Title
Addressing Mental Health Symptoms Among COVID-19 Healthcare Workers: A Heart Rate Variability Biofeedback Pilot Study.

Journal
Stress medicine, 40(6)

Authors
Lee, Darlene
Erande, Ashwini
Christodoulou, Georgia
et al.

Publication Date
2024-12-01

DOI
10.1002/smi.3502

Peer reviewed

Stress and Health

WILEY

RESEARCH ARTICLE OPEN ACCESS

Addressing Mental Health Symptoms Among COVID-19 Healthcare Workers: A Heart Rate Variability Biofeedback Pilot Study

Darlene Lee | Ashwini Erande | Georgia Christodoulou | Shaista Malik

Susan Samueli Integrative Health Institute, University of California at Irvine, Irvine, California, USA

Correspondence: Darlene Lee (darlenl1@hs.uci.edu)

Received: 18 November 2023 | **Revised:** 3 September 2024 | **Accepted:** 21 October 2024

Funding: Funding for this project was provided by the University of California at Irvine COVID Research Fund.

Keywords: autonomic nervous system | biofeedback | health personnel | psychological | psychology | stress

ABSTRACT

Psychological stress among frontline healthcare workers (HCWs) increased during the COVID-19 pandemic, elevating mental health risks. Heart rate variability biofeedback (HRV-BF) is an evidence-based intervention with potential to reduce psychological burden on frontline HCWs; however, no studies have examined its use among this population since the pandemic began. We designed a trial to assess the effects of a brief HRV-BF intervention delivered via telemedicine on measures of anxiety, depression and stress, and heart rate variability, compared to an in-person intervention. We hypothesised that the telemedicine intervention would be non-inferior to the in-person intervention. Using a randomized comparison trial design, we tested a 10-day brief heart rate variability biofeedback intervention among frontline HCWs during the COVID-19 pandemic. They received remote, 30-min guided sessions every other day and were taught methods of heart rate variability biofeedback. Depression, anxiety and stress were assessed at baseline, 10 days, and 40 days with additional measures of anxiety measured before and after each session. HRV scores were collected at baseline, as well as during the course of the 10 days. Multilevel modelling was used to examine the change in depression, anxiety, stress and HRV scores across multiple time points and session types (telemedicine vs. in-person). There was no significant differences between telemedicine (n = 32) and in-person (n = 15) interventions on the main outcomes. Both session types showed a significant decrease in depression, anxiety and stress scores across the entire intervention, and HRV scores significantly increased across both groups. Anxiety levels also significantly decreased after each session. The non-inferiority of the telemedicine intervention to a comparable in-person intervention affirms its promise for decreasing anxiety, depression and stress among frontline HCWs and may offer a cost-effective and feasible tool to use in crises situations.

1 | Introduction

Psychological stress among healthcare workers (HCWs) has long been a concern. Prior to the COVID-19 pandemic, numerous studies have documented the vulnerability of HCWs, such as physicians and nurses, to burnout, anxiety, depression, suicidality and stress-related somatic concerns (Dutheil et al. 2019; Maharaj, Lees, and Lal 2018; Shanafelt et al. 2015), particularly those working in emergency departments (Adriaenssens et al. 2011) and other frontline environments within the healthcare system. Studies done during previous epidemics and pandemics have highlighted fears and stressors of HCWs (Khalid et al. 2016). During the COVID-19 pandemic, data has pointed to increased risk for mental health issues such as anxiety and depression (Lai et al. 2020; Zhu et al. 2020) and highlighted the need for effective interventions to address stress among frontline COVID-19 HCWs (Chen et al. 2020). Alongside previous coronavirus epidemics such as SARS and MERS, as well as influenza and Ebola, the SARS-CoV-2 pandemic increased rates of depression, anxiety and stress among HCWs (Chigwedere et al. 2021; Magnavita et al. 2021; Preti et al. 2020; Saragih et al. 2021; Shreffler, Petrey, and Huecker 2020; Spoorthy, Pratapa, and Mahant 2020; Thatrimontrichai, Weber, and Apisarnthanarak 2021; Vizheh et al. 2020). Frontline HCWs, women and nurses appear to be most severely affected (Chigwedere et al. 2021; Danet 2021), and trainees such as medical students, nursing trainees and residents are particularly vulnerable, with greater prevalence and risk for anxiety, depression and stress (Dyrbye et al. 2014; Quek et al. 2019; Zhou et al. 2020). Although COVID surges have passed, the impact of the pandemic and the increased risk for mental health issues among frontline HCWs remains (Yılmaz-Karaman, Yastıbaş-Kaçar, and Ece İnce 2023).

Acute stress may be defined as 'the non-specific response of the body to any demand upon it' (Serban 2012). Experiences of acute stress lead to increased sympathetic nervous system (SNS) activity and lowered parasympathetic nervous system (PNS) activity (Marques, Silverman, and Sternberg 2010). For many years, psychometric measures have been used to assess the subjective experience of both acute and chronic stress. In recent years, heart rate variability (HRV) has gained utility as a psychometric biomarker, capable of demonstrating the impact of stress on the autonomic nervous system (ANS). HRV reflects the natural acceleration and deceleration in heart rate over time. Due to the sensitivity to changes in the ANS, HRV is often used as a biomarker of stress regulation, as well as physiologic and/or emotional self-regulation (Visted et al. 2017); it is also considered a transdiagnostic biomarker of psychopathology and mental illness (Laborde, Mosley, and Thayer 2017). While an in-depth explanation of HRV indices is beyond the scope of this paper, HRV analyses are generally described in the time domain, frequency domain, or non-linear indices (Laborde, Mosley, and Thayer 2017). Both time and frequency-based metrics of HRV are shown to change in response to psychological stressors (Kim et al. 2018). Autonomic 'flexibility', or the ability to shift between high and low arousal states in response to the environment is correlated with higher HRV (Appelhans and Luecken 2006). HRV is thus widely accepted as a measure of autonomic balance and parasympathetic nervous system power (McCraty et al. 2009; Rajendra Acharya et al. 2006; Shaffer and Ginsberg 2017). Several HRV indices are thought to be correlated with parasympathetic nervous system activity (which may also be referred to as vagal tone or vagally mediated HRV)—and the time-domain measure RMSSD is often accepted as the best assessment of vagal tone (Laborde, Mosley, and Thayer 2017). Vagal tone is implicated as central to psychophysiological health and is identified as such in various theories in psychophysiologic research (Laborde, Mosley, and Thayer 2017). An additional measure known as coherence, or cardiac coherence, is also used in the literature (McCraty and Zayas 2014). While the coherence measure is unrelated to standard HRV metrics, it is calculated based on HRV power spectrum (McCraty and Childre 2010). While RMSSD cannot be extrapolated from coherence, coherence as a measure is related to increased parasympathetic activity (McCraty and Childre 2010) and thus can provide a window into behavioural health driven by vagally mediated HRV.

A number of interventions aimed at supporting the mental health and wellbeing of frontline HCWs during the COVID-19 pandemic have been examined in the literature. They may be loosely categorised as peer support-based (Albott et al. 2020)/ peer coaching strategies (Rosen et al. 2022), some of which originate in efforts to support military personnel, mindfulness-based (Burton et al. 2017; Chmielewski, Łoś, and Łuczyński 2021), or apps and web-based tools (López-Pineda et al. 2022). Prior to the pandemic, meta-analyses have identified smart phone apps and web-based tools utilising efficacious approaches as a means to address stress and anxiety among HCW trainees and professionals (Pospos et al. 2018). However, there remains no consensus on solutions to stress-related concerns of HCWs and the need for cost effective, replicable solutions remains, though initial attempts to query health and social care professionals have identified flexible support systems (Billings et al. 2021).

Biofeedback is a process by which an individual's physiological measures under voluntary or involuntary control, some of which reflect sympathetic nervous system activation, are shown to them as they are trained to increase voluntary control over these measures for the purposes of improving health and performance (Schwartz and Andrasik 2017). Heart rate variability biofeedback (HRV-BF) is a form of cardiorespiratory biofeedback. During HRV-BF, a patient is given real-time heart rate data and guided through breathing exercises to activate parasympathetic activity, maximising respiratory sinus arrhythmia (P. M. Lehrer and Gevirtz 2014), and producing a state of parasympathetic activity and calm alertness. With increased parasympathetic activity on the heart (and thus increased HRV), HRV-BF aims to modulate the elevations in sympathetic tone that can occur with stress and negative emotions (P. M. Lehrer and Gevirtz 2014). Commercially available portable HRV sensors provide real time data and 'scoring' based on device algorithms, aiding in the learning and training process. 'Scoring' may include HRV indices or related indices such as coherence. This type of scoring allows for enhanced usability and real-time feedback to individuals using certain biofeedback programs targeting HRV. HRV-BF is generally administered in-person with self-directed maintenance practices expected and encouraged in between (Khazan 2013; P. Lehrer et al. 2013). HRV-BF has been used in many settings to address stress and stress-related conditions including anxiety, depression, PTSD and headaches (Goessl, Curtiss, and Hofmann 2017; Herhaus et al. 2021; Karavidas et al. 2007; Lin et al. 2016, 2019; Patron et al. 2013, 2020; Prinsloo et al. 2013; Steffen et al. 2017), including studies which use HRV-BF devices which give coherence feedback and those that examine the effect of HRV-BF on the coherence measure (Buchanan and Reilly 2019; Ginsberg, Berry, and Powell 2010; Lemaire et al. 2011; Pipe et al. 2012; Trousselard et al. 2016). In healthcare settings, HRV-BF interventions have shown improvement in measures of stress (Buchanan and Reilly 2019; Lemaire et al. 2011; Pipe et al. 2012) and have been postulated as a potential strategy to reduce the psychologic burden on frontline HCWs during the pandemic (Aristizabal et al. 2020). However, no studies have examined the use of HRV-BF among HCWs since the pandemic began.

