University of Zurich[UZH]

Zurich Open Repository and Archive
University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2023

Exhaustion and cardiovascular risk factors: the role of vagally-mediated heart rate variability

Wekenborg, Magdalena K ; Künzel, Richard G ; Rothe, Nicole ; Penz, Marlene ; Walther, Andreas ; Kirschbaum, Clemens ; Thayer, Julian F ; Hill, LaBarron K

Abstract: Purpose Exhaustion symptoms are known to be associated with cardiovascular disease (CVD) risk; however, the underlying mechanisms remain unclear. Autonomic imbalance, as indicated by reductions in vagally-mediated heart rate variability (vmHRV), appears to be a valid candidate for such a biological link, as it has been associated with both exhaustion symptoms and CVD risk and mortality. Methods The present study examined a potential mediation of vmHRV on the association between exhaustion symptoms and self-reported CVD risk factors as well as the age dependency of this mediation in a large, heterogeneous sample of the Dresden Burnout Study (N = 388; 72.9% females; Mage = 42.61, SD = 11.67). Results Results indicate that exhaustion symptoms were indirectly associated with CVD risk factors through vmHRV even after adjusting for well-known confounders (i.e., sex, body mass index, depressive symptoms). Moreover, this pattern was significant only among middle-aged (i.e., 54.27 years) and older individuals. Conclusions Our findings add to growing evidence that autonomic imbalance may be a key biological link between exhaustion symptoms and CVD risk in middle-aged and older individuals. Implications for public health are discussed.

DOI: https://doi.org/10.1016/j.annepidem.2023.09.008

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-254497
Journal Article
Published Version

The following work is licensed under a Creative Commons: Attribution 4.0 International (CC BY 4.0) License.

Originally published at:
Wekenborg, Magdalena K; Künzel, Richard G; Rothe, Nicole; Penz, Marlene; Walther, Andreas; Kirschbaum, Clemens; Thayer, Julian F; Hill, LaBarron K (2023). Exhaustion and cardiovascular risk factors: the role of vagally-mediated heart rate variability. Annals of Epidemiology, 87:93-99.e2.
DOI: https://doi.org/10.1016/j.annepidem.2023.09.008

Annals of Epidemiology 87 (2023) 93–99

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: sciencedirect.com/journal/annals-of-epidemiology

Exhaustion and cardiovascular risk factors: the role of vagally-mediated heart rate variability

Magdalena K. Wekenborg, PhD [a,b,*,1], Richard G. Künzel, M. Sc. [a,1], Nicole Rothe, PhD [a], Marlene Penz, PhD [c], Andreas Walther, PhD [d], Clemens Kirschbaum, PhD [a], Julian F. Thayer, PhD [e], LaBarron K. Hill, PhD [f]

[a] Chair of Biological Psychology, Faculty of Psychology, TU Dresden, Dresden, Germany
[b] Else Kröner Fresenius Center for Digital Health, Faculty of Medicine and University Hospital Carl Gustav Carus, Dresden, Germany
[c] Institute of Education and Psychology, Johannes Kepler University, Linz, Austria
[d] Clinical Psychology and Psychotherapy, University of Zurich, Zürich, Switzerland
[e] Department of Psychological Science, School of Social Ecology, University of California, Irvine
[f] Department of Psychology, North Carolina Agricultural & Technical State University, Greensboro

ARTICLE INFO

Article history:
Received 20 June 2023
Received in revised form 18 September 2023
Accepted 20 September 2023
Available online 23 September 2023

Keywords:
Exhaustion
Cardiovascular disease
Heart rate variability
Parasympathetic nervous system
Autonomic imbalance
Age

ABSTRACT

Purpose: Exhaustion symptoms are known to be associated with cardiovascular disease (CVD) risk; however, the underlying mechanisms remain unclear. Autonomic imbalance, as indicated by reductions in vagally-mediated heart rate variability (vmHRV), appears to be a valid candidate for such a biological link, as it has been associated with both exhaustion symptoms and CVD risk and mortality.
Methods: The present study examined a potential mediation of vmHRV on the association between exhaustion symptoms and self-reported CVD risk factors as well as the age dependency of this mediation in a large, heterogeneous sample of the Dresden Burnout Study (N = 388; 72.9% females; M_{age} = 42.61, SD = 11.67).
Results: Results indicate that exhaustion symptoms were indirectly associated with CVD risk factors through vmHRV even after adjusting for well-known confounders (i.e., sex, body mass index, depressive symptoms). Moreover, this pattern was significant only among middle-aged (i.e., 54.27 years) and older individuals.
Conclusions: Our findings add to growing evidence that autonomic imbalance may be a key biological link between exhaustion symptoms and CVD risk in middle-aged and older individuals. Implications for public health are discussed.

© 2023 Elsevier Inc. All rights reserved.

Purpose

Cardiovascular disease (CVD) remains the leading contributor to global disease burden and a major cause of global morbidity and mortality [1–3]. While CVD-related mortality is particularly high in low- and middle-income countries, high-income countries have consistently achieved decreases over the past 30 years [2]. Strikingly, a recent update on the Global Burden of Cardiovascular Diseases Report revealed renewed increases in CVD rates in some high-income countries, including the UK, over the past 5 years [2]. Furthermore, high premature CVD mortality has been found to be the main reason for Germany's lagging life expectancy compared to other high-income countries, especially among higher aged workers [4]. Interestingly, recent studies have associated the work stress–related burnout syndrome and its core symptom, emotional exhaustion, with an elevated risk for CVD [5–9]. After the tremendous impact of aging alone, the most important biological CVD risk factors hypertension [10], hypercholesterolemia [11], and diabetes [12] have also been linked to burnout and exhaustion. Consequently, the German Cardiac Society has recently recommended the integration of stress and exhaustion screening in preventive cardiac care [13].

* Corresponding author. TU Dresden, Department of Psychology, Zellescher Weg 19, D-01069 Dresden, Germany.
E-mail addresses: magdalena.wekenborg@tu-dresden.de (M.K. Wekenborg), richard.kuenzel@gmx.de (R.G. Künzel), nicole.rothe@tu-dresden.de (N. Rothe), marlene.penz@jku.at (M. Penz), andreas.walther@tu-dresden.de (A. Walther), clemens.kirschbaum@tu-dresden.de (C. Kirschbaum), jfthayer@uci.edu (J.F. Thayer), hill.871@gmail.com (L.K. Hill).
[1] These authors contributed equally to the work.

https://doi.org/10.1016/j.annepidem.2023.09.008
1047-2797/© 2023 Elsevier Inc. All rights reserved.

