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Editorial

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Abbreviations:
ANS: Autonomous nervous system; aRMT: Active remote measurement technology; CIBER: Centro de Investigación Biomédica en Red; HR: Heart rate; HRV: Hear rate variability; KCL: King's College London; LED: light-emitting diode; MDD: Major depressive disorder; mHR: mean HR; PPG: photoplethysmography; pRMT: passive remote measurement technology; PHQ-8: 8-item patient health questionnaire; RADAR-CNS: Remote assessment of disease and relapse – central nervous system; RADAR-MDD: Remote assessment of disease and relapse – major depressive disorder; RMT: remote monitoring technology; stdHR: Standard deviation Heart Rate; VUmc: Vrije Universiteit Medisch Centrum

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The usability of daytime and night-time heart rate dynamics as digital biomarkers of depression severity

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Abstract

Background. Alterations in heart rate (HR) may provide new information about physiological signatures of depression severity. This 2-year study in individuals with a history of recurrent major depressive disorder (MDD) explored the intra-individual variations in HR parameters and their relationship with depression severity.

Methods. Data from 510 participants (Number of observations of the HR parameters = 6666) were collected from three centres in the Netherlands, Spain, and the UK, as a part of the remote assessment of disease and relapse-MDD study. We analysed the relationship between depression severity, assessed every 2 weeks with the Patient Health Questionnaire-8, with HR parameters in the week before the assessment, such as HR features during all day, resting periods during the day and at night, and activity periods during the day evaluated with a wrist-worn Fitbit device. Linear mixed models were used with random intercepts for participants and countries. Covariates included in the models were age, sex, BMI, smoking and alcohol consumption, antidepressant use and co-morbidities with other medical health conditions.

Results. Decreases in HR variation during resting periods during the day were related with an increased severity of depression both in univariate and multivariate analyses. Mean HR during resting at night was higher in participants with more severe depressive symptoms.

Conclusions. Our findings demonstrate that alterations in resting HR during all day and night are associated with depression severity. These findings may provide an early warning of worsening depression symptoms which could allow clinicians to take responsive treatment measures promptly.

Introduction

Major depressive disorder (MDD) is a highly common mental disorder, globally affecting approximately 265 million people of all ages (James et al., 2018). MDD is often associated with poor health outcomes (Penninx, Milaneschi, Lamers, & Vogelzangs, 2013) and non-adherence to medications and treatments (DiMatteo, Lepper, & Croghan, 2000). Further, MDD is often comorbid with medical conditions such as cardiovascular diseases (CD) (Correll et al., 2017; Lett et al., 2004; Penninx, 2017; Penninx et al., 2001). Numerous studies

have shown that both MDD and CD potentially share underlying pathophysiological disturbances such as systemic inflammation, autonomic dysfunction of hypothalamic-pituitary-adrenal (HPA) axis (Angermann & Ertl, 2018), and immune system dysregulation (Halaris, 2017).

HR parameters may be used as diagnostic and predictive biomarkers of depression severity. A key indicator of the autonomous nervous system (ANS) function is the heart rate (HR) variability (HRV), consisting of the fluctuations in either the instantaneous HR or the length of heartbeats intervals. Increased variability indicates an improved autonomic nervous system regulation (Berntson et al., 1997). A reduced resting HRV has been related to difficulties in emotion regulation (Williams et al., 2015). Previous studies have also reported that individuals with MDD have a reduced resting mean HRV (Kemp & Quintana, 2013; Koenig, Kemp, Beauchaine, Thayer, & Kaess, 2016; Nabi et al., 2011). More severe depressive symptoms have been associated with elevated HR (Carney et al., 2008; Carney, Freedland, & Veith, 2005; Nabi et al., 2011) and reduced HRV (Caldwell & Steffen, 2018; Hartmann, Schmidt, Sander, & Hegerl, 2019; Kemp et al., 2010). Some studies reported that HR differences between individuals with MDD and without MDD might be more evident at night (Carney et al., 2008; Taillard, Lemoine, Boule, Drogue, & Mouret, 1993). Furthermore, people with MDD frequently report irregularities in sleep/wakes states (Walker, Walton, DeVries, & Nelson, 2020), which can also affect HR. However, most of these studies have several significant limitations: (i) either they were conducted in individuals of the general population including those without a diagnosis of MDD (Nabi et al., 2011; Silva et al., 2020); (ii) included only a small study population (Hartmann et al., 2019; Li, Hu, Shen, Xu, & Retcliffe, 2015; Narziev et al., 2020; Silva et al., 2020); or (iii) were conducted under laboratory conditions such as using electrocardiography (ECG) in hospital or research settings (Hartmann et al., 2019; Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012; Koch, Wilhelm, Salzmann, Rief, & Euteneuer, 2019; Koenig et al., 2016; Nabi et al., 2011).

The recording of the ECG during daily life and long periods has several limitations. For example, the electrodes of the ECG, can cause skin irritation in long recordings due to its wet compound and adhesive properties, or the gel might dry, resulting in a reduction of the contact between the electrode and the skin negatively affecting the quality of the recording. There are other types of electrodes that are not adhesive but they are highly sensitive to motion artefacts. Morever, Holter devices used for long data acquisitions interfere with the daily life routine, being unfeasible for continuous monitoring (Dias & Cunha, 2018).

Wrist worn devices that are available today may facilitate the measurement of HR in naturalistic conditions. These technologies have several advantages over previous devices, including being non-invasive, low burden, low cost, and allowing the acquisition and processing in near-real time of a large amount of information. In fact, these technologies are able to provide 24 h of HR monitoring, comfortable design and allowed to worn constantly (Castaneda, Esparza, Ghamari, Soltanpur, & Nazeran, 2018; Lam, Aratia, Wang, & Tung, 2020; Nelson & Allen, 2019).

All devices based on the photoplethysmographic (PPG) signal, obtained by illuminating the skin with the light from a light-emitting diode (LED) and then measuring the amount of light reflected to a photodiode to detect blood volume changes in the capillaries above the wrist (Subasi, 2019) from which HR information can be derived. The feasibility of deriving HRV from the PPG signal instead of the ECG signal has been widely investigated. In general, HRV derived from the PPG can be used as a surrogate of HRV derived from the ECG, when pulses can be accurately detected from the PPG, but this is challenging when PPG is recorded at wrist during daily life, mainly due to the sensitivity of PPG to movement artefacts. Only few studies have validated HRV derived from wrist PPG and always in resting conditions (i.e. Hernando, Roca, Sancho, Alesanco, & Bailón, 2018). However, many studies have validated the use of HR series provided by these devices to provide mean HR estimates over different periods of time (Fuller et al., 2020; Liu et al., 2022; Nazari, Macdermid, Sinden, Richardson, & Tang, 2019; Nelson & Allen, 2019). Despite the fact that these devices, based on wrist PPG, do not usually allow the study of HRV, they can still be useful to study HR trends and slow dynamics during the day, and might provide an indicator of ANS regulation of HR.

In order to analyse the use of wrist-worn technologies in assessing individuals with a history of recurrent MDD, the Remote Assessment of Disease and Relapse – Central Nervous System (RADAR-CNS) (www.radar-cns.org) project, involving the patients, took the decision to use a commercially available device which is minimally invasive, easy to use and has the sensitivity and precision to generate the desired multimodal information (i.e. HR, activity, sleep) (Owens, 2020; Polhemus et al., 2020; Simblett et al., 2019). In this project, a wrist worn fitness wearable device was used to track the HR dynamics during the whole day, outside the medical environment. This device makes use of the PPG signal from which HR is estimated using a proprietary algorithm and output at different time intervals. HR can vary significantly over 24 h and under different conditions (Shaffer & Ginsberg, 2017), so it is essential to take this information into account when analysing and interpreting HR dynamics as a marker of ANS.

This study assessed the relationship of HR parameters during different periods of the day and night and different activity levels with depression severity in a cohort of individuals with a recent history of recurrent MDD. Our first objective was to explore and test the association of HR parameters with the severity of depression. Based on previous literature, we expected that an increase in mean HR and reduced HR variation during the day would be related to an increased depression severity across the follow-up. Furthermore, we expected a similar pattern during the resting periods of the night: an increased mean HR and reduced HR variation associated with higher level of depression. The second objective was to examine whether this relationship can be affected by an individual's characteristics (age, gender body mass index (BMI), smoking and alcohol habit, comorbidity with medical health conditions and antidepressant medication). We also expected that these factors might impact on the association between HR changes and depression severity.

