Received: 13 April 2023 | Revised: 6 December 2023 | Accepted: 8 January 2024

DOI: 10.1111/psyp.14533

ORIGINAL ARTICLE

PSYCHOPHYSIOLOGY SPR WILEY

Real-time heart rate variability biofeedback amplitude during a large-scale digital mental health intervention differed by age, gender, and mental and physical health

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Funding information
National Institute of Mental Health, Grant/Award Number: R01AG057184, R01AG059677, R01AG080652, R01DK132870, R21AG080414, R24AG048024, R33AT009333, R44MH126836 and U24AG072699

Abstract

Heart rate variability biofeedback (HRVB) is an efficacious treatment for depression and anxiety. However, translation to digital mental health interventions (DMHI) requires computing and providing real-time HRVB metrics in a personalized and user-friendly fashion. To address these gaps, this study validates a real-time HRVB feedback algorithm and characterizes the association of the main algorithmic summary metric—HRVB amplitude—with demographic, psychological, and health factors. We analyzed HRVB data from 5158 participants in a therapist-supported DMHI incorporating slow-paced breathing to treat depression or anxiety symptoms. A real-time feedback metric of HRVB amplitude and a gold-standard research metric of low-frequency (LF) power were computed for each session and then averaged within-participants over 2 weeks. We provide HRVB amplitude values, stratified by age and gender, and we characterize the multivariate associations of HRVB amplitude with demographic, psychological, and health factors. Real-time HRVB amplitude correlated strongly ($r = .93$, $p < .001$) with the LF power around the respiratory frequency (~0.1 Hz). Age was associated with a significant decline in HRVB ($\beta = -0.46$, $p < .001$), which was steeper among men than women, adjusting for demographic, psychological, and health factors. Resting high- and low-frequency power, body mass index, hypertension, Asian race, depression symptoms, and trauma history were significantly associated with HRVB amplitude in multivariate analyses (p's $< .01$). Real-time HRVB amplitude correlates highly with a research gold-standard spectral metric, enabling automated biofeedback delivery as a potential treatment component of DMHIs. Moreover, we identify demographic, psychological, and health factors relevant to building an equitable, accurate, and personalized biofeedback user experience.

KEYWORDS

biofeedback, epidemiology, mental health services, psychophysiology

1 | INTRODUCTION

Approximately 40% of US adults in 2021 reported symptoms of depression and anxiety that significantly impact daily functioning and quality of life (Vahratian et al., 2021) Heart rate variability biofeedback (HRVB) is a promising, evidence-based adjunctive intervention that can make a clinically significant contribution to treating these mental health symptoms (Alayan et al., 2018; Burlacu et al., 2021; Costa Vital et al., 2021; Fournié et al., 2021; Goessl et al., 2017; Lehrer et al., 2020; Pizzoli et al., 2021). This study enables digital HRVB with machine-learning-based biofeedback by validating a real-time algorithm and by characterizing individual differences relevant to improving the equity, accuracy, and personalization of digital HRVB.

Higher HRV is considered a marker of psychobiological resilience that predicts lower morbidity and mortality (Fang et al., 2020; Shaffer & Meehan, 2020). Breathing at a slow pace close to 0.1 Hz, or six breaths per minute, has been shown to maximize respiration-induced HRV (Cooke et al., 1998). Moreover, brain networks involved in regulating emotions overlap with those involved in regulating HRV (Mather & Thayer, 2018; Thayer et al., 2012). Indeed, a recent clinical trial demonstrated that 5 weeks of HRVB (or slow-paced breathing with biofeedback) improved functional connectivity within brain networks involved in the generation and regulation of emotions (Nashiro et al., 2022). Therefore, HRVB may directly target cardiac autonomic training and emotion regulation, thereby complementing standard therapeutic approaches.

To automate user feedback during an HRVB session, one must identify what metric defines success or informs the user whether they have generated large HRV oscillations at any given moment. In research studies, successful HRVB practice is often quantified using the spectral power in the low-frequency (LF) domain (0.04–0.15 Hz) (Camm et al., 1996), where higher spectral values reflect higher amplitude HRV oscillations (Lehrer et al., 2020). However, this computation requires at least 2 min of data and yields edge effects, both of which preclude providing accurate feedback in real time. Moreover, the standard LF range of 0.04–0.15 Hz is too broad to properly guide the user experience. Specifically, users are typically instructed to match the pace of their breath to a pacer set to 0.1 Hz; hence, using the full LF range, a user breathing only half as fast as the prescribed pace (e.g., 0.05 Hz instead 0.1 Hz) would receive feedback that their performance was successful, when in fact they were not breathing in time with the pacer. When users observe that the algorithm fails to detect whether they are correctly following the directions, this undermines their trust in the treatment program. Fortunately, it is not necessary to utilize the full LF range for this algorithm because slow-paced breathing recruits the majority of the power in the LF range into a narrow band around the breathing frequency.

In frequency-domain analyses, a complex signal may be mathematically represented as the summation of sine waves distributed across a frequency spectrum (Downey, 2014). Thus, LF may be approximated around the breathing frequency by fitting a bounded, nonlinear curve-fitting algorithm (e.g., Levenberg–Marquardt algorithm) (Brown & Dennis, 1971; Gavin, 2022; Lu et al., 2019) using a sinusoidal function with bounds of .08–.12 Hz around the frequency parameter. The fitted model would yield a sine wave amplitude parameter (i.e., half the peak-to-trough amplitude), which should be highly correlated with spectral power computed within the same frequency range. This may enable a mobile application (app) to run a real-time algorithm as part of a digital intervention and feed back the HRVB amplitude metric using much shorter windows of data (e.g., 30 s).