Regrettably, the biological underpinnings linking stress-related exhaustion and CVD risk factors are still not fully understood. Nevertheless, it is likely that the autonomic nervous system (ANS) plays a vital role, as it is involved in both the etiology of CVD and the bodily response to stress [14]. In healthy individuals, the response to acute stress and environmental challenges is regulated by the dynamic balance between energy provision and energy restoration through the two branches of the ANS: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), respectively. Under chronic stress, the SNS influence becomes predominant leading to a decline in PNS function which can result in autonomic imbalance [15]. A significant biomarker of autonomic imbalance is reduced vagally-mediated heart rate variability (vmHRV) which is commonly conceptualized as high-frequency changes of the interbeat intervals (IBI) between consecutive heart beats [16]. These high-frequency changes, occurring in milliseconds, are primarily modulated by the vagus nerve due to chemical and anatomical differences [17], making vmHRV a relatively pure biomarker of PNS activity [16].

Previous studies, including our own, have shown associations between vmHRV and both exhaustion [18–20] and established CVD risk factors including hypertension, hypercholesterolemia, and diabetes [14]. Furthermore, these associations might be influenced by age, as age surpasses all other CVD risk indicators as a predictor of clinical events [21]. Additionally, age has been negatively related to vmHRV [22] and positively correlated with exhaustion symptoms, albeit inconsistently [23–26] Taken together, previous research indicates a potential age-related mediating role of vmHRV in the relationship between exhaustion symptoms and CVD risk. However, to the best of our knowledge, no previous study has examined this indirect relationship.

Therefore, in the present study, we aimed to examine the following two hypotheses: (1) vmHRV mediates the positive association between exhaustion symptoms and CVD risk, and (2) age moderates the direct and/or indirect effects of exhaustion on CVD risk through vmHRV, in a large, heterogeneous sample from the Dresden Burnout Study (DBS).

Methods

Participants and procedure

This study is based on data from a subsample of the ongoing DBS [27], a large-scale prospective investigation of biopsychological risk and protective factors associated with burnout. A comprehensive description of the study design and procedure can be found elsewhere [27]. Briefly, the cohort consists of socioeconomically diverse German speaking participants between 18 and 68 years of age who took part in an online and a subsequent biomarker assessment. Data of the present subsample were collected between September and December 2017. Altogether, N = 423 participants accepted our invitation to the biomarker assessment which lasted approximately 50 minutes and was conducted between 7 AM and 7 PM. Participants were instructed to refrain from excessive physical activity, drinking alcohol, and smoking 24 hours before the study session. After arriving at the laboratory, participants signed consent forms and were provided with heart rate devices (Polar RS800TM, Polar Electro, Oy, Kempele, Finnland). To obtain a baseline measure of vmHRV, participants were led to a separate room, where 6 minutes of seated resting heart rate was recorded. Demographic, health-related, and psychological variables were collected 1 week before the biomarker assessment via an online questionnaire. Complete data were the perquisite for inclusion in the present data analyses, resulting in a sample of N = 392. The DBS has been approved by the local ethics committee of the TU Dresden. All participants provided informed consent. Participants received a monetary compensation of 15 €.

Self-report measures

Exhaustion symptoms were measured with the German version (MBI-GS-D [28]) of the Maslach Burnout Inventory-General Survey (MBI-GS [29]). The five exhaustion related items of the MBI-GS are rated on a 7-point Likert scale (0 = never, 6 = daily) and summed to provide an unweighted exhaustion score. Higher scores represented higher severity of exhaustion symptoms. To assess the general mental state of the sample, depression symptoms were assessed with the German version of the Patient Health Questionnaire-9 (PHQ-9 [30]) and anxiety symptoms were assessed using the German version of the Generalized Anxiety Disorder-7 Questionnaire (GAD-7 [31]). Investigator-generated items were used to assess sociodemographic and health-related factors, namely age (in years), biological sex at birth (sex), height (cm) and weight (kg) to calculate body mass index (BMI), smoking (yes/no), alcohol drinking (yes/no), and caffeine intake (yes/no), as associations of these variables with vmHRV have frequently been reported. Participants self-reported any physician diagnosed medical conditions. A cumulative CVD risk score was calculated as the sum of the presence (1) or absence (0) of three primary biological CVD risk factors hypertension, hypercholesterolemia, and diabetes which are consistently part of established CVD risk score models [32] and are globally used for epidemiological CVD risk estimation by the World Health Organization [33]. The assessment of the absence or presence of these risk factors (hypertension [yes/no]; high cholesterol [yes/no], diabetes [yes/no]) was conducted through self-reports (i.e., “Have you been diagnosed by a physician with the following health conditions?”), which have demonstrated reliability in previous epidemiological studies [34, 35]. The utilization of a risk score was preferred due to previous research suggesting that sum scores provide more informative predictions regarding CVD compared to individual risk factors [36]. We employed a simple sum score because established CVD risk scores typically incorporate biological data (i.e., systolic and diastolic blood pressure, cholesterol) as well as information regarding, lifestyle-related (e.g., physical activity) and nonmodifiable (e.g., family history of CVD) risk factors [37] which were not investigated in the DBS.

Vagally-mediated heart rate variability

During the entire biomarker assessment, the Polar RS800 CX system (Polar Electro OY, Kempele, Finland) was employed to obtain IBI and heart rate data. The device consists of a watch unit and a chest-worn apparatus containing electrodes which record R-R intervals at a sampling frequency of 1000 Hz. These data are transmitted and stored to the watch for later inspection, processing, and analysis. The Polar RS800 CX system has demonstrated moderate to acceptable test-retest reliability over a 2-week interval in previous population-based German samples, yielding time domain metrics of heart rate variability showing greater consistency (Intra-class Correlation Coefficient range 0.50–0.70) relative to frequency domain parameters (Intra-class Correlation Coefficient range 0.10–0.60) [38]. Of the complete IBI timeline, only the initial 335 seconds of the seated resting condition, which was recorded at the end of the biomarker assessment procedure, was analyzed in the present study. This interval was chosen in order to avoid potential anticipatory fears with respect to a venipuncture which was also part of the biomarker assessment for a different study objective. To have a comparable time window from all participants, we decided to take the first 335 seconds, since this time window has been shown

to obtain valid vmHRV estimates [16, 39] and was available from all subjects.

