Factors Associated with Longitudinal Psychological and Physiological Stress in Health Care Workers During the COVID-19 Pandemic: Observational Study

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Submitted to: Journal of Medical Internet Research
on: June 16, 2021

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Abstract

Background: The Coronavirus Disease 2019 (COVID-19) pandemic has resulted in a high degree of psychological distress in health care workers (HCWs). There is a need to characterize which HCWs are at an increased risk of developing psychological sequela from the pandemic.

Objective: In the current study the objectives were to determine characteristics associated with longitudinal perceived stress in HCWs and to determine whether changes in heart rate variability (HRV), a measure of autonomic nervous system (ANS) function, associate with features protective against longitudinal stress.

Methods: HCWs across seven hospitals in New York City (NYC) were prospectively followed in an ongoing observational digital study using the custom Warrior Watch Study App. Participants wore an Apple Watch for the duration of the study measuring HRV throughout the follow up period. Surveys measuring perceived stress, resilience, emotional support, quality of life, and optimism were collected at baseline and longitudinally.

Results: Three hundred and sixty-one participants (mean [SD] age, 36.8 [10.1] years; 246 [69.3%] female) were enrolled. Multivariate analysis found NYC COVID-19 case count to be associated with increased longitudinal stress (P=0.008). Baseline emotional support, quality of life and resilience were associated with decreased longitudinal stress (P <0.001). A significant reduction in stress during the 4-week period after COVID-19 diagnosis was observed in the highest tertial of emotional support (P =0.03) and resilience (P =0.006). Participants in the highest tertial of baseline emotional support and resilience had significantly reduced amplitude and acrophase of the circadian pattern of longitudinally collected HRV.

Conclusions: High resilience, emotional support, and quality of life place HCWs at reduced risk of longitudinal perceived stress and have a distinct physiological stress profile. Our findings support the use of these characteristics to identify HCWs at risk of the psychological and physiological stress effects of the pandemic.

(JMIR Preprints 16/06/2021:31295)
DOI: https://doi.org/10.2196/preprints.31295

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Author Contributions: RPH, MD, GN, ZAF developed the study concept. RPH assisted with the drafting of the manuscript. RPH MD, LT, KHC, MZ, EG, SK, DH, AB, RP, CC, RMF, BES, DC, EPB, JWM, LK, MSF, GNN, ZAF critically revised the manuscript for important intellectual content. RPH MD, LT, KHC, MZ, EG, SK, DH, AB, RP, CC, RMF, BES, DC, EPB, JWM, LK, MSF, GNN, ZAF provided final approval of the version of the manuscript to be published and agree to be accountable for all aspects of the work. All authors approve the authorship list. All authors had full access to all the data in the manuscript and had final responsibility for the decision to submit for publication. RPH, ZAF, MSF, MD, and LT have verified the underlying data.

Journal: JMIR
Paper Type: Article
Word Count: 3000
Tables and Figures: 2 Figures, 3 Tables, 1 Supplementary Figure, 3 Supplementary Tables

ABSTRACT:

Background: The Coronavirus Disease 2019 (COVID-19) pandemic has resulted in a high degree of psychological distress in health care workers (HCWs). There is a need to characterize which HCWs are at an increased risk of developing psychological effects from the pandemic. Given differences in the response of individuals to stress, evaluation of both the perceived and physiological consequence of stressors provides a comprehensive evaluation of its impact.

Objective: In the current study the objectives were to determine characteristics associated with longitudinal perceived stress in HCWs and to determine whether changes in heart rate variability (HRV), a marker of autonomic nervous system (ANS) function, associate with features protective against longitudinal stress.

Methods: HCWs across seven hospitals in New York City (NYC) were prospectively followed in an ongoing observational digital study using the custom Warrior Watch Study App. Participants wore an Apple Watch for the duration of the study measuring HRV throughout the follow up period. Surveys measuring perceived stress, resilience, emotional support, quality of life, and optimism were collected at baseline and longitudinally.

Results: Three hundred and sixty-one participants (mean [SD] age, 36.8 [10.1] years; 246 [69.3%] female) were enrolled. Multivariate analysis found NYC COVID-19 case count to be associated with increased longitudinal stress (*P*=0.008). Baseline emotional support, quality of life and resilience were associated with decreased longitudinal stress (*P* <0.001). A significant reduction in stress during the 4-week period after COVID-19 diagnosis was observed in the highest tertial of emotional support (*P* =0.03) and resilience (*P* =0.006). Participants in the highest tertial of baseline emotional support and resilience had a significantly different circadian pattern of longitudinally collected HRV compared to subjects in the low or medium tertial.

Conclusions: High resilience, emotional support, and quality of life place HCWs at reduced risk of longitudinal perceived stress and have a distinct physiological stress profile. Our findings support the use of these characteristics to identify HCWs at risk of the psychological and physiological stress effects of the pandemic.

Keywords: Wearable Device; COVID-19; Stress; Heart Rate Variability; Psychological

INTRODUCTION

Increasing rates of SARS-CoV2 infections and hospitalizations, growing workloads, and concern regarding personal protective equipment have resulted in a large psychological burden on health care workers (HCWs).[1] Prior pandemics' have had psychological effects on HCWs, increasing post-traumatic stress, depression and anxiety.[1-3] However, the scale and duration of the Corona Virus Disease 2019 (COVID-19) pandemic further amplifies the risk of these adverse outcomes. Cross sectional studies have demonstrated that front line HCWs are at a high risk of depression, anxiety, insomnia and distress compared to the general population.[4-6] HCWs on wards serving patients with COVID-19 reported higher levels of stress, exhaustion, depressive mood and burnout.[7, 8] However, there is limited longitudinal data on the pandemics' psychological impact on this group, limited data across health care occupations, no means to identify which HCWs are at risk of developing psychological sequela over time, and no objective evaluation of the stress response in HCWs. Identification of at risk HCWs will allow for appropriate allocation of mental health resources.

