

Assessing the effects of sociodemographic, clinical, and mental health conditions on COVID severity and duration

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Abstract

Background Although mortality and hospitalization rates have declined since the onset of the pandemic, Coronavirus Disease 2019 (COVID) remains a public health threat with a substantial proportion of individuals burdened with prolonged symptoms. Early in the pandemic, multiple studies identified underlying risk factors associated with adverse acute COVID outcomes, however, as the pandemic has progressed fewer studies have evaluated predictors of symptom severity, illness duration, and the development of post-acute sequela of COVID. Additionally, relatively few studies have addressed sociodemographic risk factors as opposed to physical comorbidities, especially with regards to mental health comorbidities and HIV status. This study aims to address these gaps by evaluating clinical and patient-level predictors of COVID-19 symptom severity and duration in a contemporary cohort in the US.

Methods In this study, 90 adults diagnosed with COVID were recruited between 2022 and 2025 to evaluate longitudinal dynamics of infection. Factors contributing to COVID severity and duration were analyzed from initial diagnosis (within 7 days of testing positive) to symptom resolution (up to day 140). Univariable Poisson regressions were used to estimate the effect of baseline characteristics (sociodemographics, SARS-CoV-2 vaccination status, and comorbidities) on Relative Risk (RR) for COVID duration and severity. Adjustment sets of covariates were determined via partially directed acyclic graph, with analysis for robustness based on variation of causal assumption in calculating adjusted Relative Risk (aRR) using multivariable Poisson regressions.

Results Of participants 62% were Hispanic, 87% were vaccinated against SARS-CoV-2, 71% were female, and 9% were living with HIV. Univariate analysis revealed that COVID severity was highly associated with having a longer time to COVID vaccination, post-traumatic stress disorder (PTSD), sleep apnea, suicidal behavior, pneumonia, and being female. Longer COVID duration was associated with suicidal behavior, being Hispanic as compared to white non-Hispanic, PTSD, bipolar disorder, having a history of sleep apnea, HIV infection, and being female. Driven causal multivariable analysis confirmed nineteen of the variables (63%) which showed

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higher relative risk of heightened severity and sixteen of the variables (53%) which showed higher relative risk of prolonged COVID duration.

Conclusions Our work highlights the association of sociodemographic factors and physical and mental health comorbidities with heightened COVID severity and development of post-acute sequela of COVID.

Clinical trial number Not applicable.

Keywords COVID · SARS-CoV-2 · HIV · PASC · COVID severity · Comorbidities · Mental health · Long COVID · Causal assumptions · Effect estimation

Introduction

Deaths and hospitalizations from Coronavirus Disease 2019 (COVID) have markedly declined since their incidence peaked in 2021, yet the disease continues to pose a significant threat to public health, especially for patients burdened with post-acute sequelae of COVID (PASC) [1–3]. Though the specific etiology remains uncharacterized, PASC is commonly classified as the persistence of symptoms for at least three months past COVID onset and is associated with the occurrence of specific symptoms as well as overall heightened severity during acute infection [4].

The risk of severe COVID and PASC is higher for women, elderly patients, racial and ethnic minorities, patients with limited access to healthcare, patients experiencing socioeconomic deprivation, and for patients with chronic health conditions such as COPD, diabetes, and mental health disorders [4, 5]. Conversely, being vaccinated against COVID is protective against development of PASC [6]. Research to examine the interplay between patient comorbidities and sociodemographic risk factors is necessary to understand the drivers of disease outcomes such as PASC, and to individualize therapeutic interventions [7, 8]. Additionally, while much of the early pandemic research focused on acute COVID, defined as the period of symptoms up to 30 days from COVID onset [9], far fewer studies have been conducted in the years following the global relaxation of attention to COVID with few of those employing causal interpretation over standard statistical association, constituting an increasing gap as the virus continues to evolve. Using modeling techniques with robust assessment on variations of causal assumptions, we examine how the interactions of multiple factors, notably focusing on less thoroughly investigated factors such as mental health comorbidities and HIV status, impact the relative risk of increased COVID severity and prolonged COVID duration within a diverse cohort of participants followed longitudinally from acute infection until symptom resolution.

Materials and methods

This study includes individual-level data from ‘A Comprehensive Translational Initiative on Novel Coronavirus’ (ACTION) longitudinal study. Participants were recruited between 2022 and 2025 in Miami, Florida, USA and preliminary procedures have previously been described [10]. The overall objective of ACTION was to recruit individuals into a longitudinal cohort to examine immunological responses, psychosocial factors, and PASC among individuals affected by COVID, as well as serve as a robust platform for future multidisciplinary SARS-CoV-2 research.

Ethical considerations

This study was approved by the University of Miami Institutional Review Board (#20200340). All participants provided written informed consent prior to enrolling in the study and undergoing any study-related activities.

Permission was obtained from the medical providers and hospitals prior to visiting participants recruited on in-patient hospital units.

Participant recruitment, screening, and enrolment

Participants were recruited from the University of Miami Health System and affiliated hospitals (University of Miami Hospital and Jackson Memorial Hospital), and other community sites, including the Miami Center for AIDS Research clinical core research units, local COVID testing sites, consent-to-contact databases, and clinics and community health centers via social media and word-of-mouth. Due to the high prevalence of HIV in Miami, the current study's recruitment included an oversampling of people living with HIV (PWH) compared to the general COVID population, to allow for comparisons by HIV status [11].

Eligibility criteria for screening included being over the age of 18, having a positive test for SARS-CoV-2 in the past seven days or having symptoms consistent with COVID, being able to speak and understand English or Spanish, and willing and able to consent to study activities. Participants were eligible for enrollment if they tested positive for SARS-CoV-2 by rapid COVID antigen test administered by trained study personnel swabbing each participant's nostril five times and confirmed via in-house SARS-CoV-2 PCR test.