Data were transferred to the Polar Precision Performance Software (Polar Electro OY, Kempele, Finland) and exported as raw IBI data for further analysis. The raw data were artifact corrected by Neurocor Ltd. & Co. KG (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 [16] using the NEUROCOR precision HRV-Algorithm. During this analysis step, artifacts in Electrocardiogram-recordings are marked and corrected without violation of the phasing of the overall time of the signal. Subsequently, vmHRV measures were calculated. Preliminary analyses revealed high positive correlations between the root mean square of successive differences in the time intervals between consecutive heart beats (measurement of the time between two consecutive R-waves in the ECG waveform (RR) intervals - the time elapsed between two successive R waves of the electrocardiogram combination of three of the graphical deflections seen on a typical electrocardiogram (Q wave, R wave, and S wave) (QRS) complex - the time elapsed between two successive R waves of the electrocardiogram QRS complex (RMSSD) [ms]) and high-frequency heart rate variability (hf-HRV [ms²]; r = 0.94; P < .001). In the following analysis, RMSSD was used to operationalize hf-HRV as it is an approved short-term measure of vmHRV which is robust against respiratory influences [40].

Statistical analysis and data exclusion

RMSSD values at rest were not normally distributed, thus log transformations were applied to reduce skewness the time elapsed between two successive R waves of the electrocardiogram QRS complex, logarithmized (lnRMSSD). Four extreme values (lnRMSSD values ± 3 SD) were excluded, resulting in a final sample of N = 388. Descriptive statistics were computed to characterize the sample, and associations between the study variables were quantified by computing Pearson's correlations (r).

To test our first hypotheses, we conducted a conditional process (i.e., mediation) analysis which is based on standard multiple linear regression, using the PROCESS macro (Model 4) [41], including age, sex, regular consumption of alcohol and caffeine, smoking, and BMI as covariates. We tested our second hypothesis, by conducting a moderated mediation analysis based on multiple, linear regression analyses with the PROCESS macro (Model 59) [41] that included sex, regular consumption of alcohol and caffeine, smoking, and BMI as covariates. We chose Model 59 as it also yields indices of conditional indirect effects, which have been recommended as useful parameters in the context of models incorporating both moderation and mediation [41]. The moderated mediation is considered significant if the boot-strapped CIs of the respective indirect effects do not contain zero (95% bias-corrected confidence intervals from 10,000 resamples of data [41]). Although controlling for sex in our analyses, we further conducted sensitivity analyses for both hypotheses in sex-specific submodels, respectively, as previous research indicates sex differences in exhaustion, vmHRV and CVD risk [42–44]. The significance level was set to P = .05. All analyses were performed using IBM SPSS Statistics 22 [45] and the SPSS add-on PROCESS version 2.15 [41].

Results

Descriptive statistics and correlation analyses

Descriptive statistics for the sample and correlations of the variables used are presented in Table 1. The average age of participants in our sample was 42.61 (SD = 11.67; range: 20–68 years), with 72.9% of female participants. With respect to exhaustion symptoms, the sample exhibited a wide range of the emotional exhaustion score (0–6), with 35.6% reporting serious exhaustion symptoms (exhaustion > 3.2) according to a frequently used cut-off value for the presence of exhaustion operationalized using the MBI-GS [46]. With respect to the general mental state of the sample, participants reported on average no to mild depressive symptoms (M = 7.72; SD = 4.38) as well as no to mild general anxiety symptoms (M = 6.06; SD = 4.42).

Indirect effect of exhaustion symptoms on CVD risk through vmHRV

To test our first hypothesis, we examined if vmHRV mediates the association between exhaustion symptoms and CVD risk. In the first stage of the mediation model (path a: exhaustion symptoms − vmHRV) there was a significant negative association between exhaustion symptoms and vmHRV even after adjusting for well-known covariates (Table 2). A negative association between vmHRV and CVD risk was found in the second stage of the mediation model, although not statistically significant (P = .08; Table 2). Neither the positive association between exhaustion symptoms and CVD risk in the direct path (path c: $B \leq -0.01$, SE = 0.02, 95% confidence interval (CI) [−0.04, 0.03]) nor the positive association between exhaustion symptoms and CVD risk mediated by vmHRV in the indirect path ($ab \leq 0.01$, SE ≤ 0.01, 95%CI [< −0.01, 0.01]) were significant. Importantly, age was the only covariate significantly associated with the respective dependent variables in all three steps of the mediation model (path a and b: Table 2; path c: B = 0.02, SE < 0.01, P < .001).

Moderation effects of age on the indirect effect of exhaustion symptoms on CVD risk through vmHRV

To examine our second hypothesis, we conducted a moderated mediation model (Fig. 1) to test if age moderates the association between exhaustion symptoms and CVD risk through vmHRV in the direct (path f: exhaustion symptoms − CVD risk) and/or the indirect path (path d: exhaustion symptoms − vmHRV and path e: vmHRV − CVD risk).

As depicted in Table 3, age moderated the second stage of the indirect association between exhaustion symptoms and CVD risk through vmHRV (path e: F(1377) = 11.34, P < .001; R^2 = 0.02). Simple slope tests revealed that individuals aged 30.94 years old and younger exhibited a negative association between vmHRV and CVD risk, although not significant (Fig. 2). Individuals with an age of 42.61 years and above exhibited a negative association between vmHRV and CVD risk; however, this association was precise only in individuals aged 52.27 years and older (β_{simple} = −0.26, SE = 0.07, P < .001, 95%CI = [−0.40, −0.12]; Fig. 2). No significant moderation of age were found for the direct association between exhaustion symptoms on CVD risk (path f: F(1377) = 0.10, P = .75; R^2 = 0.002), and the first stage of the indirect association of exhaustion symptoms on CVD risk through vmHRV (path d: exhaustion symptoms − vmHRV; F(1379) = 0.30, P = .58; R^2 = 0.001).

Finally, results indicate that vmHRV mediated the association between exhaustion symptoms and CVD risk. As depicted in Table 4, we found a positive, although not significant indirect association between exhaustion symptoms and CVD risk through vmHRV and a negative association between exhaustion symptoms and CVD risk through vmHRV among individuals aged 42.61 years and older, that was significant only among individuals aged 54.27 years and older.

