

Review article

Exploring the dynamic relationships between nocturnal heart rate, sleep disruptions, anxiety levels, and depression severity over time in recurrent major depressive disorder

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ABSTRACT

Background: Elevated night resting heart rate (HR) has been associated with increased depression severity, yet the underlying mechanisms remain elusive. This study aimed to investigate the mediating role of sleep disturbance and the influence of anxiety on the relationship between night resting HR and depression severity.

Methods: This is a secondary data analysis of data collected in the Remote Assessment of Disease and Relapse (RADAR) Major Depressive Disorder (MDD) longitudinal mobile health study, encompassing 461 participants

Abbreviations: ANS, Autonomic nervous system; aRMT, Active remote measurement technology; CIBER, Centro de Investigación Biomédica en Red; HR, Heart rate; GAD, Generalised Anxiety Disorder; IDS-SR, Inventory of Depressive Symptomatology – Self Report; KCL, King's College London; MDD, Major depressive disorder; mHR, mean HR; PPG, photoplethysmography; pRMT, passive remote measurement technology; 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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Anxiety
Sleep disturbance

(1774 observations) across three national centers (Netherlands, Spain, and the UK). Depression severity, anxiety, and sleep disturbance were assessed every three months. Night resting HR parameters in the 2 weeks preceding assessments were measured using a wrist-worn Fitbit device. Linear mixed models and causal mediation analysis were employed to examine the impact of sleep disturbance and anxiety on night resting HR on depression severity. Covariates included age, sex, BMI, smoking, alcohol consumption, antidepressant use, and comorbidities with other medical conditions.

Results: Higher night resting HR was linked to subsequent depressive severity, through the mediation of sleep disturbance. Anxiety contributed to an exacerbated level of sleep disturbance, subsequently intensifying depression severity. Anxiety exhibited no direct effect on night resting HR.

Conclusions: Our findings underscore the mediating role of sleep disturbance in the effect of night resting HR on depression severity, and anxiety on depression severity. This insight has potential implications for early identification of indicators signalling worsening depression symptoms, enabling clinicians to initiate timely and responsive treatment measures.

1. Introduction

Major depressive disorder (MDD) is a common mental disorder, globally affecting approximately 265 million people of all ages internationally (James et al., 2018). The intricate relationship between psychological stress and depression is outlined by the diathesis-stress model (Monroe and Simons, 1991). As the predisposition to depression (diathesis) increases, attributed to either biological or psychological factors, individuals become psychologically more vulnerable. Consequently, the threshold of stress required to precipitate an episode of depression decreases (Kemp et al., 2010; Kontaxis et al., 2021).

The physiological response to acute stress is associated with changes in the autonomic nervous system (ANS). The ANS regulates heart rate (HR) to respond to changing circumstances (Thayer et al., 2011). During rest, sleep, or emotional tranquillity, the ANS reduces HR (typically to 60–75 bpm) (Gordan et al., 2015) and during sleep the HR may decrease to below normal from 40 to 60 bpm. The resting HR appears altered in people with depression (Carney et al., 2008; Koenig et al., 2016) indicating potential dysregulation of psychological arousal in the presence of emotional or environmental stressors (Kemp et al., 2010).

This disorder is often accompanied by physiological abnormalities, such as increased HR and reduced HR variability (Carney et al., 2008; Correll et al., 2017; Lett et al., 2004; Nabi et al., 2011), both during sleep and wake states (Pawlowski et al., 2017; Saad et al., 2019). Notably, these HR irregularities may be more pronounced during nighttime, a period shielded from external influences like daytime stressors, physical activity, and cognitive processing.

Extended periods of stress play a vital role in the development of MDD, and this may be mediated by concurrent anxiety experienced by up to 40 % of people with depression (Angermann and Ertl, 2018; Felez-Nobrega et al., 2022; Möller, 2002; Rashid et al., 2023; Tiller, 2013). Elevated anxiety levels may lead to increased release of stress hormones, such as adrenaline, heightening HR in response to everyday stressors (Kim et al., 2018; Steimer, 2002; Zou et al., 2022). Consequently, the coexistence of anxiety and depressive disorders may result in less favorable paths in the progression of depressive symptoms (Gaspersz et al., 2018).