Advances in digital technology provide a means to address these limitations. Smart phone Apps can administer surveys and integrate wearable devices, such as the Apple Watch, to monitor the autonomic nervous system (ANS), a primary component of the stress response. ANS function can be ascertained through measurement of heart rate variability (HRV), a measure of the parasympathetic and sympathetic nervous systems impact on cardiac contractility through calculation of changes in the beat to beat intervals.[9] Systems such as the ANS promote adaption to stressors. However, the cumulative burden of stress, or allostatic load, can alter and impair the response of these systems and result in deleterious physical effects on processes ranging from immune function to cardiovascular health. Given large differences in the response of individuals to stress, evaluation of both the perceived and physiological consequence of the stressor provides a more comprehensive evaluation of its impact and an understanding of who is at risk from the deleterious physical effects of chronic stress.[10] In response to the COVID-19 pandemic we launched the Warrior Watch Study, comprised of our custom iOS App which integrates survey metrics with physiological signatures acquired from the Apple Watch. The aim of the study was to understand the longitudinal perceived and physiological stress response in HCWs through the course of the pandemic.

METHODS

Study Design

This was an observational cohort study. The primary objective of the study was to identify characteristics associated with longitudinal stress in HCWs. The secondary aim was to determine whether changes in HRV associate with features protective against longitudinal stress development. HCWs across 7 hospitals in NYC (The Mount Sinai Hospital, Morningside Hospital, Mount Sinai West, Mount Sinai Beth Israel, Mount Sinai Queens, New York Eye and Ear Infirmary, Mount Sinai Brooklyn) were eligible. Participants had to be current employees of one of the participating hospitals, ≥18 years of age, have an iPhone Series 6 or higher and be willing to wear an Apple Watch Series 4 or higher. An underlying autoimmune disease or the use of medications that interfere with ANS function were exclusionary. This study was approved by the institutional review board at Mount Sinai. Informed consent was obtained from all participants.

Study Procedures

Participants downloaded the custom Warrior Watch Study App to their iPhones and completed eligibility questions prior to signing electronic consent. Through the Warrior Watch App, surveys were completed at enrollment and then longitudinally throughout the course of the study. At enrollment demographic information and whether subjects had a diagnosis of anxiety or depression were collected. Psychological well-being was assessed through structured surveys evaluating perceived stress (Perceived Stress Scale- 4 [PSS-

4])[11], resilience (Connor-Davidson Resilience Scale-2 [CD-RISC-2])[12], emotional support (2-item Patient-Reported Outcomes Measurement Information System [PROMIS] questionnaire)[13], quality of life (2-item Global Health and Quality of Life [QOL])[14], and optimism (Life Orientation Test)[15] (**Supplementary Table 1**). Diagnosis of COVID-19 was defined as a positive SARS-CoV-2 nasal PCR swab reported by a study subject.

To longitudinally evaluate subjects, daily surveys were administrated via the study App to collect COVID-19 related symptoms and severity, degree of COVID-19 exposure at work, types of patient care at work, whether participants left their home each day, if public transportation was used, the number of people that participants interact with each day, the results of any COVID-19 nasal PCR or antibody tests, whether the subject was quarantined, if childcare needs were required and if the subject was hospitalized. To enable trending of psychological well-being, subjects were prompted to complete the PSS-4 and 2-item General Health and QOL survey weekly. Participants were instructed to wear the Apple Watch for at least 8 hours per day throughout the study period.

Outcome Measures, Instrumentation, and the Wearable Device

HRV, a physiological marker of stress, was collected via the Apple Watch, while subjective outcome measures were assessed through standardized surveys. The Apple Watch Series 4 or 5 was worn by subjects on the wrist to capture HRV and was connected via blue tooth to the participants iPhone. A photoplethysmogram (PPG) sensor on the Apple Watch pairs a green LED light with a light sensitive photodiode to generate time series peaks.[16] The Apple Watch and Apple Health app calculates HRV using the standard deviation of NN intervals (SDNN) from the time differences between heart beats, categorized as the Interbeat Interval. SDNN is a time domain index reflecting sympathetic and parasympathetic nervous system activity.[9] This is recorded by the Apple Watch during approximately 60 second recording periods (ultra-short period). Ultra-short term analyses of HRV can be reliably performed for monitoring mental health.[17] In accordance with current HRV guidelines we did not compare SDNN values obtained from recordings of different duration and we used one measuring device (Apple Watch) to assure standardization of the equipment.[18]

The PSS-4 measures perceived stress. It is a four-question survey that is scored from 0-16. Higher scores correlate with elevated perceived stress. The scale evaluates an individual’s confidence in handling problems, whether individuals feel difficulties are piling up, whether things are felt to be going in the way of the individual, and one's sense of control.[11]

The CD-RISC-2 measures resilience. It is a 10-question survey that is scored up to 40 points, with higher scores correlating to higher resilience. It includes questions about coping, bouncing back from adversity, whether an individual gets discouraged, and adaptation to change.[12]

The 2-item emotional support PROMIS questionnaire is a 2-question survey enquiring about whether individuals have someone to listen to them when they need to talk and someone they trust to discuss their feelings with. It is scored on a scale from 2-10 points.[13]

The 2-item Global Health and QOL questionnaire asks individuals to grade how their health and quality of life are in general, with higher scores correlating with lower health and QOL.[14]

The Life Orientation Test assess subject optimism. It is comprised of 6 questions that asks individuals whether he or she expect the best in uncertain times, whether he or she expects things to go wrong, and whether more good is expected to happen compared to bad.[15]

Statistical Analysis

Survey Analyses

To account for gaps created by unanswered weekly surveys and allow comparison for each patient, we created a chronological variable called a 'period'. To account for participants having different time windows between each weekly survey, a period was assigned to each weekly survey according to participants' starting and ending date. When a participant's survey was completed less than 7 days from their previous survey date, the day after the previous survey date was regarded as the starting window date for the next period. When a participant's survey was done 7 days or more apart from the previous survey date, the starting window date was set to 6 days prior to the current survey date. To integrate weekly psychological metrics and daily risk/health metrics, results of the daily surveys were summarized by the periods defined by the weekly surveys. Daily survey data was summarized for each period, eg: mean number of risk days per period, mean number of days left home per period. To examine associations between the NYC COVID-19 case-count and perceived stress raw NYC case-count data was obtained and summarized as a mean case-count per period.[19]

