alcohol use rates may vary freely over time, but total lifetime use may only increase or stagnate. As such, participants with the greatest mean alcohol use rate up to the onset of tapering can exhibit at cross-section both the highest LAE and the lowest TLFB or PEth.

In the NOAH cohort, the association between TLFB and the DI58 was mitigated as LAE increased due to competition between TLFB and LAE for deficit accumulation within the DI58. Participant LAE and TLFB were co-associated with a 8-item set of symptomatic deficits, which included “Appetite loss” and “Difficulty Swallowing,” and other deficits that likely deter recent alcohol use. Alcohol sick-quitting among PLWH may be considered a distinct construct of frailty (i.e. geriatric syndrome) that manifests through these 7 health deficits. Overall, we propose a negative feed-back model whereby lifelong alcohol use increases the incidence of aging-related deficits that, in turn, discourage alcohol use later in life.

Previous studies have alluded to or proposed a model of reverse causality to explain an inverse relationship between alcohol use and frailty acquisition in the general population^{49,50}. These findings in NOAH contribute to the growing recognition that assigning participants to low or no recent consumption rate reference categories without consideration of their broader alcohol use history may bias inference on the influence of alcohol use on adverse health outcomes^{29,51}.

In contrast to our prediction²², we observed no significant association between lifetime alcohol exposure and the VACS 2.0 although recent alcohol use trended towards a significant positive association. The VACS is a prognostic index validated to predict mortality in the general PLWH population^{22,52} rather than biological aging⁵³, which encompasses domains of aging in excess of mortality such as morbidity⁵⁴. These results suggest that lifelong alcohol use may increase risk for frailty without altering longevity. Future longitudinal sampling may better clarify the relationship between frailty and mortality risks among PLWH who consume alcohol.

Our study is limited in part by reliance on participant recall of past alcohol consumption and lack of consideration of medication use. Distant past recall is generally less accurate than

recent event recall, which is especially problematic in medication histories⁵⁵. Nonetheless, retrospective lifetime drinking history (LDH) data correlates well with prospectively-collected alcohol use data^{56,57}, and the LDH instrument has been tested for reliability^{29,33} and validity⁵⁸. The modified LDH used herein examined alcohol intake on a per decade basis instead of between major life events. The former schema appears to correlate well with the latter⁵⁹. Medication exposure is being modeled in NOAH longitudinal studies.

In summary, we have identified cross-sectional associations between frailty and alcohol exposure over two exposure windows in PLWH. Increasing lifetime alcohol use was linked to biological aging and phenotypic frailty. Conversely, decreasing recent alcohol use was associated with frailty, which may reflect a process of alcohol use tapering with increasing chronological and biological age. Increasing lifetime alcohol use and decreasing recent use were associated with similar health deficits that suggest a specific picture of alcohol-associated sick-quitting and frailty among PLWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest and Source of Funding

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Figure 1. Retrospective per-decade alcohol consumption throughout the life-course of the New Orleans Alcohol Use and HIV cohort.

Boxplots indicating per-decade total kilograms alcohol exposure are plotted (n=365). Boxes span the interquartile range (IQR). The horizontal line indicates the median value. Whiskers are 1.5 x IQR in length.

Figure 2. The effect of recent alcohol exposure on the 58-item deficit index score stratified by lifetime alcohol exposure within the New Orleans Alcohol Use and HIV cohort.

An effect display is plotted above ($n=350$). Scattered points represent the $\log_{10}$ grams 30-day alcohol timeline follow-back (TLFB) and lifetime alcohol exposure (LAE) rank-percentile (%ile) component-plus-residual effect scores on the 58-item deficit index (DI58) shifted by the linear effect of all other extended model co-variables evaluated at their mean value. Each panel represents the estimated association between TLFB and the DI58 within tertiles of LAE. The x-axis is inverted to illustrate the direction of increasing DI58 for both TLFB and LAE. Residuals were calculated from a Gamma-family, log-link, generalized linear model. The solid line is a locally estimated scatterplot smoothing fit of the scattered component-plus-residual points. The slope and uncertainty envelope of the dashed line reflects the independent effect of LAE and TLFB on the DI58 score and 95%-confidence, respectively, after adjustment for extended model exposures. Collinearity between the solid and dashed lines suggests the approximate fit of the modeled LAE and TLFB relationship to the data.