Method

Study design and sample

This study uses data collected from the RADAR-MDD study, as a part of the research RADAR-CNS project. The study was co-developed with service users in our Patient Advisory Board. They were involved in the choice of measures, the timing and issues of engagement and have also been involved in developing the analysis plan and representative (s) are authors of this paper and critically reviewed it.

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The RADAR-MDD study explored the use of active and passive remote monitoring technology (RMT), including a wrist-worn Fitbit device to track disease course in people with a recent history of recurrent MDD (with the latest episode within the past 2 years) and follow them up for a 2 years. The active and passive data are collected via the active and passive RMT and then send into the RADAR-base platform (Ranjan et al., 2019). For the Fitbit data, they are uploaded to the vendor data warehouse and provided to developers via a Web API. Getting these data into the RADAR system is achieved by implementing a server-side Kafka Source Connector, which continuously queries data from the vendor's Web API and dumps it into Kafka inside the RADAR-base platform; this approach can be used to integrate other Web API/OAuth2 data sources [GitHub. (2019-03-04). RADAR-base/RADAR-REST-fitbit https://github.com/RADAR-base/RADAR-REST-fitbit website].

The full protocol has already been published (Matcham et al., 2019; Matcham et al., 2022). The RADAR-MDD is a multi-centre cohort study involving 623 individuals recruited from three sites: Centro de Investigación Biomédica en Red (CIBER); Barcelona, Vrije Universiteit Medisch Centrum (VUmc), Amsterdam) and the King's College London (KCL). Participants were recruited through primary and secondary mental health care networks (Barcelona and London) and through existing research cohorts (participants from Amsterdam were partially recruited through Hersenonderzoek.nl (https://hersenonderzoek.nl/) and other ways such as advertisements in the https://www.radar-cns.org/participate and mental health charity websites. The study was approved by the ethical committees of participating centres and all participants provided written consent.

Instruments

Depression severity

Depression severity was assessed with the Patient Health Questionnaire 8 items (PHQ-8) (Kroenke et al., 2009) instrument delivered through an app installed in an Android smartphone (Ranjan et al., 2019). Participants were asked by push-notification to complete the PHQ-8 every two weeks. The PHQ-8 score ranges from 0 to 24 (increasing severity). A cut-off score of $\geqslant$10 is the most recommended cut-off point for 'clinically significant' depressive symptoms (severe or moderate depression = 1; *v.* no depression or mild depression = 0), which means that the participant is likely to meet diagnostic criteria for a depressive episode (or moderate and severe depression) in the previous two weeks (Kroenke et al., 2009). Ratings below 10 are usually defined as an asymptomatic state or sub-threshold (no or mild depression). Internal consistency was calculated with Cronbach's alpha, and it was 0.91.

Heart rate features

HR parameters, such as the mean or the standard deviation, were computed daily from the HR signal provided by Fitbit charge 2 and 3 (Fitbit Inc, San Francisco, CA, USA), which is obtained from the PPG sensor of the device with a a narrowest resolution up to 5 s between samples. This device was previously demonstrate proven to accurately measuring HR (Fuller et al., 2020; Liu et al., 2022; Nazari et al., 2019; Nelson & Allen, 2019). The HR values were not estimated when the Fitbit was not worn. HR was computed during the whole day (24 h) and just at night (from 00:00 to 05:59), as well as just during resting periods and during active periods separately. The HR during nighttime calculated by the Fitbit was strongly associated with resting HR at night (00:00–05:59) ($\rho = 0.94$, $p < 0.0001$). However, a previous study (i.e.(Stucky et al., 2021) proved that the Fitbit underestimated the sleep transition dynamics. For this reason, we selected period from 00:00 to 05:59 as a conservative night time that might work for a large part of the population.

Resting periods were defined when the number of steps and activity level, derived from the accelerometer data were equal to 0.

A total of seven HR features were derived for each day: total mean and standard deviation of HR (mHR/day and stdHR/day), mean and standard deviation of HR during the resting period (resting mHR/day and resting stdHR/day, respectively), mean and standard deviation of HR during resting period at night (resting mHR/night and resting stdHR/night, respectively) and mean HR for the activity periods (activity mHR) (Table 1). We computed the average of the each of the daily HR parameters in the week before the PHQ-8 assessment across the follow-up. An example of the HR parameters for an individual with different depression score during the study was represented in Fig. 1. (Fig. 1). One week mean was considered appropriate to smooth day-to-day variability, especially during weekdays and weekend

Sociodemographic, smoking habits and medical health conditions

Information about sociodemographic (age, gender, education years, marital status) and medical history including heaviness of smoking index (yes/no), and current alcohol habit (yes/no) measured trough the questionnaire Alcohol use disorders identification test (Daeppen, Yersin, Landry, Pecoud, & Decrey, 2000) during all the follow-up, self-reported BMI and comorbidity with

Table 1. Features legend: HR parameters derived from the Fitbit

Variable	No Observations	Features
mHR/day	6666	Mean HR data across all day (24 h)
Std HR/day	6666	Standard deviation of HR data across all day (24 h)
Resting mHR/day	6613	Mean HR during resting periods, identified by activity level = resting and number of steps = 0 during the day (24 h)
Resting stdHR /day	6613	Standard deviation of HR during resting periods during the day (24 h)
Resting mHR/night	6261	Mean HR during resting periods at night time.
Resting stdHR/ night	6261	Standard deviation of HR during resting periods, identified by number of steps = 0 only during night time (0:00–05:59)
Activity mHR/day	6466	Mean of HR during activity periods (the physical activity was classified as lightly, moderate and vigorous).

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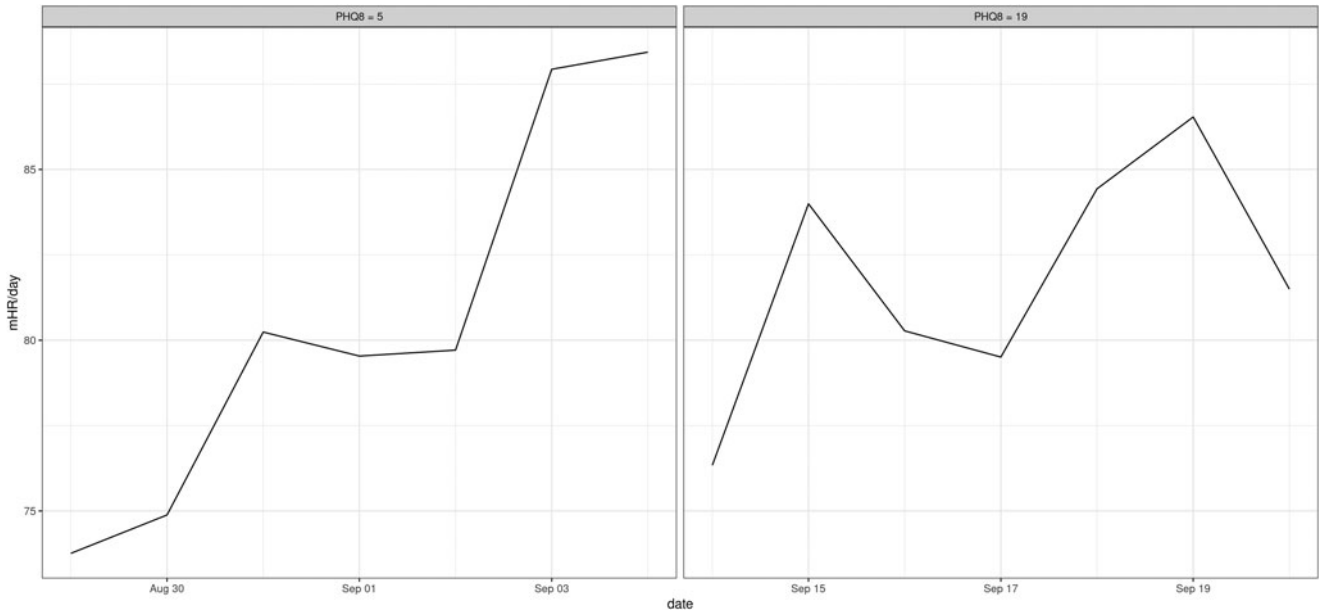

Figure 1. An example of 7-day mean HR prior to the PHQ-8 assessment from the same participant at the mild depression level (left) and moderately severe level (right) during the follow-up.

pre-existing medical health conditions(yes/no), and current antidepressant medications (yes/no) during the study were collected through a the Research Electronic Data Capture (REDCap) package during the enrolment session (Harris et al., 2019, 2009).