Occupation Classification

The occupation of each participant was collected at enrollment. Due to the pandemic, the roles and responsibilities of these occupations may have changed when compared to non-pandemic job descriptions. We therefore created a new occupation metric to identify which participants were seeing patients during the study. Occupation was calculated as follows: 1) Daily clinical occupation was calculated from the daily survey where participants classified the type of patient or non-patient care responsibilities that day. Those who reported either (a) exposure to patient areas but without patients diagnosed with or being evaluated for COVID-19, or (b) exposure to areas with patients confirmed to have COVID-19 or being investigated for COVID-19 infection, were assigned as clinical for that day. Those who responded they were at work but not caring for patients or those who were working remotely were classified as non-clinical for that day. 2) If a participant had one or more clinical days in a period, that participant is assigned as clinical for that period. 3) If a participant has one or more clinical periods over the entire study, then they are deemed as either clinical non-trainee or clinical trainee. To be classified as a clinical trainee a participant had to be either a resident or fellow. All other occupations were classified as staff.

Statistical Modeling

To model longitudinal changes in stress, we used linear mixed-effect models. Fixed effects included time invariant covariates (gender, age, occupation, baseline resilience, optimism and quality of life) and time variant covariates (COVID-19 diagnosis, SARS COVID-19 antibody positive test, mobility variables). A continuous First Order Autoregressive correlation structure (over period) was found to be suitable to our data significantly increasing the likelihood function (LRT $P<0.001$) and leading to minimal Akaiki information criterion (AIC)/Bayesian information criterion (BIC). Model coefficients were estimated using a restricted maximum likelihood approach (REML) method using R's *nlme* packages. Hypothesis of interest were tested using contrasts through the capabilities of the *emmeans* package.

Univariate models tested the association of each variable with longitudinal stress and identified associated factors. Variables with *P*<0.10 in the marginal ANOVA test were considered significant and included in the multivariate analysis. Although in univariate models random effects include only the intercept, in multivariate models, a random effect for the NYC case burden was found to be significant (LRT<0.001), indicating heterogeneity in the association of this variable with stress across subjects.

Heart Rate Variability Modelling

HRV captured from the Apple Watch demonstrated a sparse non-uniform sampling and circadian pattern making it amenable to analysis via a COSINOR model. This approach models the daily HRV circadian rhythm over a period of 24 hours which can be described using the circadian parameters: (1) Midline Statistic of Rhythm (MESOR), a rhythm-adjusted mean, (2) amplitude, a measure of half the extent of variation within a day, and (3) acrophase, measure of the time of overall high values recurring in each day. This allows testing of the effect that model covariates have on HRV. A COSINOR model used the non-linear function $Y(t) = M + A\cos ¿\, t/\tau + \phi) + e_i(t)$, where τ is the period (τ =24h), M is the MESOR, A is the amplitude and Φ is the Acrophase. This can be transformed into the linear model $x = \sin(2\pi t/\tau), z = \sin ¿\, t/\tau)$, with HRV written as $Y(t) = M + \beta x t + \gamma z t + e_i(t)$. We identified a subject specific daily pattern measuring departures from this pattern as a function of emotional support, resilience, and other covariates of interest. Utilizing a mixed effect COSINOR model HRV, the introduction of random effects intrinsically models the correlation due to the longitudinal sampling. Covariates, C, were introduced as fixed effects using the equation $HRV_{it} = M + a_0 C_i + ¿_2 C_i ¿ . x it + ¿_3 C_i . ¿ z it + W_{it} . \theta_i + e_i(t)$. As we have described previously to test if the COSINOR curve differs between two populations of interest we performed the bootstrapping procedure where for each iteration we (1) fit a linear mixed-effect model using REWL (2) estimated the marginal means for each group defined by a covariate (3) estimated marginal means for each group using the inverse relationship, and (4) defined the bootstrapping statistics as a pairwise difference between groups.[20] COSINOR models were used to estimate HRV MESOR, amplitude and acrophase for participants based on emotional support and resilience tertials (low, medium and high). COSINOR model covariates included time, gender, age, BMI, baseline emotional support, baseline resilience, optimism and stress, with the participant serving as a random intercept.

RESULTS

Three hundred sixty-one HCWs were enrolled in this ongoing observational study between April 29th and September 29th, 2020, when data was censored for analysis (**Table 1**). Occupations were classified as (1) clinical non-trainees: participants who reported caring for a patient on any daily survey and not a resident or fellow, (2) clinical trainee: a resident or fellow, (3) staff: participants who did not report caring for patients on a daily survey. Participants had a mean age of 37 years, were 69.3% female and were followed for a mean of 60 days (IQR 21-98 days). Clinical trainees had higher baseline resilience, compared to clinical non-trainees (*P*=0.03) and staff (*P*=0.01), higher optimism (*P*=0.04) and emotional support (*P*=0.01) compared to staff, and higher emotional support compared to clinical non-trainees (*P*=0.01) (**Supplementary Table 2**).