Table 1
Demographic and health-related characteristics (means, standard deviations, percentages, and intercorrelations [N = 388])

	Mean	SD	%	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. Age (y)	42.61	11.67	—	—	−.03	.27*	.04	−.04	.16*	.05	.30*	.18*	.33*	.41*	−.49*
≤29	—	—	17.0	—	—	—	—	—	—	—	—	—	—	—	—
30–39			25.0												
40–4950–59			23.2												
≤60			28.6												
			6.2												
2. Sex (male)	—	—	27.1	—	—	−.05	−.08	−.01	−.09	.05	−.06	−.001	.02	−.02	.06
3. BMI (kg/m²)	25.55	5.04	—	—	—	—	.09	.03	.04	.09	.34*	.12†	.18*	.34*	-.21*
4. Alcohol consumption (yes)	—	—	91.5	—	—	—	—	.07	.26*	−.04	−.02	−.004	−.08	−.05	−.02
5. Smoking (yes)	—	—	13.7	—	—	—	—	—	.09	.04	.01	.02	−.02	.01	−.14*
6. Caffeine consumption (yes)	—	—	86.6	—	—	—	—	—	—	−.10†	−.02	.02	.04	.02	−.07
7. Exhaustion	2.85	1.47	—	—	—	—	—	—	—	—	−.01	.10†	.05	.05	−.18*
8. High Blood pressure (yes)	—	—	15.7	—	—	—	—	—	—	—	—	.14*	.20*	.77*	−.21*
9. Diabetes (yes)	—	—	2.8	—	—	—	—	—	—	—	—	—	.24*	.50*	−.21*
10. High cholesterol (yes)	—	—	10.6	—	—	—	—	—	—	—	—	—	—	.72*	−.18*
11. CVD risk	0.29	0.58	—	—	—	—	—	—	—	—	—	—	—	—	-.29*
Score 0	—	—	76.8	—	—	—	—	—	—	—	—	—	—	—	—
Score 1			18.0												
Score 2			4.4												
Score 3			0.8												
12. VmHRV‡	37.08	23.55	—	—	—	—	—	—	—	—	—	—	—	—	—

BMI = body mass index; CVD = cardiovascular disease; vmHRV = vagally-mediated heart rate variability, operationalized as root mean square of successive differences in the time intervals between consecutive heart beats (RR intervals - the time elapsed between two successive R waves of the electrocardiogram QRS complex) at rest [RMSSD], logarithmized.

* $P < .001$.

† $P < .05$.

‡ Intercorrelations were calculated with lnRMSSD.

Table 2
Results of mediation analyses of exhaustion symptoms on CVD risk through vmHRV (Model 4; N = 388)

	Outcome variables			
	vmHRV		CVD risk	
	Estimate (SD)	95% CI	Estimate (SD)	95% CI
Constant	4.74 (0.18)*	4.39; 5.09	−0.55 (0.31)	−1.16; 0.07
Control variables				
Age	−0.02 (< 0.01)*	−0.02; −0.01	0.02 (< 0.01)*	0.01; 0.02
Sex	0.07 (0.06)	−0.05, 0.18	< −0.01 (0.06)	−0.12; 0.11
BMI	−0.01 (< 0.01)	−0.02, < 0.01	0.03 (< 0.01)*	0.01; 0.04
Alcohol consumption	0.02 (0.09)	−0.16; 0.21	−0.17 (0.10)	−0.37; 0.02
Smoking	−0.26 (0.07)*	−0.40, −0.11	< 0.01 (0.08)	−0.14; 0.16
Caffeine consumption	0.02 (0.08)	−0.13; 0.18	−0.05 (0.08)	−0.21; 0.11
Main effects				
Exhaustion	−0.06 (0.02)*	−0.09; −0.02	< −0.01 (0.02)	−0.04; 0.03
VmHRV	—	—	−0.09 (0.05)	−0.20; 0.01
Model fit statistics				
F-value	F(7380) = 22.36*	—	F(8379) = 14.81†	—
R^2	0.29	—	0.24	—

BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; vmHRV = vagally-mediated heart rate variability, operationalized as root mean square of successive differences in the time intervals between consecutive heart beats (RR intervals- the time elapsed between two successive R waves of the electrocardiogram QRS complex) at rest [RMSSD], logarithmized.

‡$P < .05$.

* $P < .001$.

† $P < .01$.

Sensitivity analysis

Lastly, we conducted sensitivity analyses including only female (n = 283) and male (n = 105) subsets, respectively. Regarding our first hypothesis, we found a significant negative association between exhaustion symptoms and vmHRV and a negative but insignificant association between vmHRV and CVD risk in both subsets, after adjusting for relevant covariates (Supplementary Tables 1 and 2). Neither the negative direct association between exhaustion symptoms on CVD risk (male: $B = -0.04$, SE = 0.04, 95%CI [−0.11, 0.04]; female: $B \geq -0.01$., SE = 0.02, 95%CI [−0.04, 0.04]) nor the indirect association of exhaustion symptoms on CVD risk mediated by vmHRV were statistically significant (male: $B \leq 0.01$., SE = 0.01, 95%CI [−0.01, 0.03]; female: $B = 0.01$., SE ≤ 0.01, 95%CI [> −0.01, 0.01]).

Regarding our second hypothesis, we observed a positive association between exhaustion and CVD risk through vmHRV among men in all age groups, although insignificant (Supplementary Table 3). Among women, we found a positive, but insignificant association between exhaustion and CVD risk through vmHRV among individuals aged 42.37 years and older. This association was negative but insignificant in individuals aged 30.42 years and younger (Supplementary Table 4).

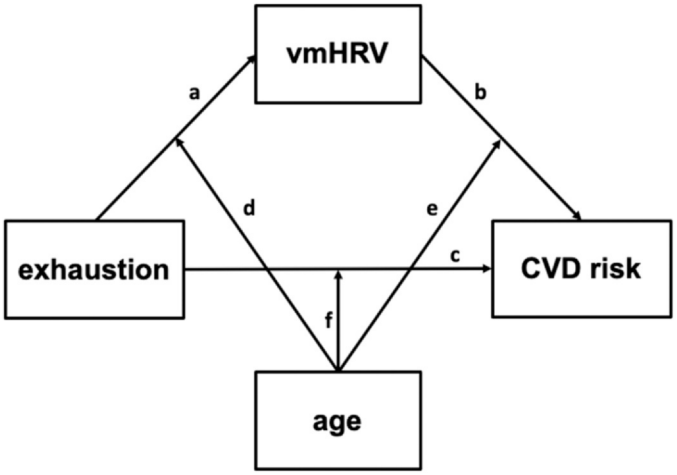

Fig. 1. Hayes Process Model 59 [35]. Conditional indirect effect of exhaustion on cardiovascular disease (CVD) risk through vagally-mediated heart rate variability (vmHRV; operationalized as root mean sum of squares of successive differences in the time intervals between consecutive heart beats (RR intervals - the time elapsed between two successive R waves of the electrocardiogram QRS complex) [RMSSD], logarithmized) moderated by age.