This study builds upon existing literature regarding the effectiveness of HRV-BF in addressing stress and stress-related conditions and tests an adaptation of established heart rate variability biofeedback training in the form of a 10-day brief intervention delivered by telemedicine, measuring both psychologic measures of anxiety, depression and stress, and physiologic measures of heart rate variability. It adapts traditional HRV-BF training protocols from their usual length in the order of weeks (P. Lehrer et al. 2013) to a brief, compressed 10-day format and further adapts it to a telemedicine format. While there have been published reports of virtually guided biofeedback for ergonomic or rehabilitative purposes (Carrión Pérez et al. 2015; Golebowicz et al. 2015; Rogante et al. 2010) and the use of apps which incorporate HRV-BF training (Economides et al. 2020), there have, to our knowledge, been no published literature regarding real time, virtual HRV-BF. Given the advantages of telemedicine for infection control and increased accessibility, it has true relevance to addressing pandemic-relates stressors challenging frontline HCWs. Our aim was to compare the one-on-one HRV-BF telemedicine intervention to an identical in-person intervention, with the hypothesis that the telemedicine HRV-BF intervention is non-inferior to the in-person intervention, and that both interventions positively influence outcomes of anxiety, depression, stress and HRV coherence in frontline COVID-19 HCWs.

2 | Methods

2.1 | Participant Sampling

A convenience sample was recruited from among staff and faculty at the University of California Irvine Medical Center in Orange, CA. Initial mass recruitment emails were sent to all staff and targeted recruitment emails to UCI Health, UCI School of Medicine and UCI School of Nursing. In addition, flyers were placed in breakrooms at UCI Douglass Hospital, and listing was displayed on the UCI School of Medicine Center for Clinical Research (CCR) and UC Irvine Health Clinical Trials webpages. Interested participants contacted research staff by email or phone and were screened via telephone for eligibility. Inclusion criteria included: UCI Health nursing and medical trainees, and residents and fellows involved in direct COVID-19 care at the UCI Medical Center between the ages of 18–65. Exclusion criteria included: (1) individuals with structural heart disease and/or arrhythmia, (2) individuals with severe OCD (severe neurosis is often a contraindication for biofeedback treatment (Cosio 2015)) and (3) individuals without Bluetooth compatible smartphone or tablet device. The verbal consent process, including an explanation of the research purpose and procedures, was completed by research staff. Consented participants were then randomized into either in-person (IP) or telemedicine groups (TM) using a table generated by an online randomisation tool (Research Randomiser, randomizer.org) and scheduled for required research sessions by research staff. All recruitment and consent materials were reviewed and approved by the University of California at Irvine Institutional Review Board, Human Research Protections. See Figure 1 for Strobe Diagram depicting the recruitment, consent and enrolment process.

Sample size was calculated using an online tool (clincalc) to conduct a power analysis and determine minimum sample size. Sample size was calculated based on a hypothesis of non-inferiority. We targeted a 2:1 telemedicine to in-person ratio due to greater use of remote visits in the midst of the COVID-19 pandemic, and because we were testing the virtual/telemedicine intervention.

2.2 | Study Design

This study was a randomized controlled trial (both prospective and comparison) comparing a remote (telemedicine) (TM) biofeedback intervention to an *identical* in-person (IP) intervention. Because of the nature of the comparison groups, blinding was not possible. Each group received a 10-day training consisting of five unique 30-min one-on-one sessions with a trained biofeedback practitioner, occurring every other day. TM sessions were conducted via Zoom; IP sessions were conducted on-site at the Medical Center. The sessions were designed and delivered by a biofeedback practitioner (certified by the Biofeedback Certification International Alliance), who trained two additional certified biofeedback practitioners to assist with the delivery of the TM sessions using scripted guides, and who delivered all of the IP sessions. The intervention included educational components describing the definition of biofeedback (Schwartz and Andrasik 2017), the physiology of stress and chronic stress including the HPA axis and autonomic nervous system (P. M. Lehrer and Gevirtz 2014; Veldhuis, Sharma, and Roelfsema 2013; Yerkes 1908), and the scientific basis for heart rate variability (P. M. Lehrer and Gevirtz 2014; McCraty and Shaffer 2015) as well as training in diaphragmatic breathing, slow paced diaphragmatic breathing and heart rate variability biofeedback (Steffen et al. 2017; Zaccaro et al. 2018), including coaching on how to use techniques as coping strategies in daily life. Heart rate variability biofeedback instruction was modelled upon instruction outlined in the literature (Khazan 2013; P. Lehrer et al. 2013) guiding participants to breathe according to visual breath pacer, whilst viewing visual feedback of changes in heart rate on their smartphone screen and trying to maximise amplitude of heart rate waves (P. Lehrer et al. 2013), as well as visual signals of HRV coherence displayed on the screen. Additionally, participants were coached to incorporate the use of self-induced positive emotions as described in McCraty (McCraty and Shaffer 2015) alongside breath practices (McCraty et al. 1998; Soer et al. 2015). Session content is summarised in Table 1. On days between sessions, participants were instructed to view brief videos created specifically for the intervention which reinforced content of sessions. Each participant received a portable, Bluetooth compatible HRV-BF device (Inner Balance, HeartMath, Boulder Creek, CA) to use during sessions. The device gives both visual and auditory feedback. In addition to HRV-BF performed during sessions, participants were asked to practice HRV-BF techniques using the device synced to a smartphone app independently for 10 min twice daily for the

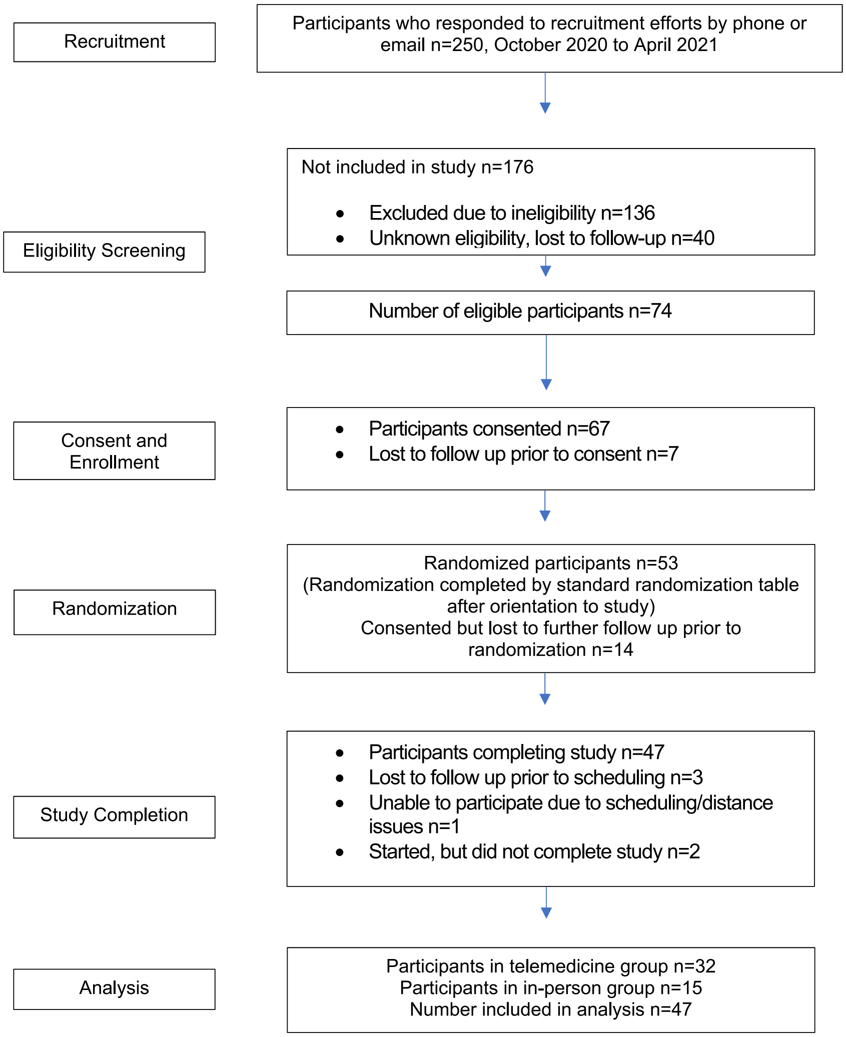

FIGURE 1 | Strobe diagram of recruitment, consent and enrolment process.

TABLE 1 | Summary of intervention by session.

Session number	Content
1	Introduction to the autonomic nervous system, biofeedback and HRV-BF
	Introduction to diaphragmatic breathing
2	Review of diaphragmatic breathing
	Instruction on pursed lips breathing and slowing the breath
	Introduction to slow paced breathing, education on overbreathing
	Introduction to using positive emotion
3	Introduction to HRV-BF and use of Inner Balance
	Education on HRV measures and coherence
	HRV-BF practice
	Discussion of how to use techniques
4	HRV-BF practice
	Stress challenge and continued discussion of how/when to use techniques
5	HRV-BF practice
	Stress challenge
	Wrapping up and moving forward

duration of the 10-day intervention, and to incorporate techniques as coping strategies during stressful situations. Participants were also encouraged to practice beyond this amount. Twice daily text messages were sent to all participants to remind them to practice techniques and to view relevant videos. The study was conducted between November 2020 and May 2021, during the height of the COVID-19 pandemic. The intervention is innovative both in its adaptation of traditional HRV-BF training protocols, but also in its specific adaptation to a telemedicine format.

3 | Measures

The Depression Anxiety Stress Scale (DASS), a 42-question validated assessment tool that measures negative emotional states of depression, anxiety and stress (using three subscales), including symptoms of autonomic arousal, within the last week (Lovibond and Lovibond 1995), was administered to participants before and after the 10-day intervention, as well as 30 days after completion of the intervention (40 days after baseline). The DASS instrument has been shown to be reliable and valid in both clinical and non-clinical samples (Brown et al. 1997; Crawford and Henry 2003). In our sample, Chronbach's alpha for the baseline DASS measurement was 0.94, 0.87 and 0.92 for Depression, Anxiety and Stress, respectively.

