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Short communication

High-frequency variability in heart rate is related to COVID-19-associated worries six years later

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ABSTRACT

Elevated resting heart rate variability (HRV) in the high frequency range has been proposed to be protective against worrying when facing environmental stressors. Yet, prospective studies using real-life stressors are still scarce.

The present study set out to replicate the previous finding of reduced resting HRV predicting COVID-19-associated worries in a larger, more homogenous sample over a longer period of time ($N = 123$; age: 42.32 [*SD*:10.72]; 65.9 % female; average time lag: six years). In addition, we were interested in investigating the specificity of this effect with respect to worry content, other physiological markers of autonomic functions, and additional potentially relevant covariates with a special focus on a potential moderating effect of sex on this association.

In regression analyses adjusting for age, sex, BMI and smoking status, the interaction between HRV and sex was significant, with women depicting a stronger association between HRV and COVID-19 associated worries. Further sensitivity analyses revealed the specificity of the effect for HRV as distinct from mean heart rate, as well as its dependence on previous COVID-19 infection, but not COVID-19 vaccination status and chronic stress level.

These data are in line with theories that propose that higher HRV levels can be protective against the deleterious effects of real-life environmental stressors. However, our results also point to the specificity of this effect, especially with respect to worry content and sex.

1. Introduction

The current SARS-CoV-2 (severe acute respiratory syndrome coronavirus type 2) pandemic provides many potential triggers for worries. Even though worries can form part of everyday normal life, when these worries become excessive, they pose a threat to mental and physical health (Clancy et al., 2020; Ottaviani et al., 2016). Interestingly, the pandemic does not increase worrying in all individuals, indicating the existence of protective and vulnerability factors with regard to the handling of these massive environmental stressors. High vagal tonus, operationalized as fast beat-to-beat changes in heart rate (i.e., high frequency heart rate variability [HRV]) during a seated resting condition, has been suggested to be a protective factor that enables flexible, adaptive behaviour when confronted with external stressors, which, following the model of neurovisceral integration, leads to a more effective coping with this stressor and a consequently reduced chronic stress level (Thayer & Lane, 2009). HRV results from the interplay of the two branches of the autonomic nervous system, namely the sympathetic (SNS) and the parasympathetic (PNS) nervous system on the heart. Due to differences in neurotransmitter signalling, only the PNS (via the vagus nerve) is able to modulate the heart rate (HR) on a time scale of milliseconds (Berntson et al., 1997; Kuo et al., 2005; Saul, 1990), and therefore it has been suggested that high-frequency variability in HR constitutes a measure of vagal function (Thayer & Lane, 2009). Yet divergent empirical findings challenge this suggestion (Grossman & Kollai, 1993).

Still, there is accumulating evidence of a link between reduced tonic HRV and an enhanced tendency to worry (Chalmers et al., 2016;

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Ottaviani et al., 2016), although longitudinal studies with real life stressors are sparse. The present SARS-CoV-2 pandemic offers the opportunity to investigate the role of resting HRV for the development of worry in response to a stressor.

Recently, Makovac et al. (2021) demonstrated that reduced resting HRV collected between May 2018 and October 2019 ($n = 66$) predicted worrying during COVID-19 lockdown in 2020 operationalized with an item that was constructed by the authors and collected every 2 h during wake for 2 consecutive days, using electronic diaries.

The present study set out to investigate the replicability of this effect in a larger, more heterogeneous sample over a larger time period within the scope of the Dresden Burnout Study (DBS). In addition, we were interested in a more precise characterisation of this effect, with respect to specific worry content, other physiological measures of autonomic function, as well as further relevant covariates.

Our first hypothesis was that HRV would be negatively associated with COVID-19-associated worries six years later. Our second hypothesis was that this relationship would be more pronounced in women compared to men, as previous research indicates that the behavioural relevance of resting HRV in terms of a flexible reaction to environmental demands is higher in women than in men (Williams et al., 2019). In addition, we examined the specificity of the presumed effect for HRV as distinct from mean heart rate (mHR; de Geus et al., 2019), as well as the role of previous COVID-19 infection, COVID-19 vaccination status, and general chronic stress level.