Data analysis

First, we described the sociodemographic characteristics reporting frequencies and percentages for categorical variables. Categorical comparisons were made with the χ^2 test. Median with standard deviation (Std) and interquartile ranges (IQR) were reported for continuous variables. Differences by country in continuous variables were explored with the Kruskal–Wallis test. Spearman correlation (ρ) was calculated between the HR parameters and PHQ-8 to assess the association without considering the clustered structure of repeated observations per individual. We also looked at the association between the PHQ-8 and the number of observations to explore if depression severity was negatively related to the assessment rate (i.e. patients with severe depression might be significantly less likely to complete the assessment because of their symptoms of abulia and apathy). Second, we compared the HR parameters between the observations in individuals with severe or moderate depression = 1; *v.* no depression or mild depression = 0) to discover HR features explaining the variance of PHQ-8. Cohen's d effect size was calculated for the comparisons: the effect size is considered as small, medium, and large using the 0.2, 0.5 and 0.8 cut-offs. Finally, linear mixed models with PHQ-8 as the outcome were computed, in two steps. In both, random intercepts for the participant and country levels were included as random effects, and data normalisation (*z* score) of the HR parameters was performed within-participants, so estimates in the mixed models indicate the effect of changes in the HR parameters from the participant-specific mean. In the first step a mixed model was computed separately for each HR feature (mean and standard deviation of HR during the day, resting periods, resting at night and activity periods), having that feature and the baseline of PHQ-8 (first measure of PHQ-8 in the dataset for each participant) as independent variables. In the second step various HR features were included as predictors simultaneously together with the baseline of PHQ-8 to estimate their joint effect. Further, in the second step, sociodemographic and clinical factors were also included as covariates to test their effect in the model, specifically age and BMI as continuous variables and gender, smoking, alcohol and antidepressant consumption, and medical comorbidity as dichotomous variables. All analyses were performed using the R software package 'lme4'(Bates, Mächler, Bolker, & Walker, 2015) software R (R Core Team, R Development Core Team, & R Core Team, 2016).

Results

Descriptive analyses

A total of 510 participants (with a total number of HR observations of 6666) in relationship to HR were included in the analyses. The majority of participants were female ($n = 386$, 76%) and the median age was 50 years old (mean 46.6, std 15.1). About half of the participants were single, separated or widowed (268, 53%). The majority were receiving antidepressant medication during the follow-up (84.3%). The median education years were 15 (Mean: 15.4, std 6.6). The mean BMI was 26 (IQR: 7.6). The sociodemographic information across sites is shown in the online Supplementary materials (Table S1). Only 21.1% ($N = 107$) reported smoking habits at enrolment. More than half ($N = 284$, 56%) reported comorbidity with medical conditions (please see details in online Supplementary materials Table S2). The Table 2 displays the descriptives of the variables included in the statistical models.

Spearman correlation between depression severity and HR features, and comparison between two groups with different current depression severity

Depression severity, as measured with the PHQ-8 was positively related to total mHR/day ($\rho = 0.13$) and negatively related to the total stdHR/day ($\rho = -0.21$), ($p < 0.001$) (Fig. 2). The same pattern of correlations was observed during the resting

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Table 2. Baseline, clinical and HR features

Variable		Median or *N* (%)	IQR	Min	Max
Age		50	27	18	76
Gender (Female) (*n*, %)		386 (75.7)			
BMI		26	7.6	14	71.7
PHQ-8		9.00	10.00	0	24
Smoking status (yes) (*N*, %)		107 (21.1)			
Alcohol habit (yes) (*n*, %)		7982 (87.4)			
Antidepressant (yes) (*n*, %)		7768 (84.3)			
Comorbidity (yes) (*n*, %)		284 (56)			
HR parameters	Period	Median	IQR	Min	Max
mHR	Day	75.55	11.82	46.62	132.65
stdHR	Day	12.70	3.93	0.00	40.18
Resting mHR	Day	73.64	11.80	46.63	132.65
Resting stdHR	Day	11.46	4.18	0.00	39.26
Activity mHR	Day	81.87	14.19	44.63	135.06
Resting mHR	Night	66.70	12.42	43.16	124.65
Resting stdHR	Night	5.05	2.30	0.00	23.72

Note: m, mean; IQR, interquartile ranges; std, standard deviation.

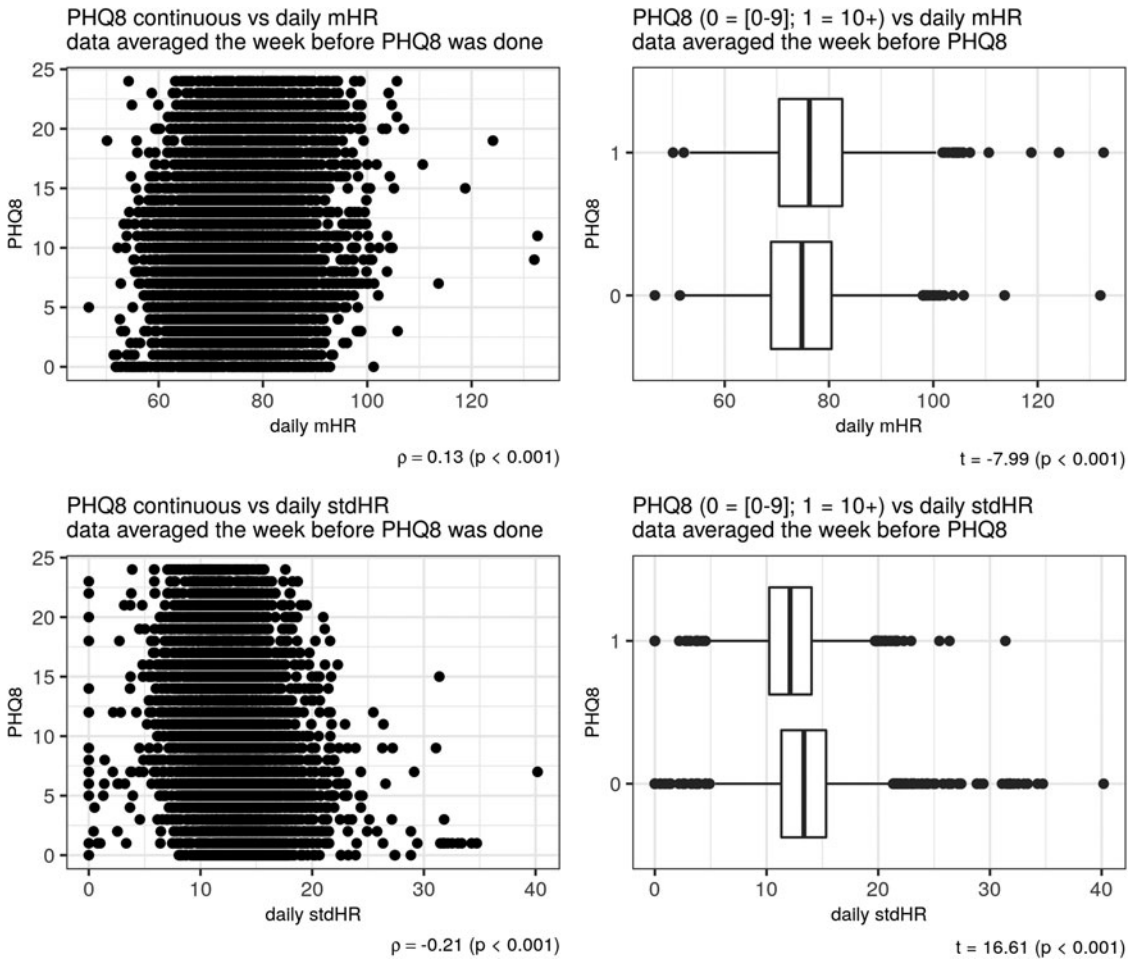

Figure 2. Depression and HR during the day. Scatter plot on the left side showed a correlation between PHQ-8 and mHR (above) and between PHQ-8 and stdHR (below). Boxplots on the right showed a comparison on total mHR (above) and total stdHR (below) between the groups depression v. no depression.

