

UC Irvine

UC Irvine Previously Published Works

Title

The Longitudinal Association of Reduced Vagal Tone With Burnout.

Permalink

<https://escholarship.org/uc/item/3d28c8gz>

Journal

Psychosomatic Medicine, 81(9)

Authors

Wekenborg, Magdalena

Hill, LaBarron

Thayer, Julian

et al.

Publication Date

2019

DOI

10.1097/PSY.0000000000000750

Peer reviewed



Published in final edited form as:

Psychosom Med. 2019 ; 81(9): 791–798. doi:10.1097/PSY.0000000000000750.

The Longitudinal Association of Reduced Vagal Tone with Burnout

Magdalena K. Wekenborg, M.Sc.¹, LaBarron K. Hill, PhD^{2,3}, Julian F. Thayer, PhD⁴, Marlene Penz, PhD¹, R. Arne Wittling, PhD⁵, Clemens Kirschbaum, PhD¹

¹Department of Psychology, TU Dresden, Germany

²Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

³Center for the Study of Aging and Human Development, Duke University Medical Center, Durham, NC, USA

⁴Department of Psychology, The Ohio State University, Columbus, USA

⁵ZNF - Center for Neuroscience Research NPO, Trier, Germany

Abstract

Objective: Previous research indicates a link between burnout symptoms and reduced vagally-mediated heart rate variability (HRV); however, the directionality of this relationship, is still largely unknown. The objective of the present study was to examine the longitudinal relationship between HRV and burnout symptoms over one year, with a special focus on the emotional exhaustion [EE] burnout sub-dimension which remains inadequately distinguished from overlapping with depressive symptoms.

Methods: Here we present HRV and behavioural data from 167 individuals (mean age 43.43, SD 11.78 years; 30.5% male) who attended two biomarker samplings (T1 and T2) of the Dresden Burnout Study approximately twelve months apart.

Results: In hierarchical linear regression analyses, T1 HRV significantly inversely predicted T2 overall burnout symptoms ($\beta = -0.16$; $p = 0.03$), and EE ($\beta = -0.23$; $p = 0.02$), adjusting for age, sex, BMI, adverse health behaviors, and depressive symptoms. Importantly, only high EE at T1 ($\beta = -0.22$; $p = 0.04$), and not the T1 MBI total score, predicted reductions in HRV from T1 to T2.

Conclusion: We report for the first time longitudinal evidence that HRV is associated with changes in burnout symptoms, independently of depressive symptoms. Results suggest vagal-dysfunction being predictive and specific for burnout symptoms, making HRV a promising starting point for the explanation of bio-physiological mechanisms underlying burnout symptoms and cardiovascular diseases (CVD). The finding of only EE at T1 being predictive for changes in HRV underscores the importance of exhaustion for modulations in autonomic regulation.

Corresponding Author: Magdalena Wekenborg, TU Dresden, Department of Psychology, Zellescher Weg 19, D-01069 Dresden, GERMANY, fon: +49 351 463 36359, fax: +49 351 4633 7274, magdalena.wekenborg@tu-dresden.de.

Conflict of interests

The authors report no conflicts of interest.

Keywords

Burnout; exhaustion; heart rate variability; longitudinal study; vagal function

1. Introduction

Over 40 years ago burnout emerged as an important manifestation of chronic work stress characterized by exhaustion (1); however, to date little is known regarding its impact on physiological systems regulating body functions over time. The lack of a concrete, universally-accepted scientific definition of burnout has been one of the main factors contributing to difficulties in aggregating findings across studies of this phenomenon. The current gold standard measure which has been used by the vast majority of studies on burnout, the Maslach Burnout Inventory (MBI) (2), defines burnout as a composite of three distinct sub-domains: the core dimension emotional exhaustion (EE), cynicism, and reduced personal accomplishment. There is keen interest in understanding the psychophysiological mechanisms underlying burnout, as burnout shows growing incidence rates in western countries (3). In addition to its impact on mental health and quality of life (4), burnout also has been associated with physical illness such as musculoskeletal disorders (5) and gastrointestinal problems(6). Importantly, growing evidence has linked burnout with an increased risk of cardiovascular diseases (CVD) (7, 8), the leading cause of morbidity and mortality in western countries (9).

Based on the notion that the autonomic nervous system (ANS) is involved in both stress reactivity and cardiovascular regulation (10), modulations in autonomic function appear to be a valid starting point for the search for physiological underpinnings of burnout in general and its association with CVD, in particular. Heart rate variability (HRV) is a non-invasive physiological index of ANS function (11). It is defined as differences in the time intervals between consecutive heart beats which result from the interplay of its two branches: the sympathetic nervous system (SNS), which facilitates energy mobilization, and the parasympathetic nervous system (PNS), which enables energy conservations via the vagus nerve. Due to differences in neurotransmitter signalling, the vagus nerve is able to modulate the heart rate on a time scale of milliseconds, whereas the SNS responses are much slower (12–14), making high-frequency changes in HRV a relatively pure measure of vagal function. In healthy individuals, the SNS and the PNS are in dynamic balance, allowing fast energy provision if need, but also a rapid decline to energy restoration after termination of the challenge. Chronic stress, however, has been shown to be associated with an imbalance of these two branches resulting in excessive energy demands and insufficient recovery opportunities for the organism as a consequence of an hypoactive vagus (15–17).

Research on burnout and vagally-mediated HRV (HRV), however, is still quite scarce. The little existing epidemiological research on the association between burnouts symptoms, measured using the MBI, and basal HRV revealed mixed results. In a recent study, our group reported associations between modulations in basal autonomic function, indexed by reduced HRV at rest and burnout symptoms in a large, population-based sample (18), which is in line with one previous study (19). However, there are also findings of increased HRV after a

simulated mentally demanding workday among individuals with burnout compared to controls (20), as well as three studies which failed to find any significant associations between burnout and HRV (21–23). Potential reasons for these inconsistent findings include small and selective samples with respect to sex, age and professional subgroups, as well as the afore-mentioned lack of a universally-accepted definition of burnout. Moreover, there has been relatively consistent evidence that the EE sub-domain of burnout, characterized by a loss of energy as a consequence of emotional strain, might be of special relevance for modulations in vagal tone. Even though, our study was the first to explicitly reveal EE-specific associations with modulations in vagal function (18), implicit support for the important role of EE is provided by previous research which has shown the exhaustion dimension of burnout to be more consistently associated with HRV, relative to cynicism and reduced personal accomplishment (19, 20, 24, 25). Further support for the special role of exhaustion for modulations in vagal function comes from previous studies outside of the burnout framework (26–28).