Factors Associated with Longitudinal Stress

The primary aim of the study was to assess the factors associated with longitudinal perceived stress. Univariate analysis evaluated the relationship between baseline demographics and prospectively collected survey metrics with longitudinal perceived stress (**Table 2**). Baseline factors including resilience, optimism, emotional support, quality of life, male gender, and age were significantly associated with lower longitudinal stress. Baseline anxiety/depression, body mass index (BMI), weight, and asthma were significantly associated with increased longitudinal stress. Longitudinal quality of life (*P* <0.001) was associated with reduced longitudinal stress, while the mean number of COVID-19 cases in NYC (*P*=0.004) was positively associated with increased longitudinal stress. Occupation classification (staff vs clinical non-trainee, *P*=0.81; staff vs clinical trainee, *P*=0.15; clinical non-trainee vs clinical trainee, *P*=0.17), mean number of days caring for patients (*P*=0.88) and treatment of patients with COVID-19 (*P*=0.73) were not associated with longitudinal stress. We observed a significant reduction of stress during the 4-week period following diagnosis (*P*=0.014) and over the follow up period (*P*=0.04). Multivariable analysis found only NYC COVID-19 case count to be significantly associated with increased longitudinal stress (*P*=0.008). The drop in stress during the 4-week period following COVID-19 diagnosis was not significant (*P*=0.23), however we noted a borderline significant increase in stress following the 4-week period after a COVID-19 diagnosis (*P*=0.05). Baseline emotional support, baseline quality of life and baseline resilience were associated with decreased longitudinal stress (*P*<0.001) (**Figure 1**).

NYC COVID-19 case count and the 4-week period after a COVID-19 diagnosis via nasal PCR were further explored in the context of emotional support and resilience. Participants were stratified into emotional support tertials (low, medium, high). A significant reduction in stress during the 4-week period after COVID-19 diagnosis occurred only in participants in the highest tertial of emotional support (effect estimate -0.97, *P*=0.03), but not in the medium (effect estimate -0.62, *P*=0.48), and low tertials (effect estimate 0.08, *P*=0.93) (**Supplementary Figure 1A**). A significant trend between COVID-19 case count in NYC and longitudinal stress was observed only in the high tertial emotional support group (estimate 1.22, *P*=0.005), not in the low (estimate -1.45, *P*=0.26) or medium (estimate 0.98, *P*=0.16) tertials (**Supplementary Figure 1b**). Stratification of the cohort into tertials for resilience demonstrated a significant reduction in stress during the 4-week period after COVID-19 diagnosis via nasal PCR in the high (estimate -1.78, *P*=0.006) but not medium (estimate 0.33, *P*=0.64) and low tertials (estimate -0.60, *P*=0.25) (**Supplementary Figure 1c**). The impact of COVID-19 case counts in NYC demonstrated a borderline significant relationship with stress in the medium (estimate 1.29, *P*=0.098) and high (estimate 1.14, *P*=0.09), but not in the low resilience group (estimate 0.72, *P*=0.21) (**Supplementary Figure 1d**).

Physiological Stress Response

Our secondary aim of the study was to evaluate whether features that buffer against perceived stress result in physiological differences in the stress response of HCWs. We fit a COSINOR model evaluating differences in HRV (SDNN) (**Supplementary Table 3**). Significant reduction in the amplitude of the circadian pattern of SDNN was observed between participants with high compared to medium (*P*<0.001) and low (*P*=.008) emotional support (**Figure 2a and 2b**). There was a significant reduction in the acrophase of the circadian pattern of SDNN in participants with high emotional support compared to those with medium (*P*<0.001) and low (*P*=0.004) emotional support. Significant changes in the circadian pattern of SDNN was also observed when the cohort was stratified based on baseline resilience (**Figure 2c and 2d**). The amplitude of the circadian pattern of SDNN was significantly lower in subjects with high resilience compared to those with low (*P*<0.001) and medium (*P*<0.001) resilience. Similarly, the acrophase of participants with high resilience was significantly reduced compared to those with medium (*P*<0.001) and low (*P*=0.048) resilience (**Table 3**).

DISCUSSION

Principal Results and Comparison with Prior Work

In summary, to the best of our knowledge, we conducted the first study identifying HCW characteristics that correlate with longitudinal stress during the COVID-19 pandemic and identify employees at risk of psychological sequela. We found worsening longitudinal stress is associated with the number of COVID-19 cases in the community, highlighting the effect of the environmental stressor. Baseline emotional support, resilience and quality of life defined which HCWs were prone to perceived longitudinal stress, not occupation class, and characterized a unique ANS stress profile.

In line with our findings, prior work shows that emotional support and resilience buffer against stress.[21, 22] Resilience, defined as a reduced vulnerability to environmental stressors and the ability to overcome difficulty, is crucial to establishing social relationships and is tied to social support, which also acts as an environmental protective factor against adversity.[23-25] In addition to demonstrating their stress protective effect in multivariate analysis, when we further evaluated NYC COVID-19 case count, a factor associated with longitudinal stress over time, we again found that those with lower emotional support or resilience were vulnerable with a dynamic stress response uncoupled from the environmental COVID-19 stressor. Similarly, the transient reduction in stress that occurs after a COVID-19 diagnosis only occurs in those with high emotional support and resilience. Importantly, these latter findings highlight how high resilience or high emotional support can minimize the impact of factors associated with longitudinal stress in HCWs.

A strength of our study is the objective assessment of this observation through longitudinal HRV measurements. HRV is a marker of physiological stress on the ANS. Repeated stressors that are felt to be unmanageable and overwhelming may lead to an impaired stress response characterized by altered autonomic and hypothalamic-pituitary-adrenal axis function.[26, 27] Buffers to stress, such as resilience, have also been shown to be impact ANS function and are associated with an activation of the sympathetic nervous system that is sufficient to respond to a stressor but not to a degree that results in the development of negative psychological effects.[19,] Resilience has been shown to moderate the relationship between perceived stress and the hypothalamic pituitary adrenal axis, which acts as a primary mediator of the physiological stress response.[28] Studies evaluating resilience have demonstrated an associated characteristic ANS profile, with higher vagal indices and with a baseline sympathovagal balance shifted toward parasympathetic predominance.[27, 29] Resilience has been associated with modulation of sympathetic nervous system activation allowing for an adequate response to a stressor but with moderation of the degree of activation and the rapidity of its return to baseline. This allows for a stable emotional response and reduced chronic anxiety.[27, 30, 31] Our findings extend these observations into HCWs during the COVID-19 pandemic. We found that buffers of stress, such as high resilience or high emotional support, were characterized by a physiologically distinct ANS profile confirming their impact on how individuals respond to stressors. These findings substantiate the effect these features have on longitudinal stress in HCWs in multiple dimensions, reaffirming their importance not only in the perception of stress but also in how HCWs are physiologically affected by the COVID-19 pandemic stressor.