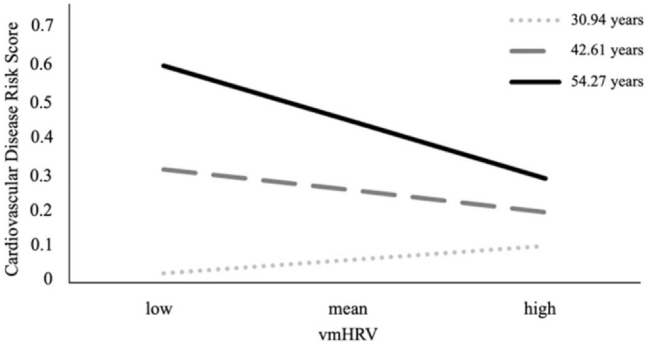

Fig. 2. Interaction of vagally-mediated heart rate variability (vmHRV; operationalized as root mean sum of squares of successive differences in the time intervals between consecutive heart beats (RR intervals - the time elapsed between two successive R waves of the electrocardiogram QRS complex) [RMSSD], logarithmized) and age on cardiovascular disease risk score. Simple slope effects representing the moderated relation between vmHRV and age on the cardiovascular disease risk score at low (M − 1 SD), average (M), and high (M + 1 SD) age levels.

Discussion

This study aimed to examine the potential role of vmHRV as a biological link between exhaustion symptoms and CVD risk. Our results indicate that vmHRV partially mediated the association between exhaustion symptoms and CVD risk, but only among middle-aged and older individuals in our study.

The findings regarding our first hypothesis are partly consistent with previous research. On the one hand, they align with the growing body of research that focuses on the integral role of deficient vagal inhibitory influence of ANS regulation, in addition to markers of SNS dominance, in understanding the pathophysiological mechanisms linking psychosocial factors to CVD morbidity and mortality risk [14]. On the other hand, they are inconsistent with previous findings of associations between vmHRV and CVD risk [14], which might be explained by the large influence of age on vmHRV and CVD risk which we considered in our second hypothesis.

In our second hypothesis, we found that vmHRV mediates the association between exhaustion symptoms and CVD risk, although

Table 4
Conditional indirect effects of exhaustion on CVD risk through vmHRV at mean ± 1 SD values of age

Age	Effect	SE	BootLLCI	BootULCI
30.94	−0.004	0.003	−0.011	0.002
42.61	0.004	0.004	−0.002	0.013
54.27	0.014	0.008	0.001	0.033

BootLLCI = Bootstrap Lower Limit of Confidence Interval; BootULCI = Bootstrap upper Limit of Confidence Interval; CVD = cardiovascular disease; vmHRV = vagally-mediated heart rate variability.

Table 3
Results of mediation analysis of exhaustion on CVD risk through vmHRV moderated by age (Model 59; N = 388)

	Outcome variables			
	vmHRV		CVD risk	
	Estimate (SD)	95% CI	Estimate (SD)	95% CI
Constant	4.64 (0.26)*	4.12; 5.15	−2.52 (0.73)*	−3.95; −1.10
Control variables				
Sex	0.07 (0.06)	−0.05; 0.18	−0.02 (0.06)	−0.14; 0.09
BMI	−0.01 (0.01)	−0.02; < 0.01	0.03 (0.01)*	0.02; 0.04
Alcohol consumption	0.03 (0.09)	−0.16; 0.21	−0.19 (0.10)†	−0.38, < −.01
Smoking	−0.26 (0.07)*	−0.41; −0.11	0.01 (0.08)	−0.15, 0.16
Caffeine consumption	0.02 (0.08)	−0.13; 0.17	−0.05 (0.08)	0.21; 0.11
Main effects				
Age	−0.02 (< 0.01)*	−0.03; −0.01	0.06 (0.02)*	0.03; 0.09
Exhaustion	−0.02 (0.07)	−0.16; 0.11	−0.03 (0.07)	−0.17; 0.11
VmHRV	—	—	0.49 (0.18)‡	0.13; 0.84
Interaction effects				
Exhaustion * age	> −0.01 (< 0.01)	> −0.01; < 0.01	< 0.01 (< 0.01)	> −0.01; < 0.01
VmHRV * age	—	—	−0.01(< 0.01)*	−0.02, < −0.01
Model fit statistics				
F-value	F(8379) = 19.56*		F(10,377) = 13.35*	
R^2	0.29		0.26	

BMI = body mass index; CVD = cardiovascular disease; vmHRV = vagally-mediated heart rate variability, operationalized as root mean square of successive differences in the time intervals between consecutive heart beats (RR intervals - the time elapsed between two successive R waves of the electrocardiogram QRS complex) at rest [RMSSD], logarithmized.

* $P < .001$.
† $P < .05$.
‡ $P < .01$

age-dependent, with precise indirect associations observed only in individuals aged 54.27 years and older. Interestingly, we found a significant moderation of age only in the association between vmHRV and CVD risk, but not in the association between exhaustion symptoms and vmHRV or exhaustion symptoms and CVD risk. This finding is in accordance with the current knowledge in this research area, where the age-dependency of cardiovascular health [21] and vmHRV [22] is well established, while exhaustion symptoms do not appear to show a strong age dependency. Prior studies have reported only small correlations between age and exhaustion symptoms [25]. Our results support the notion that age plays a stronger role in biomarkers of ANS imbalance and CVD risk than in exhaustion symptoms. This age-dependent association may be explained by previous findings suggesting that measurable modifications in CVD risk only occur after long-lasting and persistent changes in physiological markers, such as autonomic imbalance [47].