Procedures

Participants were asked to complete at least six study visits across 15 days from enrollment at baseline (day 0, within 7 days of initial COVID positive test) and follow-up visits (days 1, 6, 9, 12, 15). Participants with ongoing symptoms or a positive PCR test on day 15 were asked to complete additional visits at days 45, 75, 105, and 140 until symptom resolution and PCR negativity, with eligibility for additional visits being determined during preceding visits. At baseline, participants completed a self-administered or interviewer-administered questionnaire on sociodemographic information, health history and comorbidities, mental and behavioral health, and COVID-19 vaccination. The questionnaire used in this study was an adaptation of instruments previously used by the study team in studies that have been previously described [10, 12]. Symptoms related to COVID were self-reported at each study visit. Saliva and nasal swabs were collected at each visit, with blood samples additionally collected at baseline and day 15 via venous puncture. Follow-up visits were conducted remotely, and participants were provided with instructions for self-collection and with self-collection tools (2 mL tubes and oral swabs for saliva and nasal samples). These were retrieved via courier service. Saliva and nasal swabs were used to conduct a SARS-CoV-2 PCR test and a rapid antigen test, respectively. Total RNA was extracted from nasal samples in a sterile Biosafety Cabinet level 2 (bsl-2) using the Zymo Quick-RNA Viral kit (#R1034), and SARS-CoV-2 RNA was quantified via qPCR using the Volcano 3G enzyme from Medix Biochemica (#8100 M), FAM reporter dye-labeled probe (ACATTGGCACCCGCAATCCTGCT), forward primer (TGCTAACAAAGACGGCATCA), and reverse primer (GTAGCACGATTGCAGCATTG), using the following cycling conditions: 88 °C 30 s, (88 °C 5 s; 60 °C 20 s; 72 °C 15 s) x45 cycles. All qPCR steps were conducted in a separate lab space utilized only for qPCR to minimize possibility of contamination. Blood samples were also used to confirm HIV status using a third-generation rapid HIV Antibody test.

Variables

Baseline predictors

Baseline characteristics were evaluated as predictors of COVID severity and duration. Variable inclusion was determined using frequency cut-offs, i.e., excluding variables with a frequency of 5% and lower. Sociodemographic data, symptoms, and comorbidities were self-reported. Comorbidity data was cross-checked using medical

record abstraction whenever possible. Sociodemographic variables and mental and physical health comorbidity categorizations are specified in the supplemental methods.

Mental health

Depression was assessed via the Center for Epidemiologic Studies Depression Scale CES-D and anxiety was assessed via the Patient-Reported Outcomes Measurement Information System (PROMIS) Emotional Distress—Anxiety—Short Form, which was administered by a study coordinator [13, 14]. Other mental health comorbidities, e.g., post-traumatic stress disorder (PTSD), bipolar disorder, and suicidal behavior, were self-reported and abstracted from participant medical records.

Outcome measures

COVID severity

The primary outcome of interest was a weighted COVID severity score, measured as the cumulative symptom burden over the course of infection, where the weighting was derived from the RECOVER study [9]. Participants selected their symptoms from a list developed by study investigators based on both clinical expertise and review of the literature (Supplemental File 1). The RECOVER cohort criteria and scoring was analyzed to address individual symptoms which were identified as being differentially expressed in PASC patients and thus could serve as indicators of potential risk of PASC. Since the RECOVER symptom list was not identical to study assessments, symptoms were ascribed by similarity to original categorization. RECOVER-based weighting is specified in the supplemental methods.

COVID duration

The secondary outcome of interest was COVID duration (operationalized as the final timepoint at which continuous symptoms were resolved, and participants had an undetectable SARS-CoV-2 PCR.) Patients who did not complete all required visits were assigned a final timepoint corresponding to the visit following their last attendance. Additionally, individual participants with discrete participation periods due to reinfection following prior participation were considered as separate COVID events and analyzed independently.

Statistical analysis

Descriptive analyses were conducted to characterize the sample at baseline. Continuous variables were summarized using the median and interquartile range (IQR), while categorical variables were presented as counts and percentages.

Univariable and multivariable Poisson regressions were used to estimate the effect of each of the baseline characteristics on COVID severity and duration. Of note, there was no censoring on COVID duration since it was known for each participant when the symptoms would be resolved, and deaths were excluded. Relative risk, adjusted relative risk, and 95% Confidence Intervals (CIs) were calculated and reported. The multivariable analysis was performed to account for potential confounding, guided by a partially directed acyclic graph (pDAG) representing plausible causal relationships among the study variables/exposures and the outcomes, created through literature evidence and experts' consensus (Supplemental Fig. 1 and Supplemental File 2) [15]. An adjustment set for each exposure was then selected using the generalized adjustment criterion [16].

As a sensitivity analysis, aware that the experts' causal assumptions may not be fully consistent, we systematically generated variations of the pDAG by selecting a series of paired nodes which would be considered directionally ambiguous and disambiguated each arrow by assessing each node individually in relation to the set of all

nodes connected to either node in the pair. Beginning with the chosen node, arrows are added or removed over successive generations from a pool of nodes, each time creating/removing an average of 1.4 edges and setting directions randomly, with prioritization of double-edged arrows, and repeating the addition/removal of arrows an average of 1.5 times picking the node drawn to previously as a new origin node, each time removing previously used nodes from the pool. This process was repeated three times for each pair of nodes, with a total of thirty node pairs being processed. We then tested if the aRRs maintained their directions/effects through an ensemble, a posteriori distribution based on all point estimates obtained from each modified pDAG. Potential effect modification was assessed by introducing interaction terms between vaccination status and selected covariates (prior COVID infection, age, obesity, cumulative comorbidities, and vaccination dose history) in multivariable models. Stratum-specific adjusted relative risks (aRRs) were estimated from the combined main and interaction effects.