Sleep disturbance is a core symptom of MDD (Jansson-Fröjmark and Lindblom, 2008), with a majority of individuals ($N = 3287$) (Geoffroy et al., 2018) reporting various sleep complaints, including insomnia (85.2 %) and hypersomnia symptoms (47.5 %). These disturbances manifest in different forms, such as initial, middle, terminal insomnia, or hypersomnia (Perlis and Gehrman, 2013). At the same time, pathophysiological mechanisms responsible for any of these associations between depression, HR alteration, and sleep and anxiety symptoms are poorly understood.

Moreover, individuals with comorbid MDD and heightened anxiety may particularly struggle with sleep, impacting their ability to initiate or maintain sleep (Cox and Olatunji, 2016). Elevated HR has been correlated with prolonged time to fall asleep and diminished sleep quality (Nilsson et al., 2001), with sleep disruptions linked to cardiovascular

deterioration and altered autonomic neuro-cardiac modulation (Reyes del Paso et al., 2013; Sauvet et al., 2010).

A recent review (Correia et al., 2023) have highlighted limitations in existing studies, emphasizing the need for longitudinal and mediation analyses to elucidate the relationships between depression, HR alterations, sleep, and anxiety symptoms. Previous research often employed cross-sectional designs, and few studies were conducted specifically in MDD populations. Moreover, experimental circumstances, such as hospital settings using electrocardiography (ECG) (Eddie et al., 2020; Ottaviani et al., 2015; Saad et al., 2019; Yang et al., 2011) and short follow-up periods (< of 1 month) (Leistedt et al., 2011), further limit the understanding of these associations. Recording the ECG during daily life and long periods has several limitations most seriously participant acceptability. Wrist-worn devices that are available today facilitate the measurement of HR, derived from pulse photoplethysmography (PPG), 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 of a large amount of information in near-real time.

The present study represents a secondary analysis of the Remote Assessment of Disease and Relapse-Major Depressive Disorder (RADAR-MDD) dataset (Matcham et al., 2019, 2022). Previous findings from this dataset identified associations between increased night resting HR (Siddi et al., 2023) and sleep disturbance (Zhang et al., 2021; Matcham et al., 2023) with depression severity in individuals with a history of recurrent MDD during a 24-month follow-up.

In this longitudinal study, we aim to test the following main hypotheses (Fig. 1):

- 1) Anxiety contributes to elevate night-resting HR (arrow a)
- 2) Increases in anxiety (arrow b), night resting HR (arrow c) and sleep disturbance (arrow f) are associated with an increase in depression severity.
- 3) Anxiety (arrow d) and night-resting HR (arrow e) contributes to elevate the sleep disturbance.

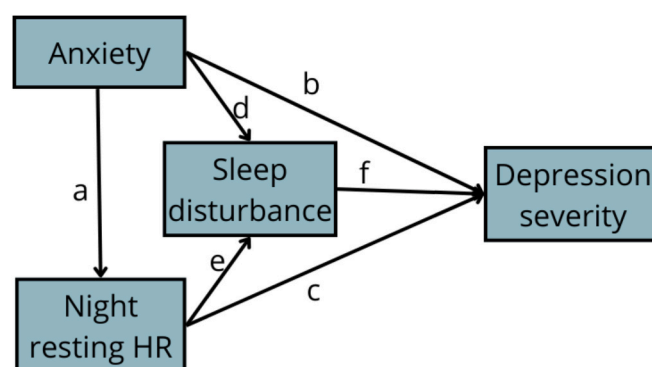


Fig. 1. Causal diagram proposed according to the hypothesis.

2. Methods

2.1. Study design and participants

RADAR-MDD is an international, multicentre, longitudinal, observational cohort study in people with a history of recurrent MDD (the protocol was published here (Matcham et al., 2019), followed up for a median of 541 days (interquartile range.(IQR): 401–730 days) (Matcham et al., 2022). Participants were recruited from three recruitment sites: Centro de Investigación Biomédica en Red (CIBER, Barcelona), King's College London (London, UK); Amsterdam University Medical Centre, location VUmc (Amsterdam, The Netherlands). The RADAR-MDD study, as a part of the research RADAR-CNS project (<https://www.radar-cns.org/>), was co-developed with service users in our Patient Advisory Board (PAB) (Polhemus et al., 2020; Simblett et al., 2019, 2020). The PAB were involved in the choice of measures, devise, the timing and issues of engagement and have been involved in developing the analysis plan and representative (s) are authors of the papers.