Due to implications of sex-specific effects on exhaustion, vmHRV, and CVD risk reported in previous studies [42–44], we conducted sensitivity analyses with sex-specific subsets. In accordance, we found age-dependent indirect associations between exhaustion and CVD risk through vmHRV in both subsets. Although the direction of associations remained the same except for 1 weak estimate in men, statistical significance was not reached in either subset. This is possibly due to the considerably lower statistical power in the subsets compared to the full sample. The association between persistent exhaustion-related physiological changes and CVD risk we observed may extend to a public health level. In a comparative analysis of life expectancy in high-income countries, Jasilionis et al. [4] concluded that Germany's poor longevity performance compared to other high-income countries is primarily attributed to premature cardiovascular mortality, particularly among middle-aged and older individuals who work. These results underline our findings demonstrating a significant association between chronic work-related exhaustion and CVD risk among older individuals, but not younger ones. While predicting morbidity and mortality was beyond the scope of this study, our results shed light on the biological underpinnings between psychosocial factors and CVD. Longitudinal studies are needed to validate the causal assumptions of the proposed mediation model. In addition, future research should explore complementary biological pathways, such as the hypothalamic-pituitary-adrenal axis which has also been associated with exhaustion symptoms [48] and CVD risk factors.

The present study has several limitations which should be considered. First, the present study represents a cross-sectional analysis utilizing a single wave of the DBS, and thus no conclusions about causality or directionality can be drawn. Nevertheless, longitudinal evidence from this cohort has previously documented linkages between burnout/exhaustion and reduced vmHRV at 1 and 3 year intervals [20,49], both confirming the findings of observation documented in previous investigations (e.g., [6, 8]).

Second, we operationalized CVD risk as the cumulative occurrence of self-reported physician diagnosed hypertension, hypercholesterinaemia, and diabetes, three of the most prevalent and commonly comorbid biological risk factors for severe and fatal cardiovascular outcomes [32, 33]. This is not without controversy as established CVD risk scores include lifestyle-related risk factors such as smoking or family history of CVD, as well [32]. Family history of CVD was not recorded in our sample, and rates of smoking across the sample were relatively low and higher among men (14.3%) than women (13.4%). Because diagnosis is based on self-report, there may be a greater likelihood of outcome misclassification. On balance, it is equally feasible that some participants unknowingly carried a risk factor or diagnosis, and thus, did not endorse these items (i.e., underreporting) which heightens the probability of effect underestimation. Nevertheless, self-reports of physician diagnoses, as well as the summation of self-reported diagnosis and symptoms, are a common tool in population-based and epidemiologic studies when more invasive and/or expensive screening and assessment may not be practical. Furthermore, the prevalence of hypertension, hypercholesterolemia, and diabetes in our sample is comparable to those reported among larger population-based German samples [50–52].

Third, as discussed in the published DBS protocol [27], one aim of the simple inclusion criteria was to facilitate recruitment of a professionally, socioeconomically, and clinically/medically diverse sample which expected concomitant variation in burnout symptomatology. Thus, at least with respect to similarly aged working individuals in Germany and likely other industrialized nations/countries, our findings may bear greater than average generalizability. However, the lower number of male participants, reliance on a simple index of CVD risk, and cross-sectional nature of the present may limit this extensibility.

In conclusion, our findings suggest that vmHRV mediates the association between exhaustion symptoms and CVD risk among middle-aged and older individuals, relative to younger individuals in a large heterogeneous sample. Though additional replication and longitudinal studies are needed to confirm this pattern, these observations may hold important implications for prevention and treatment strategies to address the recent increases of CVD in high-income countries [2] and eventually reduce its global burden.

Funding

M.K.W. was supported by the Postdoc Starter Kit of the Graduate Academy, TU Dresden, Germany.

CRediT authorship contribution statement

Magdalena K. Wekenborg: Conceptualization, investigation, methodology, formal analysis, writing original draft. **Richard G. Künzel:** Methodology, formal analysis, writing original draft. **Nicole Rothe:** Investigation. **Marlene Penz:** Conceptualization, investigation. **Andreas Walther:** Investigation. **Clemens Kirschbaum**: Conceptualization, supervision. **Julian F. Thayer:** Review. **LaBarron K. Hill:** Methodology, supervision, review. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Data availability

Due to privacy/ethical restrictions, the data used in the development of this study is not publicly available, but access to it can be granted upon reasonable request to the corresponding author.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

References

[1] Joseph P, Leong D, McKee M, et al. Reducing the global burden of cardiovascular disease, part 1: the epidemiology and risk factors. Circ Res 2017;121(6):677–94. https://doi.org/10.1161/CIRCRESAHA.117.308903

[2] Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol 2020;76(25):2982–3021. https://doi.org/10.1016/j.jacc.2020.11.010

[3] Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396(10258):1204–22. https://doi.org/10.1016/S0140-6736(20)30925-9

[4] Jasilionis D, van Raalte AA, Klüsener S, Grigoriev P. The underwhelming German life expectancy. Eur J Epidemiol 2023;38(8):1–12. https://doi.org/10.1007/s10654-023-00995-5

[5] Ahola K, Pulkki-Råback L, Kouvonen A, Rossi H, Aromaa A, Lönnqvist J. Burnout and behavior-related health risk factors: results from the population-based Finnish Health 2000 study. J Occup Environ Med 2012;54(1):17–22. https://doi.org/10.1097/JOM.0b013e31823ea9d9

[6] 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(8):840–7. https://doi.org/10.1097/PSY.0b013e31826c3174

[7] 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(3):327–53. https://doi.org/10.1037/0033-2909.132.3.327

[8] Toppinen-Tanner S, Ahola K, Koskinen A, Väänänen A. Burnout predicts hospitalization for mental and cardiovascular disorders: 10-year prospective results from industrial sector. Stress Health 2009;25(4):287–96. https://doi.org/10.1002/smi.1282

[9] Toppinen-Tanner S, Ojajärvi A, Väänänen A, Kalimo R, Jäppinen P. Burnout as a predictor of medically certified sick-leave absences and their diagnosed causes. Behav Med 2005;31(1):18–32. https://doi.org/10.3200/BMED.31.1.18-32

[10] von Känel R, Princip M, Holzgang SA, et al. Relationship between job burnout and somatic diseases: a network analysis. Sci Rep 2020;10(1):1–7. https://doi.org/10.1038/s41598-020-75611-7

[11] Koertge JC, Ahnve S, Schenck-Gustafsson K, Orth-Gomér K, Wamala SP. Vital exhaustion in relation to lifestyle and lipid profile in healthy women. Int J Behav Med 2003;10(1):44–55. https://doi.org/10.1207/s15327558ijbm1001_04

[12] Räikkönen K, Keltikangas-Järvinen L, Adlercreutz H, Hautanen A. Psychosocial stress and the insulin resistance syndrome. Metabolism 1996;45(12):1533–8. https://doi.org/10.1016/s0026-0495(96)90184-5

[13] Albus C, Waller C, Fritzsche K, et al. Significance of psychosocial factors in cardiology: update 2018: position paper of the German Cardiac Society. Clin Res Cardiol 2019;108(11):1175–96. https://doi.org/10.1007/s00392-019-01488-w

[14] Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol 2010;141(2):122–31. https://doi.org/10.1016/j.ijcard.2009.09.543

[15] 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(2):747–56. https://doi.org/10.1016/j.neubiorev.2011.11.009

[16] Task Force. Heart rate variability standards of measurement, physiological interpretation, and clinical use Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17:354–81.