A second major challenge is how to feed back the HRVB amplitude in a manner that is easily interpretable to the user. User experience research shows that complex health information is best delivered using a simple color-coded score with short-word descriptors (Brockman et al., 2021). With a real-time algorithm, a digital intervention could apply a threshold to a rolling window calculation of HRVB amplitude within an app. For example, the app could dynamically change the color of the breathing pacer, thereby helping the patient learn when they are performing HRVB correctly and optimizing their training.

If the thresholds are not personalized, however, then real-time algorithms could result in biases against individuals with lower HRV due to age, gender, and mental or physical health factors. For example, because resting HRV generally declines with age (Jandackova et al., 2016; Natarajan et al., 2020), applying a one-size-fits-all threshold might prevent older users from achieving positive feedback, even when they may be doing HRVB effectively. Consequently, this may lead to reduced patient engagement or effectiveness among certain populations (Lambert et al., 2018; Schilling et al., 2021). Nevertheless, it is not yet known whether HRVB amplitude also declines with age, as do resting HRV metrics.

Gender also impacts the trajectory of age-related decline in HRV. In resting HRV assessments, women exhibit less power in the LF range and more in the HF range compared to men (Koenig & Thayer, 2016). However, men's LF also declines faster than women's with age (Jandackova et al., 2016; Stein et al., 1997). Moreover, slow-paced breathing with biofeedback evokes complex interactions across several bodily systems, which differ from a resting state. Hence, to ensure an equitable, accurate, and personalized user experience, real-world studies are needed to establish whether HRVB amplitude is impacted by demographic, psychological, and health factors, including gender, race and ethnicity, mental health symptom severity, cardiometabolic conditions, and other medical comorbidities (Aschbacher et al., 2017; Berg et al., 2021; Fournié et al., 2021; Kemp et al., 2010; Mason et al., 2019).

To address this gap, this study developed age- and gender-stratified estimates for real-time HRVB amplitude among a large sample of patients ($N = 5158$) who participated in a digital mental health intervention (DMHI) incorporating HRVB to treat symptoms of depression and anxiety (Economides et al., 2020). The primary hypothesis was that greater age would be associated with lower HRV amplitude scores while doing biofeedback training, even when adjusting for other demographic, psychological, and health factors (Almeida-Santos et al., 2016; Monahan, 2007; Reardon & Malik, 1996; Umetani et al., 1998). The secondary hypothesis was that age would interact with gender to predict HRV amplitude during biofeedback, such that younger men would have higher amplitudes than younger women, but men would also show greater age-associated decline (Abhishekh et al., 2013; Jandackova et al., 2016; Koenig & Thayer, 2016; O'Neal et al., 2016; Shaffer & Ginsberg, 2017). We additionally explored the extent to which other demographic, psychological, and health factors were associated with HRV amplitude during biofeedback.

2 | METHODS

2.1 | Study sample

The sample included 5158 people who participated in a DMHI called the Meru Health Program (MHP) between August 1, 2020 and August 1, 2022. Referral to the MHP was through healthcare providers and employee assistance programs. Inclusion criteria determined during a clinical intake included: (1) having at least mild levels of depression, anxiety, or burnout; (2) owning a smartphone; (3) no active substance use disorder; (4) no severe active suicidal ideation with a specific plan or severe active self-harm; (5) no history of psychosis or mania; and (6) being 18 years of age or older. Additional inclusion criteria for this study were participation in at least one HRVB session with a minimum recording length of 4 min, which exceeds the recommended minimum length of 2 min per published guidelines (Shaffer & Ginsberg, 2017).

Patients consented to participate and have their collected and de-identified data used for research purposes when accepting the MHP privacy practices. Data were stored in Health Insurance Portability and Accountability Act-compliant electronic medical records that include protected health information. All data were encrypted in transit and at rest. Institutional review board exemption for this study was obtained from the Pearl Institutional Review Board (21-MERU-114). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2 | HRVB module

In the second week of the program, participants begin self-administering HRVB via the MHP app using a HeartMath® Bluetooth photoplethysmography (PPG) sensor, which was sent to each participant prior to starting the intervention. The sensor was medical grade with real-time autogain control, which collected PPG data from the ear lobe with a sampling rate of 125 Hz and transmitted the raw interpulse intervals. PPG measured at the ear lobe has previously been shown to provide accurate interpulse intervals for HRV measurement (Lu et al., 2009).

First, each participant participated in a 3-min resting assessment in a supine position, from which we computed resting HRV metrics. During the following log-in, each participant received a brief written introduction to HRVB and slow-paced breathing, including how to use the sensor, and was then asked to complete introductory content via the MHP app, during which they could set a daily time as a reminder to engage with the practice. All participants were assigned to a pace of six breaths per minute, which appears to optimize respiratory-induced HRVB oscillations for most individuals (Vaschillo et al., 2002). During each HRVB session, participants were guided by a visual pacer that expanded during inhalation and contracted during exhalation (see Video S1). Participants received additional auditory cues in the form of recorded breath sounds that matched the rate of the visual pacer. At the end of the practice, participants were shown a summary feedback screen detailing the session duration and time spent in low versus high levels of respiratory-induced modulation of HRV (i.e., termed "resonance" in the app, with low resonance defined as falling below a given HRVB amplitude cutoff). Content video instructions featured a concise scientific explanation of the relationship between heart rate, breathing, and the body's ability to self-regulate. Participants who struggled with lightheadedness were given a video about how to avoid hyperventilation (called "over-breathing" in the app).