While these initial findings provide some support for the potential role of autonomic function in burnout, the directionality of their association is still not entirely clear, as previous evidence supports the possibility for both directions. Notably, chronic stress has been shown to precede reductions in HRV (see 29). However, there also is empirical evidence of reductions in HRV increasing the risk for poorer cardiovascular, and overall health (30), as well as more recent research demonstrating that vagal stimulation partially ameliorates psychopathological symptoms that overlap with burnout (i.e., 31). Collectively, these latter findings offer consistent support for the notion that reductions in vagal tone precede psychological symptomatology.

To our knowledge, there has been only one previous study of the longitudinal association between HRV and burnout symptoms, a one-year follow-up in patients after their first acute coronary syndrome conducted by Zhang et al. (25). Notably, these researchers found that baseline burnout symptomatology was inversely associated with a 24-hour ambulatory assessment of HRV at four time points during a one-year period. However, these results are somewhat limited, given the selective sample composition, as well as the fact that these researchers only examined the predictive value of burnout symptoms on HRV and not vice versa. In view of the still scarce knowledge on the association between burnout symptoms and autonomic regulation, the present study examined the time sequence of changes in burnout symptoms and HRV between a first visit (T1) and 1-year follow-up (T2) in a large population-based sample. Drawing on our previous findings (18), we were particularly interested in the role of EE,

Given the ongoing debate as to whether or not burnout and depression represent distinct pathological entities (32, 33), we also examined the potential confounding role of depressive symptoms for the association between burnout and HRV, as depressive symptoms have been shown to depict both, a considerable symptomatic overlap with burnout (34), as well as negative association with HRV (for review see 35).

2. Material and methods

2.1 Participants

The current study included participants from the ongoing Dresden Burnout Study (DBS), a large-scale longitudinal study designed to systematically assess societal and biopsychological risk factors of burnout. Recruitment strategies and design of the DBS are described in detail elsewhere (36). Briefly, participants were recruited via public media and the civil register of the city of Dresden. Inclusion criteria were restricted to age 18–68 years and German language skills. The DBS includes an online assessment of a range of psychosocial factors via the official study homepage (www.dresdner-burnout-studie.de). HRV-data used in the present study were obtained during an annual in-person biomarker assessment to which DBS participants with residence in Dresden and within a 60 km radius around the city were invited. 446 participants accepted our invitation to participate in the first biomarker sampling that was conducted from September to October 2015 (T1), whereas only 403 participants had complete data on all demographic, health-related, and psychological variables and could therefore be included in the analyses¹. For the second visit, which was conducted from October to November 2016 and January to February 2017, 507 participants accepted our invitation (T2). Altogether, 173 participants attended both, T1 and T2. During data analysis, 6 participants were excluded due to artefactual heart rate recordings resulting in a final sample of N = 167. Detailed sample characteristics for T1 and T2 are summarized in Table 1. Statistical comparisons did not reveal significant differences between participants who completed visit 2 and the original sample at T1 with respect to sample characteristics (e.g., age, sex, BMI, MBI total score; see Table 1). All participants received a monetary reward of 15 € at T1 and T2.

All participants gave written informed consent. The study protocol was approved by the ethics committee of the TU Dresden and conducted in accordance with the Declaration of Helsinki.

2.2 Protocol

Within one week prior to the biomarker sampling, participants completed an online questionnaire assessing burnout symptoms, depressive symptoms, and provided information on sociodemographic and health-related factors. Laboratory sessions lasted approximately 50 minutes and were conducted between 7 am and 7 pm. These sessions included: a blood draw and hair sample collection (data reported elsewhere, see (37, 38), and assessment of heart rate data.

2.3 Assessment of self-report measures

Covariates were selected based on previously demonstrated associations with HRV in the literature and included: age, sex, BMI, alcohol and caffeine consumption (yes/no), and smoking (yes/no) (39–43).

¹For results of cross-sectional analyses of HRV and burnout symptoms at T1 see (18)

Burnout symptoms were measured with the German version (MBI-GS-D; [44]) of the *Maslach Burnout Inventory-General Survey* (MBI-GS; [45]), the most frequently used burnout measure in the field. The MBI-GS consists of 16 items forming three subscales (EE, cynicism, reduced personal efficacy). The items are rated on a 7-point Likert scale (0 = never, 6 = daily). Given that there is no solid clinical cut-off value established to define high or low burnout, the weighted MBI total score ($[0.4*EE + 0.3*CY + 0.3*Per]$) previously introduced by Kalimo, Pahkin (46), as well as the EE sub score were considered as continuous variables.

Depressive symptoms were assessed with the German version (PHQ-9-D; [47]) of the Patient Health Questionnaire (PHQ-9; [48]). The PHQ-9 consists of nine items, which are scored on a 4-point ranking scale (0 = not at all, 3 = nearly every day), quantifying the frequency, over the last two weeks, of each of the nine diagnostic criteria for a depressive disorder defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; [49]). The nine items are summed to form a continuous variable, with higher scores representing higher severity of depression.

2.3 Assessment of heart rate data

HRV was assessed via recording of continuous heart rate (beat-to-beat) intervals, using a wireless chest transmitter and a wrist monitor recorder (Polar RS800CX, Polar Electro OY, Kempele, Finland), with which participants were provided immediately after arriving at the laboratory and signing the consent forms. Of the complete inter-beat interval (IBI) timeline, recorded during the whole biomarker sampling procedure with a frequency of 1000 Hz, only a 335s period of the seated resting condition was analysed in the present study. A seated rest condition seems especially suited to examine burnout associated changes in autonomic function, as this experimental setting has previously been shown to enable assessment of HRV as a trait-like marker of vagal function (50).