Figure 3. 58-item deficit index clustering according to lifetime alcohol exposure, recent 30-day alcohol exposure, and additional co-variables within the New Orleans Alcohol Use and HIV cohort.

A) A pruned co-variate model (n=350) was selected based on whether extended model (n=350) terms were statistically significantly associated ($p < .050$) with deficit clustering by permutational analysis of variance (ANOVA). B) Ordination of a redundancy analysis between the reported 58 deficits comprising the 58-item deficit index (DI58) and the pruned co-variate model. Arrows point in the direction of a positive association between the indicated co-variate and neighboring deficits. Deficits and co-variables separated by a 90° angle lacked an association while those at 0° or 180° were positively and negatively associated, respectively. The percent variation explained by each axis is listed in the axis title. Overall, the constraining model explained 8% of the total variation in reported deficit prevalence. C) Profile 95% confidence intervals (CI) of the LAE x TLFB interaction term in the pruned co-variate model after removing the symptom, medical diagnosis, or activities of daily living (ADL) deficits. Abbreviations: body mass index (BMI), African American (AA), Hepatitis C virus (HCV) co-infection, detectable HIV viral load (VL), CD4 Immunodeficiency (CD4), lifetime alcohol exposure (LAE), 30-day Alcohol Timeline Follow-back (TLFB), days (d) or years (y) of substance use (Sub.), and pack-years (P-Y) and current (Cur.) smoke tobacco use (Smo.).

Table 1:

New Orleans Alcohol Use and HIV Study cohort characteristics, means, and frequencies of analyzed variables are stratified by subject sex.

Variable	Female (N = 113)	Male (N = 252)	P-value*
Demographic			
Age (y), <i>mean ± sd</i>	48.0 ± 9.8	48.4 ± 10.6	0.510
African American Race, %	85.8	82.5	0.526
Body Mass Index, <i>mean ± sd</i>	30.3 ± 9.2	25.9 ± 5.2	<.001
HIV			
CD4 >350 cells / μ L, %	76.6	72.4	0.483
Viral Load <20 copies / mL, %	67.3	69.6	0.759
ART Adherence >90%, %	83.5	86.8	0.674
Alcohol			
Lifetime use (g), <i>mean ± sd</i>	230,441.3 ± 348,537.4	369,521.1 ± 446,388.7	<.001
30-day use (g), <i>mean ± sd</i>	463.7 ± 1,085.2	799.7 ± 1,395.0	0.001
PEth** (ng/ μ L, n=353), <i>mean ± sd</i>	97.3 ± 232.2	233.6 ± 553.1	<.001
Any Alcohol Therapy Received, %	1.8	11.5	0.004
Smoke Tobacco			
Current use, %	53.1	64.3	0.047
Pack-years, <i>mean ± sd</i>	11.5 ± 15.0	14.4 ± 16.8	0.040
Other Substance***			
30-day use (d), <i>mean ± sd</i>	7.7 ± 13.1	7.6 ± 13.7	0.847
Lifetime use (y), <i>mean ± sd</i>	21.4 ± 22.3	22.7 ± 23.5	0.506
Frailty			
58-item Deficit Index, <i>mean ± sd</i>	0.18 ± 0.09	0.16 ± 0.08	0.009
Phenotypic Frailty Index (n=351)			
Frail, %	11.0	7.9	0.446
Pre-Frail, %	55.1	51.2	0.262
Not Frail, %	33.9	40.9	0.586
Veterans Aging Cohort Study Index 2.0			
Total Score (n=354), <i>mean ± sd</i>	46 ± 17.2	44.1 ± 16.2	0.286
White Blood Cells (cells / nL), <i>mean ± sd</i>	5.3 ± 1.6	5.5 ± 2.1	0.619
Albumin (g / dL), <i>mean ± sd</i>	4.0 ± 0.3	4.1 ± 0.3	<.001
Hemoglobin (g / dL), <i>mean ± sd</i>	12.5 ± 1.5	13.8 ± 1.5	<.001
eGFR (mL / min / 1.73 m ²), <i>mean ± sd</i>	91.0 ± 25.8	93.3 ± 24.8	0.357
FIB-4, <i>mean ± sd</i>	1.3 ± 0.8	1.5 ± 1.3	0.082
Hepatitis-C infection, %	20.4	15.9	0.369