[17] Berntson GG, Thomas Bigger Jr J, Eckberg DL, et al. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 1997;34(6):623–48. https://doi.org/10.1111/j.1469-8986.1997.tb02140.x

[18] de Vente W, van Amsterdam JG, Olff M, Kamphuis JH, Emmelkamp PM. Burnout is associated with reduced parasympathetic activity and reduced HPA axis responsiveness, predominantly in males. Biomed Res Int 2015;2015:431725. https://doi.org/10.1155/2015/431725

[19] Kanthak MK, Stalder T, Hill LK, 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(5):475–84. https://doi.org/10.5271/sjweh.3647

[20] Wekenborg MK, Hill LK, Thayer JF, Penz M, Wittling RA, Kirschbaum C. The longitudinal association of reduced vagal tone with burnout. Psychosom Med 2019;81(9):791–8. https://doi.org/10.1097/PSY.0000000000000750

[21] Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med 2006;355(25):2631–9. https://doi.org/10.1056/NEJMoa055373

[22] Reardon M, Malik M. Changes in heart rate variability with age. Pacing Clin Electrophysiol 1996;19(11):1863–6. https://doi.org/10.1111/j.1540-8159.1996.tb03241.x

[23] Ahola K, Honkonen T, Isometsä E, et al. Burnout in the general population. Soc Psychiatry Psychiatr Epidemiol 2006;41(1):11–7. https://doi.org/10.1007/s00127-005-0011-5

[24] Brewer EW, Shapard L. Employee burnout: a meta-analysis of the relationship between age or years of experience. Hum Resour Dev Rev 2004;3(2):102–23. https://doi.org/10.1177/1534484304263335

[25] Gómez-Urquiza JL, Vargas C, De la Fuente EI, Fernández-Castillo R, Cañadas-De la Fuente GA. Age as a risk factor for burnout syndrome in nursing professionals: a meta-analytic study. Res Nurs Health 2017;40(2):99–110. https://doi.org/10.1002/nur.21774

[26] Tuuli P, Karisalmi S. Impact of working life quality on burnout. Exp Aging Res 1999;25(4):441–9. https://doi.org/10.1080/036107399243922

[27] Penz M, Wekenborg MK, Pieper L, et al. The Dresden Burnout Study: Protocol of a prospective cohort study for the bio-psychological investigation of burnout. Int J Methods Psychiatr Res 2018;27(2):e1613. https://doi.org/10.1002/mpr.1613

[28] Büssing A, Glaser J. Deutsche Fassung des Maslach burnout inventory–General survey (MBI-GS-D). Munich: München, Technische Universität, Lehrstuhl für Psychologie; 1999.

[29] Schaufeli WB, Leiter MP, Maslach C, Jackson SE. Maslach Burnout Inventory-General Survey (MBI-GS). In: Maslach C, Jackson SE, Leiter M, editors. The Maslach Burnout Inventory – Test Manual. Consulting Psychologists Press; 1996.

[30] Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606–13. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

[31] Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092–7. https://doi.org/10.1001/archinte.166.10.1092

[32] Willis A, Davies M, Yates T, Khunti K. Primary prevention of cardiovascular disease using validated risk scores: a systematic review. J R Soc Med 2012;105(8):348–56. https://doi.org/10.1258/jrsm.2012.110193

[33] Kaptoge S, Pennells L, De Bacquer D, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Health 2019;7(10):e1332–45. https://doi.org/10.1016/S2214-109X(19)30318-3

[34] Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. J Clin Epidemiol 2004;57(10):1096–103. https://doi.org/10.1016/j.jclinepi.2004.04.005

[35] Barber J, Muller S, Whitehurst T, Hay E. Measuring morbidity: self-report or health care records? Fam Pract 2010;27(1):25–30. https://doi.org/10.1093/fampra/cmp098

[36] Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1991;121(1):293–8. https://doi.org/10.1016/0002-8703(91)90861-b

[37] NHLBI. Understand your risk for heart disease. Heart-Healthy Living. ⟨https://www.nhlbi.nih.gov/health/heart-healthy-living/risks⟩ [accessed 24.3.2022].

[38] Williams DP, Jarczok MN, Ellis RJ, Hillecke TK, Thayer JF, Koenig J. Two-week test–retest reliability of the Polar® RS800CX™ to record heart rate variability. Clin Physiol Funct Imaging 2017;37(6):776–81. https://doi.org/10.1111/cpf.12321. Epub 2016 Jan 27.

[39] Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health 2017;5:258. https://doi.org/10.3389/fpubh.2017.00258

[40] Hill L, Siebenbrock A, Sollers J, Thayer JF. Are all measures created equal? Heart rate variability and respiration – biomed 2009. Biomed Sci Instrum 2009;45:71–6. PMID: 19369742.

[41] Hayes AF. Introduction to mediation, moderation, and conditional process analysis: a regression-based approach. New York, NY: Guilford Publications,; 2017. ISBN 9781462549030.

[42] Busch MA, Kuhnert R. 12-Month prevalence of coronary heart disease in Germany. J Health Monit 2017;2(1):58. https://doi.org/10.17886/RKI-GBE-2017-018

[43] Hapke U, Maske U, Scheidt-Nave C, Bode L, Schlack R, Busch M. Chronischer Stress bei Erwachsenen in Deutschland. Bundesgesundheitsbl 2013;56:749–54. https://doi.org/10.1007/s00103-013-1690-9

[44] Koenig J, Thayer JF. Sex differences in healthy human heart rate variability: a meta-analysis. Neurosci Biobehav Rev 2016;64:288–310. https://doi.org/10.1016/j.neubiorev.2016.03.007

[45] IBM. Statistical Package for the Social Sciences; 2013.

[46] Maslach C, Jackson SE, Leiter MP. Maslach Burnout Inventory manual. 2nd ed., Consulting Psychologists Press,; 1997.