Our findings have implications for how HCWs can be assessed for the pandemic's detrimental psychological effects, through screening for an individual's degree of resilience and social support. Evaluation of these characteristics will assist health care institutions in allocating often limited psychological support services to at-risk individuals. Importantly, one of these features, resilience, is modifiable through targeted interventions. This provides an opportunity to build resilience in HCWs who are found to have low resilience. While further studies are needed on the impact of such interventions in HCWs, they may mitigate the physiological impact of longitudinal stress. Several resilience building interventions have demonstrated to be effective in HCWs,[32, 33] however, our findings linking HRV alterations with degree of resilience, makes HRV focused resilience building exercises an attractive option.[34]

Strengths and Limitations

Strengths of the study are its multicenter longitudinal study design. Furthermore, the number and type of longitudinal variables we capture allows for a robust multivariate analysis. Lastly, the incorporation of ANS parameters provide an objective assessment of the stress response. However, there are several limitations to our study. The Apple Watch provides HRV data in one-time dimension (SDNN) limiting evaluation of other metrics with outcomes of interests. The Apple Watch also provides HRV sampling sporadically throughout the day. While our modelling accounts for this, a denser sampling would allow expanded analyses. Additionally, HRV can be impacted by many environmental factors which cannot be fully accounted for in such studies. While we tried to control for relevant covariates, there is the potential for unmeasured factors to impact our results.

Conclusions

We identified features associated with longitudinal perceived stress in HCWs during the COVID-19 pandemic. NYC COVID-19 case count was significantly associated with increased longitudinal perceive stress and baseline emotional support, quality of life and resilience were associated with decreased longitudinal perceived stress. Furthermore, high resilience and high social support impacted the physiological stress response and were associated with a unique autonomic nervous system profile. This demonstrates the importance of resilience and social support on both perception of stress and its physiological impact.

Acknowledgments:

Support for this study was provided by the Ehrenkranz Lab For Human Resilience, the BioMedical Engineering and Imaging Institute, The Hasso Plattner Institute for Digital Health at Mount Sinai, The Mount Sinai Clinical Intelligence Center and The Dr. Henry D. Janowitz Division of Gastroenterology.

Conflicts of Interest:

RPH declares consulting fees from HealthMode,Inc, Janssen Pharmaceuticals, Takeda Pharmaceuticals. Research support from Intralytix Inc. and a Crohn's and Colitis Foundation Career Development Award (grant number 607934).

MD declares no competing interests.

LT declares no competing interests.

KHC declares no competing interests.

MZ declares no competing interests.

EG declares no competing interests.

SK declares no competing interests.

DH declares no competing interests.

AB declares no competing interests.

RP declares no competing interests.

CC declares no competing interests.

RMF declares no competing interests.

BES declares no competing interests.

DC is co-inventor on patents filed by the Icahn School of Medicine at Mount Sinai (ISMMS) relating to the treatment for treatment-resistant depression, suicidal ideation and other disorders. ISMMS has entered into a licensing agreement with Janssen Pharmaceuticals, Inc. and it has and will receive payments from Janssen under the license agreement related to these patents for the treatment of treatment-resistant depression and suicidal ideation. Consistent with the ISMMS Faculty Handbook (the medical school policy), Dr. Charney is entitled to a portion of the payments received by the ISMMS. Since SPRAVATO has received regulatory approval for treatment-resistant depression, ISMMS and thus, through the ISMMS, Dr. Charney, will be entitled to additional payments, beyond those already received, under the license agreement. Dr. Charney is a named co-inventor on several patents filed by ISMMS for a cognitive training intervention to treat depression and related psychiatric disorders. The ISMMS has entered into a licensing agreement with Click Therapeutics, Inc. and has and will receive payments related to the use of this cognitive training intervention for the treatment of psychiatric disorders. In accordance with the ISMMS Faculty Handbook, Dr. Charney has received a portion of these payments and is entitled to a portion of any additional payments that the medical school might receive from this license with Click Therapeutics. Dr. Charney is a named co-inventor on a patent application filed by the ISMMS for the use of intranasally administered Neuropeptide Y (NPY) for the treatment of mood and anxiety disorders. This intellectual property has not been licensed. Dr. Charney is a named co-inventor on a patent application in the US, and several issued patents outside the US filed by the ISMMS related to the use of ketamine for the treatment of post-traumatic stress disorder (PTSD). This intellectual property has not been licensed.

JWM declares no competing interests.

E.P. Bottinger reports consultancy agreements with Deloitte and Roland Berger; ownership interest in Digital Medicine E.Böttinger GmbH, EBCW GmbH, and Ontomics, Inc.; receiving honoraria from Bayer, Bosch Health Campus, Sanofi, and Siemens; and serving as a scientific advisor or member of Bosch Health Campus and Seer Biosciences Inc

LK declares research funding from Abbvie and Pfizer, consulting for Abbvie and Pfizer, equity ownership/stock options MetaMe Health, Trellus Health MSF declares no competing interests.

MSF declares no competing interests.

G.N. Nadkarni reports employment with, consultancy agreements with, and ownership interest in Pensieve Health and Renalytix AI; receiving consulting fees from AstraZeneca, BioVie, GLG Consulting, and Reata; and serving as a scientific advisor or member of Pensieve Health and Renalytix AI.

ZAF discloses consulting fees from Alexion, GlaxoSmithKline and Trained Therapeutix Discovery; Research funding from Daiichi Sankyo; Amgen; Bristol Myers Squibb; Siemens Healthineers. ZAF receives financial compensation as a board member and advisor to Trained Therapeutix Discovery and owns equity in Trained Therapeutix Discovery as co-founder.