Before and after each session, the State Trait Anxiety Inventory (STAI Form Y-1, S-Anxiety) was administered and collected, a validated 20-item questionnaire indicating feelings in the present moment (Spielberger 1983; Spielberger, Gorsuch, and Lushene 1970). The STAI instrument has been used extensively and is translated into 48 languages. Chronbach's alpha for the STAI measure in our sample after the first session was 0.67, consistent with the range of estimates of reliability and validity for this measure reported in the literature, which range from 0.31 to 0.86 (Barnes, Harp, and Jung 2002; Kabacoff et al. 1997; Julian 2011).

HRV coherence score was collected at baseline using the HeartMath Inner Balance sensor and accompanying software app (HeartMath, Boulder Creek, CA). Conventional time and frequency based HRV measures were not collected due to the limitations of the sensor and app, which were chosen for ease of use and user interface. We also collected HRV coherence from participants' independent sessions, to further characterise HRV data throughout the intervention and as fidelity checks to document completion of independent practice; these scores were transmitted by text message as screen shots. The HRV coherence score is a number which reflects how stable, regular and repeating the user's heart rhythm is at a single frequency between 0.04 and 0.24 Hz (3–15 cycles per minute, calculated by a mathematical algorithm internal to the software app, ranging from 0 to 16; formulated as: (Peak Power/[Total Power − Peak Power]) (McCraty and Shaffer 2015). HRV coherence is associated with the experience of positive emotions, self-regulatory ability and a general sense of well-being (McCraty and Zayas 2014). As discussed in the Introduction, the HRV coherence measure is not related to standard HRV metrics, but does correlate with an increase in parasympathetic activity (McCraty and Childre 2010), therefore does reflect changes to ANS balance.

3.1 | Statistical Analyses

Chi-square statistics were conducted to compare demographics and baseline measures by session type (telemedicine [TM] versus in-person biofeedback [IP]). To assess the association between session type and the outcome measures over time, multilevel modelling (MLM) was used to account for repeated measures with covariate adjustment. MLM is more flexible than repeated measures ANOVA, as it can accommodate uneven data structures, missing data and unequal variances (Peugh 2010). More specifically, MLM for repeated measures uses maximum likelihood estimation to account for any missing data and is appropriate with small sample sizes (Pugh, Brown, and Enserro 2022). Multilevel models are robust to missing data under the assumption that the data are missing at random (MAR) or missing completely at random (MCAR). To verify this, we conducted Little's MCAR test, where a non-significant result suggests that the data are MCAR (Li 2013).

We modelled three different repeated outcomes: HRV coherence, DASS total score and STAI. DASS subscale scores were not examined in MLMs due to smaller sample sizes and convergence issues, so alternatively we calculated unadjusted within-group effect sizes for each DASS subscale to explore the intervention's distinct association with change in stress, depression and anxiety. For each of the three outcomes, two-level models were specified (level 1: repeated measures within-person, level 2: between-person factors including time, session type, the time × session type interaction and covariates). The interaction between time and session type allows the exploration of whether the effect of the intervention from pre-to post-measurement differed significantly by session type. All multilevel models were adjusted for the potential confounders age, gender and race. Because our data collection tool collected age ranges rather than absolute age, age was included in the model as a categorical rather than continuous variable.

Time was modelled differently across models depending on the timing of measurement in the study. In the model of HRV coherence, consistent with recommendations of HRV analyses (Laborde, Mosley, and Thayer 2017) time was modelled as a continuous measure of days (1 through 10). In the DASS model, time was modelled categorically, reflecting three time points-pre-session, post-session (at day 10), and at 30 days post-session. In order to assess potential differences in effect across sessions in the STAI model, time was modelled as binary pre-versus post-intervention, with separate models for each session. For all models, random intercepts were included to account for subject-specific baseline differences. Random effects (slopes) were not modelled given that our focus was on group differences by session type rather than subject-specific effects. Restricted maximum likelihood estimation (REML) was used due to the small sample size (Raudenbush and Bryk 1992). Marginal means estimated from multilevel models were used to generate plots over time using the emmeans package in R.

To establish noninferiority of the telemedicine sessions relative to the in-person sessions for the DASS and STAI outcomes, a margin must be determined to set the maximum allowable mean difference of the change in outcomes after the intervention between groups, beyond which telemedicine would be considered inferior to in-person (Cuzick and Sasieni 2022). The margin should depend on several factors including the magnitude of other benefits of the alternative treatment as well as severity of the endpoint (e.g., a small margin should be chosen for an outcome such as mortality) (Cuzick and Sasieni 2022). A non-inferiority margin of 5 points for the DASS scale was selected based on prior research finding this to be the change score related to a minimum clinically important difference (Yohannes et al. 2022). A noninferiority margin of 8 points for the STAI scale was selected based on research showing an eight-point difference being the threshold to ensure reliable change beyond measurement error, and another study finding that 10 points was the minimal important difference value for change on the STAI measure (Corsaletti et al. 2014; Fisher and Durham 1999). We selected 8 points as the margin to be slightly more conservative (more stringent) in the present noninferiority analysis. The confidence interval approach (aka fixed margin method) was used to test for non-inferiority (Althunian et al. 2017; Mascha and Sessler 2011). Estimates of the mean difference and 95% confidence intervals were derived from multilevel model estimates of the interaction between session type (TM) and time, consistent with recommendations on noninferiority analysis for repeated measures data (Mascha and Sessler 2011). Lower scores are better for the DASS and STAI outcomes, so when calculating the difference as TM minus IP, the upper bound of the 95% confidence interval should be no greater than the IP mean plus the margin (+5 points) to establish noninferiority.

While DASS subscales could not be used as outcomes in multilevel models, we calculated Hedge's *G* effect sizes (TM vs. IP) to assess the intervention's association with change in the distinct dimensions of stress, anxiety and depression by session type. All analyses were performed in R (Version 4.4.1).

TABLE 2 | Baseline characteristics and outcomes by session type.

	Session type	
	Telemed[a]	**In person**[a]
Variable	***n* (%)**	
Overall	32 (68.9)	15 (31.9)
Age		
18–24	3 (9.7)	1 (6.7)
25–34	20 (64.5)	12 (80)
35–65	8 (25.08)	2 (13.3)
Missing	1 (3.1)	0 (0%)
Gender		
Female	22 (71)	9 (60)
Male	8 (25.8)	6 (40)
Prefer not to answer	1 (3.1)	0 (0)
Missing	1 (3.1)	0 (0)
Race		
Asian	16 (64)	8 (72.7)
White	6 (24)	1 (9.1)
Others	3 (12)	2 (18.2)
Missing	7 (21.9)	4 (26.7)
	Mean (SD)	
DASS total score	24.5 (20.6)	25.5 (19.0)
DASS depression	6.9 (8.9)	6.9 (7.9)
DASS anxiety	5.7 (6.4)	6.1 (5.7)
DASS stress	12.0 (8.5)	12.5 (9.2)
STAI	38.9 (12.5)	36.7 (10.9)
HRV coherence	1.9 (1.1)	1.6 (0.5)

[a]All baseline differences by session type non-significant.

4 | Results

Demographics and baseline (pre-intervention) outcomes are depicted in Table 2. Participants in the telemedicine versus in-person session types did not significantly differ in age, gender, or race. The telemedicine group had slightly lower total DASS scores but slightly higher STAI scores and HRV coherence at baseline, though differences were not statistically significant. Thirty-two (68%) participated in the TM session and 15 (31.9%) participated in the IP session. A large portion of the study participants, 32 out of total 47 study participants, were from the age group of 25–34, and almost half identified as Asian. Information regarding sample socioeconomic status was not collected [not available].

There were some missing questionnaires which contributed to missing data. Across 5 sessions, there were 7 missing pre-session STAI questionnaires, with no more than 2 missing per session. Across the 5 sessions, there were 12 missing post questionnaires ranging from 1 to 4 questionnaires per session; with some participants missing both pre and post of a session and some missing only pre or post for a single session. There was data missing for 2 cases for each of the 3 DASS measurements—DASS pre-intervention, DASS 10-day and DASS 30-day; though not the same individuals (6 different participants). Little's MCAR test suggested the data were missing completely at random ($p = 0.63$), validating the missingness assumption required to produce unbiased estimates from the multilevel model. Further, findings from unadjusted analyses of mean differences and from adjusted analyses in the mixed models that include cases with incomplete data (described below) support the same conclusions, indicating that missing data did not bias our estimates or conclusions.

Within-group intervention effect sizes for the depression, anxiety and stress subscales of the DASS measure show that the intervention effect was small to moderate for all subscales in the TM group, with stress being the subscale most impacted in this session type (Table 3). Conversely, the intervention effect was negligible in the IP group for both the stress and anxiety subscales, while the depression subscale was most impacted in this group (though only to a small degree). Estimates from adjusted models for DASS total score and STAI indicate group differences

TABLE 3 | Within-group intervention effect size[a] (Hedge's G) across DASS subscales.

DASS subscale	Telemedicine	In-person
Stress	0.5 (medium)	0.1 (negligible)
Anxiety	0.3 (small)	0.1 (negligible)
Depression	0.3 (small)	0.4 (small)

[a]Effect sizes calculated based on raw mean differences from baseline to 10-day follow-up.

TABLE 4 | Mean difference and effect size for DASS and STAI measures by session type.