Twenty-one participants (23.33%) did not provide income data, thirteen participants (14.44%) were missing vaccination dates, and four participants (4.44%) were missing height and weight information, all of which were imputed using Multivariate Imputation by Chained Equations (MICE) using the mice R package [17] (Supplemental File 3). Two participants (2.08%) were missing symptom data on day 12 which was filled with symptom data from the previous timepoint. Twelve participants (12.5%) were missing vaccine booster data and were set to having zero boosters. Analyses were conducted using the R language for statistical computing R version 4.4.2 [18], including the dagitty [19], ggdag [20], and ggraph [21] libraries.

Results

Of the 90 enrolled participants, 88 participants were retained in the study through Visit 5 (day 15) with 54 completing additional visits, and with the final follow-up visit occurring on approximately Day 140 ($n=18$).

Sociodemographics

Participants ($n=90$) were primarily female ($n=64$, 71.1%) and were mostly Hispanic/Latino ($n=56$, 62.2%), with remaining participants being non-Hispanic White ($n=13$, 14.4%) and non-Hispanic Black ($n=21$, 23.3%). Age was sorted into the following distinct groups: under 30 ($n=17$, 18.8%), 30 to 50 ($n=30$, 33.3%), 50 to 65 ($n=27$, 30%), and over the age of 65 ($n=16$, 17.8%). Marital status was categorized as being either married ($n=42$, 46.7%) or not married ($n=48$, 53.3%). Socioeconomic status and education were self-reported and binned into groups as described in Supplemental Table 1.

Comorbidities, COVID history and vaccination, and mental health

Eight participants (8.9%) were living with HIV, of which seven (87.5%) were currently taking antiretrovirals, with the median timeframe since HIV diagnosis being roughly 22 years. All participants living with HIV for whom CD4 T-cell count data was available had above 200 CD4 cells/mm³, with a median value of 1099 CD4 cells/mm³ (IQR 900–1153). Additional health comorbidities included obesity (40%), hypertension (42.2%), diabetes (34.4%), hypercholesterolemia (52.2%), cardiovascular conditions (thrombotic events [10%], arrhythmia [13.3%], heart failure [7.8%], and cardiovascular disease [14.4%]), pulmonary conditions (pneumonia [27.8%], COPD [23.3%]), chronic kidney disease (18.8%), chronic liver disease (6.7%), and thrombotic events (10%). Sixty-two participants (68.88%) had longer time to COVID vaccination, eleven (12.22%) had never received a COVID vaccination, and seventeen participants (18.88%) had a recent COVID vaccination. Forty-nine participants (54.44%) had received more than two COVID vaccine doses. Mental health conditions included depression (25.6%), anxiety (31.1%), PTSD (11.1%), bipolar disorder (11.1%), and suicidal behavior (8.9%) (Fig. 1). Prior COVID infection was reported by fifty-five participants (61.1%).

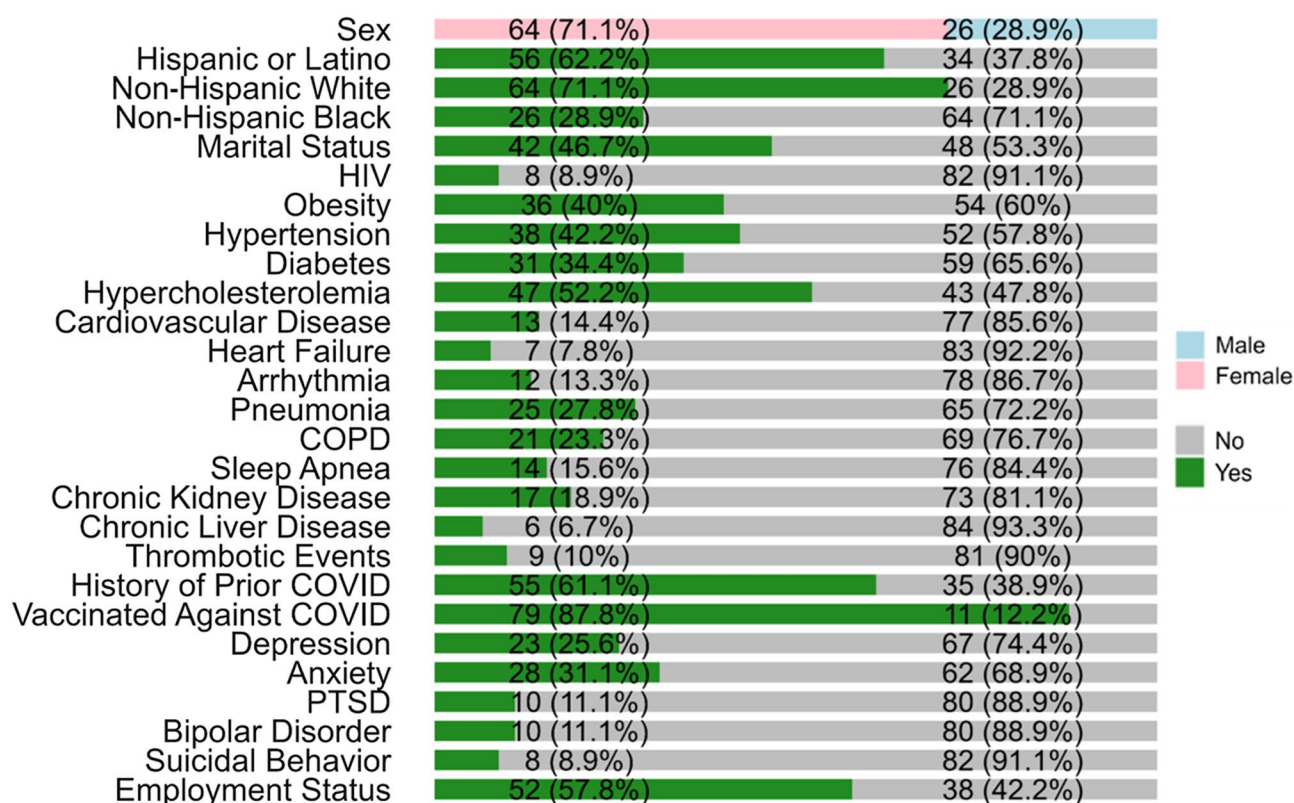


Fig. 1 ACTION3 demographics. Demographic composition, comorbidities, COVID history, and vaccination status of study participants ($N=90$). Alt text: graphical representation of ACTION study population demographics with percentage bars describing percentage of study representing that group

COVID symptoms, severity, and duration

The median COVID duration was 15 (IQR: 10.5–70.5) days. The median cumulative weighted COVID severity score was 9 (IQR: 4–17) at baseline and 14 (IQR: 9.5–21) over the duration of COVID-19. Over 20% of the participants (19 of 90 participants) experienced symptoms lasting longer than 100 days with 15 of 90 participants (16.7%) experiencing COVID durations that reached the maximum timepoint for our study of 140 days. Symptoms experienced by participants at some point over the course of COVID infection included generalized symptoms, respiratory, neurological, and skin conditions and are illustrated in Fig. 2.