[47] McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998;338(3):171–9. https://doi.org/10.1056/NEJM199801153380307

[48] Kudielka B, Bellingrath S, Hellhammer D. Cortisol in burnout and vital exhaustion: an overview. G Ital Med Lav Ergon 2006;28(1):34–42. PMID: 19031555.

[49] Wekenborg MK, Schwerdtfeger A, Rothe N, et al. Determining the direction of prediction of the association between parasympathetic dysregulation and exhaustion symptoms. Sci Rep 2022;12(1):10648. https://doi.org/10.1038/s41598-022-14743-4

[50] Neuhauser H, Adler C, Rosario A, Diederichs C, Ellert U. Hypertension prevalence, awareness, treatment and control in Germany 1998 and 2008–11. J Hum Hypertens 2015;29(4):247–53. https://doi.org/10.1038/jhh.2014.82

[51] Born S, Heidemann C, Kunert R, Scheidt-Nave C. 12-Monats-Prävalenz des bekannten diabetes mellitus in Deutschland. J Health Monitoring 2017;2(1):48. https://doi.org/10.17886/RKI-GBE-2017-008

[52] Scheidt-Nave C, Du Y, Knopf H, et al. Verbreitung von Fettstoffwechselstörungen bei Erwachsenen in Deutschland. Bundesgesundheitsbl 2013;56:661–7. https://doi.org/10.1007/s00103-013-1670-0

Supplementary material

Supplementary Table 1
Results of mediation analyses of exhaustion symptoms on CVD risk through vmHRV among male participants (Model 4; N = 105)

	Outcome variables			
	vmHRV		CVD risk	
	Estimate (SD)	95% CI	Estimate (SD)	95% CI
Constant	4.59 (0.40)*	3.81; 5.37	−0.80 (0.62)	−2.02; 0.43
Control variables				
Age	−0.02 (< 0.01)*	−0.03; −0.01	0.01 (< 0.01)†	< 0.01; 0.02
BMI	> −0.01 (0.01)	−0.03; 0.02	0.06 (0.01)*	0.03; 0.08
Alcohol consumption	0.09 (0.24)	−0.38; 0.58	−0.35 (0.25)	−0.84; 0.14
Smoking	−0.12 (0.14)	−0.41; 0.16	0.20 (0.15)	−0.09; 0.49
Caffeine consumption	−0.09 (0.19)	−0.47; 0.28	−0.27 (0.19)	−0.65; 0.11
Main effects				
Exhaustion	−0.10 (0.03)‡	−0.17; −0.04	−0.04 (0.04)	−0.11; 0.04
VmHRV	—	—	−0.08 (0.10)	−0.28, 0.13
Model fit statistics				
F-value	F(6,98) = 5.09*	—	F(7,97) = 6.84*	—
R^2	0.24	—	0.33	—

BMI = body mass index; CVD = cardiovascular disease; vmHRV = vagally-mediated heart rate variability, operationalized as root mean square of successive differences in the time intervals between consecutive heart beats (RR intervals - the time elapsed between two successive R waves of the electrocardiogram QRS complex) at rest [RMSS], logarithmized.
* $P < .001$
† $P < .05$
‡ $P < .01$.

Supplementary Table 2
Results of mediation analyses of exhaustion symptoms on CVD risk through vmHRV among female participants (Model 4; N = 283)

	Outcome variables			
	vmHRV		CVD risk	
	Estimate (SD)	95% CI	Estimate (SD)	95% CI
Constant	4.83 (0.19)*	4.46; 5.20	-0.39 (0.36)	−1.10; 0.32
Control variables				
Age	−0.02 (< 0.01)*	−0.03, −0.02	0.02 (< 0.01)*	< 0.01; 0.02
BMI	−0.01 (< 0.01)	−0.02; < 0.01	0.02 (< 0.01)*	0.01, 0.03
Alcohol consumption	0.01 (0.10)	−0.19; 0.22	−0.13 (0.11)	−0.34; 0.08
Smoking	−0.31 (0.09)*	−0.48; −0.14	−0.08 (0.09)	−0.26; 0.10
Caffeine consumption	0.05 (0.09)	−0.12; 0.22	−0.01 (0.09)	−0.17; 0.18
Main effects				
Exhaustion	−0.04 (0.02)†	−0.08, > −0.01	> −0.01 (0.02)	−0.04; 0.04
VmHRV	-	-	−0.12 (0.06)	−0.24; 0.01
Model fit statistics				
F-Value	F(6276) = 21.48*		F(7275) = 11.91*	
R^2	0.32		0.23	

BMI = body mass index; CVD = cardiovascular disease; vmHRV = vagally-mediated heart rate variability, operationalized as root mean square of successive differences in the time intervals between consecutive heart beats (RR intervals - the time elapsed between two successive R waves of the electrocardiogram QRS complex) at rest [RMSS], logarithmized.
‡$P < .01$.
* $P < .001$
† $P < .05$.

Supplementary Table 3
Conditional indirect effects of exhaustion on CVD risk through vmHRV among male participants at mean ± 1 SD values of age (N = 105)

Age	Effect	SE	BootLLCI	BootULCI
32.34	0.001	0.009	−0.019	0.018
43.24	0.007	0.013	−0.018	0.035
54.14	0.017	0.037	−0.051	0.099

BootLLCI = Bootstrap Lower Limit of Confidence Interval; BootULCI = Bootstrap upper Limit of Confidence Interval

Supplementary Table 4
Conditional indirect effects of exhaustion on CVD risk through vmHRV among female participants at mean ± 1 SD values of age (N = 283)

Age	Effect	SE	BootLLCI	BootULCI
30.42	-0.004	0.004	−0.014	0.003
42.37	0.005	0.004	−0.001	0.015
54.32	0.011	0.010	−0.007	0.033

BootLLCI = Bootstrap Lower Limit of Confidence Interval; BootULCI = Bootstrap upper Limit of Confidence Interval

Supplementary Table 5
Missingness of included variables in the full sample (N = 423)

	N	*n* missing	% missing
1. Age (y)	422	1	0.24
2. Sex (male)	423	0	0.00
3. BMI (kg/m²)	421	2	0.47
4. Alcohol consumption (yes)	422	1	0.24
5. Smoking (yes)	417	6	1.42
6. Caffeine consumption (yes)	419	4	0.95
7. Exhaustion	421	2	0.47
8. High blood pressure (yes)	419	4	0.95
9. Diabetes (yes)	411	12	2.84
10. High cholesterol (yes)	413	10	2.36
12. VmHRV (lnRMSSD)	423	0	0.0