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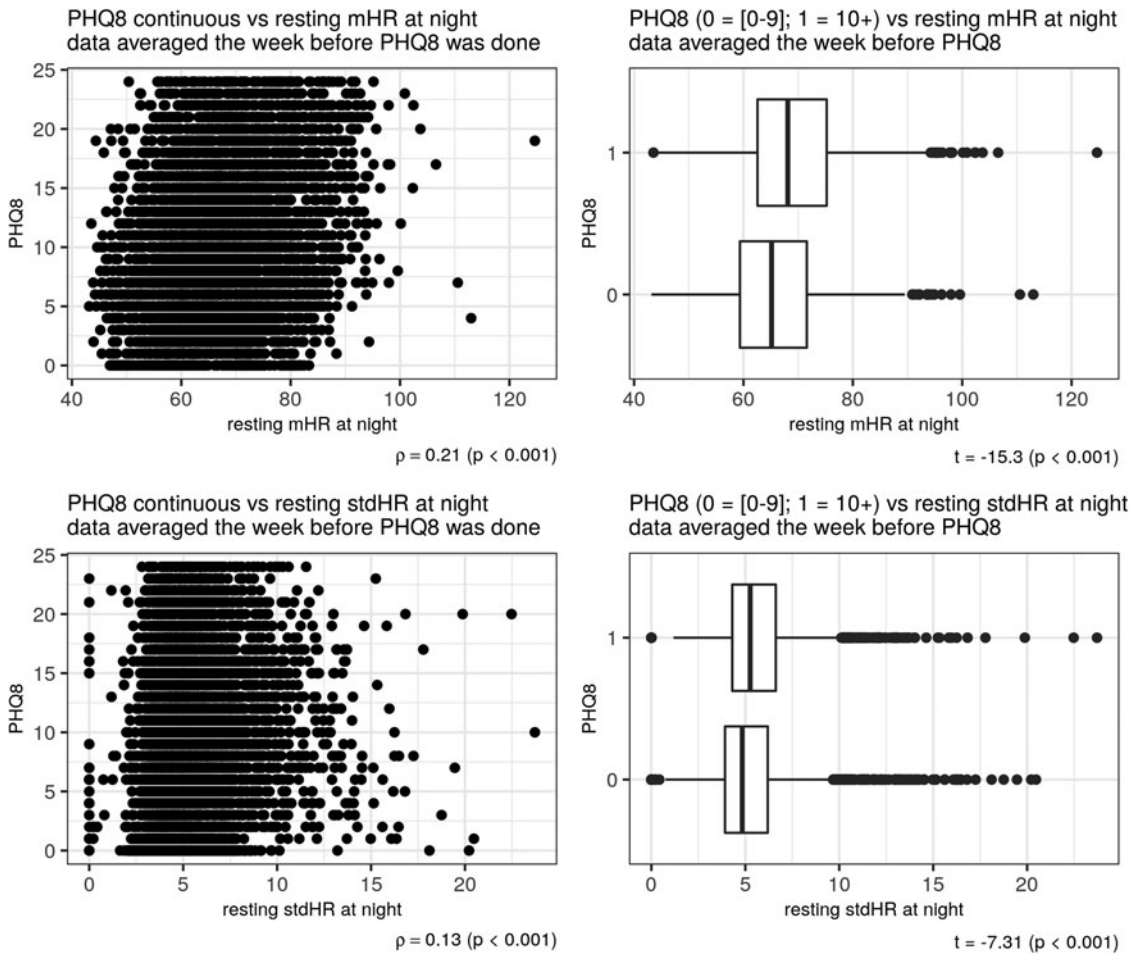

Figure 3. Depression and resting HR at night. Scatter plot on the left side showed a correlation between PHQ-8 and mHR (above) and between PHQ-8 and stdHR (below). Boxplots on the right side showed a comparison on mHR (above) and stdHR (below) between the groups depression v. no depression.

period: depression severity was positively related to resting mHR/day ($\rho = 0.17$) and negatively related to resting stdHR/day ($\rho = -0.12$) ($p < 0.001$). During the activity period, depression severity was positively related to activity mHR during all day but with a small correlation ($\rho = 0.03$, $p = 0.001$). During the night, depression severity was positively related with both measures: resting mHR/night ($\rho = 0.21$) and resting stdHR/night ($\rho = 0.13$) ($p < 0.001$). In fact, participants with no depression or mild depression (PHQ-8 < 10) and moderate or severe depression (PHQ-8 ⩾ 10) severity had different total mHR/day ($t = -7.99$, *Cohen's* $d = -0.20$) and total stdHR/day (t = 16.61, *Cohen's* $d = 0.41$) (Fig. 2) ($p < 0.001$); resting mHR/night ($t = -15.30$, *Cohen's* $d = -0.39$) and resting stdHR/night ($t = -7.31$, *Cohen's* $d = -0.18$) ($p < 0.001$) (Fig. 3). However, we did not find any significant difference in activity mHR/day ($t = -1.67$, $p = 0.09$).

We did not find any significant association between depression severity as assessed with the PHQ-8 and the number of observations ($\rho = -0.08$, $p = 0.07$).

Linear multilevel regression analyses for each of the HR parameters

The models included the PHQ-8 rating as dependent variable and each of the HR features and the baseline of PHQ-8 as independent variables. The within-participant coefficient z-scores of the mHR/day ($\beta = -0.18$) and stdHR/day ($\beta = -0.34$) were negatively associated with depression severity (Table 3). We also observed a similar pattern for resting mHR/day ($\beta = -0.14$) and resting stdHR/day ($\beta = -0.32$), both were negatively associated with depression severity. While, resting mHR/night was positively associated with depression severity ($\beta = 0.09$). On the other hand, no association was found for resting stdHR/night and depression severity.

Linear multilevel regression analyses for each of the HR parameters adjusting for all parameters and covariates.

The Table 4 shows the results of the multilevel analysis including mean and standard deviation of HR during the day, and resting HR during the night as independent variables (Model 1). Table 4 does shows the same model when adding the sociodemographic and clinical characteristics (adjusted model). The findings are consistent in the two models. Increases in mHR/day ($\beta = -0.23$) and stdHR/day ($\beta = -0.30$) were associated with a decrease on PHQ-8, while the increasing resting mHR/night ($\beta = 0.19$) was related with an increase on PHQ-8. We then replicated the analyses, replacing the HR during all day with HR at resting state during the day (Table 5). We observed similar patterns for resting HR during the day: depression severity was negatively related to resting mHR/day ($\beta = -0.16$) and resting stdHR ($\beta = -0.30$), while a positive association was observed with resting mHR/night ($\beta = 0.14$, $p = 0.04$)

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Table 3. Multilevel analyses for exploring the associations between the HR features and the depressive symptoms severity (PHQ-8)

Features	β	s.e. (95% CI)	p value
mHR/day	−0.18	0.04 (−0.26 to −0.10)	<0.0001
stdHR/day	−0.34	0.04 (−0.42 to −0.26)	<0.0001
Resting mHR/day	−0.14	0.04 (−0.22 to −0.06)	0.0004
Resting stdHR/day	−0.32	0.04 (−0.40 to −0.24)	<0.0001
Resting mHR/night	0.09	0.04 (0.01–0. 17)	0.037
Resting stdHR/night	−0.01	0.04 (−0.09 to 0.07)	0.824
Activity mHR/day	−0.05	0.04 (−0.13 to 0.03)	0.215

Note: each model includes a HR parameter together with the baseline PHQ-8 as independent variables to predict.
PHQ-8 changes (continuous variable).

(Table 5). No significant findings were found for resting stdHR at night. Depression severity was negatively associated with age ($\beta = -0.03,\ p = 0.01$) and positively to medical health condition ($\beta = 1.12,\ p < 0.0001$).

We then replicated the previous analyses including mHR during the activity period and the resting mHR/day and resting mHR/night to confirm that the activity mHR does not have an association with depression severity (Table 6). Resting mHR/day and resting mHR/night maintained their association with depression severity, as also the other two covariates did, but activity mHR/day was not associated to depression severity (adjusted model).

Discussion

To the best of our knowledge, this is the first study exploring the association between depression severity and HR changes using a wearable device in a sample of people with MDD during a long-term period of monitoring. The two main findings of this study are: first, lower resting HR variation measured with the standard deviation of HR during the day is associated with higher depression severity; and second, resting mean HR at night increases with depression severity. These relationships were maintained when we adjusted for gender, age, smoking and alcohol habits, also pre-existing comorbid medical health conditions, and antidepressant treatment.

These findings are consistent with the study hypotheses. A previous study demonstrated that individuals with more severe depression were less active and did not perform moderate and vigorous activities that increase the HR during the day (Kandola, Lewis, Osborn, Stubbs, & Hayes, 2020). Accordingly, one possible explanation could, therefore, be that individuals with MDD have low physical activity. The relationship was maintained when we also adjusted for mean HR during activity periods.