The raw data were transferred to the Polar Precision Performance Software (Polar Electro OY, Kempele, Finland) and exported as raw IBI data for artefact correction conducted by the *Center for Neuroscience Research Trier*, Germany, according to the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (11) using the NEUROCOR® “precisionHRV”-Algorithm (17). During this analysis step, artefacts in the ECG derived RR-Intervals are marked and corrected without violation of the phasing and of the overall time of the signal. Subsequently, mean heart rate (mHR) and HRV measures were calculated. RMSSD was used to operationalize the differences between the RR-intervals of successive heartbeats and is calculated of the square root of the mean of the sum of the squares of differences between adjacent RR intervals. It reflects high frequency variation in heart rate. It is approved for short-term measure of HRV reflecting vagal cardiac influence and its robustness against breathing patterns (11, 50–52). RMSSD values at rest were not normally distributed, thus log transformations were applied to reduce skewness. In order to examine potential differences between different HRV operationalisations, we conducted all analyses with RMSSD and high-frequency [HF-] power HRV (frequency band: 0.15 – 0.4Hz). Since results were virtually identical for RMSSD and HF-HRV, only results for RMSSD are reported.²

2.4 Statistical analysis and data exclusion

The primary interest in this study was to examine longitudinal association patterns between burnout and HRV. In a first step, we removed extreme values of HRV (± 3 SD from the mean of the log-scaled values), leaving a total of $n = 167$ participants.

A series of hierarchical regression models were constructed to examine longitudinal associations between HRV and burnout symptoms. Since there is no convincing evidence regarding the causal direction of the association between burnout symptoms and autonomic function, we decided to test both directions. To avoid multiple testing we focused our analysis on the MBI total score and its EE sub-dimension, as EE has been previously shown to be of special relevance for vagal function (18). In order to account for the high multicollinearity among the MBI total score and EE, separate hierarchical regression analyses were conducted for these measures.

Given the availability of two waves of data, a change-score regression approach was used (53). In the present analyses, the T2-T1 change score for either, the MBI total score, the EE sub-domain, or HRV was first regressed on age, sex, BMI, alcohol consumption, smoking, depressive symptoms and the T1 value of the respective outcome (Basic model); with the focal predictor added in a second step (Model 1: MBI total score change score predicted by T1HRV; Model 2: EE change score predicted by T1 HRV; Model 3: HRV change score predicted by T1 MBI total score; Model 4: HRV change score predicted by T1 EE). All statistical analyses were conducted using IBM SPSS Statistics v. 22 (SPSS Inc., Chicago, IL, USA), significance was set at $p < 0.05$.

3. Results

Demographic and health characteristics of the sample and descriptive statistics (means and SDs) of the assessed variables at T1 and T2 are presented in Table 1. The sample at T2 was characterized by 30.5 % men and a mean age of 43.4 years (SD 11.8; range: 23–68).

Regression coefficients examining the longitudinal associations between HRV and burnout symptoms are reported in Table 2 to Table 4.

3.1 Predictive value of HRV on the temporal changes of burnout symptoms

Results of the hierarchical regression model evaluating the predictive value of T1 HRV on the temporal changes of the MBI total score are presented in Table 2. Both, T1 age ($\beta = 0.20$, $p = .007$) and depressive symptoms ($\beta = 0.23$, $p = .035$) were positively associated with change in burnout, whereas the T1 MBI total score ($\beta = -0.62$, $p < .001$) was significantly inversely associated with change in the MBI total score. Altogether the basic model accounted for 28.7% of the variance ($p < .001$) of the change in the MBI total score. In Model 1, adding T1 HRV to the regression model accounted for an additional 2.1 % of the variance in changes in the MBI total score ($\beta = -0.16$, $p = .030$). High levels of HRV at T1 were predictive of a decrease in the MBI total score³.

²Coefficient of correlation between HF-HRV and RMSSD: (1) at T1: .93, $p < .001$; (2) at T2: .94, $p < .001$; (3) T2-T1 difference score: .89, $p < .001$.

Regression results for the predictive value of T1 HRV on changes in EE are presented in Table 3. The hierarchical regression model at stage one (Basic model) was nearly identical to the basic model predicting changes in the MBI total score. Together the basic model predictors accounted for 25.7 % of the variation in temporal change of EE ($p < .001$). In Model 2, adding T1 HRV to the regression model accounted for an additional 4.6 % of the variance in change in EE ($\beta = -0.23, p = .002$). Participants with high levels of T1 HRV were likely to report a decline in EE⁴.

3.2 Predictive value of burnout symptoms on the temporal changes of HRV

Results of the hierarchical regression models evaluating the predictive value of burnout symptoms on the temporal changes of HRV between T1 and T2 are presented in Table 4. The hierarchical regression model revealed at stage one (Basic model) that age ($\beta = -0.30, p < .001$) and T1 HRV ($\beta = -0.44, p < .001$) were significantly negative correlated with change in HRV from T1 to T2. Altogether the basic model accounted for 22.3% of the variance ($p < .001$).

In Model 3, the T1 MBI total score did not account for a significant amount of additional variance in change in HRV ($R^2 = .14; p = .46$). In Model 4, adding T1 EE to the regression model accounted for an additional 2.1% of the variation in the temporal change of HRV ($\beta = -0.22, p = .040$), suggesting that higher levels of baseline EE prospectively predicted a decrease in HRV between T1 and T2.

Discussion

Growing evidence indicates an increasing prevalence of burnout in industrialized nations and further implicates burnout as a potential risk factor for a range of negative health outcomes (e.g. cardiovascular disease [CVD]). The aim of the present study was to examine longitudinal associations between burnout symptoms and HRV over a one-year period in an age-diverse population-based sample. We found that lower baseline HRV significantly predicted increases in burnout symptomatology overall, as well as with regard to EE. Furthermore, higher EE, but not total burnout symptomatology, predicted reduced levels of HRV. These associations were independent of demographic and health-related factors, depressive symptoms and T1 outcome scores (i.e., burnout symptoms, HRV). These findings suggest that decreased vagal activity may precede an increase in burnout symptoms, however, only the emotional exhaustion component of burnout was predictive of a decrease in HRV over time. While further replication studies are needed to confirm the precise directionality of this association, our results add to and extend previous findings demonstrating a link between burnout and vagally-mediated cardiac autonomic functioning.

Although significant negative cross-sectional associations between burnout symptoms and vagal tone have been previously reported (18,19), to the authors knowledge, this is the first study to provide empirical support for the predictive value of HRV on burnout symptoms.