2.3 | Intervention

The MHP incorporates self-guided modules with interactions with a dedicated, licensed clinical therapist through a smartphone app. The MHP lasts 12 weeks and contains evidence-based practices derived from cognitive behavioral therapy, behavioral activation therapy, mindfulness, sleep therapy, nutritional psychiatry, and HRVB (Economides et al., 2019, 2020). Participant HRVB sessions were done through the app, with guidance from the real-time algorithm controlling the pacer, rather than from a live clinician.

2.4 | Demographics and psychological factors

Demographic variables included self-declared gender (25% male, 73% female, 2% gender expansive) and age (mean = 40 years, range = 18–76 years). Psychological factors included chronicity of major depressive episodes (MDE; none, single, recurrent) and the presence of any lifetime traumatic events (yes/no). Depression and anxiety symptoms were measured on a biweekly basis with the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 Scale (GAD-7), respectively (Table 1). Both questionnaires have excellent psychometric properties and clinical utility (Kroenke et al., 2001; Löwe et al., 2004, 2008; Spitzer et al., 2006).

2.5 | Health factors

Participants were invited to self-report their weight and height, from which body mass index (BMI) was computed (mean = 28, range = 16–68), as well as physician-diagnosed medical conditions including heart disease, hypertension, diabetes (type I, II, or gestational) or prediabetes, high cholesterol, autoimmune disease, respiratory conditions (e.g., asthma), cancer or malignancy, or liver disease (see Table 1). The average resting heart rate was 72 (range = 45–116).

2.6 | Algorithm for real-time HRVB amplitude

A detailed description of the real-time HRVB algorithm, developed by the first author and used to empirically derive HRVB amplitude, is provided in the Supplementary Methods section. Supplementary code resources can be found in online repositories (https://github.com/meruhealth/meru-publications/tree/main/hrvb_toward_precision_care). Using Kubios as a guideline, data cleaning was automated using real-time

TABLE 1 Descriptive statistics of patient population ($N = 5158$).

Characteristics	*n* (%)
Age, mean (std)	40.057 (10.927)
Gender	
Male	1288 (24.971%)
Female	3775 (73.187%)
Expansive	95 (1.842%)
Race	
White	3620 (70.182%)
American Indian	30 (0.582%)
Asian	609 (11.807%)
Black	196 (3.800%)
Hispanic	294 (5.700%)
Other	310 (6.010%)
Declined	99 (1.919%)
Major Depressive Episode Chronicity	
None	2060 (39.938%)
First	1048 (20.318%)
Recurrent	2050 (39.744%)
Trauma history	
No	2687 (52.094%)
Yes	2471 (47.906%)
Psychological symptoms, mean (std)	
Baseline depression (PHQ-9)	10.986 (5.754)
Baseline anxiety (GAD-7)	11.102 (4.759)
Physiological factors, mean (std)	
Resting heart rate	71.856 (11.518)
Resting high-frequency power (ln)	5.522 (1.129)
Resting low-frequency power (ln)	5.874 (1.142)
Health factors*	
Body mass index, mean (std)	27.549 (6.845)
Hypertension	642 (12.447%)
Heart disease	123 (2.385%)
Diabetes or prediabetes	427 (8.278%)
High cholesterol	440 (8.530%)
Cancer or malignancy	234 (4.537%)
Chronic pain	182 (3.528%)
Autoimmune disease	504 (9.771%)
Respiratory conditions	722 (13.998%)
Liver disease	105 (2.036%)

*Participants can have more than one condition.

filtering algorithms to interpolate missing data and remove global outliers, ectopic beats (using a modified Kamanth filter), and movement artifacts (Tarvainen et al., 2014). Next, we applied a rolling window application of a time-bounded Levenberg–Marquardt (LM) algorithm for nonlinear curve-fitting (Aschbacher et al., 2023; Brown & Dennis, 1971; Gavin, 2022; Lu et al., 2019), which utilized a sine function to fit four parameters: amplitude, omega (angular frequency), phase, and the mean heart rate.

2.7 | HRVB amplitude and success rate metrics

The final HRVB amplitude score for each participant session was computed as the median amplitude parameter over all session windows. Finally, we averaged each participant's HRVB amplitude metrics over their first 2 weeks of practice to derive a more trait-like index reflecting individual characteristics such as age and gender while minimizing circadian and state-like variation.

Furthermore, to mathematically simulate whether the pacer would deliver an equitable user experience regardless of age, we computed the percentage of time that a participant's feedback would indicate successful task performance (i.e., high-amplitude HRV oscillations), by quantifying whether the amplitude parameters exceeded a threshold of 2.0 for all session windows. Henceforth, we refer to this metric as the HRVB success rate. A threshold value of 2.0 was chosen because it was already being used in the app at the study start.