Outcome	Adjusted mean difference TM-IP (95% CI)
DASS total score	
Baseline	−3.6 (−15.5 to 8.3)
10 days	−5.3 (−15.1 to 4.5)
30 days	−2.5 (−12.5 to 7.5)
STAI	
Post-session 1	−3.3 (−10.4 to 3.8)
Post-session 2	3.2 (−3.0 to 9.4)
Post-session 3	−2.4 (−7.9 to 3.2)
Post-session 4	−2.8 (−9.9 to 4.4)
Post-session 5	0.5 (−5.8 to 6.7)
HRV coherence days 1–10	0.01 (−0.1 to 0.1)

Note: Adjusted mean difference reflects the multilevel model estimates.
Abbreviations: IP = in-person; TM = telemedicine.

in change in scores post-intervention are not statistically significant, as indicated by the confidence intervals that all cross the null value 0 in Table 4—adjusted mean differences. Based on the noninferiority margins of 5 points for the DASS measure and 8 points for the STAI measure, noninferiority can be concluded for the 10-day post-intervention follow up measurement of DASS and for the STAI across all sessions except the second. Non-inferiority was not established for the 30-day follow up DASS measure nor the STAI measure after the second session, as the upper bound of the confidence interval exceeded the non-inferiority margin. Predicted means for all outcomes over time and by session type are shown in Figures 2–4. Results depict notable reductions in state anxiety scores after each session as well as DASS scores at each post-intervention measurement.

Examination of the estimated marginal means obtained from the MLM revealed that all participants showed increasing trend of HRV coherence across 10 timepoints during the study and that means were higher for the participants from the TM group compared to those from the IP group, though not statistically significant (Figure 4).

5 | Discussion

This study uses validated psychological measures of anxiety, depression and stress in conjunction with physiological measures of HRV to assess a brief heart rate variability biofeedback intervention on a sample of COVID-19 frontline trainees, comparing a remote telemedicine approach to in-person sessions. In both the telemedicine group and the in-person group, we found that the measure of HRV coherence (McCraty 2017), increased successively across the 10-day intervention period, with overall higher measures among the telemedicine group (though not statistically significant). This confirmed our original hypothesis that a brief HRV-BF telemedicine intervention delivered over the course of 10 days was non-inferior to an identical in-person intervention. The overall upward trend in HRV coherence is not surprising, given that the practices associated with HRV-BF are aimed to increase vagal tone, thus increasing vagal inhibition of heart rate during expiration phase of respiration. However, the higher HRV coherence measures among the telemedicine groups raises the possibility that the telemedicine intervention may in some ways be superior, as the interventions are otherwise identical. We postulate that the remote nature of the telemedicine intervention offset some of the stressors experienced by participants, allowing them to benefit more greatly from the intervention. The study was done at the height of the COVID-19 pandemic (data collected from November 2020 to June 2021), a time during which stressors upon frontline HCWs were at their peak. It is possible that those in the telemedicine group benefited more greatly from the intervention because the intervention fit much more seamlessly into their schedules, while those in the in-person group may have had the added stress of adhering to the schedule of visits. It is also possible that in-person visits caused additional stress because of fears regarding the transmission of COVID-19, or that the wearing of masks, which was required at the time, adversely affected the comfort of participants or ease of completing breathing exercises during the in-person sessions.

As mentioned previously, the HRV measure assessed in this intervention is independent of standard time and frequency measures for HRV (Shaffer and Ginsberg 2017), and rather a measure of cardiac coherence, the harmonic wavelike properties of a heart rate over time (McCraty 2017; McCraty and Zayas 2014). The limitations of the study conditions precluded recording baseline HRV from which to derive measures of total HRV (time and frequency-based measures). The coherence measure was assessed by the device software (EmWave Inner Balance) and is based on the formula of coherence ratio is formulated as: (Peak Power/[Total Power − Peak Power]) according to the low frequency peak on an HRV power spectrum (McCraty and Shaffer 2015) and was measured during slow paced breathing practices which were taught in the intervention. Thus, it does not necessarily represent total amount of HRV as time-based measures of HRV such as SDNN or RMSSD would, but rather an individual's emotional state [or their ability to evoke a particular emotional state] (McCraty 2017; McCraty and Shaffer 2015). While states of higher HRV cardiac coherence have been linked to positive emotions such as appreciation and compassion (McCraty et al. 1995; Tiller, McCraty, and Atkinson 1996) and cardiac coherence (measured as 'coherence' in the study device and cited as 'HRV coherence' in this study), activated by the practice of slow-paced breathing due to respiratory sinus arrhythmia, or the natural variation of heart rate over the breath cycle has been linked to increased self-regulation (McCraty and Zayas 2014), the lack of relationship between coherence and standard HRV metrics limits the interpretation of our results.

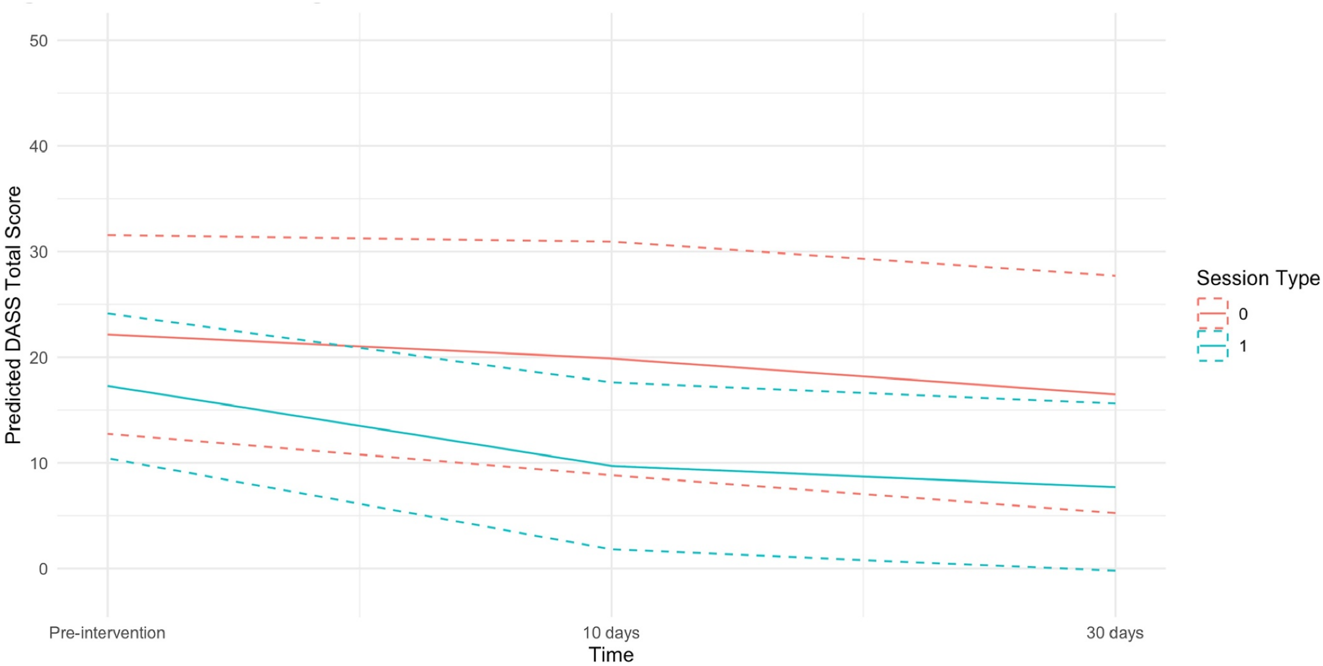

FIGURE 2 | Estimated marginal means of DASS total score. This figure depicts estimated DASS total scores across time (baseline, after 10-day intervention, then 30 days after the intervention) for in-person and telemedicine groups, with 95% confidence intervals. Error bands are represented by dashed lines and are based on 95% confidence intervals.

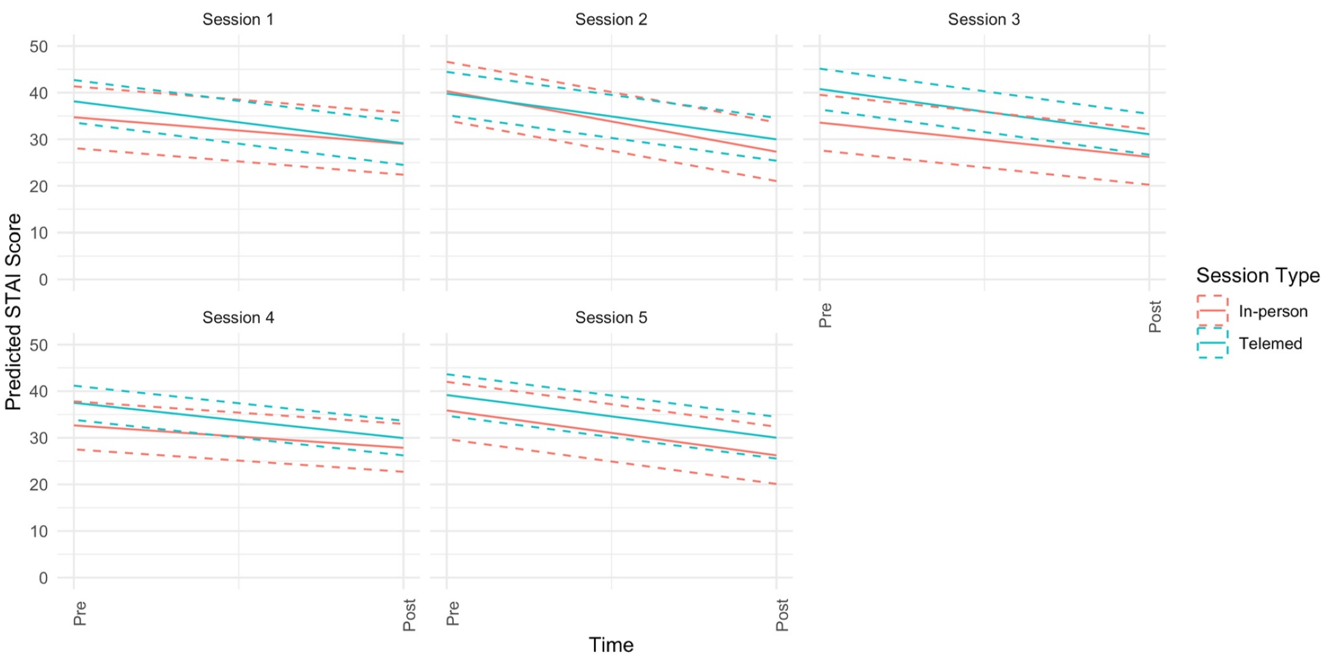

FIGURE 3 | Estimated marginal means of STAI score. This figure shows estimated STAI scores for each of the five intervention sessions (pre and post) for in-person and telemedicine groups, with 95% confidence intervals. Error bands are represented by dashed lines and are based on 95% confidence intervals.