2. Methods

Participants were a subsample from the DBS, a large longitudinal study on psychological, societal and biological risk factors of burnout symptoms which started in 2015. Study details have been published elsewhere (Penz et al., 2018). Participants were recruited German-wide through public media platforms and the civil register of the city Dresden. In order to accrue a heterogeneous sample composition, an age between 18 and 68 years and sufficiently fluent German language were the only inclusion criteria. The DBS consists of a German-wide conducted online assessment of a range of psychosocial factors via the official study homepage (www.dresdner-burnout-studie.de). In addition, annual in-person sampling of several biological variables (biomarker assessments) are conducted with participants from Dresden and surrounding areas (Saxony, Germany). HR data used in the present study, as well as relevant demographic- and health-related factors were obtained during the first biomarker assessment of the DBS (T0; conducted between September and October 2015). COVID-19-associated worries were assessed during an DBS online survey, which was conducted between April and June 2021 (T1). During April and June 2021, COVID-19 incidences were particularly high in Saxony.

The subsample of the present study was selected based on available HR data at T0 and complete data on COVID-19-associated worries at T1, resulting in a sample of $N = 124$. The DBS was designed according to ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 and approved by the ethic committee of TU Dresden. Participants received a monetary compensation of €15 for the in-person biomarker assessment.

2.1. Study design and procedure

2.1.1. Biomarker assessments (T0; September–October 2015)

$N = 446$ DBS participants accepted our invitation to the biomarker assessment in 2015. It lasted approximately 50 min and was conducted between 07:00–19:00 h. Information on demographic- and health-related factors were collected one week before biomarker assessments with online questionnaires. After arriving at the laboratory, participants signed informed consent sheets and were provided with heart rate devices. The seated resting HR data was collected in $N = 403$ participants at the end of the biomarker assessment procedure.

2.1.2. DBS online survey (T1; April–June 2021)

$N = 981$ DBS participants accepted our invitation to participate on the German-wide DBS online survey in 2021, and were provided with questionnaires, after logging in on the study homepage.

2.2. Assessment of self-report measures

2.2.1. COVID-19-associated worries

In the absence of validated questionnaires in German language, COVID-19-associated worries were assessed using three items that were constructed by the authors: (1) I am worried about my economic future because of Corona; (2) I am worried about the health of relatives and/or friends because of Corona; (3) I am worried about my own health because of Corona. The three items were scored on a six-point ranking scale (1 = does not apply at all; 6 = Applies completely). In addition, a simple averaged score was calculated over all three worry items (worry score) with higher scores representing higher COVID-19-associated worries. Cronbach's alpha of the worry score was 0.73, thus suggesting acceptable reliability.

2.2.2. Covariates

To ensure comparability of the results, the same co-variates were selected as in the study of Makovac et al. (2021) (i.e., age, sex, BMI, smoking status [yes/no]), all collected at T0.

In addition, previous COVID-19 infections (yes/no), current COVID-19 vaccination status (yes/no), as well as chronic stress level were assessed at T1, in order to be able to take these into account within the scope of sensitivity analyses. The latter was operationalized using the total score of the 10-item German version (PSS-10; Schneider et al., 2020) of the Perceived Stress Scale (Cohen et al., 1983). The 10 items of the PSS-10 are scored on a 5-point rating scale (0 = never to 4 = very often). The sum of the 10 items represents the total score, whereby higher values indicate a higher participant's level of perceived stress over the last month.