2.8 | HRV frequency-domain metrics

HRV frequency-domain metrics were computed using a Lomb–Scargle analysis applied retrospectively to the entire session's cleaned inter-beat interval series (Delane et al., 2016), followed by natural log transformation. For resting assessments, we used the standard HF (0.15–0.40 Hz) and LF domains (0.04–0.15 Hz) (Camm et al., 1996). However, for HRVB session analysis, we used the same subset of the frequency range to measure LF during HRV biofeedback as was used in the real-time algorithm, henceforth referred to as HRVB LF (0.08–0.12 Hz). This was done to (1) enable a direct comparison of HRVB amplitude with the LF metric, by ensuring they were both measured across the same frequency band and (2) ensure that the frequency band appropriately reflected the prescribed breathing pace.

2.9 | Statistical analyses

2.9.1 | Validation of HRVB amplitude

Pearson correlations were computed among the HRV metrics to test whether HRVB amplitude would exhibit strong convergent validity by correlating highly (>0.80) with HRVB LF around the breathing frequency (0.08–0.12 Hz; Figure 2), and strong discriminant validity by exhibiting small to moderate correlations (0.20–0.35) with resting HRV (Table 2). We focused on resting HF as the best indicator for discriminant validity in this context (Figure S5), because during normal breathing at rest, the respiration-associated changes in HRV will contribute to HF rather than LF.

2.9.2 | Age-stratified HRVB metrics

Values for HRVB amplitude stratified by age were generated by first classifying age into roughly 5-year bins (but grouping individuals 65–80 in one final bin due to smaller cell sizes) and computing descriptive statistics. To test the bivariate associations of age with various HRV metrics, we computed the Pearson correlation table among age and HRV metrics: resting heart rate, HF and LF power, LF power around the breathing frequency, and HRVB amplitude. For inferential statistical tests, we utilized the natural log-transformed variables for HRVB amplitude and LF power to improve the normality of the distributions.

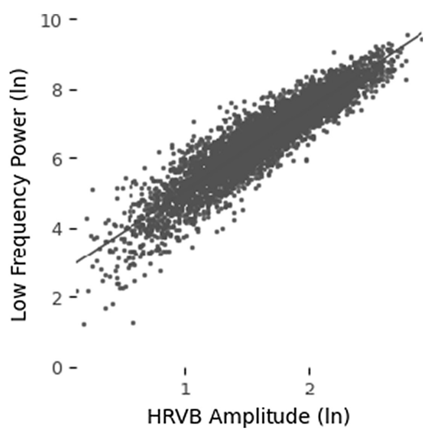

FIGURE 2 The association between HRVB amplitude and low-frequency power during HRVB. The Pearson correlation for this association is $r = .93$, $p < .001$, supporting measurement and construct validity of this metric, HRVB amplitude during biofeedback, computed using a novel algorithm, designed for real-time use. HRVB amplitude and LF (0.08–0.12 Hz), both measured during biofeedback, were natural log-transformed to improve normality.

TABLE 2 Pearson correlations among age and HRV metrics at rest and during biofeedback.

N = 5158	Age	HRVB amplitude (ln)	HRVB LF (.08–.12 Hz ln)	Resting heart rate	Resting LF (ln)	Resting HF (ln)
Age	–	−0.479	−0.429	−0.065	−0.227	−0.300
HRVB Amplitude (ln)	–	–	0.926	−0.046	0.329	0.389
HRVB LF (.08–.12 Hz ln)		–	–	−0.264	0.392	0.454
Resting heart rate	–	–	–	–	−0.306	−0.356
Resting HF (ln)	–	–	–	–	–	0.764
Resting LF (ln)	–	–	–	–	–	–

Note: All *p*-values <.001 due to large sample size; hence, we focus the interpretation on the *r*-values as indications of effect size. HRVB amplitude reflects the median amplitude of the fitted sinusoidal model across all rolling windows, which is half the peak-to-trough height, per the classic definition of sine wave parameters (see supplement for details). HRVB LF reflects the low-frequency power extracted in the frequency band around the prescribed breathing pace of six breaths per minute (0.08–0.12). Resting high-frequency (HF) and low-frequency (LF) power were calculated using standard frequency band definitions (see methods).

Abbreviation: HRVB, Heart rate variability biofeedback.

2.9.3 | Multivariate associations and choice of covariates

To evaluate whether increasing age would remain significantly associated with reduced HRVB amplitude, even when controlling for a variety of other demographic, psychological, and health factors, we tested a series of three nested multivariate linear regression models. All models used the natural log-transformed HRVB amplitude score as the main outcomes. Each nested model tested a broader set of covariates as follows: Model (1) Age, gender, and an age-by-gender interaction; Model (2) Variables from Model 1 plus race/ethnicity and psychological factors; and Model (3) Variables from Model 1 and 2 plus health factors and resting HRV metrics. Covariates were chosen based on prior literature regarding factors impacting HRV and the ultimate goal of building an equitable algorithm. Model 1 specifically tested the hypothesis that the slope of age-associated decline in HRVB amplitude will differ among women versus men. We tested this hypothesis by entering the following independent variables into a linear regression model: age (continuous), gender (female, male, expansive), and the interaction between age and gender. Models 2 and 3 were conducted separately, in anticipation of the fact that health factors used in Model 3 might attenuate the effects of psychological factors like prior history of trauma and MDEs on the outcome, which can only be identified with the current nested design.