Abbreviations

AIC: Akaiki information criterion
ANS: Autonomic Nervous System
COVID-19: Corona Virus Disease 2019
HCWs: Health Care Workers
HRV: Heart Rate Variability
MESOR: Midline Statistic of Rhythm
NYC: New York City
PSS-4: Perceived Stress Scale- 4
CD-RISC-2: Connor-Davidson Resilience Scale-2
PPG: Photoplethysmogram
PROMIS: Patient-Reported Outcomes Measurement Information System
QOL: Quality of Life
REML: restricted maximum likelihood approach
SDNN: standard deviation of NN intervals

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Figure 1. Multivariate analysis of factors associated with longitudinal stress. The scatter plot shows estimated coefficients (±confidence intervals) for variables used in the multivariate analysis. Stars indicate that variable has significant (*P*<0.05) association with longitudinal stress while crosses indicate a borderline significant relationship (*P*<0.10). Positive association is indicated in blue, negative association in red.

Figure 2. Exploring the relationship between HRV, emotional support and resilience. Plots (A, C) show mean (± 95% Confidence Intervals) HRV MESOR, Amplitude and Acrophase for participants with low, medium and high emotional support (A) or resilience (C). Stars indicate significant differences between groups. Plots (B, D) show average daily circadian HRV rhythm for participants with low, medium and high emotional support (B) or resilience (D). (+*P*<0.1, * *P*<0.05, ** *P*<0.01, *** *P*<0.001).

Table 1. Baseline demographic characteristics of the total cohort and by occupation category.

	Total Cohort (n=361)	**Staff (n=65)**	**Clinical Non-Trainee (n=217)**	**Clinical Trainee (n=40)**
Age, mean (SD)	36.8 (10.1)	36.5 (11.0)	37.8 (10.4)	31.1 (3.6)
Body Mass Index, mean (SD)	25.7 (5.8)			
Female Gender (%)	246 (69.3)	43 (66.2)	158 (73.8)	20 (51.3)
Race (%)				
Asian	90 (24.9)	14 (21.5)	49 (22.6)	14 (35.0)
Black	33 (9.1)	3 (4.6)	23 (10.6)	4 (10.0)
Other	47 (13.0)	7 (10.8)	31 (14.3)	6 (15.0)
White	132 (36.6)	26 (40.0)	80 (36.9)	15 (37.5)
Ethnicity (%)				
Hispanic	59 (16.3)	15 (23.1)	34 (15.7)	1 (2.5)
Baseline Positive SARS-CoV-2 nasal PCR (%)	22 (6.1)	2 (3.1)	16 (7.4)	2 (5.0)
Baseline Positive SARS-CoV-2 serum antibody (%)	35 (9.7)	6 (9.2)	22 (10.1)	2 (5.0)
Baseline Smoking Status (%)				
Current/Past smoker	48 (13.5)	10 (15.4)	31 (14.5)	0 (0.0)
Never/Rarely smoker	307 (86.5)	55 (84.6)	183 (85.5)	39 (100.0)
Baseline Immune Suppressing Medication (%)	4 (1.4)	0 (0.0)	4 (1.9)	0 (0.0)
Anxiety or Depression	73 (20.6)	16 (24.6)	43 (20.1)	7 (17.9)
Baseline Survey Metrics, mean (SD)				
PSS-4	5.3 (3.1)	5.3 (3.1)	5.5 (2.9)	5.4 (3.1)
CD-RISC	5.7 (1.4)	5.4 (1.5)	5.7 (1.4)	6.2 (1.3)
Optimism	19.1 (4.2)	18.4 (4.3)	18.8 (4.2)	20.1 (3.7)
Emotional Support	6.8 (1.5)	6.7 (1.7)	6.8 (1.5)	7.6 (0.9)
Quality of Life	7.8 (1.5)	7.5 (1.4)	7.8 (1.4)	8.0 (1.5)
Baseline Medical Conditions				
Asthma	41 (11.4)	13 (20)	19 (8.8)	5 (12.5)
Chronic Lung Disease	1 (0.3)	0 (0.0)	0 (0.0)	1 (2.5)
Heart Disease	1 (0.3)	1 (1.5)	0 (0.0)	0 (0.0)

Cancer	2 (0.6)	0 (0.0)	2 (0.9)	0 (0.0)
Diabetes Mellitus	6 (1.7)	2 (3.1)	4 (1.8)	0 (0.0)
Hypertension	20 (5.5)	5 (7.7)	11 (5.1)	0 (0.0)
Pneumonia	7 (1.9)	1 (1.5)	5 (2.3)	1 (2.5)

Table 2. Univariate analysis of factors associated with longitudinal perceived stress.

	Effect Estimate	**P value**
Baseline Resilience	-0.84	<0.001
Baseline Optimism	-0.34	<0.001
Baseline Emotional Support	-0.62	<0.001
Baseline Quality of Life	-0.71	<0.001
Longitudinal Quality of Life	-0.80	<0.001
Baseline Anxiety/Depression	1.27	<0.001
Baseline Body Mass Index	0.07	0.001
Male Gender	-0.94	0.002
Mean New York City Case Count Per Period	0.82	0.004
No Positive Corona Virus Nasal PCR at Baseline	0.91	0.114
2 Week Period Post Positive Corona Virus Nasal PCR	-0.18	0.615
4 Week Period Post Positive Corona Virus Nasal PCR	-0.82	0.014
2 Week Period Post Positive Corona Virus Antibody	-0.36	0.191
4 Week Period Post Positive Corona Virus Antibody	-0.10	0.71
Any Period Post Positive Corona Virus Nasal PCR	-0.85	0.04
2 Week Period Post Positive Corona Virus PCR or Antibody	-0.25	0.28
Any Period Post Positive Corona Virus Antibody	-0.26	0.36
Weight	0.02	0.04
Age	-0.03	0.047
Baseline Asthma	0.89	0.045
Baseline Heart Disease	3.37	0.186
Baseline Hypertension	-0.34	0.58
Baseline Diabetes	-0.20	0.85
Mean Symptomatic Days Per Period	0.32	0.07
Staff vs Clinical Non-Trainee	-0.03	0.81
Staff vs Clinical Trainee	0.43	0.15
Clinical vs Clinical Trainee	0.60	0.17
Any Period Post Positive Corona Virus PCR or Antibody	-0.47	0.07
Height	-0.03	0.08
Mean Days Travelled Per period	-0.09	0.58
Days Left Home Per Period	-0.05	0.08
No Immune Suppressing Medication at Baseline	-1.80	0.17
No Child Care Needs at Baseline	-0.39	0.23
Smoking at Baseline	0.53	0.20
Mean Days Hospitalized Per Period	-1.66	0.27
Mean Days Treating COVID-19 Positive Patients Per Period	0.22	0.28
Number of Days Left Home	-0.02	0.30
Asian vs Black	0.02	0.97
Asian vs Other	-0.34	0.47
Black vs Other	-0.36	0.55