³Adding mHR at T1 as an additional predictor did not significantly change the result pattern: mHR: $\beta = -.12; p = .20$; HRV: $\beta = -.23, p = .01$

⁴Adding mHR at T1 as an additional predictor did not significantly change the result pattern: mHR: $\beta = -.003; p = .97$; HRV: $\beta = -.24, p = .01$

The only other study to examine this longitudinal association between burnout and HRV mainly assessed indices of HRV that do not specifically reflect vagal modulation of HR. Although HF-power was measured, the other indices reported in this study were the standard deviations of NN intervals [SDNN], low frequency power [LF], very low power [VLF], ultra low frequency power [ULF], and total power [TP] (25). Beyond this, Zhang et al. (25) did not assess HRV at baseline and were therefore unable to investigate the longitudinal effects of baseline vagal function on burnout symptoms. The finding of HRV being predictive of subsequent incident burnout symptoms accords, however, with the model of neurovisceral integration (15), as well as with polyvagal theory (54) which both suggest that healthy affective and social behaviour depends on flexible autonomic regulation, which can be indexed by HRV.

Indeed, empirical examinations of the neurovisceral integration model revealed that HRV was associated with a set of cortical and subcortical structures comprising the central autonomic network (CAN) known to be involved in emotion and self-regulation (i.e., frontal cortex, amygdala) (55). Over time a deficit in these regulatory abilities may promote maladaptive emotional, cognitive, and behavioural patterns, potentially elevating burnout symptoms. In fact, there is preliminary evidence showing that modulations in vagal activity predict changes in affective states sharing conceptual overlap with burnout. For example, there are indications for a positive effect of vagus nerve stimulation on depressive symptomatology (for review see [31]). Determining the aetiological significance of HRV in burnout may have important implications for the mechanisms underlying previously reported associations between burnout and CVD (7,56).

In the present study HRV predicted burnout symptoms, even with depressive symptoms included as a covariate. In addition to providing some of the first indications that HRV may be a valid biomarker for burnout diagnosis and treatment monitoring, these findings also provide support for discriminant validity between burnout and depression. The argument for discriminant validity with respect to depressive symptoms is of special relevance when searching for appropriate biological markers of burnout symptoms, given the ongoing debate on the differentiability of burnout from depression. Within this debate, burnout has been described as an unambiguously distinct pathological entity, a precursor of depression, and as a non-stigmatising synonym for depression (32, 41, 57). Our results support previous efforts to differentiate the two entities based on biological markers (37). It seems, however, to be important, *how* depression is conceptualized. For instance, Zhang et al. (25) found significant longitudinal associations between burnout symptoms and HRV independent of depressive symptomatology, employing a depression measure which focused on the cognitive rather than the somatic symptoms of depression. This is in line with a previous study using a subset of participants from the DBS, which reported that somatic, rather than cognitive symptoms of depression partially attenuated the cross-sectional associations between burnout symptoms and autonomic modulation (18). In contrast, a recent longitudinal study showed HRV to be predictive of cognitive depressive symptoms (58).

Taken together with our present finding of significant effects when adjusting for depressive symptoms operationalized using a composite measure of cognitive and somatic symptoms, these previous results illustrate the lack of clarity as to whether domain-specific depressive

symptomatology may have a differential overlap with burnout and how this may impact the ability to detect unique effects for burnout in association with health and disease. These open questions underline the importance for future research on delineating the role of vagal dysfunction in being able to distinguish between single symptoms rather than aggregated syndrome scores. This is of special importance not only for disentangling the burnout and depression concepts but also for the exploration of the bio-physiological mechanisms underlying associations between CVD and both, burnout and depression (55, 59–61), given previous findings that somatic depressive symptoms may be more predictive of CVD mortality and morbidity than cognitive depressive symptoms (62–64).

As there was little previous evidence to clearly indicate the directionality of burnout - HRV relationships, we used each factor as both the outcome and the focal predictor. Our finding that EE was not only predicted by T1 HRV, but did also, in contrast to total burnout symptomatology, prospectively predict changes in vagal tone, confirms previous suggestions that EE may be uniquely associated with vagal dysfunction in burnout (18). This is in line with the study by Zhang et al. (25) which revealed high burnout symptoms at baseline, operationalized using the Copenhagen Burnout Inventory (CBI) (65), a measure which focuses exclusively on the exhaustion dimension of burnout, to be predictive of decreases in HRV during a one-year period. However, since Zhang et al. (25) included solely Chinese patients following acute coronary syndrome in their study, the generalizability of these results may be limited. As HRV is associated with coronary morbidity and mortality (18), our findings support the previous suggestion that decreased HRV might be a plausible psycho-physiological pathway between burnout and the recurrence of coronary events and potentially CVD mortality. In addition, consideration of our finding for EE with the results of several large epidemiological studies which revealed a notable contribution of exhaustion to recurrent coronary events and mortality after CVD (10, 66–70), further supports the notion that reductions in EE (e.g., via prevention/psychotherapy) may be a useful approach to attenuate the deleterious effects of burnout on cardiovascular health. Clearly, additional experimental and interventional studies are needed to explore this possibility.

Limitations

There are some limitations to the present study that should be considered. First, while we adjusted for a large variety of potential confounders, there remain other potentially important factors (i.e., medication intake, chronic disease, sleep quality) which were not assessed. For instance, since we did not assess clinical endpoints, we were unable to explicitly test effects of burnout symptoms and HRV on CVD incidence over time. Future research incorporating valid and comprehensive medical and psychosocial examinations, as well as a more comprehensive assessment of potential confounders (e.g., caffeine intake, alcohol consumption) is needed. In addition, while our longitudinal design is a definite strength, the time span of one year may be too short to draw firm conclusions regarding the potential longer-term impact of burnout on HRV or to observe relatively large changes in burnout. Subsequent data on the present sample, as well as additional longitudinal research in clinical populations may help to inform these constraints. Third, while the MBI-GS remains the current ‘gold standard’ measure for assessing burnout, the lack of consensus regarding definitional burnout criteria remains a drawback in the field (71). Moreover, there has been

some methodological critique of the MBI-GS (72–74), primarily regarding the underlying factor structure of the instrument. Nonetheless, the 3-factor model of the MBI has shown considerable reliability compared to proposed 1- or 2 factor models (75, 76), and based on its wide use in the burnout research area, the MBI appears to be the most valid research tool in the field at the moment.

In conclusion, our findings indicate that lower HRV is predictive of increased burnout symptoms one year later, suggesting that the examination of autonomic function may be a promising starting point for research on the physiological mechanisms underlying associations between burnout and CVD. Importantly, this effect remained significant even when adjusting for depressive symptoms, further demonstrating that the association between burnout and CVD risk may be independent of previously noted longitudinal associations between HRV and depression. In addition, our findings for the role of EE as both predictor and consequence of reduced HRV confirms its central role in burnout.