At odds with the study hypothesis, we also observed decrease in daily mean HR and daily resting HR associated with more severe depression. However, this finding was only present in the regression analysis. Accordingly, this association between mean HR/day and depression severity could have been affected by Simpson's paradox, given that the direction of the correlation between the two parameters changed from positive in the bivariate analyses to negative in the regression analyses when the HR data were within-participants normalised. The negative association was

Table 4. Mixed model with HR features during the day (24 h) and night related to depression severity and sociodemographic covariates

	Model 1				Adjusted Model			
Features	β	s.e.	95% CI	p value	β	s.e.	95% CI	p value
Baseline PHQ-8	0.72	0.03	0.67–0.77	*<0.0001*	0.69	0.03	0.63–0.75	<0.001
mHR/day	−0.23	0.07	−0.38 to −0.09	*0.001*	−0.24	0.07	−0.39 to −0.09	0.001
stdHR /day	−0.30	0.06	−0.41 to −0.19	*<0.0001*	−0.29	0.06	−0.40 to −0.18	<0.0001
Resting mHR/night	0.19	0.07	0.05–0.33	*0.006*	0.18	0.07	0.04–0.32	0.01
Resting stdHR/night	0.003	0.05	−0.09 to 0.09	*0.93*	0.02	0.05	−0.07 to 0.11	0.68
Age					−0.03	0.01	−0.05 to −0.01	0.01
Gender (women)[a]					−0.14	0.37	−0.88 to 0.59	0.71
BMI					0.01	0.02	−0.04 to 0.05	0.84
Smoking habits					0.44	0.42	−0.39 to 1.27	0.30
Alcohol					−0.22	0.35	−0.9 to 0.48	0.54
Comorbidity					1.12	0.34	0.46–1.78	<0.001
Antidepressant					−0.21	0.22	−0.64 to 0.21	0.32
R^2 marginal	0.487				R^2 marginal		0.749	
AIC	33 347.92				AIC		32 446.4	
BIC	33 401.85				BIC		32 547.1	
Adjusted ICC	0.512				Adjusted ICC		0.497	

Note: Model 1. Daily measure of HR and HR during nighttime parameters were included together with the baseline PHQ-8 as independent variables in this model. Adjusted model includes all the previous independent variables and covariates.
[a]The reference group is men.

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Table 5. Linear mixed model with resting HR features during the day (24 h) and night related to depression severity and sociodemographic covariates

	Model 1				Adjusted Model			
Features	β	S.E.	(95% CI)	p value	β	S.E.	(95% CI)	p value
Baseline PHQ-8	0.72	0.03	0.67– 0.77	*<0.0001*	0.69	0.03	0.64–0.75	<0.001
Resting mHR/day	−0.16	0.07	−0.31 to −0.01	*0.03*	−0.17	0.08	−0.33 to −0.02	0.02
Resting stdHR/day	−0.30	0.06	−0.43 to −0.19	*<0.0001*	−0.32	0.06	−0.44 to −0.20	<0.001
Resting mHR/night	0.14	0.07	0.004–0.28	*0.04*	0.13	0.07	−0.01 to 0.27	0.07
Resting stdHR/night	0.05	0.05	−0.04 to 0.14	*0.28*	0.07	0.05	−0.02 to 0.17	0.13
Age					−0.03	0.01	−0.05 to −0.01	0.01
Gender(women)[a]					−0.15	0.38	−0.89 to 0.59	0.69
BMI					0.005	0.02	−0.04 to 0.05	0.84
Smoking habits					0.43	0.42	−0.40 to 1.26	0.30
Alcohol					−0.23	0.35	−0.92 to 0.46	0.52
Comorbidity					1.12	0.34	0.45–1.78	<0.001
Antidepressant					−0.24	0.22	−0.67 to 0.18	0.27
R^2 marginal	0.487				R^2 marginal		0.501	
AIC	32 505.1				AIC		32 448.09	
BIC	32 505.1				BIC		32 548.79	
Adjusted ICC	0.509				Adjusted ICC		0.498	

Note. Model 1. Resting HR measures during the day and night were included together with the baseline PHQ-8 as independent variables, Adjusted model: previous parameters were then included in this model with covariates.
[a]The reference group is men.

Table 6. Linear mixed model with mean HR features during the day (24 h) and night related to depression severity and sociodemographic covariates

	Model 1				Adjusted Model			
Features	β	S.E.	95% CI	p value	β	S.E.	95% CI	p value
Baseline PHQ-8	0.72	0.03	0.67–0.77	<0.0001	0.69	0.03	0.64–0.75	<0.001
Resting mHR/day	−0.40	0.06	−0.52 to −0.28	<0.0001	−0.42	0.06	−0.54 to −0.30	<0.001
Resting mHR/night	0.37	0.06	0.25–0.48	<0.0001	0.36	0.06	0.25–0.48	<0.001
Activity mHR/day	−0.06	0.04	−0.15 to 0.02	0.18	−0.04	0.05	−0.13 to 0.05	0.42
Age					−0.03	0.01	−0.05 to −0.01	0.02
Gender (women)[a]					−0.15	0.37	−0.88 to 0.59	0.69
BMI					0.01	0.02	−0.04 to 0.05	0.84
Smoking habits					0.43	0.42	−0.40 to 1.26	0.32
Alcohol habit					−0.20	0.35	−0.89 to 0.50	0.58
Comorbidity					1.10	0.34	0.44–1.76	0.001
Antidepressant					−0.22	0.22	−0.64 to 0.21	0.32
R^2 marginal	0.488				R^2 marginal		0.502	
AIC	31 888.51				AIC		31 885.92	
BIC	31 942.08				BIC		31 986.35	
Adjusted ICC	0.507				Adjusted ICC		0.496	

Note. Model 1: Resting and activity HR measures were included together with the baseline PHQ-8 as independent variables, Adjusted model: Previous parameters were then included in this model with covariates.
[a]The reference group is men.

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also maintained when the predictors were analysed separately, when they were introduced together and then adjusted with the covariates. Further research may be needed to advance in the relation between HR and depression severity.

One possible explanation of the relationship between HR and depression severity may be that passive behaviours, such as watching TV, listening to music or any other activity that do not include movements, may be more frequent in individuals when more depressed (Hallgren et al., 2020). Another explanation might be that a low resting mean HR might be provoked by the effect of the medication; however we did not observe any effect of antidepressant medication when adjusted for it.. Studies conducted both in humans and animals reported that potentially adverse effects of antidepressant interactions could lead to an abnormal decrease in the HR (Ababneh, Ritchie, & Webster, 2012; Azizi, Elyasi, & Roodposhti, 2019; Woroń, Siwek, & Gorostowicz, 2019). However, a recent meta-analysis found that HR alterations were not fully explained by antidepressant use alone (Brown et al., 2018).

During the night, the high resting mean HR was associated with higher depression severity. In the resting state during the night non-activity periods were included, but they can correspond to awake stages where HR could be higher than expected for the night time. It is well-known that people with MDD suffer of sleeping difficulties, especially insomnia, that would be one explanation of the high mean HR. In healthy individuals, resting mean HR decreases significantly during the night due to parasympathetic predominance during sleep (Mancia et al., 1983). This decrease may be less pronounced in individuals with MDD and related to depression severity. Previous studies have also demonstrated that increasing resting mean HR is a significant predictor of mortality in people with MDD and heart failure (Carney et al., 2016; Lau et al., 2021; Nabi et al., 2011). We did not find any association between the resting HR variation during the night and depression severity. Further studies are warranted to explore if the HR variation in relation to depression severity fluctuates according to the different sleep stages.

As we expected, we observed that low HR variation during all day resting periods was related to increased depression severity over time. A low HR variation indicates that the body is under stress from psychological events, or other internal or external stressors. The reduced resting HR variation may depend on a failure of the parasympathetic control via the vagal nerve (Olshansky, Sabbah, Hauptman, & Colucci, 2008) that restores the body from overworking and prior accumulated stress (Kemp & Quintana, 2013; Kim, Cheon, Bai, Lee, & Koo, 2018).

Decreased HR variation, especially during the resting period is associated with increased cardiovascular risk and mortality across different age groups (Brown et al., 2018; Koch et al., 2019; Koenig et al., 2016) and it is reported in different medical health conditions (Galinier et al., 2000; Tessier et al., 2017). In our group, we observed that depression severity was positively associated with various comorbid medical conditions including cardiovascular disease, metabolic and digestive disease rheumatic disease, pulmonary disease and neurological disorders and other (i.e. psychiatric, as anxiety, eating disorders and other medical conditions. MDD is frequently comorbid with cardiovascular disease (Carney et al., 2005; Penninx, 2017), long diseases (Yohannes, Willgoss, Baldwin, & Connolly, 2010), metabolic syndrome (Pan & Hu, 2013; Vancampfort et al., 2014), and neurological disorder (Raskind, 2008). This comorbidity might impact the prognosis and management of depression and increase risk of mortality.