White vs Asian	0.01	0.99
White vs Black	0.03	0.96
White vs Other	-0.34	0.45
No Positive COVID-19 Antibody at Baseline	0.03	0.69
Days Caring for Patients With COVID-19	0.01	0.73
Interacted With 1-3 People Outside The Home Per Day	0.01	0.97
Interacted With 4-9 People Outside The Home Per Day	0.01	0.96
Interacted With ≥10 People Outside The Home Per Day	-0.11	0.64
Mean Days Quarantined Per Period	-0.20	0.80
Total Symptomatic Days Per Period	0.01	0.85
Days Working Weighted Based on Patient Exposure	0.03	0.69
Days Hospitalized Per Period	0.07	0.88
Days Quarantined Per Period	-0.03	0.90
Mean Number of Days Left the House Per Period	0.03	0.90
Mean Days Working this Period	0.02	0.88
Sum of the Severity of COVID-19 Symptoms Per Period	-0.001	0.96
Mean Severity of COVID-19 Symptoms This Period	0.08	0.14

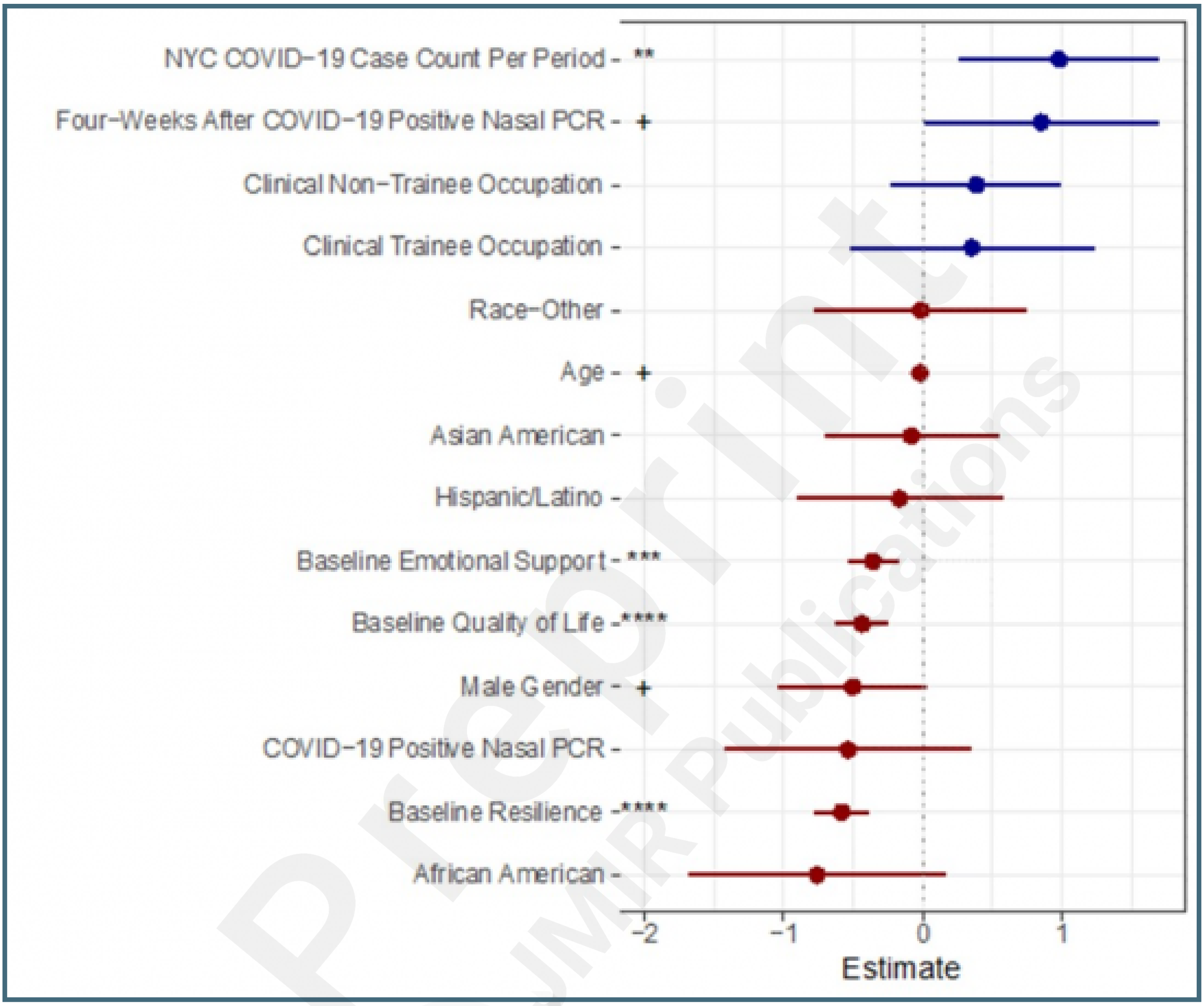
Table 3. Comparison of mean HRV parameters stratified based upon emotional support and resilience tertials.