Conflicts of Interest and Source of Funding

The authors report no conflicts of interest. This work was supported by the TU Dresden's Institutional Strategy ("The Synergetic University"), which is funded by the Excellence Initiative of the German Federal and State Governments. M.K.W. was supported by the German Academic Scholarship Foundation. L.K.H was supported by funding from the National Institutes of Health/National Heart, Lung, and Blood Institute (HL121708).

Acronyms:

ANS	autonomic nervous system
BMI	body mass index
CBI	Copenhagen Burnout Inventory
CVD	cardiovascular disease
DBS	Dresden Burnout Study
EE	Maslach Burnout Inventory – General scale, emotional exhaustion sub-dimension
HF	high-frequency
HRV	heart rate variability
IBI	inter-beat interval
LF	low-frequency
MBI	Maslach Burnout Inventor
MBI-GS	Maslach Burnout Inventory – General Survey
PHQ-9	Patient Health Questionnaire, depression sum-score
PNS	parasympathetic nervous system

RMSSD	root mean square of successive difference between heart beats
SNS	sympathetic nervous system
VLF	very low-frequency
HRV	vagally-mediated heart rate variability

Literature

1. Freudenberger HJ. Staff burn-out. *J Soc Issues* 1974;30:159–65.
2. Maslach C, Jackson SE. The measurement of experienced burnout. *J Org Behav* 1981;2:99–113.
3. Maske UE, Riedel-Heller SG, Seiffert I, Jacobi F, Hapke U. Häufigkeit und psychiatrische Komorbiditäten von selbstberichtetem diagnostiziertem Burnout-Syndrom. *Psychiatr Prax* 2016;43:18–24. [PubMed: 25158142]
4. Jackson SE, Maslach C. After-effects of job-related stress: families as victims. *J Org Behav* 1982;3:63–77.
5. Honkonen T, Ahola K, Pertovaara M, Isometsä E, Kalimo R, Nykyri E, Aromaa A, Lönnqvist J. The association between burnout and physical illness in the general population—results from the Finnish Health 2000 Study. *J Psychosom Res* 2006;61:59–66. [PubMed: 16813846]
6. Kim H, Ji J, Kao D. Burnout and physical health among social workers: a three-year longitudinal study. *Social Work* 2011;56:258–68. [PubMed: 21848090]
7. Toker S, Melamed S, Berliner S, Zeltser D, Shapira I. Burnout and risk of coronary heart disease: a prospective study of 8838 employees. *Psychosom Med* 2012;74:840–7.
8. Melamed S, Shirom A, Toker S, Shapira I. Burnout and risk of type 2 diabetes: a prospective study of apparently healthy employed persons. *Psychosom Med* 2006;68:863–9.
9. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, AlMazroa MA, Amann M, Anderson HR, Andrews KG. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2013;380:2224–60.
10. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol* 2010;141:122–31. [PubMed: 19910061]
11. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;93:1043–65. [PubMed: 8598068]
12. Berntson GG, Bigger J, Eckberg D, Grossman P, Kaufmann P, Malik M, Nagaraja H, Porges S, Saul J, Stone P, van der Molen M, Bigger JT, Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, van der Molen MW. Heart rate variability: origins, methods, and interpretative caveats. *Psychophysiology* 1997;34:623–48. [PubMed: 9401419]
13. Saul JP. Beat-to-beat variations of heart rate reflect modulation of cardiac autonomic outflow. *Physiology* 1990;5:32–7.
14. Kuo TB, Lai CJ, Huang Y-T, Yang CC. Regression analysis between heart rate variability and baroreflex-related vagus nerve activity in rats. *J Cardiovasc Electrophysiol* 2005;16:864–9. [PubMed: 16101628]
15. Thayer JF, Lane RD. Claude Bernard and the heart–brain connection: further elaboration of a model of neurovisceral integration. *Neurosci Biobehav Rev* 2009;33:81–8. [PubMed: 18771686]
16. Schweiger E, Wittling W, Genzel S, Block A. Relationship between sympathovagal tone and personality traits. *Pers Individ Dif* 1998;25:327–37.
17. Wittling W, Wittling A. *Herzschlagvariabilität: Frühwarnsystem [heart rate variability: early warning system]*. Heiligenstadt, Germany: Eichsfeld Verlag; 2012.
18. Kanthak MK, Stalder T, Hill L, Thayer JF, Penz M, Kirschbaum C. Autonomic dysregulation in burnout and depression: evidence for the central role of exhaustion. *Scand J Work Environ Health* 2017;43:475–84.