The study protocol emphasised to study participants the importance of not only learning and practicing the techniques taught in study sessions, but employing these tactics in times of stress, emphasising stressful situations in the workplace, in this case the COVID-19 frontline milieu. The fact that telemedicine participants showed overall higher coherence could reflect better comprehension and retention of the skills taught in study sessions, leading to correct use of the techniques during practice, and implementation of techniques during stressors at work, increasing their ability to self-regulate and to weather the stressful situations they were experiencing.

Measures of depression, anxiety and stress (DASS instrument) also improved over the course of the 10-day intervention, and

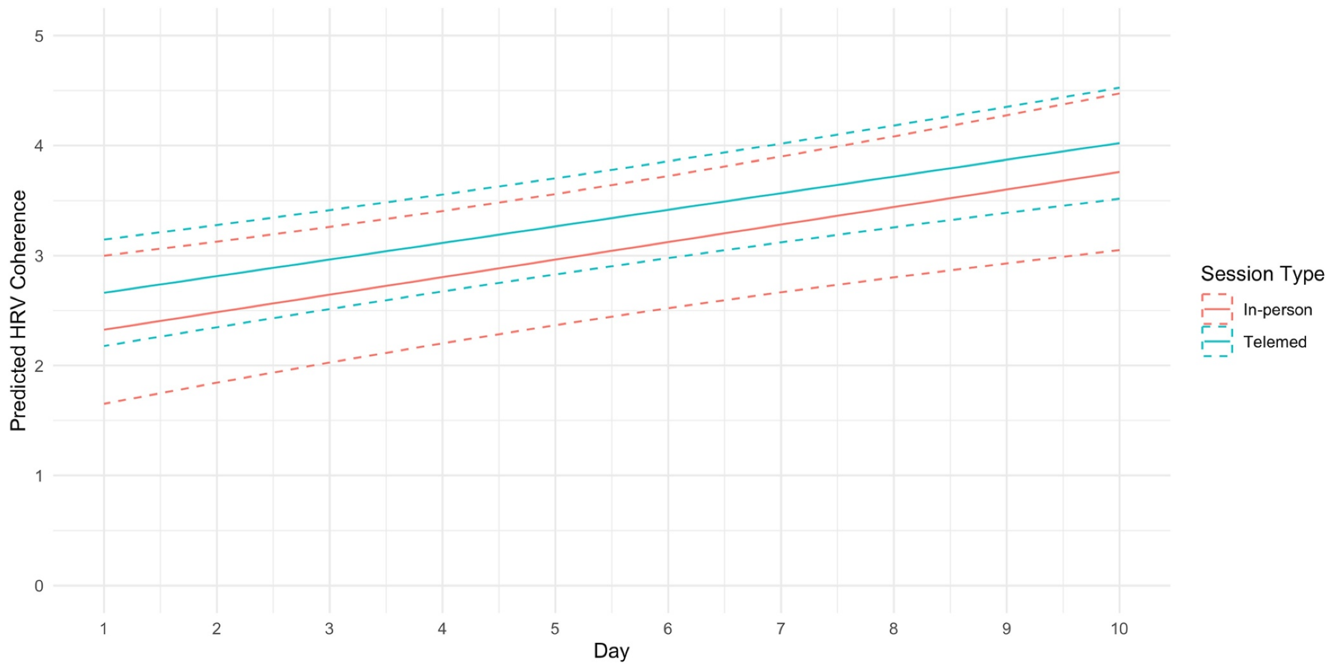

FIGURE 4 | Estimated marginal means of HRV coherence. This figure depicts estimated HRV coherence scores across days of the intervention for in-person and telemedicine groups with 95% confidence intervals. Error bands are represented by dashed lines and are based on 95% confidence intervals.

showed a sustained effect at 30-day follow-up. While previous studies have shown some sustained effects of biofeedback (not specific to HRV-BF) on tension headache (Nestoriuc et al. 2008), there is less evidence of sustained effects with regards to mental health despite meta-analyses showing efficacy in reducing symptomology (Goessl, Curtiss, and Hofmann 2017; Pizzoli et al. 2021). As was the case with HRV measures, those in the telemedicine group appear to have overall lower depression, anxiety and stress scores. Since the study population was randomized, this difference may be due to the conditions in which they completed the mental health assessment instruments. While DASS scores can be broken into subscores reflective of depression, anxiety and stress, we were limited by small sample size in our ability to examine the subscores in fully adjusted multilevel models.

Our use of the 'state' anxiety subset of the State Trait Anxiety Inventory (STAI Form Y-1, S-Anxiety) (Spielberger 1983) allowed us to assess the effect of a single session, independent of the overall intervention or follow-up, on participants' level of anxiety. All five of the sessions for both groups showed an improvement in anxiety state. The 'state' subset of the STAI has a cutoff of 40 points for clinically significant anxiety state. A drop of 10 points can have true clinical consequence and benefit for participants. Whether benefit was derived from the education delivered during each session, practicing the techniques of heart rate variability biofeedback, or the interaction with research staff is more difficult to determine. Measurements of total HRV (time or frequency-based measures) would allow us to correlate this further in our next study.

Nevertheless, our results suggest that even one brief session could contribute to lower levels of anxiety in this population. Taken alongside previous studies which showed that even a single session of HRV-BF results in improvements in HRV measures (Lin et al. 2020; Prinsloo et al. 2013), we may extrapolate that gains in HRV may accompany the improvements in anxiety. Despite the fact that traditional HRV-BF protocols rely on approximately 5–10 weeks (Khazan 2013; P. Lehrer et al. 2013) to train individuals in the techniques of HRV-BF (slow paced breathing), an abbreviated and compressed protocol such as ours shows promise, and may be more feasible among populations such as first responders/frontline HCWs in crisis situations.

There are some limitations of our study. First, the pilot study was planned and designed without the guidance of intervention development frameworks such as the ORBIT framework (Czajkowski et al. 2015) or the MRC framework (Bleijenberg et al. 2018). Additional limitations relate to data collection. Due to the limitations of the smartphone app and portable HRV-BF device used, we were unable to capture time or frequency-based measures of HRV, only the measure of coherence (see Measures for specific formula for coherence). This hampered our capacity to assess the effect of the intervention specifically on autonomic balance and to correlate these changes with improvements in mental health, as well as our ability to compare to many other published studies on HRV-BF and generalise our results. Furthermore, coherence measures were taken during paced breathing exercises, rather than in a resting state, prohibiting assessment of the impact of the intervention on resting HRV.

The complexity of the intervention presents a limitation as it is difficult to discern the mechanisms at work. Because the intervention contains multiple components including real-time and video education, breathing instruction, the use of positive emotion and HRV-BF, it is difficult to disentangle the effects of each, particularly because there is no control group. The study population was highly educated, making the findings potentially less generalisable. Furthermore, the in-person, condensed intervention has not been tested against established, published protocols of similar number of sessions such as Lehrer's 5 session protocol (P. Lehrer et al. 2013). While commercially available HRV biofeedback interventions such as the one used in this study have the benefit of ease of delivery, considerations for choice of hardware should include the data available for analysis, as well as the ability to tailor the device to support simplicity of the intervention protocol.

Other limitations relate to the fidelity of the delivery of the intervention. The intervention was delivered by three different individuals, according to scripted guides developed by the primary biofeedback practitioner. However, the study lacked fidelity checks to ensure consistency in the delivery. Finally, the small sample size is a limitation of the study. However, the greater number of telemedicine visits in our sample show that the significant treatment effect shown in this group is very promising. Despite the limits of the study, given the magnitude of stressors shouldered by frontline HCWs during the COVID-19 pandemic, and the potential for similar situations should other pandemics strike, our study significantly contributes to efforts to support resilience among HCWs by teaching them simple, easy to learn and effective techniques that can lower anxiety, stress and depression. The utility of a telemedicine intervention makes it a highly feasible, cost-effective and easily scalable intervention with ease of delivery. While this study examined trainees, residents and fellows, it has implications for all HCWs and first responders. Future studies should validate these findings in a larger randomized controlled trial. Using the ORBIT model (Czajkowski et al. 2015), we would consider our intervention to be a Phase II preliminary testing phase as we translated an existing in-person intervention, biofeedback, to a virtually-delivered intervention. Per the ORBIT model, future studies (phase III) efficacy studies would be the next step. A larger randomized controlled trial would benefit from guidance offered by intervention development framework tools to ensure rigorous design, including establishing the equivalence of the in-person intervention to published protocols. Given the evidence that slow paced breathing without HRV-BF may have similar effects on HRV measures as with HRV-BF (as well as on other markers of emotion), future research on this intervention may benefit from a control group of slow-paced breathing or other singular components of this intervention to clarify effects. Future larger studies would also benefit from correlating improvements in mental health measures with time and frequency domain HRV metrics in addition to coherence.

Author Contributions

Darlene Lee was involved in the conceptualisation of the research question and design, data curation, acquisition of funding, investigation, methodology, project administration, creation of study resources, writing original manuscript, final review and revision of manuscript. Ashwini Erande was involved with data curation, formal analysis of the data, methodology, validation and visualisation of data, writing parts of the original manuscript, and editing and final review of the manuscript. Georgia Christodoulou was involved with formal analysis and validation of the data, supervision of data analysis, critical review, commentary and revision of the manuscript. Shaista Malik was involved with conceptualisation of the research question and design, funding acquisition, supervision of the project as a whole, writing, including critical review, commentary and revision.