3 | RESULTS

3.1 | Participant characteristics

Table 1 describes the participant characteristics for the demographic, psychological, and health factors. Figure S1 illustrates the Lomb–Scargle algorithm across the low-frequency (0.04–0.15 Hz) and high-frequency (0.15–0.40 Hz) ranges for one representative participant. Figure S2 visualizes short rolling windows of data using the bounded Levenberg–Marquardt model for a representative participant.

3.2 | Age-stratified HRVB metrics

Figure 1 and Table S1 provide the data for the mean HRVB amplitude and 95% confidence interval for every age category, binned in 5-year intervals, except for the first and last bins. For comparison, Figure S3 also visualizes the mean HRVB LF power (0.08–0.12 Hz ln) by age category. The HRVB success rate (i.e., percentage of time a user was informed that their performance was successful in increasing HRV during a session) declined steadily from 84% to 52% when comparing participants aged 40–45 years to those aged 65–80 years (Figure S4).

3.3 | Associations of age with HRV

Increasing age was significantly associated with decreases in all HRV metrics in Pearson correlation analyses (Table 2; r's: −.23 to −.48, all p's < .001), including those taken during both resting assessment HRVB sessions.

3.4 | Convergent and divergent validity of HRVB amplitude

As hypothesized, HRVB amplitude was highly correlated (r = .93, p < .001) with HRVB LF (0.08–0.12 Hz; Figure 2),

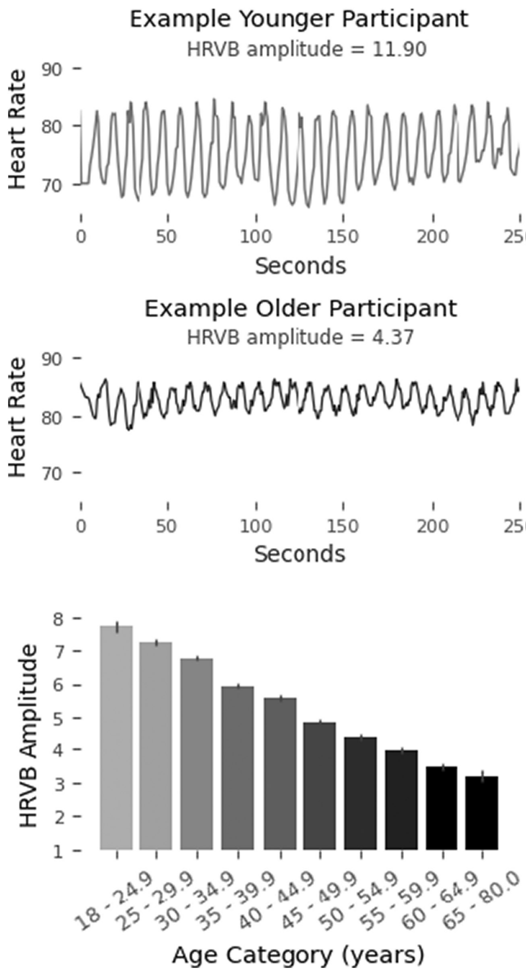

FIGURE 1 The association of age with HRVB amplitude: Example waveforms and aggregate data. Example waveforms of instant heart rate data for one younger participant (between 20 and 29) and one older participant (over 65) during HRV biofeedback are shown above, with their respective HRVB amplitude scores indicated. The bar graph displays the association between age categories and the mean HRVB amplitude values with standard errors. Supplementary Tables provide age-stratified values in the entire sample and for each gender subgroup.

demonstrating high convergent validity. Moreover, HRV amplitude during biofeedback exhibited small to moderate correlations (r's: .33–.39, $p < .001$) with HRV metrics during the resting state (Table 2; Figure S5), thereby demonstrating that HRVB amplitude, calculated with our real-time algorithm, is a unique metric independent of resting HRV.

3.5 | Model 1: Age and gender

Our primary hypothesis that age and gender would exhibit a significant interaction predicting HRVB amplitude was supported (Model 1, Table 3; $p < .001$), with an adjusted R^2 of 23%. As hypothesized, age-related decline in HRVB amplitude was attenuated (or flatter) for participants of female versus male gender. Simple effects follow-up analyses in each gender subgroup revealed that women's HRVB amplitudes decline less steeply with age ($\beta = -0.019$, 95% CI $= -0.020$, 0.018, $p < .001$) compared to men's ($\beta = -0.023$, 95% CI $= -0.026$, -0.021, $p < .001$) and the gender expansive subgroup ($\beta = -0.023$, 95% CI $= -0.029$, -0.017, $p < .001$). Estimates stratified by age and gender identity may be found in Tables S1–S4.

3.6 | Model 2: Demographic and psychological factors

As hypothesized, age- and gender-associated declines in HRVB amplitude remained significant in multivariate analyses adjusting for demographic and psychological factors ($p < .01$; Table 3; see methods for covariate selection). Moreover, participants self-reporting their race as Asian, other, or "declined to state" exhibited significantly lower HRVB amplitude than Whites (p's $< .01$), whereas Blacks and Hispanics did not significantly differ from Whites. Interestingly, baseline depression symptoms and trauma history were associated with significantly lower HRVB amplitude (p's $< .01$), while anxiety symptoms and past MDE severity were not (p's $> .05$). The Pearson correlation between baseline depression and anxiety symptoms was $r = .55$, $p < .01$. Notably, the adjusted R^2 for Model 2 was 26%, improving only 3% relative to nested Model 1, indicating that self-reported race and baseline psychological status exerted small effects.