Four participants reported unique symptom profiles for discrete COVID episodes, which were considered separate reinfections. Symptom burden generally decreased over time with respiratory symptoms and ear, nose, and throat symptoms being the most prevalent symptom categories at baseline and gradually decreasing at later timepoints. Neurological symptoms were recorded in sustained moderate prevalence across all timepoints and became the most prevalent symptom category from day 15 onwards (Supplemental Fig. 2).

Crude associations with COVID severity and duration

Univariable analysis identified several comorbidities associated with an increased RR of COVID severity (Fig. 3). The strongest five predictors in terms of effect, selecting all those with a conventional p -value < 0.05 , were longer time to COVID vaccination as compared to recent COVID vaccination (RR 1.76 95% CI: 1.51–2.05), PTSD (RR 1.64 95% CI: 1.45–1.86), sleep apnea (RR 1.61 95% CI: 1.43–1.81), suicidal behavior (RR 1.58 95% CI: 1.37–1.83), and pneumonia (RR 1.58 95% CI: 1.44–1.75). Being married (RR 0.9 95% CI: 0.82–0.99) and

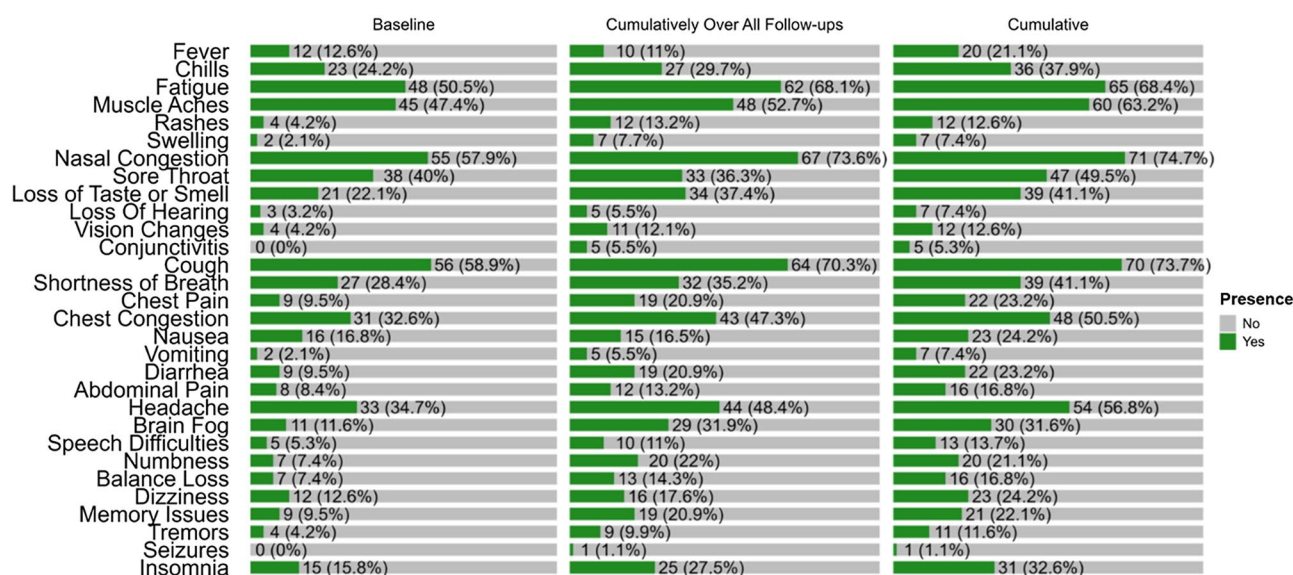


Fig. 2 Distribution of COVID symptoms stratified by timepoint. Distribution of COVID symptoms stratified by timepoint, i.e., at baseline, cumulatively over the follow-up visits, and cumulatively over the whole observation periods. Alt text: graphical representation of COVID symptoms over the different time periods represented by discrete columns and with percentage bars describing presence of symptoms experienced by ACTION participants

higher average income (RR 0.97 95% CI: 0.95–0.99) were the only variables with a conventional p -value < 0.05 associated with a decreased relative risk of heightened symptom burden. Being HIV positive (RR 1.06 95% CI: 0.90–1.25) and being female (RR 1.52 95% CI: 1.35–1.71) were additionally associated with increased RR of COVID severity, although only being female had a conventional p -value < 0.05 .

The strongest five variables associated with increased RR of prolonged COVID duration ($p < 0.05$) included: suicidal behavior (RR 1.84 95% CI: 1.71–1.99), Hispanic as compared to non-Hispanic white ethnicity (RR 1.78 95% CI: 1.62–1.95), PTSD (RR 1.56 95% CI: 1.45–1.68), bipolar disorder (RR 1.54 95% CI: 1.43–1.66), and sleep apnea (RR 1.51 95% CI: 1.41–1.61). Higher educational attainment (RR 0.94 95% CI: 0.92–0.96) was the only variable associated with decreased relative risk of prolonged infection with a conventional p -value < 0.05 . Being HIV positive (RR 1.16 95% CI: 1.06–1.27) and being female (RR 1.31 95% CI: 1.23–1.40) were additionally associated with increased RR of COVID duration with a conventional p -value < 0.05 .