Acknowledgements

The authors wish to acknowledge Arvin Jenab for his assistance in the conception of our research question, Jessica Tobin for support with data analysis, and Brenna Champlin, Maddison Thivierge and Alexandra Carlton for their assistance in the research study.

Ethics Statement

Our study was approved by the Human Subjects Protection Committee at the University of California, Irvine.

Consent

All study participants provided informed consent prior to enrolling in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Open Science Transparency Statement

This pilot study was not formally registered, and the analysis plan was not formally pre-registered. The materials of this study are not publicly available. De-identified data, the analytic code and materials can be made available by contacting the corresponding author.

References

Adriaenssens, J., V. De Gucht, M. Van Der Doef, and S. Maes. 2011. "Exploring the Burden of Emergency Care: Predictors of Stress-Health Outcomes in Emergency Nurses." *Journal of Advanced Nursing* 67, no. 6: 1317–1328. https://doi.org/10.1111/j.1365-2648.2010.05599.x.

Albott, C. S., J. R. Wozniak, B. P. McGlinch, M. H. Wall, B. S. Gold, and S. Vinogradov. 2020. "Battle Buddies: Rapid Deployment of a Psychological Resilience Intervention for Health Care Workers During the COVID-19 Pandemic." *Anesthesia & Analgesia* 131, no. 1: 43–54. https://doi.org/10.1213/ane.0000000000004912.

Althunian, T. A., A. de Boer, R. H. H. Groenwold, and O. H. Klungel. 2017. "Defining the Noninferiority Margin and Analysing Non-inferiority: An Overview." *British Journal of Clinical Pharmacology* 83, no. 8: 1636–1642. https://doi.org/10.1111/bcp.13280.

Appelhans, B. M., and L. J. Luecken. 2006. "Heart Rate Variability as an Index of Regulated Emotional Responding." *Review of General Psychology* 10, no. 3: 229–240. https://doi.org/10.1037/1089-2680.10.3.229.

Aristizabal, J.-P., R. Navegantes, E. Melo, and A. Pereira. 2020. "Use of Heart Rate Variability Biofeedback to Reduce the Psychological Burden of Frontline Healthcare Professionals Against COVID-19." *Frontiers in Psychology* 11: 572191. https://doi.org/10.3389/fpsyg.2020.572191.

Barnes, L. L. B., D. Harp, and W. S. Jung. 2002. "Reliability Generalization of Scores on the Spielberger State-Trait Anxiety Inventory." *Educational and Psychological Measurement* 62, no. 4: 603–618. https://doi.org/10.1177/0013164402062004005.

Billings, J., N. Abou Seif, S. Hegarty, et al. 2021. "What Support Do Frontline Workers Want? A Qualitative Study of Health and Social Care Workers' Experiences and Views of Psychosocial Support During the

COVID-19 Pandemic." *PLoS One* 16, no. 9: e0256454. https://doi.org/10.1371/journal.pone.0256454.

Bleijenberg, N., J. M. de Man-van Ginkel, J. C. A. Trappenburg, et al. 2018. "Increasing Value and Reducing Waste by Optimizing the Development of Complex Interventions: Enriching the Development Phase of the Medical Research Council (MRC) Framework." *International Journal of Nursing Studies* 79: 86–93. https://doi.org/10.1016/j.ijnurstu.2017.12.001.

Brown, T. A., B. F. Chorpita, W. Korotitsch, and D. H. Barlow. 1997. "Psychometric Properties of the Depression Anxiety Stress Scales (DASS) in Clinical Samples." *Behaviour Research and Therapy* 35, no. 1: 79–89. https://doi.org/10.1016/s0005-7967(96)00068-x.

Buchanan, T. M., and P. M. Reilly. 2019. "The Impact of HeartMath Resiliency Training on Health Care Providers." *Dimensions of Critical Care Nursing* 38, no. 6: 328–336. https://doi.org/10.1097/DCC.0000000000000384.

Burton, A., C. Burgess, S. Dean, G. Z. Koutsopoulou, and S. Hugh-Jones. 2017. "How Effective Are Mindfulness-Based Interventions for Reducing Stress Among Healthcare Professionals? A Systematic Review and Meta-Analysis." *Stress and Health* 33, no. 1: 3–13. https://doi.org/10.1002/smi.2673.

Carrión Pérez, F., M. S. Rodríguez Moreno, L. Carnerero Córdoba, M. C. Romero Garrido, L. Quintana Tirado, and I. García Montes. 2015. "Telerehabilitation to Treat Stress Urinary Incontinence. Pilot Study." *Medical Clinics of North America* 144, no. 10: 445–448. https://doi.org/10.1016/j.medcli.2014.05.036.

Chen, Q., M. Liang, Y. Li, et al. 2020. "Mental Health Care for Medical Staff in China During the COVID-19 Outbreak." *Lancet Psychiatry* 7, no. 4: e15–e16. https://doi.org/10.1016/s2215-0366(20)30078-x.

Chigwedere, O. C., A. Sadath, Z. Kabir, and E. Arensman. 2021. "The Impact of Epidemics and Pandemics on the Mental Health of Healthcare Workers: A Systematic Review." *International Journal of Environmental Research and Public Health* 18, no. 13: 6695. https://doi.org/10.3390/ijerph18136695.

Chmielewski, J., K. Łoś, and W. Łuczyński. 2021. "Mindfulness in Healthcare Professionals and Medical Education." *International Journal of Occupational Medicine & Environmental Health* 34, no. 1: 1–14. https://doi.org/10.13075/ijomeh.1896.01542.

Corsaletti, B. F., M.-D. G. L. Proença, G. K. W. Bisca, J. C. Leite, L. M. Bellinetti, and F. Pitta. 2014. "Minimal Important Difference for Anxiety and Depression Surveys After Intervention to Increase Daily Physical Activity in Smokers." *Fisioterapia e Pesquisa* 21, no. 4: 359–364.

Cosio, D., and E. H. Lin. 2015. "Biofeedback: Information for Pain Management." *Practical Pain Management* 15, no. 4.

Crawford, J. R., and J. D. Henry. 2003. "The Depression Anxiety Stress Scales (DASS): Normative Data and Latent Structure in a Large Non-Clinical Sample." *British Journal of Clinical Psychology* 42, no. Pt 2: 111–131. https://doi.org/10.1348/014466503321903544.

Cuzick, J., and P. Sasieni. 2022. "Interpreting the Results of Non-inferiority Trials – A Review." *British Journal of Cancer* 127, no. 10: 1755–1759. https://doi.org/10.1038/s41416-022-01937-w.

Czajkowski, S. M., L. H. Powell, N. Adler, et al. 2015. "From Ideas to Efficacy: The ORBIT Model for Developing Behavioral Treatments for Chronic Diseases." *Health Psychology, American Psychological Association* 34, no. 10: 971–982. https://doi.org/10.1037/hea0000161.

Danet, A. 2021. "Psychological Impact of COVID-19 Pandemic in Western Frontline Healthcare Professionals. A Systematic Review." *Medical Clinics of North America* 156, no. 9: 449–458. (Impacto psicológico de la COVID-19 en profesionales sanitarios de primera línea en el ámbito occidental. Una revisión sistemática.). https://doi.org/10.1016/j.medcli.2020.11.009.

Dutheil, F., C. Aubert, B. Pereira, et al. 2019. "Suicide Among Physicians and Health-Care Workers: A Systematic Review and Meta-Analysis." *PLoS One* 14, no. 12: e0226361. https://doi.org/10.1371/journal.pone.0226361.

Dyrbye, L. N., C. P. West, D. Satele, et al. 2014. "Burnout Among U.S. Medical Students, Residents, and Early Career Physicians Relative to the General U.S. Population." *Academic Medicine* 89, no. 3: 443–451. https://doi.org/10.1097/acm.0000000000000134.

Economides, M., P. Lehrer, K. Ranta, et al. 2020. "Feasibility and Efficacy of the Addition of Heart Rate Variability Biofeedback to a Remote Digital Health Intervention for Depression." *Applied Psychophysiology and Biofeedback* 45, no. 2: 75–86. https://doi.org/10.1007/s10484-020-09458-z.

Fisher, P. L., and R. C. Durham. 1999. "Recovery Rates in Generalized Anxiety Disorder Following Psychological Therapy: An Analysis of Clinically Significant Change in the STAI-T Across Outcome Studies since 1990." *Psychological Medicine* 29, no. 6: 1425–1434. https://doi.org/10.1017/s0033291799001336.

Ginsberg, J. P., M. E. Berry, and D. A. Powell. 2010. "Cardiac Coherence and Posttraumatic Stress Disorder in Combat Veterans." *Alternative Therapies in Health & Medicine* 16, no. 4: 52–60.

Goessl, V. C., J. E. Curtiss, and S. G. Hofmann. 2017. "The Effect of Heart Rate Variability Biofeedback Training on Stress and Anxiety: A Meta-Analysis." *Psychological Medicine* 47, no. 15: 2578–2586. https://doi.org/10.1017/S0033291717001003.

Golebowicz, M., Y. Levanon, R. Palti, and N. Z. Ratzon. 2015. "Efficacy of a Telerehabilitation Intervention Programme Using Biofeedback Among Computer Operators." *Ergonomics: The Official Publication of the Ergonomics Research Society* 58, no. 5: 791–802. https://doi.org/10.1080/00140139.2014.982210.

Herhaus, B. P., M. Siepmann, G. J. Kahaly, R. Conrad, and K. MDPetrowski. 2021. "Effect of a Biofeedback Intervention on Heart Rate Variability in Individuals With Panic Disorder: A Randomized Controlled Trial." *Psychosomatic Medicine* 84, no. 2: 199–209. https://doi.org/10.1097/psy.0000000000001031.

Julian, L. J. 2011. "Measures of Anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A)." Supplement, *Arthritis Care & Research* 63, no. S11: S467–S472. https://doi.org/10.1002/acr.20561.