2.3. Heart rate data

HR data was recorded as inter-beat intervals (IBIs) with a Polar RS800CX system via the corresponding chest belt (Polar Electro OY, Kempele, Finland) during the whole biomarker sampling procedure with a sampling frequency of 1000 Hz. Of the complete IBI timeline, only a 335-s period of seated resting condition was analysed in the present study. Previous research indicated that a seated resting condition is especially suited to assess HRV as a trait-like marker of vagal function (Bertsch et al., 2012). The data was then transferred to the Polar Precision Performance Software (Polar Electro OY, Kempele, Finland), while raw IBI data were exported for further analysis. The subsequently conducted artefact correction was 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 (1996) using the NEUROCOR "precisionHRV" Algorithm (Wittling & Wittling, 2012).

After detection of R-spikes using modified Pan-Tompkins-Algorithm, identified artefacts were corrected and mean heart rate (mHR), as well as HRV, operationalized using a well-established time domain measure (i.e., root mean square of successive differences between IBIs [RMSSD])[1] were calculated.

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[1] In addition, high-frequency HRV (HF-HRV) was calculated as the corresponding frequency domain measure reflecting parasympathetic (i.e., vagal) influence. As RMSSD and HF-HRV correlated highly ($r(121) = 0.73$; $p < .001$), results were virtually identical for RMSSD and HF-HRV, results are presented only for RMSSD.

2.4. Statistical analyses and data exclusion

RMSSD values were not normally distributed and log transformations were applied to reduce skewness. Furthermore, extreme values (lnRMSSD values ± 3 *SD*) were excluded resulting in a final sample of $N = 123$ (i.e., one participant was excluded).

To test our first hypothesis, we applied a two-step approach. In a first step, we used Spearman's Rank Order correlations between lnRMSSD at T0 and COVID-19-associated worries at T1. In order to reduce the number of conducted tests, only those COVID-19-associated worries, which depicted significant associations with lnRMSSD in the first step were taken into account for the following analyses. In a second step, we tried to replicate the findings of Makovac et al. (2021), by predicting the respective COVID-19-associated worries at T1, with lnRMSSD at T0 as the relevant independent variable while adjusting for the identical covariates used by Makovac et al. (2021), namely age, sex, BMI, and smoking status.

In order to test our second hypothesis on the sex-specificity of potentially revealed associations between lnRMSSD at T0 and COVID-19-associated worries at T1, we added an interaction term of sex and lnRMSSD at T0 to the regression analyses described above.

As the COVID-19-associated worries had an ordinal scale level, we used ordinal logistic regression analyses (OLR). Whenever the parallel lines assumption was not met, multinomial logistic regression analyses (MLR) were used.

Additionally, we performed a series of sensitivity analyses in which we separately included chronic stress, previous COVID-19 infections, as well as COVID-19 vaccination status as additional covariates within the regression analyses mentioned above. Moreover, we examined the specificity of potentially revealed effects for lnRMSSD as compared to mHR by performing all analyses mentioned above again, replacing lnRMSSD with mHR.

The significance level was set to 0.05 (two-tailed). All analyses were performed using SPSS Statistics 22 (IBM, Armonk, NY, USA).

3. Results

Table 1 provides demographic and health-related characteristics for the sample at T0 (*M* ± *SD* age: 42.31 ± 10.72; 65.9 % female) and T1 (*M* ± *SD* age: 47.93 ± 10.77). At T1, 4.9 % individuals reported that they have been tested positive for SARS-CoV-2 by PCR test in the past, 31.5 % reported that they had been vaccinated at least once against SARS-CoV-2.

With respect to the central variables of interest, on average, people reported to be the most worried about the health of family members and friends, and the least about the economic consequences of COVID-19. In fact, 43.9 % of the participants reported to not worry at all about their economic future, whereas only 5.7 % reported no worries about the health of others and 17.9 % did not worry at all about their own health. Five participants (4.1 %) reported no worries at all on the three items.

3.1. Associations between lnRMSSD and COVID-19-associated worries

To test our first hypothesis on negative associations between lnRMSSD at T0 and COVID-19-associated worries at T1, in a first step, Spearman's Rank Order correlations were calculated. As depicted in Table 2, lnRMSSD was negatively associated with COVID-19-associated economic worries, but neither with COVID-19-associated worries about family and/or friends nor with COVID-19-associated worries about one's own health.