Moreover, we also observed that younger age was associated with depression severity. Young people may endorse more affective symptoms whereas elderly people may report more cognitive changes and loss of interest (Fiske, Wetherell, & Gatz, 2009). Another study found that younger age could have a greater risk of multiple depression episodes (Fergusson & Woodward, 2002). This finding highlights the importance of a prompt and early intervention. Finally, we did not find any association of depression severity with gender. It might be due to the fact that the majority of our sample was composed of women (76%) and both women and men were diagnosed with MDD with recurrent episodes. Neither did we find an association between depression and smoking status, alcohol status and BMI in our group. One explanation could be that only a small subgroup reported smoking habits, and a few reported BMI over the normal range. Previous studies reported an association between depressive symptoms, BMI and smoking habits (Hooker, MacGregor, Funderburk, & Maisto, 2014; Strine et al., 2008; Widome et al., 2009).

Strengths and limitations

When considering these results, we should acknowledge the limitation of the device used. As stated previously, the HR data derived from the PPG are highly correlated with the HR data derived from the ECG, both HR and HRV (Gil et al., 2010; Lu et al., 2008). However, the wrist-worn device used in this study does not provide access to the PPG signal but rather to the HR series derived by proprietary algorithms at different time intervals. This does not allow for analysing HRV properly, as already stated. Wrist-based device HR determination has been shown to have a < 5% error in a range of devices and activities relative to gold-standard and closer to 1% when at rest (Shcherbina et al., 2017). The HR variation can be used as a proxy measure of HR fluctuations (Moser et al., 1994). The HR variation has already been used to explore the variation of HR in other studies (Quer, Gouda, Galarnyk, Topol, & Steinhubl, 2020; Wang, Lizardo, & Hachen, 2022). On the other hand, the Fitbit device presents different advantages: comfortable design, it can be used for an extended period and is accessible to a broad population for its low cost. Another strength of this study is the collection of daily mood data which may be superior to retrospective reports to measure depression severity in association with daily HR parameters. Moreover, we used long term longitudinal data from participants. Additional aspects to be considered when analysing the results are that the effect of some medications (i.e. beta-blockers and inhaler treatments) was not analysed; that potential adverse effect on HR might be provoked by other medications; and that various medical conditions have been included in the analysis but were not considered separately. However, the objective was only to explore how co-morbid medical condition might impact the association between HR and depression severity. Finally, depression severity may be exacerbated by anxiety symptoms. Further research should explore the impact of anxiety and sleep, among others, in the association between HR and depression severity.

Conclusion

In this paper, we have demonstrated that HR parameters may be indicators of depression severity and that it is possible to collect them on large numbers of participants and long follow-ups. From a clinical perspective, the current data suggest that reduced

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daily resting HR variability could represent a correlate of vulnerability to depression severity. Hence, the findings of specific HR biomarkers associated to depression severity fluctuations, providing a valuable tool for the early recognition or post- depressive monitoring of vulnerable individuals. An early warning of potential relapse allows clinicians to take responsive treatment promptly. This represents an opportunity to offer individual trajectories of HR parameters. Moreover, a longitudinal view of HR variations provides great personal health information in real-time and in real-world setting. Further research is needed to translate these results into meaningful clinical recommendations. These findings will be integrated in future analyses with multi-modal data collected within the RADAR-MDD study in order to develop algorithms to predict changes in clinical state.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723001034

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Competing interests. VAN and VS are employees of Janssen Research and Development LLC. PA is employed by the pharmaceutical company H. Lundbeck A/S. JMH has received economic compensation for participating in advisory boards or giving educational lectures from Eli Lilly & Co, Sanofi, Lundbeck, and Otsuka. No other authors have competing interests to declare

Availability of data and materials. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

Ababneh, D., Ritchie, H., & Webster, W. S. (2012). Antidepressants cause bradycardia and heart block in GD 13 Rat embryos in vitro. *Birth Defects Research Part B – Developmental and Reproductive Toxicology*, *95*(2), 184–193. https://doi.org/10.1002/bdrb.21003.

Angermann, C. E., & Ertl, G. (2018). Depression, anxiety, and cognitive impairment: Comorbid mental health disorders in heart failure. *Current Heart Failure Reports*, *15*, 398–410. https://doi.org/10.1007/s11897-018-0414-8.

Azizi, M., Elyasi, F., & Roodposhti, F. N. (2019). Bradycardia caused by interaction of venlafaxine and cyclosporine: A case report. *Caspian Journal of Internal Medicine*, *10*(4), 463–467. https://doi.org/10.22088/cjim.10.4.463.

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1), 1–51. https://doi.org/10.18637/jss.v067.i01.

Berntson, G. G., Thomas Bigger, J., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., … Van Der Molen, M. W. (1997). Heart rate variability: Origins methods, and interpretive caveats. *Psychophysiology*, *34*, 623–648. https://doi.org/10.1111/j.1469-8986.1997.tb02140.x.

Brown, L., Karmakar, C., Gray, R., Jindal, R., Lim, T., & Bryant, C. (2018). Heart rate variability alterations in late life depression: A meta-analysis. *Journal of Affective Disorders*, *235*, 456–466. https://doi.org/10.1016/j.jad.2018.04.071.

Caldwell, Y. T., & Steffen, P. R. (2018). Adding HRV biofeedback to psychotherapy increases heart rate variability and improves the treatment of major depressive disorder. *International Journal of Psychophysiology*, *131*, 96–101. https://doi.org/10.1016/j.ijpsycho.2018.01.001.

Carney, R. M., Freedland, K. E., Steinmeyer, B. C., Rubin, E. H., Stein, P. K., & Rich, M. W. (2016). Nighttime heart rate predicts response to depression treatment in patients with coronary heart disease. *Journal of Affective Disorders*, *200*, 165–171. https://doi.org/10.1016/j.jad.2016.04.051.

Carney, R. M., Freedland, K. E., & Veith, R. C. (2005). Depression, the autonomic nervous system, and coronary heart disease. *Psychosomatic Medicine*, *67*, S29–S33. https://doi.org/10.1097/01.psy.0000162254.61556.d5.

Carney, R. M., Steinmeyer, B., Freedland, K. E., Blumenthal, J. A., Stein, P. K., Steinhoff, W. A., … Jaffe, A. S. (2008). Nighttime heart rate and survival in depressed patients post acute myocardial infarction. *Psychosomatic Medicine*, *70*(7), 757–763. https://doi.org/10.1097/PSY.0b013e3181835ca3.

Castaneda, D., Esparza, A., Ghamari, M., Soltanpur, C., & Nazeran, H. (2018). A review on wearable photoplethysmography sensors and their potential future applications in health care. *International Journal of Biosensors & Bioelectronics*, *4*(4), 195–202. https://doi.org/10.15406/ijbsbe.2018.04.00125.

Correll, C. U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., … Stubbs, B. (2017). Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: A large-scale meta-analysis of 3,211,768 patients and 113383368 controls. *World Psychiatry*, *16*(2), 163–180. https://doi.org/10.1002/wps.20420.

Daeppen, J.-B., Yersin, B., Landry, U., Pecoud, A., & Decrey, H. (2000). Reliability and validity of the Alcohol Use Disorders Identification Test (AUDIT) imbedded within a general health risk screening questionnaire: Results of a survey in 332 primary care patients. *Alcoholism: Clinical and Experimental Research*, *24*(5), 659–665. https://doi.org/10.1111/j.1530-0277.2000.tb02037.x.

Dias, D., & Cunha, J. P. S. (2018). Wearable health devices – vital sign monitoring, systems and technologies. *Sensors* (*Switzerland*), *18*, 2414. https://doi.org/10.3390/s18082414.

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine*, *160*(14), 2101–2107. https://doi.org/10.1001/archinte.160.14.2101.

Fergusson, D. M., & Woodward, L. J. (2002). Mental health, educational, and social role outcomes of adolescents with depression. *Archives of General Psychiatry*, *59*(3), 225–231. https://doi.org/10.1001/archpsyc.59.3.225.

Fiske, A., Wetherell, J. L., & Gatz, M. (2009). Depression in older adults. *Annual Review of Clinical Psychology*, *5*(1), 363–389. https://doi.org/10.1146/annurev.clinpsy.032408.153621.

Fuller, D., Colwell, E., Low, J., Orychock, K., Tobin, M. A., Simango, B., … Taylor, N. G. A. (2020). Reliability and validity of commercially available wearable devices for measuring steps, energy expenditure, and heart rate: Systematic review. *JMIR MHealth and UHealth*, *8*(9), e18694. https://doi.org/10.2196/18694.

Galinier, M., Pathak, A., Fourcade, J., Androdias, C., Curnier, D., Varnous, S., … Bounhoure, J. P. (2000). Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. *European Heart Journal*, *21*(6), 475–482. https://doi.org/10.1053/euhj.1999.1875.