3.7 | Model 3: Full model including health status

The final Model 3 confirmed that age remained strongly negatively associated with HRVB amplitude ($p < .001$) when additionally adjusting for health factors as well as resting HRV LF and HF power. Effect size comparison (Figure S6) revealed that age accounted for the most variance in HRVB amplitude. The adjusted R^2 was 34% (+8% versus Model 2), with the largest effect sizes after age coming from resting HF and BMI (p's $\leq .001$), followed by resting LF and hypertension (p's $< .05$), while other health factors were non-significant. Having a trauma history (yes/no) became non-significant after controlling for health factors.

TABLE 3 Multivariate associations between HRVB amplitude (ln) and participant characteristics.

Characteristics	Model 1 Coefficient (*SE*)	Model 2 Coefficient (*SE*)	Model 3 Coefficient (*SE*)
Age	−.0228 (.001)**	−.0241 (.001)**	−.0188 (.001)**
Gender			
Male	Referent	Referent	Referent
Female	−.1459 (.05)**	−.1383 (.049)**	−.1009 (.046)*
Gender expansive	−.0497 (.044)	−.011 (.044)	−.0369 (.041)
Age*gender	.0034 (.001)**	.0033 (.001)**	.0025 (.001)*
Race/ethnicity			
White	–	Referent	Referent
Black	–	−.0254 (.029)	.0218 (.028)
Hispanic/Latinx	–	.0151 (.024)	.0141 (.023)
Asian	–	−.1258 (.018)**	−.1313 (.017)**
American Indian	–	−.0767 (.067)	−.0914 (.063)
Other	–	−.1133 (.024)**	−.0815 (.022)**
Declined	–	−.2014 (.041)**	−.1639 (.039)**
Psychological Factors			
Baseline PHQ-9	–	−.0074 (.001)**	−.0035 (.001)**
Baseline GAD-7	–	−.002 (.001)	−.0022 (.001)
Trauma	–	−.0279 (.012)*	−.0204 (.011)
MDE chronicity	–	−.0042 (.007)	.0039 (.006)
Physiological factors			
Resting high frequency power (ln)	–	–	.074 (.007)**
Resting low frequency power (ln)	–	–	.0253 (.007)*
Health factors			
BMI	–	–	−.0088 (.001)**
Hypertension	–	–	−.0576 (.018)**
Heart disease	–	–	−.0612 (.035)
Diabetes	–	–	−.0289 (.021)
High cholesterol	–	–	.0241 (.02)
Cancer	–	–	.0094 (.026)
Chronic pain	–	–	−.0383 (.03)
Autoimmune disorder	–	–	−.0249 (.017)
Respiratory disease	–	–	.0176 (.015)
Liver disease	–	–	.0057 (.039)

Abbreviations: BMI, body mass index; GAD, Generalized Anxiety Disorder; HRVB, heart rate variability biofeedback; MDE, major depressive episode; PHQ, Patient Health Questionnaire; *SE*, standard error.
*$p \leq .05$; **$p \leq .01$.

4 | DISCUSSION

Many studies have shown that HRVB has substantial benefits for mental and physical health (Alayan et al., 2018; Burlacu et al., 2021; Fournié et al., 2021; Lehrer et al., 2020); however, little evidence exists to guide the translation of HRVB from the clinician's office to out-of-clinic, real-time digital interventions. This is the first study to rigorously evaluate the association between a real-time HRVB metric—HRVB amplitude—with demographic, psychological, and health factors. With a cohort of over 5000 patients from across the United States who participated in a therapist-supported DMHI, this study fills an important gap by providing remote providers and participants with the expected range of values for HRVB metrics, measured in naturalistic settings and stratified by age and gender (Goessl et al., 2017; Pizzoli et al., 2021). Furthermore, we demonstrate the need for precision care algorithms by showing that without personalization, automated pacer feedback based on a one-size-fits-all HRVB metric may exhibit substantial algorithmic age biases. Specifically, this would reduce the percentage of time users would receive positive feedback from over 80% to nearly 50%, when comparing people in their early 40 or younger to people over 65 years of age. In sum, the results of this study significantly advance our ability to deliver automated, equitable, and personalized HRVB interventions at scale.

These findings are the first to show an age-related reduction of HRV metrics during biofeedback (e.g., oscillatory amplitude and LF power) in a large sample, when adjusting demographic, physiological, psychological, and health factors. Of all factors studied, age exhibited the largest independent effect on HRV amplitude during biofeedback. This finding is largely consistent with the extant literature on resting HRV assessments (Choi et al., 2020; Jandackova et al., 2016); however, they are novel in that, to our knowledge, there are no published age and gender benchmarks of HRVB metrics in large studies or real-world settings. Hence, the normal aging process appears to involve a general decline in cardiac autonomic modulation (Thayer et al., 2021), which affects HRV both at rest and during biofeedback. Prior studies including older adults have observed age-related attenuation of HRVB metrics. Interestingly, this did not preclude clinical benefits or apparently beneficial changes in the brain of similar magnitude to those of younger adults (Lehrer et al., 2006; Yoo et al., 2022). Hence, this spotlights several critical clarifications for the field, such as whether HRVB amplitude is an important determinant of clinical outcomes and whether participants with lower HRVB amplitudes may require a higher dose or practice duration to achieve similar real-world effectiveness. Alternatively, those with lower age-adjusted HRVB amplitudes at baseline may show similar (or even greater) benefits from biofeedback due to their greater need for intervention to improve autonomic cardiac control.