19. de Vente W, van Amsterdam JG, Olf M, Kamphuis JH, Emmelkamp PM. Burnout is associated with reduced parasympathetic activity and reduced HPA axis responsiveness, predominantly in males. *Biomed Res Int* 2015;2015:1–13.
20. Zanstra YJ, Schellekens JM, Schaap C, Kooistra L. Vagal and sympathetic activity in burnouts during a mentally demanding workday. *Psychosom Med* 2006;68:583–90. [PubMed: 16868268]
21. van Doornen LJ, Houtveen JH, Langelaan S, Bakker AB, van Rhenen W, Schaufeli WB. Burnout versus work engagement in their effects on 24-hour ambulatory monitored cardiac autonomic function. *Stress Health* 2009;25:323–31.
22. Henning MA, Sollers J, Strom JM, Hill AG, Lyndon MP, Cumin D, Hawken SJ. Junior doctors in their first year: mental health, quality of life, burnout and heart rate variability. *Perspect Med Educ* 2014;3:136–43. [PubMed: 24706177]
23. Jönsson P, Österberg K, Wallergård M, Hansen ÅM, Garde AH, Johansson G, Karlson B. Exhaustion-related changes in cardiovascular and cortisol reactivity to acute psychosocial stress. *Physiol Behav* 2015;151:327–37. [PubMed: 26210042]
24. Lennartsson A-K, Jonsdottir I, Sjörs A. Low heart rate variability in patients with clinical burnout. *Int J Psychophysiol* 2016;110:171–78. [PubMed: 27535344]
25. Zhang M, Liu L, Shi Y, Yang Y, Yu X, Angerer P, Kristensen TS, Li J. Longitudinal associations of burnout with heart rate variability in patients following acute coronary syndrome: a one-year follow-up study. *Gen Hosp Psychiatry* 2018;53:59–64. [PubMed: 29859340]
26. Collins S, Karasek R. Reduced vagal cardiac control variance in exhausted and high strain job subjects. *Int J Occup Med Environ Health* 2010;23:267–78. [PubMed: 20934956]
27. Keltikangas-Järvinen L, Heponiemi T. Vital exhaustion, temperament, and cardiac reactivity in task-induced stress. *Biol Psychol* 2004;65:121–35 [PubMed: 14706435]
28. Watanabe T, Sugiyama Y, Sumi Y, Watanabe M, Takeuchi K, Kobayashi F, Kono K. Effects of vital exhaustion on cardiac autonomic nervous functions assessed by heart rate variability at rest in middle-aged male workers. *Int J Behav Med* 2002;9:68–75. [PubMed: 12112997]
29. Grippo AJ., Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. *Stress* 2009;12:1–21. [PubMed: 19116888]
30. Thayer JF, Sternberg E. Beyond heart rate variability: vagal regulation of allostatic systems. *Ann NY Acad Sci* 2006;1088:361–72. [PubMed: 17192580]
31. Vonck K, Raedt R, Naulaerts J, De Vogelaere F, Thiery E, Van Roost D, Aldenkamp B, Miatton M, Boon P. Vagus nerve stimulation... 25 years later! What do we know about the effects on cognition? *Neurosci Biobehav Rev* 2014;45:63–71. [PubMed: 24858008]
32. Bianchi R, Schonfeld IS, Laurent E. Burnout–depression overlap: a review. *Clin Psychol Rev* 2015;36:28–41. [PubMed: 25638755]
33. Orosz A, Federspiel A, Haisch S, Seeher C, Dierks T, Cattapan K. A biological perspective on differences and similarities between burnout and depression. *Neuroscience & Biobehavioral Reviews* 2017;73:112–22. [PubMed: 27993607]
34. Bianchi R, Boffy C, Hingray C, Truchot D, Laurent E. Comparative symptomatology of burnout and depression. *J Health Psychol* 2013;18:782–87. [PubMed: 23520355]
35. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biol Psychiat* 2010;67:1067–74. [PubMed: 20138254]
36. Penz M, Wekenborg MK, Pieper L, Beesdo-Baum K, Walther A, Miller R, Stalder T, Kirschbaum C. The Dresden Burnout Study: protocol of a prospective cohort study for the bio-psychological investigation of burnout. *Int J Methods Psychiatr Res* 2018:e1613. [PubMed: 29611872]
37. Penz M, Kirschbaum C, Buske-Kirschbaum A, Wekenborg MK, Miller R. Stressful life events predict one-year change of leukocyte composition in peripheral blood. *Psychoneuroendocrinology* 2018;94:17–24. [PubMed: 29751249]
38. Penz M, Stalder T, Miller R, Ludwig VM, Kanthak MK, Kirschbaum C. Hair cortisol as a biological marker for burnout symptomatology. *Psychoneuroendocrinology* 2017;87:218–21. [PubMed: 28781093]

39. Hayano J, Yamada M, Sakakibara Y, Fujinami T, Yokoyama K, Watanabe Y, Takata K. Short-and long-term effects of cigarette smoking on heart rate variability. *Am J Cardiol* 1990;65:84–8. [PubMed: 2294686]
40. Rossy LA, Thayer JF. Fitness and gender-related differences in heart period variability. *Psychosom Med* 1998;60:773–81. [PubMed: 9847039]
41. Karason K, Mølgaard H, Wikstrand J, Sjöström L. Heart rate variability in obesity and the effect of weight loss. *Am J Cardiol* 1999;83:1242–7. [PubMed: 10215292]
42. Thayer JF, Hall M, Sollers JJ, Fischer JE. Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: Evidence for impaired inhibitory control of the HPA axis in heavy drinkers. *Int J Psychophysiol* 2006;59:244–50. [PubMed: 16325293]
43. Koenig J, Jarczok MN, Kuhn W, Morsch K, Schäfer A, Hillecke TK, Thayer JF. Impact of caffeine on heart rate variability: a systematic review. *Journal of Caffeine Research* 2013;3:22–37.
44. Büssing A, Glaser J. Deutsche Fassung des Maslach Burnout Inventory–General Survey (MBI-GS-D). München: Technische Universität München: Lehrstuhl für Psychologie; 1999.
45. Schaufeli WB, Leiter MP, Maslach C, Jackson SE. Maslach Burnout Inventory-General Survey. Maslach C, Jackson SE, Leiter MP, editors (3rd ed.). Palo Alto, CA: Consulting Psychologists Press; 1996.
46. Kalimo R, Pahkin K, Mutanen P, Topipinen-Tanner S. Staying well or burning out at work: work characteristics and personal resources as long-term predictors. *Work Stress* 2003;17:109–22.
47. Löwe BP, Spitzer RL. Gesundheitsfragebogen für Patienten PHQ-D: Manual; Komplettversion und Kurzform. Berlin, Germany: Pfizer GmbH; 2001.
48. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13. [PubMed: 11556941]
49. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th ed. text rev.). Washington, DC: Author; 2000.
50. Bertsch K, Hagemann D, Naumann E, Schächinger H, Schulz A. Stability of heart rate variability indices reflecting parasympathetic activity. *Psychophysiology* 2012;49:672–82. [PubMed: 22335779]
51. Hill LK, Siebenbrock A, Sollers JJ, Thayer JF. Are all measures created equal? Heart rate variability and respiration. *Biomed Sci Instrum* 2009;45:71–6. [PubMed: 19369742]
52. Penttilä J, Helminen A, Jartti T, Kuusela T, Huikuri HV, Tulppo MP, Coffeng R, Scheinin H. Time domain, geometrical and frequency domain analysis of cardiac vagal outflow: effects of various respiratory patterns. *Clin Physiol* 2001;21:365–76. [PubMed: 11380537]
53. Dalecki M, Willits FK. Examining change using regression analysis: three approaches compared. *Sociol Spectr* 1991;11:127–45.
54. Porges SW. The polyvagal perspective. *Biol Psychol* 2007; 74:116–143. [PubMed: 17049418]
55. Thayer JF, Åhs F, Fredrikson M, Sollers Iii JJ, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev* 2012;36:747–56. [PubMed: 22178086]
56. Melamed S, Shirom A, Toker S, Berliner S, Shapira I. Burnout and risk of cardiovascular disease: evidence, possible causal paths, and promising research directions. *Psychol Bull* 2006;132:327–53. [PubMed: 16719565]
57. Schonfeld IS, Bianchi R. Burnout and depression: two entities or one? *Clin Psych* 2016;72:22–37.
58. Jandackova VK, Britton A, Malik M, Steptoe A. Heart rate variability and depressive symptoms: a cross-lagged analysis over a 10-year period in the Whitehall II study. *Psychol Med* 2016;46:2121–31. [PubMed: 27181276]
59. Cohen R, Bavishi C, Haider S, Thankachen J, Rozanski A. Meta-analysis of relation of vital exhaustion to cardiovascular disease events. *Am J Cardiol* 2017;119:1211–6. [PubMed: 28215416]
60. Meijer A, Conradi H, Bos E, Anselmino M, Carney R, Denollet J, Doyle F, Freedland K, Grace S, Hosseini S. Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: individual patient data meta-analysis. *Br J Psychiatry* 2013;203:90–102. [PubMed: 23908341]