Kabacoff, R. I., D. L. Segal, M. Hersen, and V. B. Van Hasselt. 1997. "Psychometric Properties and Diagnostic Utility of the Beck Anxiety Inventory and the State-Trait Anxiety Inventory With Older Adult Psychiatric Outpatients." *Journal of Anxiety Disorders* 11, no. 1: 33–47. https://doi.org/10.1016/s0887-6185(96)00033-3.

Karavidas, M. K., P. M. Lehrer, E. Vaschillo, et al. 2007. "Preliminary Results of an Open Label Study of Heart Rate Variability Biofeedback for the Treatment of Major Depression." *Applied Psychophysiology and Biofeedback* 32, no. 1: 19–30. https://doi.org/10.1007/s10484-006-9029-z.

Khalid, I., T. J. Khalid, M. R. Qabajah, A. G. Barnard, and I. A. Qushmaq. 2016. "Healthcare Workers Emotions, Perceived Stressors and Coping Strategies During a MERS-CoV Outbreak." *Clinical Medicine and Research* 14, no. 1: 7–14. https://doi.org/10.3121/cmr.2016.1303.

Khazan, I. Z. 2013. *The Clinical Handbook of Biofeedback: A Step by Step Guide for Training and Practice with Mindfulness*. Wiley-Blackwell.

Kim, H.-G., E.-J. Cheon, D.-S. Bai, Y. H. Lee, and B.-H. Koo. 2018. "Stress and Heart Rate Variability: A Meta-Analysis and Review of the Literature." *Psychiatry Investigation* 15, no. 3: 235–245. https://doi.org/10.30773/pi.2017.08.17.

Laborde, S., E. Mosley, and J. F. Thayer. 2017. "Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research – Recommendations for Experiment Planning, Data Analysis, and Data Reporting." *Frontiers in Psychology* 8: 213. https://doi.org/10.3389/fpsyg.2017.00213.

Lai, J., S. Ma, Y. Wang, et al. 2020. "Factors Associated With Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019." *JAMA Network Open* 3, no. 3: e203976. https://doi.org/10.1001/jamanetworkopen.2020.3976.

Lehrer, P., B. Vaschillo, T. Zucker, et al. 2013. "Protocol for Heart Rate Variability Biofeedback Training." *Biofeedback* 41, no. 3: 98–109. https://doi.org/10.5298/1081-5937-41.3.08.

Lehrer, P. M., and R. Gevirtz. 2014. "Heart Rate Variability Biofeedback: How and Why Does it Work?" *Frontiers in Psychology* 5: 756. https://doi.org/10.3389/fpsyg.2014.00756.

Lemaire, J. B., J. E. Wallace, A. M. Lewin, J. de Grood, and J. P. Schaefer. 2011. "The Effect of a Biofeedback-Based Stress Management Tool on Physician Stress: A Randomized Controlled Clinical Trial." *Open Medicine* 5, no. 4: e154–e163.

Li, C. 2013. "Little's Test of Missing Completely at Random." *State Journal* 13, no. 4: 795–809. https://doi.org/10.1177/1536867x1301300407.

Lin, I. M., S.-Y. Fan, C.-F. Yen, et al. 2019. "Heart Rate Variability Biofeedback Increased Autonomic Activation and Improved Symptoms of Depression and Insomnia Among Patients With Major Depression Disorder." *Clinical Psychopharmacology and Neuroscience* 17, no. 2: 222–232. https://doi.org/10.9758/cpn.2019.17.2.222.

Lin, I. M., J.-M. Ko, S.-Y. Fan, and C.-F. Yen. 2016. "Heart Rate Variability and the Efficacy of Biofeedback in Heroin Users With Depressive Symptoms." *Clinical Psychopharmacology and Neuroscience* 14, no. 2: 168–176. https://doi.org/10.9758/cpn.2016.14.2.168.

Lin, I. M., S.-Y. Wang, S.-Y. Fan, E. Peper, S.-P. Chen, and C.-Y. Huang. 2020. "A Single Session of Heart Rate Variability Biofeedback Produced Greater Increases in Heart Rate Variability Than Autogenic Training." *Applied Psychophysiology and Biofeedback* 45, no. 4: 343–350. https://doi.org/10.1007/s10484-020-09483-y.

López-Pineda, A., I. Carrillo, A. Mula, et al. 2022. "Strategies for the Psychological Support of the Healthcare Workforce During the COVID-19 Pandemic: The ERNST Study." *International Journal of Environmental Research and Public Health* 19, no. 9: 5529. https://doi.org/10.3390/ijerph19095529.

Lovibond, P. F., and S. H. Lovibond. 1995. "The Structure of Negative Emotional States: Comparison of the Depression Anxiety Stress Scales (DASS) With the Beck Depression and Anxiety Inventories." *Behaviour Research and Therapy* 33, no. 3: 335–343. https://doi.org/10.1016/0005-7967(94)00075-u.

Magnavita, N., F. Chirico, S. Garbarino, N. L. Bragazzi, E. Santacroce, and S. Zaffina. 2021. "SARS/MERS/SARS-CoV-2 Outbreaks and Burnout Syndrome Among Healthcare Workers. An Umbrella Systematic Review." *International Journal of Environmental Research and Public Health* 18, no. 8: 4361. https://doi.org/10.3390/ijerph18084361.

Maharaj, S., T. Lees, and S. Lal. 2018. "Prevalence and Risk Factors of Depression, Anxiety, and Stress in a Cohort of Australian Nurses." *International Journal of Environmental Research and Public Health* 16, no. 1: 61. https://doi.org/10.3390/ijerph16010061.

Marques, A. H., M. N. Silverman, and E. M. Sternberg. 2010. "Evaluation of Stress Systems by Applying Noninvasive Methodologies: Measurements of Neuroimmune Biomarkers in the Sweat, Heart Rate Variability and Salivary Cortisol." *Neuroimmunomodulation* 17, no. 3: 205–208. https://doi.org/10.1159/000258725.

Mascha, E. J., and D. I. Sessler. 2011. "Equivalence and Noninferiority Testing in Regression Models and Repeated-Measures Designs." *Anesthesia & Analgesia* 112, no. 3: 678–687. https://doi.org/10.1213/ANE.0b013e318206f872.

McCraty, R. 2017. "New Frontiers in Heart Rate Variability and Social Coherence Research: Techniques, Technologies, and Implications for Improving Group Dynamics and Outcomes." *Frontiers in Public Health* 5: 267. https://doi.org/10.3389/fpubh.2017.00267.

McCraty, R., M. Atkinson, W. A. Tiller, G. Rein, and A. D. Watkins. 1995. "The Effects of Emotions on Short-Term Power Spectrum Analysis of Heart Rate Variability." *American Journal of Cardiology* 76, no. 14: 1089–1093. https://doi.org/10.1016/S0002-9149(99)80309-9.

McCraty, R., M. Atkinson, D. Tomasino, and R. T. Bradley. 2009. "The Coherent Heart Heart-Brain Interactions, Psychophysiological Coherence, and the Emergence of System-Wide Order." *Integral Review: A Transdisciplinary & Transcultural Journal for New Thought, Research, & Praxis* 5, no. 2: 10–115.

McCraty, R., B. Barrios-Choplin, D. Rozman, M. Atkinson, and A. D. Watkins. 1998. "The Impact of a New Emotional Self-Management Program on Stress, Emotions, Heart Rate Variability, DHEA and Cortisol." *Integrative Physiological and Behavioral Science* 33, no. 2: 151–170. https://doi.org/10.1007/BF02688660.

McCraty, R., and D. Childre. 2010. "Coherence: Bridging Personal, Social, and Global Health." *Alternative Therapies in Health & Medicine* 16, no. 4: 10–24.

McCraty, R., and F. Shaffer. 2015. "Heart Rate Variability: New Perspectives on Physiological Mechanisms, Assessment of Self-Regulatory Capacity, and Health Risk." *Global Advances in Health and Medicine* 4, no. 1: 46–61. https://doi.org/10.7453/gahmj.2014.073.

McCraty, R., and M. A. Zayas. 2014. "Cardiac Coherence, Self-Regulation, Autonomic Stability, and Psychosocial Well-Being." *Frontiers in Psychology* 5: 1090. https://doi.org/10.3389/fpsyg.2014.01090.

Nestoriuc, Y., A. Martin, W. Rief, and F. Andrasik. 2008. "Biofeedback Treatment for Headache Disorders: A Comprehensive Efficacy Review." *Applied Psychophysiology and Biofeedback* 33, no. 3: 125–140. https://doi.org/10.1007/s10484-008-9060-3.

Patron, E., S. Messerotti Benvenuti, G. Favretto, et al. 2013. "Biofeedback Assisted Control of Respiratory Sinus Arrhythmia as a Biobehavioral Intervention for Depressive Symptoms in Patients After Cardiac Surgery: A Preliminary Study." *Applied Psychophysiology and Biofeedback* 38, no. 1: 1–9. https://doi.org/10.1007/s10484-012-9202-5.

Patron, E., M. Munafò, S. Messerotti Benvenuti, L. Stegagno, and D. Palomba. 2020. "Not All Competitions Come to Harm! Competitive Biofeedback to Increase Respiratory Sinus Arrhythmia in Managers." *Frontiers in Neuroscience* 14: 855. https://doi.org/10.3389/fnins.2020.00855.

Peugh, J. L. 2010. "A Practical Guide to Multilevel Modeling." *Journal of School Psychology* 48, no. 1: 85–112. https://doi.org/10.1016/j.jsp.2009.09.002.

Pipe, T. B., V. L. Buchda, S. Launder, et al. 2012. "Building Personal and Professional Resources of Resilience and Agility in the Healthcare Workplace." *Stress and Health* 28, no. 1: 11–22. https://doi.org/10.1002/smi.1396.