Estimation of exposures' effects on COVID severity and duration with sensitivity analysis

We calculated potential causal effects of sociodemographic characteristics, comorbidities, COVID and vaccination history, and mental health conditions with respect to both outcomes using an expert-drawn pDAG and its variations. Table 1 shows the point estimates obtained from the initial pDAG along with 95% CIs and p -values, and Fig. 4 shows the summary of aRR estimates upon the different adjustment sets obtained from the various pDAGs, interpretable as an *a posteriori* CI.

When looking at COVID severity, the aRRs estimates for older age, being of Hispanic as well as non-Hispanic black race/ethnicity as compared to non-Hispanic white, female sex, pneumonia, hypercholesterolemia, diabetes, heart failure, COPD, sleep apnea, depression, PTSD, bipolar disorder, marital status, HIV, higher average income, obesity, and both no recent COVID vaccination and no COVID vaccination as compared to recent COVID vaccination were consistent with the main pDAG results in terms of direction of risk, i.e., increased or decreased, with some variations on the magnitude of the effect (with occasional crossing of the unit risk threshold in terms of 95% CI). Conversely, higher education level, hypertension, cardiovascular disease, thrombotic events, arrhythmia, chronic kidney disease, chronic liver disease, anxiety, suicidal behavior, history of prior COVID,

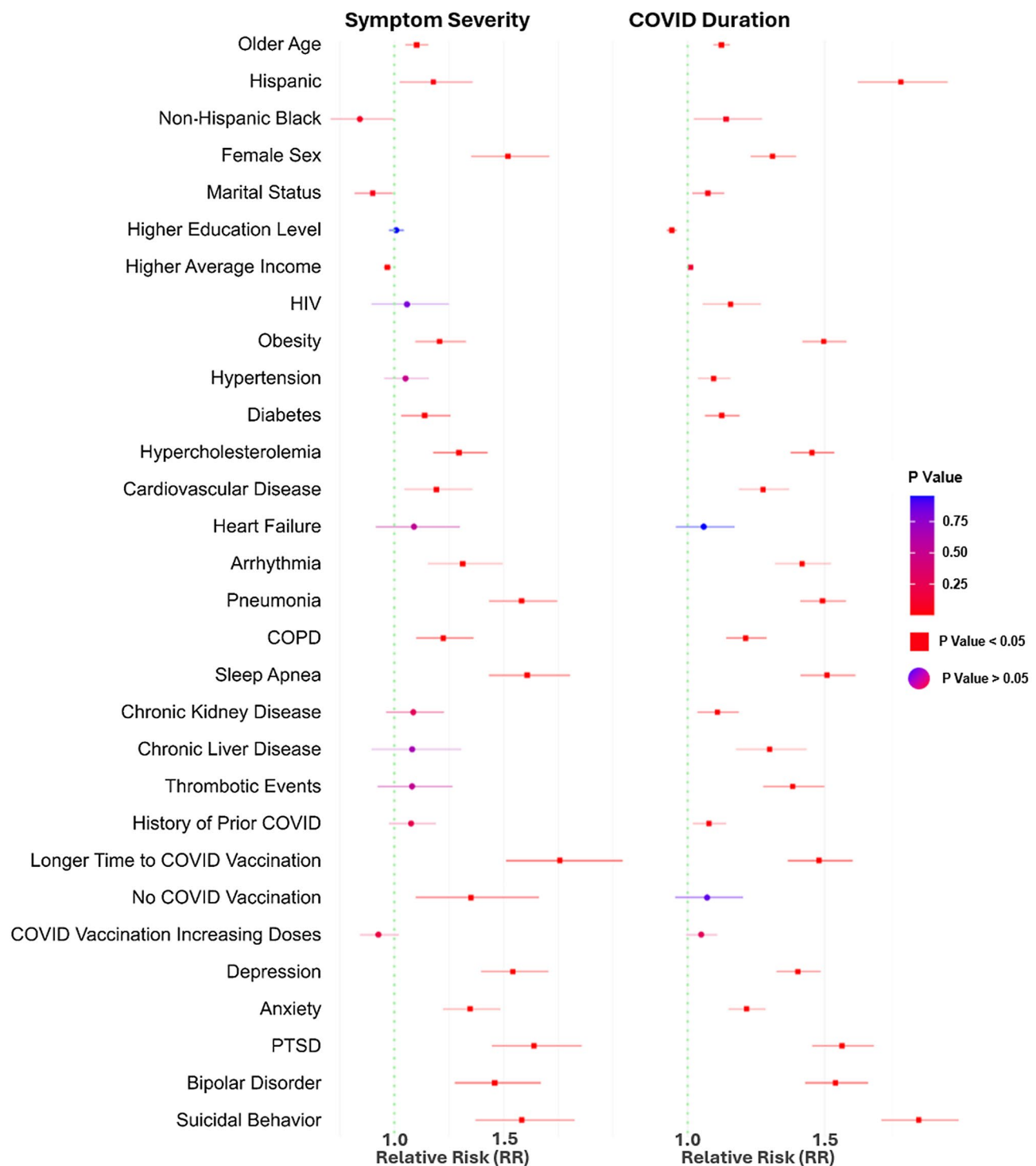


Fig. 3 Relative risk of COVID symptom severity and duration. Univariate Poisson regression on COVID symptom duration and symptom severity showing relative risks with 95% confidence intervals and continuous/discrete p-value scale. Alt text: graphical representation of relative risk of COVID symptom severity and duration for individual comorbidities and sociodemographic factors