61. Frestad D, Prescott E. Vital exhaustion and coronary heart disease risk: a systematic review and meta-analysis. *Psychosom Med* 2017;79:260–72. [PubMed: 27902666]
62. Schiffer AA, Pelle AJ, Smith OR, Widdershoven JW, Hendriks EH, Pedersen SS. Somatic versus cognitive symptoms of depression as predictors of all-cause mortality and health status in chronic heart failure. *J Clin Psychiatry* 2009;70:1667–73. [PubMed: 19646367]
63. Roest AM, Carney RM, Freedland KE, Martens EJ, Denollet J, de Jonge P. Changes in cognitive versus somatic symptoms of depression and event-free survival following acute myocardial infarction in the Enhancing Recovery In Coronary Heart Disease (ENRICH) study. *J Affect Disord* 2013;149:335–41. [PubMed: 23489396]
64. Linke SE, Rutledge T, Johnson BD, Vaccarino V, Bittner V, Cornell CE, Eteiba W, Sheps DS, Krantz DS, Parashar S. Depressive symptom dimensions and cardiovascular prognosis among women with suspected myocardial ischemia: a report from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. *Arch Gen Psychiatry* 2009;66:499–507. [PubMed: 19414709]
65. Kristensen TS, Borritz M, Villadsen E, Christensen KB. The Copenhagen Burnout Inventory: a new tool for the assessment of burnout. *Work Stress* 2005;19:192–207.
66. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. *Biol Psychol* 2007;74:224–42. [PubMed: 17182165]
67. Kop WJ, Appels A, de Leon Mendes C, Bär F. Vital exhaustion predicts new cardiac events after successful coronary angioplasty. *Psychosom Med* 1994;56:281–7. [PubMed: 7972608]
68. Koertge J, Wamala S, Janszky I, Ahnve S, Al-Khalili F, Blom M, Chesney M, Sundin Ö, Svane B, Schenck-Gustafsson K. Vital exhaustion and recurrence of CHD in women with acute myocardial infarction. *Psychol Health Med* 2002;7:117–26.
69. Smith OR, Gidron Y, Kupper N, Winter JB, Denollet J. Vital exhaustion in chronic heart failure: symptom profiles and clinical outcome. *J Psychosom Res* 2009;66:195–201. [PubMed: 19232231]
70. Volz A, Schmid J-P, Zwahlen M, Kohls S, Saner H, Barth J. Predictors of readmission and health related quality of life in patients with chronic heart failure: a comparison of different psychosocial aspects. *Int J Behav Med* 2011;34:13–22.
71. Maslach C, Jackson SE, Leiter MP. *Maslach Burnout Inventory: Manual* (2nd ed.) Paolo Alto, CA: Consulting Psychologist Press; 1986.
72. Demerouti E, Bakker AB, Nachreiner F, Schaufeli WB. The job demands-resources model of burnout. *Journal of Applied Psychology* 2001;86:499. [PubMed: 11419809]
73. Bouman AM, Brake HT, Hoogstraten J. Significant effects due to rephrasing the Maslach Burnout Inventory's personal accomplishment items. *Psychological Reports* 2002;91:825–6. [PubMed: 12530729]
74. Shirom A *Job-related burnout: a review*. Washington, DC: American Psychological Association; 2003.
75. Schaufeli WB, Bakker AB, Hoogduin K, Schaap C, Kladler A. On the clinical validity of the Maslach Burnout Inventory and the Burnout Measure. *Psychology & Health* 2001;16:565–82. [PubMed: 22804499]
76. Schutte N, Toppinen S, Kalimo R, Schaufeli W. The factorial validity of the Maslach Burnout Inventory-General Survey (MBI-GS) across occupational groups and nations. *J Occup Organ Psychol* 2000;73:53–66.

Table 1

Demographic and clinical characteristics for the sample at rest for first visit (T1) and follow-up (T2)