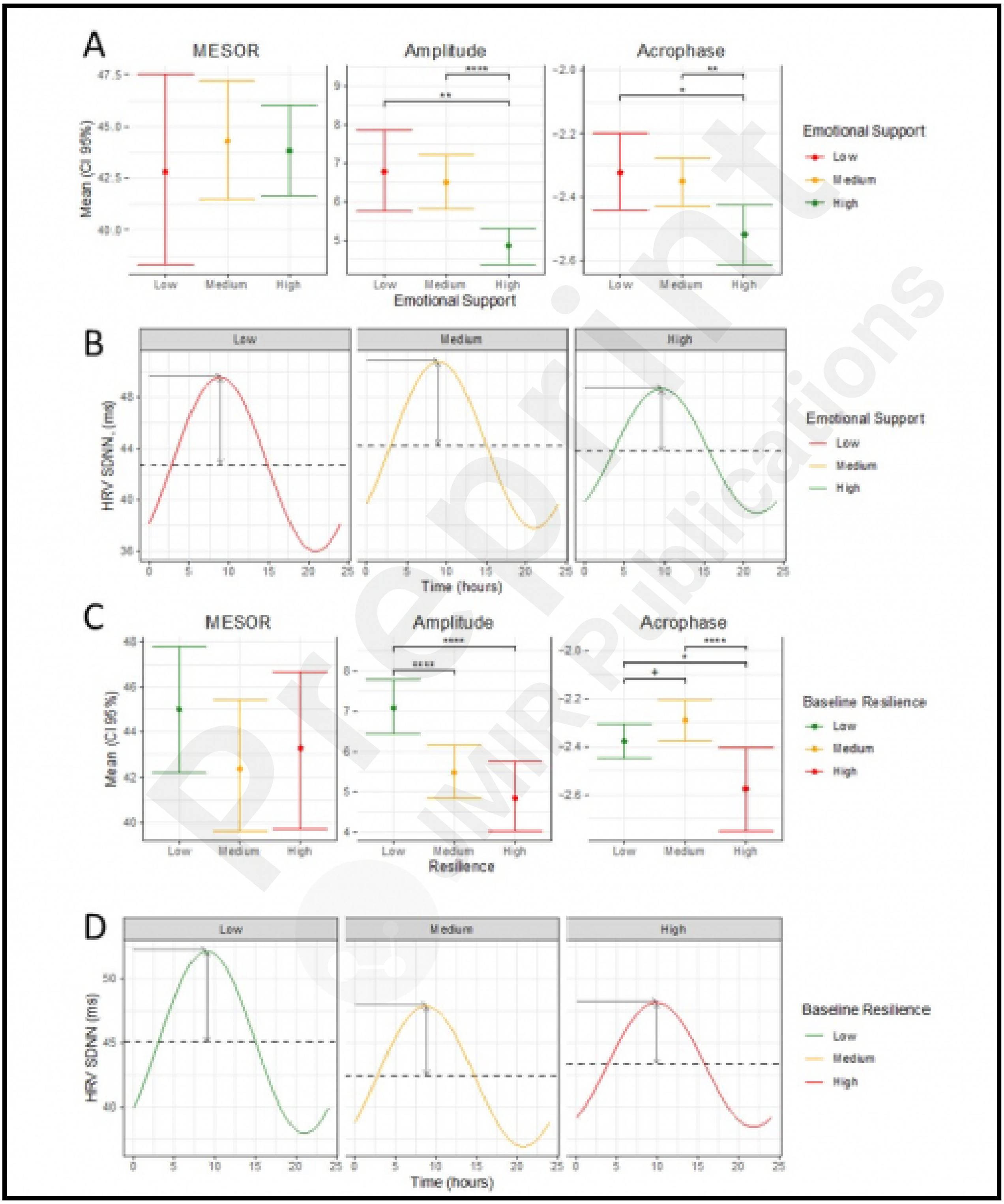
Parameter	Emotional Support Tertial Comparisons	***P*-value**	Resilience Tertial Comparisons	***P*-value**
MESOR				
	Low vs Medium	0.60	Low vs Medium	0.10
	Low vs High	0.67	Low vs High	0.46

	Medium vs High	0.78	Medium vs High	0.71
Amplitude				
	Low vs Medium	0.68	Low vs Medium	<0.001
	Low vs High	0.01	Low vs High	<0.001
	Medium vs High	<0.001	Medium vs High	0.24
Acrophase				
	Low vs Medium	0.70	Low vs Medium	0.09
	Low vs High	0.004	Low vs High	0.048
	Medium vs High	<0.001	Medium vs High	<0.001

Supplementary Files

Figures


NYC COVID−19 Case Count Per Period - **
Four−Weeks After COVID−19 Positive Nasal PCR - +
Clinical Non−Trainee Occupation -
Clinical Trainee Occupation -
Race−Other -
Age - +
Asian American -
Hispanic/Latino -
Baseline Emotional Support - ***
Baseline Quality of Life - ****
Male Gender - +
COVID−19 Positive Nasal PCR -
Baseline Resilience - ****
African American -
−2
−1
0
1
Estimate


A
MESOR
Amplitude
Acrophase
Mean (CI 95%)
Emotional Support
Low
Medium
High
B
HRV SDNN (ms)
Time (hours)
C
Resilience
Baseline Resilience
D

Multimedia Appendixes

Supplementary Figure 1. Plots (A, C) show changes in longitudinal stress following a positive COVID-19 nasal test in participants with low, medium and high emotional support (A) or resilience (C), stars indicate that change in longitudinal stress was significantly different from zero. Line plots (B, D) show relationship between New York City COVID-19 case-count and mean longitudinal stress (± Confidence Intervals) for participants with low, medium and high emotional support (B) or resilience (D), stars indicate significant trend between New York City case-count and longitudinal stress. (+P
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Supplementary material.
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