Gil, E., Orini, M., Bailón, R., Vergara, J. M., Mainardi, L., & Laguna, P. (2010). Photoplethysmography pulse rate variability as a surrogate measurement of heart rate variability during non-stationary conditions. *Physiological Measurement*, *31*(9), 1271–1290. https://doi.org/10.1088/0967-3334/31/9/015.

Halaris, A.. (2017). Inflammation-associated co-morbidity between depression and cardiovascular disease. *Current Topics in Behavioral Neurosciences*, *31*, 45–70. https://doi.org/10.1007/7854_2016_28. PMID: 27830572.

Hallgren, M., Nguyen, T., Owen, N., Stubbs, B., Vancampfort, D., Lundin, A., … Lagerros, Y. T. (2020). Cross-sectional and prospective relationships of passive and mentally active sedentary behaviours and physical activity with depression. *The British Journal of Psychiatry*, *2*, 413–419. https://doi.org/10.1192/bjp.2019.87.

Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., … Duda, S. N. (2019). The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics*, *95*, 103208. https://doi.org/10.1016/j.jbi.2019.103208.

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010.

Hartmann, R., Schmidt, F. M., Sander, C., & Hegerl, U. (2019). Heart rate variability as indicator of clinical state in depression. *Frontiers in Psychiatry*, *10* (JAN), 735. https://doi.org/10.3389/fpsyt.2018.00735.

Hernando, D., Roca, S., Sancho, J., Alesanco, Á, & Bailón, R. (2018). Validation of the Apple watch for heart rate variability measurements during relax and mental stress in healthy subjects. *Sensors*, *18*(8), 2619. https://doi.org/10.3390/s18082619.

Hooker, S. A., MacGregor, K. L., Funderburk, J. S., & Maisto, S. A. (2014). Body mass index and depressive symptoms in primary care settings: Examining the moderating roles of smoking status, alcohol consumption and vigorous exercise. *Clinical Obesity*, *4*(1), 21–29. https://doi.org/10.1111/cob.12035.

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., … Murray, C. J. L. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the global burden of disease study 2017. *The Lancet*, *392*(10159), 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7.

Kandola, A., Lewis, G., Osborn, D. P. J., Stubbs, B., & Hayes, J. F. (2020). Depressive symptoms and objectively measured physical activity and sedentary behaviour throughout adolescence: A prospective cohort study. *The Lancet Psychiatry*, *7*(3), 262–271. https://doi.org/10.1016/S2215-0366(20)30034-1.

Kemp, A. H., & Quintana, D. S. (2013). The relationship between mental and physical health: Insights from the study of heart rate variability. *International Journal of Psychophysiology*, *89*, 288–296. https://doi.org/10.1016/j.ijpsycho.2013.06.018.

Kemp, A. H., Quintana, D. S., Felmingham, K. L., Matthews, S., & Jelinek, H. F. (2012). Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: Implications for cardiovascular risk. *PLoS ONE*, *7*(2), e30777. https://doi.org/10.1371/journal.pone.0030777.

Kemp, A. H., Quintana, D. S., Gray, M. A., Felmingham, K. L., Brown, K., & Gatt, J. M. (2010). Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. *Biological Psychiatry*, *67* (11), 1067–1074. https://doi.org/10.1016/j.biopsych.2009.12.012.

Kim, H. G., Cheon, E. J., Bai, D. S., Lee, Y. H., & Koo, B. H. (2018). Stress and heart rate variability: A meta-analysis and review of the literature. *Psychiatry Investigation*, *15*(3), 235–245. https://doi.org/10.30773/pi.2017.08.17.

Koch, C., Wilhelm, M., Salzmann, S., Rief, W., & Euteneuer, F. (2019). A meta-analysis of heart rate variability in major depression. *Psychological Medicine*, *49*, 1948–1957. https://doi.org/10.1017/S0033291719001351.

Koenig, J., Kemp, A. H., Beauchaine, T. P., Thayer, J. F., & Kaess, M. (2016). Depression and resting state heart rate variability in children and adolescents – A systematic review and meta-analysis. *Clinical Psychology Review*, *46*, 136–150. https://doi.org/10.1016/j.cpr.2016.04.013.

Kroenke, K., Strine, T. W., Spitzer, R. L., Williams, J. B. W., Berry, J. T., & Mokdad, A. H. (2009). The PHQ-8 as a measure of current depression in the general population. *Journal of Affective Disorders*, *114*(1–3), 163–173. https://doi.org/10.1016/j.jad.2008.06.026.

Lam, E., Aratia, S., Wang, J., & Tung, J. (2020). Measuring heart rate variability in free-living conditions using consumer-grade photoplethysmography: Validation study. *JMIR Biomedical Engineering*, *5*(1), e17355. https://doi.org/10.2196/17355.

Lau, K., Malik, A., Foroutan, F., Buchan, T. A., Daza, J. F., Sekercioglu, N., … Alba, A. C. (2021). Resting heart rate as an important predictor of mortality and morbidity in ambulatory patients with heart failure: A systematic review and meta-analysis. *Journal of Cardiac Failure*, *27*, 349–363. https://doi.org/10.1016/j.cardfail.2020.11.003.

Lett, H. S., Blumenthal, J. A., Babyak, M. A., Sherwoob, A., Strauman, T., Robins, C., & Newman, M. F. (2004). Depression as a risk factor for coronary artery disease: Evidence, mechanisms, and treatment. *Psychosomatic Medicine*, *66*, 305–315. https://doi.org/10.1097/01.psy.0000126207.43307.c0.

Li, X., Hu, B., Shen, J., Xu, T., & Retcliffe, M. (2015). Mild depression detection of college students: An EEG-based solution with free viewing tasks. *Journal of Medical Systems*, *39*(12), 187. https://doi.org/10.1007/s10916-015-0345-9.

Liu, S., Han, J., Puyal, E. L., Kontaxis, S., Sun, S., Locatelli, P., … RADAR-CNS consortium. (2022). Fitbeat: COVID-19 estimation based on wristband heart rate using a contrastive convolutional auto-encoder. *Pattern Recognition*, *123*, 108403. https://doi.org/10.1016/J.PATCOG.2021.108403.

Lu, S., Zhao, H., Ju, K., Shin, K., Lee, M., Shelley, K., & Chon, K. H. (2008). Can photoplethysmography variability serve as an alternative approach to obtain heart rate variability information? *Journal of Clinical Monitoring and Computing*, *22*(1), 23–29. https://doi.org/10.1007/s10877-007-9103-y.

Mancia, G., Ferrari, A., Gregorini, L., Parati, G., Pomidossi, G., Bertinieri, G., … Zanchetti, A. (1983). Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circulation Research*, *53* (1), 96–104. https://doi.org/10.1161/01.RES.53.1.96.

Matcham, F., Barattieri di San Pietro, C., Bulgari, V., de Girolamo, G., Dobson, R., Eriksson, H., … Hotopf, M. (2019). Remote assessment of disease and relapse in major depressive disorder (RADAR-MDD): A multi-centre

prospective cohort study protocol. *BMC Psychiatry*, *19*(1), 72. https://doi.org/10.1186/s12888-019-2049-z.

Matcham, F., Leightley, D., Siddi, S., Lamers, F., White, K. M., Annas, P., … RADAR-CNS consortium. (2022). Remote Assessment of Disease and Relapse in Major Depressive Disorder (RADAR-MDD): Recruitment, retention, and data availability in a longitudinal remote measurement study. *BMC Psychiatry*, *22*(1), 136. https://doi.org/10.1186/s12888-022-03753-1.

Moser, M., Lehofer, M., Sedminek, A., Lux, M., Zapotoczky, H. G., Kenner, T., & Noordergraaf, A. (1994). Heart rate variability as a prognostic tool in cardiology. A contribution to the problem from a theoretical point of view. *Circulation*, *90*(2), 1078–1082. https://doi.org/10.1161/01.CIR.90.2.1078.

Nabi, H., Kivimäki, M., Empana, J.-P., Sabia, S., Britton, A., Marmot, M. G., … Singh-Manoux, A. (2011). Combined effects of depressive symptoms and resting heart rate on mortality. *The Journal of Clinical Psychiatry*, *72*(09), 1199–1206. https://doi.org/10.4088/JCP.09m05901blu.

Narziev, N., Goh, H., Toshnazarov, K., Lee, S. A., Chung, K. M., & Noh, Y. (2020). STDD: Short-term depression detection with passive sensing. *Sensors* (*Switzerland*), *20*(5), 1396. https://doi.org/10.3390/s20051396.