Table 1 Relative risk of variables with p-values

Variable	Symptom Severity		COVID-19 Duration	
	RR (95% CI)	p-value	RR (95% CI)	p-value
Age	1.1 (1.05–1.16)	6.35e-05	1.12 (1.09–1.15)	3.52e-17
Hispanic	1.18 (1.02–1.36)	0.0217	1.78 (1.62–1.95)	1.48e-34
Non-Hispanic Black	0.843 (0.709–1)	0.052	1.14 (1.02–1.27)	0.0178
Sex	1.52 (1.35–1.71)	2.75e-12	1.31 (1.23–1.4)	9.54e-17
Marital Status	0.887 (0.786–1)	0.0536	1 (0.938–1.07)	0.925
Higher Education Level	1.01 (0.975–1.04)	0.595	0.943 (0.925–0.961)	1.03e-09
Average Income	0.958 (0.934–0.983)	0.00113	1.01 (0.991–1.02)	0.448
HIV	1.28 (1.05–1.55)	0.0149	1.68 (1.51–1.87)	6.13e-21
Obesity	1.21 (1.1–1.33)	1.16e-04	1.5 (1.42–1.58)	9.95e-49
Hypertension	0.838 (0.731–0.961)	0.0114	0.908 (0.841–0.98)	0.0137
Diabetes	1.02 (0.92–1.14)	0.667	1.02 (0.961–1.08)	0.513
Hypercholesterolemia	1.23 (1.1–1.38)	2.66e-04	1.34 (1.26–1.43)	7.28e-20
Cardiovascular Disease	0.728 (0.547–0.969)	0.0293	0.943 (0.809–1.1)	0.458
Heart Failure	1.38 (1.04–1.84)	0.0268	1.1 (0.939–1.29)	0.236
Arrhythmia	1.26 (1–1.57)	0.0487	1.43 (1.26–1.63)	2.56e-08
Pneumonia	1.55 (1.39–1.74)	2.80e-14	1.5 (1.4–1.59)	2.66e-35
COPD	1.15 (1.03–1.28)	0.014	1.14 (1.08–1.22)	1.61e-05
Sleep Apnea	1.56 (1.38–1.76)	8.15e-13	1.42 (1.32–1.52)	4.70e-23
Chronic Kidney Disease	1 (0.869–1.16)	0.968	1.13 (1.04–1.23)	0.00292
Chronic Liver Disease	0.901 (0.73–1.11)	0.334	1.03 (0.919–1.15)	0.635
Thrombotic Events	1.08 (0.918–1.27)	0.36	1.39 (1.28–1.51)	1.26e-14
History of Prior COVID	0.83 (0.733–0.94)	0.0034	0.988 (0.931–1.05)	0.705
Longer Time to COVID Vaccination	1.57 (1.34–1.84)	1.70e-08	1.24 (1.14–1.35)	4.06e-07
No COVID Vaccination	1.14 (0.923–1.41)	0.224	0.92 (0.818–1.03)	0.163
COVID Vaccination Increasing Doses	0.956 (0.856–1.07)	0.428	1.02 (0.954–1.08)	0.609
Depression	1.45 (1.24–1.69)	2.32e-06	1.49 (1.36–1.62)	3.40e-19
Anxiety	0.873 (0.751–1.02)	0.0791	0.915 (0.84–0.997)	0.0433
PTSD	1.58 (1.38–1.8)	2.17e-11	1.73 (1.6–1.87)	1.36e-44
Bipolar Disorder	1.46 (1.28–1.67)	3.51e-08	1.54 (1.43–1.66)	1.03e-29
Suicidal Behavior	1.4 (1.17–1.68)	1.95e-04	1.08 (0.975–1.19)	0.14

Multivariable Poisson regression on COVID severity and duration directed by original pDAG, showing adjusted relative risks (aRR) with 95% confidence intervals (95% CI) and p-values with p-values < 0.05 being bolded

and increasing COVID vaccination doses, exhibited changes in risk direction, some with strong magnitude (e.g., anxiety and suicidal behavior), indicating that the aRRs might not be reliable due to high dependence on causal assumptions and lack of agreement on such.

The aRR estimates of COVID duration through the various pDAGs revealed the following variables were consistent with the main pDAG results in terms of direction of risk with variations on the direction and magnitude of the effect: older age, being of Hispanic as well as non-Hispanic black race/ethnicity as compared to non-Hispanic white, female sex, higher education level, pneumonia, hypercholesterolemia, thrombotic events, chronic kidney disease, sleep apnea, depression, bipolar disorder, suicidal behavior, HIV, obesity, and having no recent COVID vaccination as compared to recent COVID vaccination. Conversely, diabetes, hypertension, cardiovascular disease, heart failure, arrhythmia, COPD, chronic liver disease, anxiety, PTSD, marital status, higher average income, history of prior COVID, and both COVID vaccination increasing doses and never having received a COVID vaccination as compared to recent COVID vaccination exhibited changes in risk direction, some with strong magnitude (e.g., anxiety and heart failure), suggesting that the aRRs might not be reliable.

Interaction analyses demonstrated effect modification of the association between vaccination status and prolonged COVID duration, most notably by prior COVID infection. For earlier vaccination, the aRR was 1.04 among participants without prior COVID and 2.03 among those with prior COVID (interaction aRR = 1.95, $p = 3.22 \times 10^{-11}$). For no vaccination, the corresponding aRRs were 0.61 and 1.79 (interaction aRR = 2.94, $p = 1.72 \times 10^{-15}$). Additional interactions were observed for obesity, age, cumulative comorbidities, and vaccination