To be eligible for inclusion, individuals needed to: have had at least two episodes of MDD; have experienced with their most recent episode within the previous two years, be able to complete self-reported questionnaires via a smartphone, be fluent in English, Dutch, Catalan or Spanish; be able to give informed consent; be an Android user, or be willing to switch to use an Android phone for the duration of participation; be aged over 18 years. People who had a lifetime history of bipolar disorder, schizoaffective disorder, schizophrenia, MDD with psychotic features dementia, recent drug or alcohol misuse or a major medical illness (requiring long periods of hospitalisation), were not eligible to participate.

2.2. Procedure

The RADAR-MDD study explored the use of active and passive remote monitoring technology (RMT) and then send into the RADAR-base platform (Ranjan et al., 2019). The passive RMT included a wrist-worn Fitbit device to measure HR, physical activity and sleep and app to collect information on phone usage, GPS, Bluetooth, while in this manuscript we explored the following variables according to our hypothesis (Table 1). Recruitment took place between November 2017 and June 2020 and follow-up ceased on 30th April 2021. Participants completed the following assessments every 3 months via automated surveys delivered using (REDCap) platform (Harris et al., 2009).

2.3. Assessment

2.3.1. Depression severity

Depression was assessed as total score on the Inventory of Depressive Symptomatology – Self Report (IDSSR) (Rush et al., 2000) to capture symptom severity during the last seven days. The IDS-SR is a 30-item questionnaire, widely used in depression trials and providing detailed information on depressive symptoms, including all 9 Diagnostic and Statistical Manual (DSM) domains, symptoms commonly associated

with depression (such as irritability or pain), melancholic symptoms and atypical symptoms. Each item is rated 0–3. For this study, we excluded from the total score the items related to sleep items (Item 1 to 4) that were used to measure sleep disturbance. In this self-rated version (IDS-SR26), a cut-off-point ≥ 22 indicates the presence of clinically relevant depressive symptomatology (≥ 26 score were considered in the previous papers (Matcham et al., 2022) including the items 1–4. The new cut-off (≥ 22) distinguished between patients with clinically significant depression (Rush et al., 2000, 2003) categorized as severe or moderate, and those without depression or with only mild symptoms as the previous cut-off of ≥ 26 score (275 [59.7 %] vs 186 [40.3 %]).

2.3.2. Sleep disturbance

To assess the sleep complaints, we used the sum of the sleep subscale of the IDS-SR30 (from 1 to 4 item) (Gili et al., 2011). The first three items measure (insomnia: sleep onset insomnia, mid-nocturnal insomnia, and early morning insomnia) (Mason et al., 2020) during the last 7 days. The item 4 measure hypersomnia, where participants were asked to rate the longest period slept in a 24 h period over the last 7 days, including naps. This subscale was used previously in various studies (Kaplan et al., 2015). Each item is rated on a 0–3 Likert-type scale, with higher scores representing a greater severity of symptoms.

2.3.3. Anxiety severity

Anxiety was measured via the 7-item Generalised Anxiety Disorder questionnaire (GAD7) (Spitzer et al., 2006), used as a continuous indicator of anxiety symptom severity for the past two weeks (a total of 21, with higher scores indicating increased anxiety severity) and a total score ≥ 10 indicating significant symptoms. 181 participants reported high anxiety and 280 reported low anxiety. This threshold has previously been shown to have good levels of sensitivity and specificity (Jordan et al., 2017).

2.3.4. Night resting heart rate feature

The HR was computed from the HR signal provided by Fitbit charge 2 and 3 (Fitbit Inc., San Francisco, CA, USA), which is obtained from the photoplethysmography (PPG) sensor of the device with a narrowest resolution up to 5 s between samples. This device was previously shown to measure HR during the day accurately (Fuller et al., 2020; Liu et al., 2022; Nazari et al., 2019; Nelson and Allen, 2019) and during the night (de Zambotti et al., 2016; Haghayegh et al., 2019).

Night resting mean HR was computed during the night (from 00:00 to 05:59), and resting period was defined when the number of steps and activity level, derived from the accelerometer data, equalled 0.