* P-values were derived from Mann-Whitney U or χ^2 tests where appropriate. P<.050 are bolded.

** Phosphatidylethanol

*** Included oral or injected analgesic, barbiturate, sedative, amphetamine, crack-cocaine, hallucinogen, inhalant, and cannabis use.

Table 2:

Lifetime and recent alcohol exposures and their interaction in association with biological age, phenotypic frailty, and mortality risk among persons living with HIV, New Orleans Alcohol Use in HIV Study.

Model	Predictor	Outcome	Base (95% CI)	P	Extended (95% CI)	P
LAE & TLFB	LAE	DI58	(0.002, 0.006)	0.001	(0.001, 0.006)	0.004
		PFI	(0.004, 0.022)	0.004	(0.004, 0.023)	0.005
		VACS	(-0.002, 0.001)	0.809	(-0.003, <.001)	0.156
	TLFB	DI58	(-0.117, -0.027)	0.002	(-0.126, -0.034)	0.001
		PFI	(-0.374, -0.003)	0.047	(-0.404, -0.015)	0.035
		VACS	(-0.008, 0.058)	0.139	(-0.004, 0.065)	0.085
	LAE x TLFB	DI58	(<.001, 0.003)	0.014	(<.001, 0.003)	0.026
		PFI	(-0.003, 0.008)	0.411	(-0.004, 0.008)	0.506
		VACS	(-0.001, 0.001)	0.646	(-0.001, 0.001)	0.606
LAE & PEth	LAE	DI58	(0.001, 0.005)	0.001	(0.001, 0.005)	0.004
		PFI	(0.002, 0.018)	0.017	(0.002, 0.021)	0.019
		VACS	(-0.001, 0.002)	0.824	(-0.002, 0.001)	0.383
	PEth	DI58	(-0.154, -0.052)	<.001	(-0.163, -0.058)	<.001
		PFI	(-0.369, 0.057)	0.152	(-0.406, 0.034)	0.098
		VACS	(-0.003, 0.069)	0.072	(-0.003, 0.073)	0.069
	LAE x PEth	DI58	(>-.001, 0.003)	0.058	(>-.001, 0.003)	0.087
		PFI	(-0.007, 0.006)	0.895	(-0.008, 0.006)	0.773
		VACS	(-0.001, 0.001)	0.703	(-0.001, 0.001)	0.714

Beta-coefficient profile confidence intervals (CI) and p-values (P) representing the linear or interaction effect of recent and lifetime alcohol exposure (LAE) on the 58-item deficit index (DI58), phenotypic frailty index (PFI), and the Veterans Aging Cohort Study (VACS) index 2.0. Total-grams LAE was rank-percentile transformed. Recent alcohol exposure as measured by the 30-day total-grams alcohol timeline follow-back (TLFB) or phosphatidylethanol (PEth) was log₁₀+1-transformed. All continuous predictors were mean-centered. The LAE & TLFB model includes LAE and TLFB and their interaction as predictors. The LAE & PEth model repeats the latter model after replacing TLFB with PEth. The CI in base models account for demographic, body mass index, and HIV infection-related variables only. The CI in extended models additionally account for the effect of smoke tobacco and other substance use. Bolded values indicate a significant (p<.050) main effect term (LAE, TLFB, or PEth) or interaction effect term (LAE x TLFB or LAE x PEth). Float points were truncated at <.001. Complete cases ranged from n=332 to 354.