In a second step, ordinal logistic regression analyses were used to examine the predictive value of lnRMSSD on COVID-19-associated economic worries when adjusting for age, sex, BMI and smoking status (Table 3, Model 1; main effect model). Results indicate that even though the main effect model had a significantly better fit to the data compared to the null model ($\chi^2(5) = 13.12$, $p = .022$), lnRMSSD was not found to significantly contribute to the model ($B = -0.53$, $SE = 0.31$, Wald $= 2.91$, $p = .088$).

Table 1
Demographic and health-related characteristics for the sample at T0 and T1 ($N = 123$).

	T0 (biomarker sampling)		T1 (online survey)	
	Values	Range	Values	Range
Demographics				
Age, y, *M* (*SD*)	42.31 (10.72)	20–62	47.93 (10.77)	27–70
Female, *n* (%)	81 (65.9)	–	–	–
Health-related factors				
Smokers, *n* (%)	12 (9.8)	–	–	–
BMI, kg/m	25.93 (18.94)	17.63–41.77	–	–
PSS-10[a]			16.50 (7.82)	1–36
COVID-19 infection, yes (%)	–	–	6 (4.9)	–
COVID-19 vaccination, yes (%)	–	–	51 (31.5)	–
COVID-19-associated worries				
Worry score			2.86 (1.11)	1–6
Economic	–	–	2.04 (1.30)	1–6
Health of family/friends	–	–	3.58 (1.41)	1–6
Own health	–	–	2.97 (1.41)	1–6
RMSSD, *M* (*SD*)	36.30 (22.29)	6.23–129.17	–	–
mHR, *M* (*SD*)	70.74 (9.56)	45.97–99.66	–	–

Note. BMI = body mass index; mHR = mean heart rate; PSS-10 = Perceived Stress Scale, 10-item German version; RMSSD = root mean square of successive differences between IBIs.

[a] $N = 121$.

3.2. Interaction effects of lnRMSSD and sex on COVID-19-associated economic worries

In order to test our second hypotheses of the sex-specificity of potentially revealed associations between lnRMSSD at T0 and COVID-19-associated economic worries at T1, the respective interaction term was added to the ordinal logistic regression model described above (Table 3, Model 2; interaction effect model). The interaction effect model had a significantly better fit to the data compared to the null model ($\chi^2(6) = 18.24$, $p = .006$). The interaction between sex and lnRMSSD was found to significantly contribute to the model ($B = -1.42$, $SE = 0.64$, Wald $= 4.92$, $p = .026$), indicating that with increasing values of lnRMSSD, COVID-19 associated worries decrease stronger in women than in men (Fig. 1).

3.3. Sensitivity analyses

In order to examine the role of other potentially influencing variables in the association between lnRMSSD and COVID-19-associated economic worries, we conducted separate logistic regression analyses controlling for the PSS-10, previous COVID-19 infections, as well as COVID-19 vaccination status.

Detailed description of the results of these sensitivity analyses are depicted in the Online Supplement. Sensitivity analyses which additionally included COVID-19 vaccination status replicated the results of our original analyses with insignificant main effects of lnRMSSD and a significant interaction effect of sex and lnRMSSD on the prediction of COVID-19-associated worries. Sensitivity analyses which additionally included COVID-19 infection status resembled the results of our main analyses, however, the interaction effect of lnRMSSD and sex on the prediction of COVID-19-associated worries was not significant anymore ($B = -1.27$, $SE = 0.65$, $p = .050$).

Table 2
Spearman's Rank Order correlations between lnRMSSD, mHR, COVID-19-associated worries, sociodemographic and health-related factors ($N = 123$).