By gender, male participants exhibited a steeper age-related decline in HRVB amplitude than female participants. This finding aligns with two prior studies, which showed that LF (but not HF) power from resting HRV assessments exhibited a greater age-related decline among men than women (Jandackova et al., 2016; Stein et al., 1997). Given that HRVB enhances baroreflex sensitivity (BRS; Sakakibara et al., 2020), it is noteworthy that a prior study also reported less age-related decline in BRS among women than men (Laitinen et al., 1998). Age-associated decline in HRVB metrics was independent of age-related declines in resting HRV, which may have important mechanistic implications. Resting HF power reflects parasympathetic tone, whereas resting LF power tends to reflect the influence of the baroreflex. However, when participants slow their breathing down, these metrics reflect different physiological mechanisms associated with resonance breathing. In a resting state, natural breathing occurs in the HF range; consequently, the influence of respiration HRV is reflected in higher resting HF or root mean square of successive differences (RMSSD). In contrast, during these biofeedback sessions, the breathing rate is intentionally slowed to a pace of six breaths per minute, which impacts the LF range (Shaffer & Ginsberg, 2017). While some earlier studies have suggested that LF HRV might reflect sympathetic input, recent evidence comparing pharmacological blockade of sympathetic versus parasympathetic activity has revealed that increases in spectral power at the breathing frequency during slow-paced breathing are almost entirely vagally mediated (Kromenacker et al., 2018).

Unlike normal breathing at rest, slow-paced breathing evokes complex interactions between multiple homeostatic systems, such as respiratory sinus arrhythmia, attentional control, and the baroreflex (Shaffer & Meehan, 2020). The baroreflex loop is a feedback-regulated cardiac-brain control system that regulates short-term blood pressure changes (Man et al., 2021). HRVB actively exercises the baroreflex, thereby improving BRS (Lehrer et al., 2003; Sakakibara et al., 2020). Notably, the factors associated with reduced HRVB amplitude in this study are remarkably similar to those associated with lower BRS: older age and poorer cardiometabolic health (Ebert et al., 1992; Lehrer et al., 2003; Man et al., 2021). Thus, real-time HRVB amplitude may provide a unique biomarker of multisystemic resilience lying at the intersection of mental health and cardiometabolic disease.

We elected not to provide HRVB amplitude stratification by race because such categories are poor proxies for biological differences and may better reflect social determinants of health (SDOH) (National Academies of Sciences, Engineering, and Medicine et al., 2022). Whereas prior research suggests that racial discrimination among African Americans adversely impacts stress physiology and biomarkers of cardiovascular risk (Aschbacher et al., 2016; Hill et al., 2017), we did not find lower HRVB amplitudes among Blacks and Hispanics compared to Whites; however, we did find significantly lower HRVB amplitudes among Asians and those who reported other race or chose not to disclose their race, compared to Whites. While some researchers have posited that photoplethysmography might be less accurate among participants with darker skin tones, a recent systematic review reported that the evidence remains inconclusive, with less than half the studies reporting significant skin color-related differences in accuracy and the most comprehensive study of the full range of skin tones finding no significant difference in accuracy across skin tones (Bent et al., 2020; Koerber et al., 2022). Taken together, these findings underscore the need to further examine how SDOH may impact racial and ethnic differences in HRVB and determine strategies to improve standard reporting of race and ethnicity during clinical intakes (Rowen et al., 2022).

Consistent with prior research, we found that higher depression symptoms and the presence of trauma history were associated with lower HRVB amplitude. Surprisingly, anxiety symptoms were not a significant predictor, which might reflect comorbidity with depression or a need for more in-depth anxiety assessment. While the standardized effect sizes for these psychological factors were small in the final model (Model 3), the notable decrease in the effect sizes for depression and trauma from Model 2 to Model 3 suggests that much of their effects are mediated via resting HF power and cardiometabolic health.

Several limitations are acknowledged. Most participants of the investigated DMHI were employed and therefore able to cover program costs through health insurance, limiting the generalizability with the general US adult population. The decline of HRVB amplitude with age might conceivably be even steeper in the general population, given that the older adults in this study were more likely to be employed than retired. These participants may have had higher baseline levels of anxiety and depression than the population at large; nevertheless, psychological factors had small relationships with HRVB amplitude (Figure S6), supporting the generalizability of our age-stratified metrics. This study also did not collect data on psychotropic or cardiovascular medications, precluding our ability to adjust for additional factors that may have impacted HRVB amplitude. These limitations to external validity are offset by the high ecological validity and clinical significance of our main study findings.

This study examined differences in HRVB metrics using measures of self-declared gender identity rather than biological sex. While this may limit inferences about HRVB by sex-associated hormones, using gender identity helps promote diversity and inclusion in DMHIs. While it is possible that the effect sizes in this study may be slightly attenuated compared to highly controlled experimental studies, these data demonstrate that HRVB metrics are robust to guide and personalize the patient's biofeedback experience in real time. Moreover, this novel HRVB metric exhibited strong convergent validity with the research standard metric: LF power.