Nazari, G., Macdermid, J. C., Sinden, K. E., Richardson, J., & Tang, A. (2019). Inter-instrument reliability and agreement of Fitbit charge measurements of heart rate and activity at rest, during the modified Canadian aerobic fitness test, and in recovery. *Physiotherapy Canada*, *71*(3), 197–206. https://doi.org/10.3138/ptc.2018-25.

Nelson, B. W., & Allen, N. B. (2019). Accuracy of consumer wearable heart rate measurement during an ecologically valid 24-hour period: Intraindividual validation study. *JMIR MHealth and UHealth*, *7*(3), e10828. https://doi.org/10.2196/10828.

Olshansky, B., Sabbah, H. N., Hauptman, P. J., & Colucci, W. S. (2008). Parasympathetic nervous system and heart failure pathophysiology and potential implications for therapy. *Circulation*, *118*, 863–871. https://doi.org/10.1161/CIRCULATIONAHA.107.760405.

Owens, A. P. (2020). The role of heart rate variability in the future of remote digital biomarkers. *Frontiers in Neuroscience*, *14*, 582145. https://doi.org/10.3389/fnins.2020.582145.

Pan, A., Hu, F. B. (2013). Response to comment on: Pan *et al*. Bidirectional association between depression and metabolic syndrome: A systematic review and meta-analysis of epidemiological studies. Diabetes care 2012;35:1171–1180. *Diabetes Care*, *36*(2), e28–e28. https://doi.org/10.2337/dc12-1779.

Penninx, B. W. (2017). Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. *Neuroscience and Biobehavioral Reviews*, *74*(Pt B), 277–286. https://doi.org/10.1016/j.neubiorev.2016.07.003.

Penninx, B. W., Beekman, A., Honig, A., Deeg, D. J., Schoevers, R. A., van Eijk, J. T., & van Tilburg, W. (2001). Depression and cardiac mortality: Results from a community-based longitudinal study. *Archives of General Psychiatry*, *58*(3), 221–227. https://doi.org/10.1001/archpsyc.58.3.221.

Penninx, B. W., Milaneschi, Y., Lamers, F., & Vogelzangs, N. (2013). Understanding the somatic consequences of depression: Biological mechanisms and the role of depression symptom profile. *BMC Medicine*, *11*(1), 129. https://doi.org/10.1186/1741-7015-11-129.

Polhemus, A. M., Novák, J., Ferrao, J., Simblett, S., Radaelli, M., Locatelli, P., … Hotopf, M. (2020). Human-centered design strategies for device selection in mHealth programs: Development of a novel framework and case study. *JMIR MHealth and UHealth*, *8*(5), e16043. https://doi.org/10.2196/16043.

Quer, G., Gouda, P., Galarnyk, M., Topol, E. J., & Steinhubl, S. R. (2020). Inter- and intraindividual variability in daily resting heart rate and its associations with age, sex, sleep, BMI, and time of year: Retrospective, longitudinal cohort study of 92457 adults. *PLOS ONE*, *15*(2), e0227709. https://doi.org/10.1371/journal.pone.0227709.

Ranjan, Y., Rashid, Z., Stewart, C., Conde, P., Begale, M., Verbeeck, D., … RADAR-CNS Consortium. (2019). RADAR-base: Open source mobile health platform for collecting, monitoring, and analyzing data using sensors, wearables, and mobile devices. *JMIR MHealth and UHealth*, *7*(8), e11734. https://doi.org/10.2196/11734.

Raskind, M. A. (2008). Diagnosis and treatment of depression comorbid with neurologic disorders. *The American Journal of Medicine*, *121*(11), S28–S37. https://doi.org/10.1016/j.amjmed.2008.09.011.

R Core Team, R Development Core Team, & R Core Team. (2016). R: A language and environment for statistical computing. In R Foundation for Statistical Computing Vienna Austria.

Shaffer, F., & Ginsberg, J. P. (2017). An overview of heart rate variability metrics and norms. *Frontiers in Public Health*, *5*, 258. https://doi.org/10.3389/fpubh.2017.00258.

Shcherbina, A., Mattsson, C., Waggott, D., Salisbury, H., Christle, J., Hastie, T., … Ashley, E. (2017). Accuracy in wrist-worn, sensor-based measurements of heart rate and energy expenditure in a diverse cohort. *Journal of Personalized Medicine*, *7*(2), 3. https://doi.org/10.3390/jpm7020003.

Silva, E., Aguiar, J., Reis, L. P., Sá, J. O. E., Gonçalves, J., & Carvalho, V. (2020). Stress among Portuguese medical students: The EuStress solution. *Journal of Medical Systems*, *44*(2), 45. https://doi.org/10.1007/s10916-019-1520-1.

Simblett, S., Matcham, F., Siddi, S., Bulgari, V., Barattieri di San Pietro, C., Hortas López, J., … Wykes, T. (2019). Barriers to and facilitators of engagement with mHealth technology for remote measurement and management of depression: Qualitative analysis. *JMIR MHealth and UHealth*, *7*(1), e11325. https://doi.org/10.2196/11325.

Strine, T. W., Mokdad, A. H., Dube, S. R., Balluz, L. S., Gonzalez, O., Berry, J. T., … Kroenke, K. (2008). The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *General Hospital Psychiatry*, *2*, 127–137. https://doi.org/10.1016/j.genhosppsych.2007.12.008.

Stucky, B., Clark, I., Azza, Y., Karlen, W., Achermann, P., Kleim, B., & Landolt, H.-P. (2021). Validation of Fitbit charge 2 sleep and heart rate estimates against polysomnographic measures in shift workers: Naturalistic study. *Journal of Medical Internet Research*, *23*(10), e26476. https://doi.org/10.2196/26476.

Subasi, A. (2019). Chapter 2 - Biomedical signals. In A. Subasi (Eds.), *Practical guide for biomedical signals analysis using machine learning techniques* (pp. 27–87). Academic Press. https://doi.org/10.1016/B978-0-12-817444-9.00002-7.

Taillard, J., Lemoine, P., Boule, P., Drogue, M., & Mouret, J. (1993). Sleep and heart rate circadian rhythm in depression: The necessity to separate. *Chronobiology International*, *10*(1), 63–72. https://doi.org/10.3109/07420529309064483.

Tessier, A., Sibon, I., Poli, M., Audiffren, M., Allard, M., & Pfeuty, M. (2017). Resting heart rate predicts depression and cognition early after ischemic stroke: A pilot study. *Journal of Stroke and Cerebrovascular Diseases*, *26*(10), 2435–2441. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.05.040.

Vancampfort, D., Correll, C. U., Wampers, M., Sienaert, P., Mitchell, A. J., De Herdt, A., … De Hert, M. (2014). Metabolic syndrome and metabolic abnormalities in patients with major depressive disorder: A meta-analysis of prevalences and moderating variables. *Psychological Medicine*, *44*(10), 2017–2028. https://doi.org/10.1017/S0033291713002778.

Walker, W. H., Walton, J. C., DeVries, A. C., & Nelson, R. J. (2020). Circadian rhythm disruption and mental health. *Translational Psychiatry*, *10*, 1–13. https://doi.org/10.1038/s41398-020-0694-0.

Wang, C., Lizardo, O., & Hachen, D. S. (2022). Using Fitbit data to monitor the heart rate evolution patterns of college students. *Journal of American College Health*, *70*(3), 875–882. https://doi.org/10.1080/07448481.2020.1775610.

Widome, R., Linde, J. A., Rohde, P., Ludman, E. J., Jeffery, R. W., & Simon, G. E. (2009). Does the association between depression and smoking vary by body mass index (BMI) category? *Preventive Medicine*, *5*, 380–383. https://doi.org/10.1016/j.ypmed.2009.07.018.

Williams, D. P., Cash, C., Rankin, C., Bernardi, A., Koenig, J., & Thayer, J. F. (2015). Resting heart rate variability predicts self-reported difficulties in emotion regulation: A focus on different facets of emotion regulation. *Frontiers in Psychology*, *6*(MAR), 261. https://doi.org/10.3389/fpsyg.2015.00261.

Woroń, J., Siwek, M., & Gorostowicz, A. (2019). Adverse effects of interactions between antidepressants and medications used in treatment of cardiovascular disorders. *Psychiatria Polska*, *53*(5), 977–995. https://doi.org/10.12740/PP/OnlineFirst/96286.

Yohannes, A. M., Willgoss, T. G., Baldwin, R. C., & Connolly, M. J. (2010). Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: Prevalence, relevance, clinical implications and management principles. *International Journal of Geriatric Psychiatry*, *25*, 1209–1221. https://doi.org/10.1002/gps.2463.