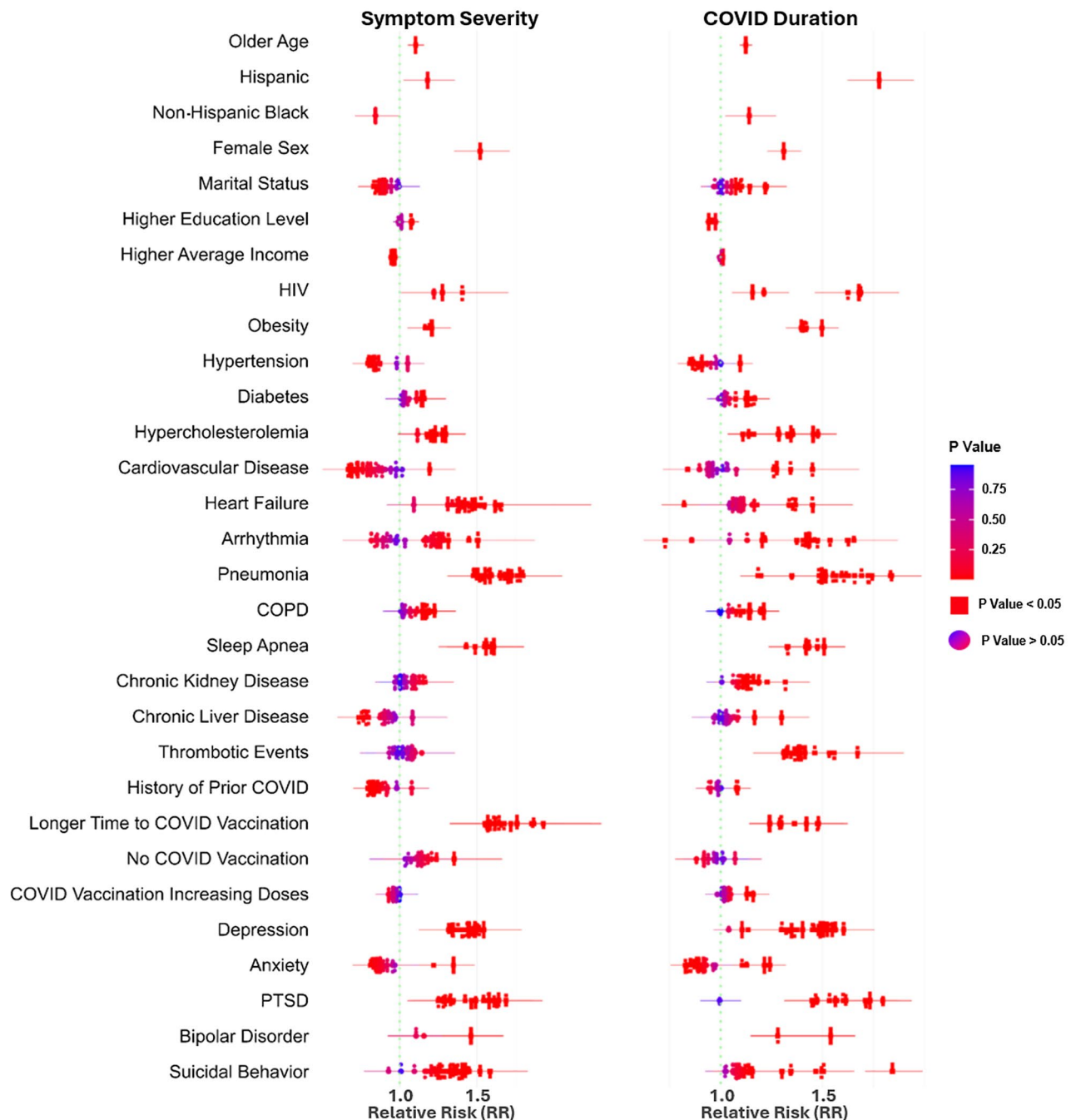


Fig. 4 Distribution of relative risks of covid symptom severity and duration according to sensitivity analysis of variation of causal assumptions. Causality-informed multivariable Poisson regression on COVID severity and duration, showing adjusted relative risks (each variable had its own adjustment set when set as exposure) with 95% CI over all shuffled aRR values and continuous/discrete p-value scale. Multiple points indicate aRR values from pDAG variations (when the causal assumptions were modified) to assess robustness. Alt text: graphical representation of relative risk of COVID symptom severity and duration for individual comorbidities and sociodemographic factors

dose history, further supporting heterogeneity in the association between vaccination status and COVID duration across participant subgroups.

Discussion

The current study includes a cohort of COVID positive adults with a broad range of sociodemographic characteristics and comorbidities exhibiting a wide variance in COVID severity over variable durations of symptoms, with contributing factors to such disparate outcomes being analyzed using a novel robust assessment based on variations of causal assumptions.

Psychiatric comorbidities emerged as a consistent risk cluster associated with increased severity across all timepoints. Depression and bipolar disorder demonstrated strong and stable associations with both COVID severity and duration. The symptom summaries of the participant group with depression were significantly higher at baseline as compared to participants without depression, and the median severity was comparable to or greater than in those without depression at the majority of timepoints (Supplemental Fig. 3). Psychiatric and mental health disorders have been associated with higher rates of hospitalization and COVID related fatality, although findings on depression's contribution to worse COVID outcomes are mixed [22, 23]. The intersection of COVID and mental health is further complicated by the impact of COVID on mental health outcomes and access to mental health resources, particularly among vulnerable patient populations [8, 24–26]. Further investigations are necessary to clarify the potential connection between specific mental health conditions.

Females showed significantly increased burden when compared to males (Supplemental Fig. 4) and being female was associated with higher relative risk of COVID severity and duration. Prior research describes unique presentations and psychosocial factors affecting women during the pandemic that may contribute to the differences by sex [27–29]. Being non-Hispanic black as compared with non-Hispanic white race/ethnicity served as a modest protective variable with lower severity across all variations, while Hispanic ethnicity was a risk factor of higher severity. This is possibly a consequence of the small portion of the study population being non-Hispanic, given the literature indicates that people who are Hispanic and non-Hispanic black experience heightened rates of COVID burden [30, 31].