5 | CONCLUSION

This study's data provides foundational information for incorporating digital HRVB into a DHMI as an adjunctive mind–body treatment component. To automate biofeedback, real-time algorithms are needed that help the end users or patient populations optimize cardiac autonomic training sessions without a clinician present. Although people expect to see their app data, they also disengage when they do not perceive the metrics as actionable and easily interpretable (Reading et al., 2018). Raw numbers and waveforms generated during biofeedback have little inherent meaning to the typical user. As such, evidence-based user experience recommends that an app translate a score into simple color-coded categories to delineate a low versus a high score (Lu et al., 2019). However, categorization without personalization risks algorithmic inequity. This study's findings therefore provide the foundational knowledge to build a precision HRVB algorithm at scale, ensuring a more equitable experience for patients regardless of age, gender, race/ethnicity, and health status, which directly aligns with the US government's Blueprint for an AI Bill of Rights (White House, 2022).

Moreover, participants in a DMHI expect their therapists to be knowledgeable about the range of expected values for real-time HRVB metrics and the factors that influence these metrics, which currently constitutes a gap in the literature. While additional work is needed to develop normative values for comparison of an individual's health status to a larger demographically matched population, these benchmarks provide needed empirical data that empowers consumers of digital HRVB products to have realistic expectations. Finally, now that this study has validated a real-time HRVB amplitude metric, outcomes studies are needed to test the real-world effectiveness of HRVB amplitude as a potential intervention mechanism for improving within-user progress and clinical improvements over time during DHMIs and other digital interventions. With the emergence of slow-paced breathing as a digital therapeutic, this study's findings demonstrate a clear need to ensure that algorithm-based biofeedback utilizes a precision care approach. Similarly, remote clinician feedback can also use these HRVB ranges to help participants interpret their scores and track their progress. Lastly, these findings illustrate that without a precision care algorithm, digital HRVB will be age-biased, thereby risking lower real-world effectiveness. These findings help pave the way for more robust and equitable HRVB metrics as a core component of translational digital medicine and precision psychiatry.

AUTHOR CONTRIBUTIONS

Kirstin Aschbacher: Conceptualization; data curation; formal analysis; investigation; methodology; software; writing – original draft; writing – review and editing. **Mara Mather:** Conceptualization; methodology; writing – review and editing. **Paul Lehrer:** Methodology; validation; writing – review and editing. **Richard Gevirtz:** Methodology; validation; writing – review and editing. **Elissa Epel:** Investigation; methodology; writing – review and editing. **Nicholas C. Peiper:** Conceptualization; funding acquisition; methodology; project administration; supervision; writing – original draft; writing – review and editing.

FUNDING INFORMATION

This study received no specific funding from any funding agency, commercial, or not-for-profit sectors. Dr. Mather reports support from the National Institutes of Health under grants R01AG080652 (PI: Mather), R01AG057184 (PI: Mather), and R21AG080414 (MPI: Ycaza Herrera, Mather). Dr. Epel reports support from the National Institutes of Health under grants R01AG059677 (MPI: Epel, Laraia), U24AG072699 (MPI: Epel, Mendes), R24AG048024 (MPI: Epel, Mendes), R33AT009333 (MPI: Hecht, Epel), and R01DK132870 (MPI: Schmidt, Epel). Dr. Peiper reports support from the National Institutes of Health under grant R44MH126836 (PI: Peiper).

CONFLICT OF INTEREST STATEMENT

The authors KA and NP report employment, salary, and stock options from Meru Health, and the authors MM, PL, RG report being scientific consultants. EE reports no conflicts of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of Meru Health or the US Department of Health and Human Services. All decisions about the research were made by the authors and unrestricted.

DATA AVAILABILITY STATEMENT

Code for this study is openly available in an online repository (https://github.com/meruhealth/meru-publications/tree/main/hrvb_toward_precision_care). De-identified data are not available in a public archive or for distribution to ensure the privacy of the program participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Table S1. Age-stratified HRVB metrics in the entire sample.

Table S2. Age-stratified HRVB metrics of self-reported female gender.

Table S3. Age-stratified HRVB metrics of self-reported male gender.

Table S4. Age-stratified HRVB metrics of self-reported expansive gender.

Figure S1. Spectral power clusters around the respiratory frequency during slow-paced breathing at 0.1 Hz (bottom), unlike during a resting assessment (top).

Figure S2. Simplified example of the bounded Levenberg-Marquardt model applied to rolling windows of instant heart rate data.

Figure S3. Association between low frequency power (0.08–0.12 Hz ln) and age.

Figure S4. HRVB success rate by age category.

Figure S5. The association between HRVB amplitude during biofeedback and high frequency power at rest.

Figure S6. Effect sizes of main effects on real-time HRVB amplitude.

Video S1. How the heart rate variability biofeedback pacer in the app works.

How to cite this article: Aschbacher, K., Mather, M., Lehrer, P., Gevirtz, R., Epel, E., & Peiper, N. C. (2024). Real-time heart rate variability biofeedback amplitude during a large-scale digital mental health intervention differed by age, gender, and mental and physical health. *Psychophysiology*, *00*, e14533. https://doi.org/10.1111/psyp.14533