	COVID-19-associated worries					
	Sum-score	Economic situation	Family/Friends	Own health	lnRMSSD	mHR
lnRMSSD	-0.14	-0.23*	-.08	-0.07		
mHR	.12	.12	.07	.12	-0.52**	–
Age	.18*	.19*	.12	.14	-0.42**	-.08
Sex	.22*	.10	.19*	.22*	.04	.08
BMI	.15	.21*	.02	.18	-0.23*	.09
Smoking status	-0.12	-0.03	.14	-0.12	-0.03	.09
PSS-10[a]	.35**	.35**	.22*	.28**	-.04	-0.03
COVID-19 infection	.02	.16	-0.04	-0.04	-0.09	< 0.001
COVID-19 vaccination	-0.06	-0.17	0.06	-0.03	0.07	-0.03

Note. BMI = body mass index; lnRMSSD = root mean square of successive differences between IBIs, log transformed; mHR = mean heart rate; PSS-10 = Perceived Stress Scale, 10-item German version.

* $p < .05$.

** $p < .01$.

[a] $N = 121$.

Table 3
Ordinal logistic regression of predicting COVID-19-associated economic worries from lnRMSSD ($N = 123$).

Predictor		*B* (*SE*)	Wald
Model 1			
	Age	0.02 (0.02)	0.97
	Sex (0 = male)	0.35 (0.36)	0.93
	BMI	0.06 (0.04)	3.47
	Smoking status	0.04 (0.59)	< 0.01
	LnRMSSD	-0.53 (0.31)	2.91
Model 2			
	Age	0.01 (0.02)	0.36
	Sex (0 = male)	5.21 (2.22)*	5.50
	BMI	0.06 (0.03)	3.36
	Smoking status	-0.11 (0.59)	0.03
	LnRMSSD	0.46 (0.54)	0.73
	LnRMSSD X Sex	-1.42 (0.64)*	4.92

Note. Cells indicate unstandardised coefficients with *SE* in brackets; BMI = body mass index; lnRMSSD = root mean square of successive differences between IBIs, log transformed. **p* < .05.

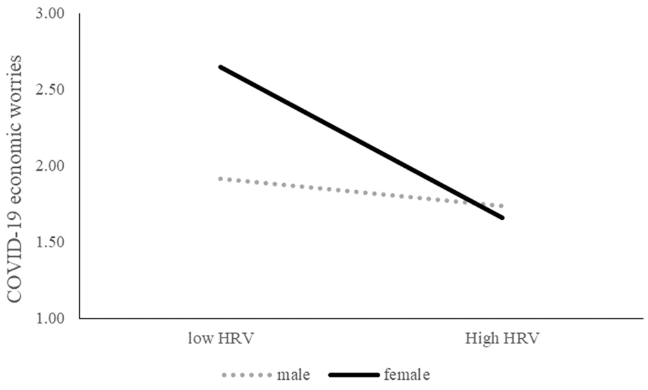

Fig. 1. Simple slopes of heart rate variability (root mean square of successive differences between IBIs [RMSSD], log transformed) predicting COVID-19-associated economic worries (scale range: 1–6) for men and women. Sample was divided based on a RMSSD median split (high HRV: RMSSD [log transformed] > 3.43; low HRV: RMSSD [log transformed] < 3.43).

As the main effect model which included the PSS-10 (Model 1) did not meet the assumption of parallel lines, a multinomial logistic regression model was used, which itself produced a warning of unexpected singularities in the Hessian matrix. We therefore decided to combine the initially five categories of the outcome variables to three categories (categories 3/4/5 were combined as they depicted the lowest endorsement), which resulted in a sufficient cell occupation in the Hessian matrix. Results revealed that higher levels in PSS-10 were significantly associated with a lower probability of worrying, whereas the interaction effect of sex and lnRMSSD remained significant after inclusion of the PSS-10 (Model 2).[2]

In addition, we were interested in the specificity of the effects found in differentiation from mHR. Conducting the same analyses, but replacing lnRMSSD with mHR revealed no significant correlations between mHR and any of the COVID-19-associated worries (Table 2), as well as no significant main or interaction effects of mHR and sex on COVID-19-associated economic worries (Online Supplement).