	T1 initial sample (N = 403)			T1 tested at both time points (N = 167)			T2 (N = 167)			Group comparison T1(N = 403) T2 (N = 167)		Group comparison T1(N = 167) T2 (N = 167)	
	N (%) or mean \pm s.d.	Range		N (%) or mean \pm s.d.	Range		N (%) or mean \pm s.d.	Range					
Demographics													
Age (years)	42.0 \pm 11.2	19–67		42.1 \pm 11.7	20–67		43.4 \pm 11.8	23–68		$F(1,569) = 1.85$,ns		$t(66) = -5.26$,s	
Male	133 (33.3)			51 (30.5)			51 (30.5)			$F(1,569) = 0.44$,ns			
BMI (kg/m ²)	25.3 \pm 4.6	17.3–42.5		24.6 \pm 4.1	17.3–39.1		24.7 \pm 4.1	15.1–38.5		$F(1,569) = 2.13$,ns		$t(66) = -1.19$,ns	
Health related factors													
Smokers	54 (13.4)			22 (13.4)			17 (10.2)			$F(1,569) = 1.10$,ns		$t(66) = 1.42$,ns	
Caffeine consumer	373 (92.6)			154 (92.2)			155 (92.8)			$F(1,569) = 0.01$,ns		$t(66) < 0.01$,ns	
Alcohol consumer	345 (85.6)			143 (85.6)			149 (89.2)			$F(1,569) = 1.31$,ns		$t(66) = -1.61$,ns	
MBI total score	2.2 \pm 1.2	0.0–5.4		2.1 \pm 1.2	0.0–4.6		2.2 \pm 1.1	0.2–5.7		$F(1,569) = 0.03$,ns		$t(66) = -1.83$,ns	
Emotional exhaustion													
Cynicism	2.0 \pm 1.5	0.0–6.0		2.0 \pm 1.5	0.0–5.8		2.1 \pm 1.4	0.0–6.0		$F(1,569) = 0.90$,ns		$t(66) = -1.77$,ns	
Reduced personal accomplishment	1.6 \pm 1.1	0.0–6.0		1.6 \pm 1.1	0.0–4.5		1.6 \pm 1.0	0.0–6.0		$F(1,569) = 0.44$,ns		$t(66) = 0.19$,ns	
PHQ-9	8.3 \pm 5.3	0.0–26.0		7.9 \pm 5.1	0.0–23.0		7.7 \pm 5.0	0.0–22.0		$F(1,569) = 1.67$,ns		$t(66) = 0.70$,ns	
HRV at rest	35.8 \pm 22.1	6.2–147.6		36.3 \pm 22.1	6.2–134.9		38.2 \pm 25.0	4.6–128.5		$F(1,569) = 1.30$,ns		$t(66) = -1.19$,ns	

Note. BMI = body mass index, MBI total score = Maslach Burnout Inventory - General Survey total score, burnout sum-score, PHQ-9 = Patient Health Questionnaire, depression sum-score, HRV = vagal-mediated heart rate variability (e.g. root mean square of successive difference between heart beats [RMSSD]). s = significant; ns = not significant.

Table 2 Hierarchical regression model predicting temporal changes in the MBI total score ($N = 167$)

Model 1									
	<i>b</i>	<i>se</i>	β	<i>p</i>	<i>b</i>	<i>se</i>	β	<i>p</i>	<i>p</i>
Age	.01	.01	.20	.007	.01	.01	.15	.15	.046
Sex	-.18	.12	-.10	.15	-.19	.12	-.11	-.11	.12
BMI	-.002	.02	-.01	.91	-.01	.01	-.03	-.03	.72
Alcohol consumption	-.08	.17	-.04	.12	-.11	.17	-.05	-.05	.51
Smoking	.26	.17	.11	.12	.29	.17	.12	.12	.085
Caffeine consumption	-.26	.23	-.08	.26	-.25	.23	-.08	-.08	.28
PHQ-9	.04	.02	.23	.035	.03	.02	.20	.20	.060
MBI total score T1	-.42	.07	-.62	<.001	-.41	.07	-.60	-.60	<.001
HRV					-.22	-.10	-.16	-.16	.030
R^2	.29**								
R^2	.02*								

Note. BMI = body mass index; MBI total score T1 = Maslach Burnout Inventory - General Survey total score; burnout sum-score at T1 biomarker sampling; PHQ-9 = Patient Health Questionnaire, depression sum-score; HRV = vagal-mediated heart rate variability (i.e. root mean square of successive difference between heart beats [RMSSD]).

* $p < .05$;

** $p < .001$

Table 3Hierarchical regression model predicting temporal changes in emotional exhaustion [EE] $N=167$)

	Model 2				<i>b</i>	<i>se</i>	β	<i>p</i>
	<i>b</i>	<i>se</i>	β	<i>p</i>				
Age	.02	.01	.23	.002	.02	.01	.16	.041
Sex	-.14	.18	-.06	.43	-.17	.18	-.07	.35
BMI	-.02	.02	-.07	.37	-.03	.02	-.09	.20
Alcohol consumption	-.35	.25	-.11	.16	-.41	.24	-.14	.095
Smoking	.44	.25	.13	.077	.50	.24	.14	.040
Caffeine consumption	-.28	.34	-.06	.41	-.26	.33	-.06	.44
PHQ-9	.05	.02	.21	.048	.04	.02	.18	.073
EE_{T1}	-.45	.08	-.58	<.001	-.44	.08	-.57	<.001
HRV					-.47	.15	-.23	.002
<i>R</i>²				.26**				
<i>R</i>²								.05*

Note. BMI = body mass index; EE_{T1} = Maslach Burnout Inventory – General Survey, emotional exhaustion sub-dimension at T1 biomarker sampling; PHQ-9 = Patient Health Questionnaire, depression sum-score; HRV = vagal-mediated heart rate variability (e.g. root mean square of successive difference between heart beats [RMSSD]).

* $p < .05$;

** $p < .001$

Table 4

Hierarchical regression models predicting temporal changes in HRV ($N = 167$)

	Basic Model			Model 2			Model 3					
	<i>b</i>	<i>se</i>	β	<i>b</i>	<i>se</i>	β	<i>b</i>	<i>se</i>	β	<i>p</i>		
Age	-.01	.004	-.30	<.001	-.01	.004	-.31	<.001	-.01	.004	-.31	<.001
Sex	.11	.08	.09	.19	.13	.09	.11	.13	.14	.09	.12	.10
BMI	.001	.01	.01	.92	.001	.01	.01	.94	.002	.01	.02	.84
Alcohol consumption	.15	.12	.10	.20	.15	.12	.10	.21	.15	.12	.10	.21
Smoking	-.16	.12	-.10	.17	-.16	.12	-.10	.18	-.16	.12	-.10	.17
Caffeine consumption	.14	.16	.07	.40	.13	.16	.06	.44	.11	.16	.05	.51
PHQ-9	-.002	.01	-.02	.82	.01	.01	.13	.26	.02	.01	.14	.18
HRV _{T1}	-.40	.07	-.44	<.001	-.40	.07	-.43	<.001	-.40	.07	-.44	<.001
MBI total score
EE
R^2	.22**											
R^2	.01											
	.02*											

Note. BMI = body mass index; EE = Maslach Burnout Inventory – General Survey, emotional exhaustion sub-dimension; MBI total score = Maslach Burnout Inventory - General Survey total score, burnout sum-score; PHQ-9 = Patient Health Questionnaire, depression sum-score sum score; HRV_{T1} = vagal-mediated heart rate variability (e.g. root mean square of successive difference between heart beats [RMSSD]) at T1 biomarker sampling.

* $p < .05$;

** $p < .001$