Pizzoli, S. F. M., C. Marzorati, D. Gatti, D. Monzani, K. Mazzocco, and G. Pravettoni. 2021. "A Meta-Analysis on Heart Rate Variability Biofeedback and Depressive Symptoms." *Scientific Reports* 11, no. 1: 6650. https://doi.org/10.1038/s41598-021-86149-7.

Pospos, S., I. T. Young, N. Downs, et al. 2018. "Web-Based Tools and Mobile Applications to Mitigate Burnout, Depression, and Suicidality Among Healthcare Students and Professionals: A Systematic Review." *Academic Psychiatry: official journal of the American Association of Directors of Psychiatric Residency Training and the Association for Academic Psychiatry* 42, no. 1: 109–120. https://doi.org/10.1007/s40596-017-0868-0.

Preti, E., V. Di Mattei, G. Perego, et al. 2020. "The Psychological Impact of Epidemic and Pandemic Outbreaks on Healthcare Workers: Rapid Review of the Evidence." *Current Psychiatry Reports* 22, no. 8: 43. https://doi.org/10.1007/s11920-020-01166-z.

Prinsloo, G. E., W. E. Derman, M. I. Lambert, and H. G. Laurie Rauch. 2013. "The Effect of a Single Session of Short Duration Biofeedback-Induced Deep Breathing on Measures of Heart Rate Variability

During Laboratory-Induced Cognitive Stress: A Pilot Study." *Applied Psychophysiology and Biofeedback* 38, no. 2: 81–90. https://doi.org/10.1007/s10484-013-9210-0.

Pugh, S. L., P. D. Brown, and D. Enserro. 2022. "Missing Repeated Measures Data in Clinical Trials." *Neuro-Oncology Practice* 9, no. 1: 35–42. https://doi.org/10.1093/nop/npab043.

Quek, T. T., W. W. Tam, B. X. Tran, et al. 2019. "The Global Prevalence of Anxiety Among Medical Students: A Meta-Analysis." *International Journal of Environmental Research and Public Health* 16, no. 15: 2735. https://doi.org/10.3390/ijerph16152735.

Rajendra Acharya, U., K. Paul Joseph, N. Kannathal, C. M. Lim, and J. S. Suri. 2006. "Heart Rate Variability: A Review." *Medical & Biological Engineering & Computing* 44, no. 12: 1031–1051. https://doi.org/10.1007/s11517-006-0119-0.

Raudenbush, S., and A. Bryk. 1992. "Hierarchical Linear Models: Applications and Data Analysis Methods."

Rogante, M., S. Silvestri, M. Grigioni, and M. Zampolini. 2010. "Electromyographic Audio Biofeedback for Telerehabilitation in Hospital." *Journal of Telemedicine and Telecare* 16, no. 4: 204–206. https://doi.org/10.1258/jtt.2010.004012.

Rosen, B., M. Preisman, H. Read, et al. 2022. "Resilience Coaching for Healthcare Workers: Experiences of Receiving Collegial Support During the COVID-19 Pandemic." *General Hospital Psychiatry* 75: 83–87. https://doi.org/10.1016/j.genhosppsych.2022.02.003.

Saragih, I. D., S. I. Tonapa, I. S. Saragih, et al. 2021. "Global Prevalence of Mental Health Problems Among Healthcare Workers During the Covid-19 Pandemic: A Systematic Review and Meta-Analysis." *International Journal of Nursing Studies* 121: 104002. https://doi.org/10.1016/j.ijnurstu.2021.104002.

Schwartz, M. S., and F. Andrasik. 2017. *Biofeedback: A Practitioner's Guide*. New York: Guilford Press.

Serban, G. 2012. *Psychopathology of Human Adaptation*. New York: Springer Science & Business Media.

Shaffer, F., and J. P. Ginsberg. 2017. "An Overview of Heart Rate Variability Metrics and Norms." *Frontiers in Public Health* 5: 258. https://doi.org/10.3389/fpubh.2017.00258.

Shanafelt, T. D., O. Hasan, L. N. Dyrbye, et al. 2015. "Changes in Burnout and Satisfaction With Work-Life Balance in Physicians and the General US Working Population between 2011 and 2014." *Mayo Clinic Proceedings* 90, no. 12: 1600–1613. https://doi.org/10.1016/j.mayocp.2015.08.023.

Shreffler, J., J. Petrey, and M. Huecker. 2020. "The Impact of COVID-19 on Healthcare Worker Wellness: A Scoping Review." *Western Journal of Emergency Medicine* 21, no. 5: 1059–1066. https://doi.org/10.5811/westjem.2020.7.48684.

Soer, R., A. B. de Jong, B. L. Hofstra, H. R. S. Preuper, and M. F. Reneman. 2015. "Does Mindfulness Improve After Heart Coherence Training in Patients With Chronic Musculoskeletal Pain and Healthy Subjects? A Pilot Study." *Global Advances in Health and Medicine* 4, no. 4: 50–55. https://doi.org/10.7453/gahmj.2015.028.

Spielberger, C. D., R. Gorsuch, E. R. Lushene, P. R. Vagg, and G. Jacobs. 1983. *Manual for the State-Trait Anxiety Inventory (Form Y1–Y2)*. Vol. IV. Palo Alto, CA: Consulting Psychologists Press.

Spielberger, C. D., R. L. Gorsuch, and R. E. Lushene. 1970. *STAI Manual for the State-Trait Anxiety Inventory: ("Self-Evaluation Questionnaire")/ by Charles D. Spielberger, Richard L. Gorsuch, Robert E. Lushene*. Palo Alto, CA: Consulting Psychologists Press.

Spoorthy, M. S., S. K. Pratapa, and S. Mahant. 2020. "Mental Health Problems Faced by Healthcare Workers Due to the COVID-19 Pandemic – A Review." *Asian Journal of Psychiatry* 51: 102119. https://doi.org/10.1016/j.ajp.2020.102119.

Steffen, P. R., T. Austin, A. DeBarros, and T. Brown. 2017. "The Impact of Resonance Frequency Breathing on Measures of Heart Rate Variability, Blood Pressure, and Mood." *Frontiers in Public Health* 5: 222. https://doi.org/10.3389/fpubh.2017.00222.

Thatrimontrichai, A., D. J. Weber, and A. Apisarnthanarak. 2021. "Mental Health Among Healthcare Personnel During COVID-19 in Asia: A Systematic Review." *Journal of the Formosan Medical Association* 120, no. 6: 1296–1304. https://doi.org/10.1016/j.jfma.2021.01.023.

Tiller, W. A., R. McCraty, and M. Atkinson. 1996. "Cardiac Coherence: A New, Noninvasive Measure of Autonomic Nervous System Order." *Alternative Therapies in Health & Medicine* 2, no. 1: 52–65.

Trousselard, M., F. Canini, D. Claverie, C. Cungi, B. Putois, and N. Franck. 2016. "Cardiac Coherence Training to Reduce Anxiety in Remitted Schizophrenia, a Pilot Study." *Applied Psychophysiology and Biofeedback* 41, no. 1: 61–69. https://doi.org/10.1007/s10484-015-9312-y.

Veldhuis, J. D., A. Sharma, and F. Roelfsema. 2013. "Age-Dependent and Gender-Dependent Regulation of Hypothalamic-Adrenocorticotropic-Adrenal Axis." *Endocrinology and Metabolism Clinics of North America* 42, no. 2: 201–225. https://doi.org/10.1016/j.ecl.2013.02.002.

Visted, E., L. Sørensen, B. Osnes, J. L. Svendsen, P.-E. Binder, and E. Schanche. 2017. "The Association Between Self-Reported Difficulties in Emotion Regulation and Heart Rate Variability: The Salient Role of Not Accepting Negative Emotions." *Frontiers in Psychology* 8: 328. https://doi.org/10.3389/fpsyg.2017.00328.

Vizheh, M., M. Qorbani, S. M. Arzaghi, S. Muhidin, Z. Javanmard, and M. Esmaeili. 2020. "The Mental Health of Healthcare Workers in the COVID-19 Pandemic: A Systematic Review." *Journal of Diabetes and Metabolic Disorders* 19, no. 2: 1967–1978. https://doi.org/10.1007/s40200-020-00643-9.

Yerkes, R. M., and D. John. 1908. "The Relation of Strength of Stimulus to Rapidity of Habit Formation." *Journal of Comparative Neurology and Psychology* 18: 459–482.

Yılmaz-Karaman, İ. G., C. Yastıbaş-Kaçar, and F. Ece İnce. 2023. "Posttraumatic Growth Levels of Healthcare Workers in Two Periods With Different Intensities of COVID-19 Pandemic." *PsyCh Journal* 12, no. 2: 297–306. https://doi.org/10.1002/pchj.599.

Yohannes, A. M., R. Casaburi, S. Dryden, and N. A Hanania. 2022. "Minimum Clinically Important Difference in the Depression Anxiety Stress Scale-21 Using an Anchor-Based Methodology in Response to Pulmonary Rehabilitation." *Chest* 162, no. 4: A2288–A2289. https://doi.org/10.1016/j.chest.2022.08.1896.

Zaccaro, A., A. Piarulli, M. Laurino, et al. 2018. "How Breath-Control Can Change Your Life: A Systematic Review on Psycho-Physiological Correlates of Slow Breathing." *Frontiers in Human Neuroscience* 12: 353. https://doi.org/10.3389/fnhum.2018.00353.

Zhou, A. Y., M. Panagioti, A. Esmail, R. Agius, M. Van Tongeren, and P. Bower. 2020. "Factors Associated With Burnout and Stress in Trainee Physicians: A Systematic Review and Meta-Analysis." *JAMA Network Open* 3, no. 8: e2013761. https://doi.org/10.1001/jamanetworkopen.2020.13761.

Zhu, Z., S. Xu, H. Wang, et al. 2020. "COVID-19 in Wuhan: Sociodemographic Characteristics and Hospital Support Measures Associated With the Immediate Psychological Impact on Healthcare Workers." *EClinicalMedicine* 24: 100443. https://doi.org/10.1016/j.eclinm.2020.100443.