4. Discussion

Previous findings of Makovac et al. (2021) provide longitudinal evidence of increased HRV being protective of COVID-19 associated worries. The findings of the present study principally support this notion in a larger, more heterogeneous sample over a time span of six instead of two years, yet with some important restrictions.

More precisely, our first hypothesis that HRV would be negatively associated with COVID-19-associated worries six years later could only be partly supported, as significant associations were found only with COVID-19-associated economic worries and only without consideration of covariates adjusted for in the analyses by Makovac et al. (2021).

Our second hypothesis that relations between HRV and COVID-19-associated worries would be more pronounced in women compared to men was supported, emphasising the previously suggested importance of considering sex with respect to both HRV (Williams et al., 2022) and worry tendency (Robichaud et al., 2003).

One might argue that our findings of the specificity of the revealed effect with respect to worry content and sex could also be interpreted as evidence against the important role of high HRV as an indicator of general flexibility to react to environmental challenges as proposed by the model of neurovisceral integration (Thayer & Lane, 2009). But there is reason to consider the importance of these findings. First and foremost, our study was a replication of previous findings. The fact that the negative predictive value of HRV was found in two completely independent studies, albeit with some restrictions, indicates its importance. Second, the fact that significant associations with COVID-19-associated worry content were found for HRV and not for mHR implies that mHR might camouflage subtle effects which are detectable using HRV. This finding is in line with a meta-analysis showing stronger associations between worry and HRV compared to HR (Ottaviani et al., 2016).

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[2] Ordinal regression analyses were used as this model met the assumption of parallel lines.

Finally, the fact that the significant interaction effect between HRV and sex in predicting COVID-19-associated economic worries remained significant in two of three sensitivity analyses that controlled for additional covariates underscores the robustness of the findings. The finding of an inclusion of previous COVID-19 infections as a covariate eliminating this effect seems more likely to be due to a lack of statistical power given the lack of associations of COVID-19 infection with HRV and COVID-19-related worries, as well as a p-value just above the significance level.

Several limitations must be considered when interpreting the current results. First, analysing associations between HRV and COVID-19-associated worries was not an original part of the DBS, which is why the conducted analyses should be evaluated as exploratory. Second, in the absence of a validated German questionnaire for assessing COVID-19-associated worries, we relied on self-generated items. Even though our analyses indicate a good reliability of the worry sum-scale, an extensive examination of the psychometric properties of the single items appears desirable. Third, due to a lack of previous studies in this particular field, this study included a relatively large number of statistical tests, which bears the risk of alpha-error accumulation. Results should therefore be interpreted with caution. Fourth, even though we adjusted for a wide range of potential covariates, we cannot rule out that other variables and conditions (e.g., previous illnesses and medication, fitness, other pandemic related variables) might have also influenced the revealed effects. Fifth, despite the fact that resting RMSSD has been considered as rather stable (Bertsch et al., 2012), opposed findings (Uhlig et al., 2020), as well as the lack of reliability studies spanning longer time periods limit the interpretability of RMSSD as a physiological trait measure. Sixth, we did not measures breathing rate. Giving the long standing controversy regarding residual inspiratory vagal activity in humans, we cannot unambiguously interpret RMSSD as an index of vagal activity.

Despite these limitations and restrictions, our finding of HRV predicting COVID-19-associated economic worries six years later confirms previous notions of the model of neurovisceral integration of high basal HRV as a potentially important resilience factor when being confronted with serious environmental stressors, at least in women (Thayer et al., 2012). As vagal-excitatory interventions have been shown to enhance HRV (e.g., physical activity, Sloan et al., 2009; nicotine–free programs, Yotsukura et al., 1998), our findings and specifications of the effect revealed by Makovac et al. (2021) may have important implications for designing prevention programs for the general public, as well as for identifying those individuals who are most vulnerable when being confronted with a global pandemic/environmental stressor.

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Disclosure of interest

The authors report no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [M.K.W.], upon reasonable request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2022.108404.

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