The finding that aRR estimates for having longer time to COVID vaccination status were consistently associated with prolonged COVID duration, while having no COVID vaccination exhibited risk direction changes for prolonged COVID duration was unexpected, but likely reflects multifactorial biases compounded by the low participation of both unvaccinated individuals and individuals who had a recent COVID vaccination. The interaction analyses suggest that the association between vaccination status and prolonged COVID duration differs across clinically relevant subgroups, particularly according to prior COVID infection history. These findings indicate substantial heterogeneity in the study population and suggest that aggregate estimates may mask important subgroup-specific associations. The few remaining unexpected estimates may reflect sparse data in some vaccination categories, selection mechanisms, and residual confounding inherent to observational studies. Importantly, large-scale studies demonstrate clear vaccine effectiveness against severe disease [32–35], while additionally showing waning protection over time in the absence of additional boosters and consequent neutralizing antibodies [36–39]. Our results therefore highlight the importance of considering time since vaccination and booster status when evaluating vaccine effectiveness in smaller observational cohorts.

This work has some limitations: (1) the sample size was relatively small compared to the number of exposures analyzed, and it is likely that our cohort is skewed due to sampling bias as recruitment occurred in connection with an academic center and the majority of the cohort was female and of Hispanic origin; (2) from a modeling standpoint, the COVID symptom burden score outcome was approximated: some of the previously used cohort study's variables, i.e., RECOVER symptoms of post-exertional malaise, thirst, palpitations, sexual desire, abnormal movements, and hair loss did not match those in this cohort and as such, differential weighting of certain symptoms may introduce bias; (3) the pDAG involved many nodes, causal assumptions, and potentially

unmeasured confounding (even with the usage of doubly edged arrows), and not all possibilities can be tested; (4) the use of MICE as well as the randomization function for parsing the DAG introduce barriers to reproducibility, however, we attempt to mitigate such by including the seed utilized for MICE imputation and all code in the github.

Interpreting how and why the magnitude and direction of causal effects change when modifying the DAG is challenging, as effects that have large variations are more difficult to trust and opposite effects could result from multiple plausible alternative hypotheses, thus exhibiting a bimodal distribution of risks. This is a caveat for all observational studies that apply causal inference methods.

Nonetheless, our framework using pDAG evaluates effects through multiple variations of causal assumptions. It is an effective approach to assess robustness of findings and potentially increase generalizability as all the effects estimated through variations of the pDAG could be summarized in a Bayesian manner (e.g., by setting priors on the pDAGs). Methods that exploit DAG variation and nonlinear estimators for estimation of average effects (e.g., bagged random causal forests) have been proposed and could be applied with this and similar study designs [40].

Conclusions

The results of our work highlight multiple unique aspects of our study. We observed a consistent association between multiple variables - most notably HIV status, female sex, Hispanic ethnicity, and mental health comorbidities - and both increased COVID severity and duration, which persisted throughout resolution of the pDAG arrow directionalities. These results suggest that attention should be paid both in future research and in clinical settings to patients from underrepresented sociodemographic backgrounds, those with relevant mental health comorbidities, PWH, and women, as they may be the most likely to suffer PASC [41].

At a time when COVID continues to pose a threat—particularly to populations experiencing comorbidities, healthcare inequities, and socioeconomic deprivation—it is essential to remain vigilant in monitoring both SARS-CoV-2 and its burden of disease. As SARS-CoV-2 evolves, ongoing surveillance of emerging mutation constellations relevant to viral pathogenicity must be paired with careful tracking of changes in symptom profiles and disease progression. Future work should integrate machine learning analysis in tandem with phylogenetic analysis to understand how changing phylogenetic dynamics of SARS-CoV-2 reflect changes related to COVID severity and duration, with the goal of informing interventions to mitigate disease severity and reduce the burden of PASC.

Abbreviations

COVID	Coronavirus Disease 2019
PASC	Post-acute sequelae of COVID
ACTION	A Comprehensive Translational Initiative on Novel Coronavirus
IQR	Interquartile range
RR	Relative risk
aRR	adjusted relative risk
CI	95% confidence intervals
pDAG	partially directed acyclic graph
PWH	People living with HIV

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Author contributions Bassett: Carried out analysis, drafted original manuscript and edited all versions of the manuscript. Alcaide: Contributions to conceptualization, methodology, investigation, and reviewing and editing the manuscript (MPI). Kaminsky: Contributions to investigation (conducting study visits and reviewing medical records for data collection) and to writing the original draft of the manuscript. Prosperi: Contributions to conceptualization, methodology, analysis, and writing, reviewing, and editing the manuscript. Collin: Contributions to analysis and to writing the original draft of the manuscript. Fernandez: Contributions to writing the first draft of the manuscript. Cherenack: Contributed to writing the first draft of the manuscript and reviewing and editing later versions. Marini: Contributions to methodology and analysis. Acosta: contributions to investigation/methodology (the main study coordinator) and contributed to reviewing and editing the manuscript. Laine: contributions to investigation/methodology (the main study coordinator) and contributed to reviewing and editing the manuscript. Beardsley: Contributions to analysis. Cash: Contributions to editing and reviewing the manuscript. Alvarado: contributions to methodology and to writing and editing the first draft of the manuscript. Sosa: Contributions to writing the first draft of the manuscript. Meyer: Contributions to writing the first draft of the manuscript. Mavian: Contributions to conceptualization and editing first draft of the manuscript. Raccamarich: Contributions to methodology and investigation (study project manager) and reviewed and edited manuscript. Stevenson: Contributions to conceptualization, methodology, and investigation (overseeing sample processing and shipment). Salemi: Contributions to conceptualization, methodology, investigation, and reviewing the manuscript. Jones: Contributions to conceptualization, methodology, investigation, and reviewing and editing the manuscript (MPI)-psychosocial perspectives.

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Data availability The datasets collected during the study as well as the corresponding analyzed data and relevant code are available at the following GitHub repository: [https://github.com/salemilab/ACTION_metadata].

Declarations

Ethics approval and consent to participate This study was approved by the University of Miami Institutional Review Board (#20200340). All participants provided written informed consent prior to enrolling in the study and undergoing any study related activities. We also obtained permission from the medical providers and hospitals prior to visiting participants recruited on in-patient hospital units.

Human ethics and consent to participate This study includes human participants, and written informed consent was obtained prior to all study activities. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the University of Miami Institutional Review Board (#20200340).

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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