A previous paper (i.e. Stucky et al., 2021) suggested that the Fitbit underestimated the sleep transition dynamics (transition from deep sleep to light sleep). For this reason, we selected the period from 00:00 to 05:59 as a conservative nighttime that might work for a large part of the population.

We computed the average of each night's resting HR parameter the 2 weeks' prior the IDS-SR26 across the follow-up, excluding the weekends before the IDS-SR26 assessment. People's behaviours follow a quasiperiodic routine during the weekdays, such as working and doing activities during the day and sleeping at night. Meanwhile, the circadian rhythm may be different during the weekends. So, we excluded weekend to avoid differences in the circadian phases between weekdays and weekends (Gander and Paine, 2016) This previous timeframe was also considered previously to detect the association between depression severity measured by the PHQ8 and sleep features in our previous study (Zhang et al., 2021).

We additionally considered the two weeks prior to the IDS-R26 completion time, considering the weekends and included in the supplementary materials.

2.3.5. Covariates

Baseline sociodemographic, smoking habits and medical health

Table 1
Features Legend: Clinical and HR parameters derived from the app and Fitbit, respectively.

Variable	Features	Assessment
Depression severity	Inventory of Depressive Symptomatology – Self Report IDS-SR 26 items	Every 3 months
Anxiety severity	Generalised Anxiety Disorder-7 items	Every 3 months
Sleep Disturbance	IDS-SR 4 items	Every 3 months
Night resting mHR	Mean HR during resting periods, identified by activity level = resting and number of steps = 0 during the night (0:00–05:59)	Every day

conditions: Information about sociodemographic (age, gender, education years, partnership status), medical or psychiatric history(yes/no), heaviness of smoking index(yes/no);and current alcohol habit (yes/no) measured through the Alcohol use disorders identification test (Daepfen et al., 2000), self-reported BMI and comorbidity with pre-existing medical or psychiatric health conditions(yes/no), antidepressant medication (yes/no), and time of assessment (every 3 months).

3. Data analysis

The analyses were conducted in four stages. First, we described the socio-demographic characteristics of the sample at enrolment (baseline) and clinical and physical variables at follow-up using appropriate summary statistics (median and inter-quartile range (IQR) for continuous variables; frequency and percentage for categorical variables). Second, Spearman correlation (ρ) was calculated between the night resting HR parameter and IDS-SR26 subscales (1–4 items) and GAD7 items to assess the association of night resting HR with depression, anxiety and sleep disturbance. We also looked at the association between the IDS-SR26 items 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). We also compared the night resting mean HR between individuals with and without significant depressive symptoms ($\text{IDS-SR26} \geq 22$) to determine whether HR explained the variance of depression severity. We conducted similar analyses in individuals with anxiety and without anxiety symptoms ($\text{GAD7} \geq 10$), and those with and without sleep disturbance ($\text{IDS1-4 mean} \geq 3$). Cohen's d effect size was calculated for the comparisons: the effect size is considered small, medium, and large using the 0.2, 0.5 and 0.8 cut-offs. Third, linear mixed models were conducted in three steps to assess the different association pathways from Fig. 1. Depression severity was the outcome (IDS-SR26 total score) and time of assessment was an explanatory variable included in all the models. In the first step, we included the night resting HR feature as the main explanatory variable (relation c; Fig. 1). The second step, night resting HR was accompanied in various models by anxiety severity (continuous variable 0 to 21), sleep disturbance (continuous variable from 0 to 12), and both together. In the third step, the covariates were included in the same previous models: age and BMI as continuous variables and gender, smoking, alcohol (categorical variables), antidepressant medication, and medical comorbidity as dichotomous variables. We also take into account the time as a covariable, each time is corresponding a 3 month which were the assessments periods. The measures of model fit, such as either the Akaike Information Criterion (AIC) or the Bayesian Information Criterion (BIC), were considered.

To demonstrate the consistencies of our previous findings, we additionally replicated the previous models, including the night resting HR computed during the 2 week including weekends prior the IDS-SR completion time (Table S3). We then conducted separate linear mixed models to see if anxiety was also associated with night resting HR (relation a; Fig. 1), and if anxiety and night resting HR were related to sleep disturbance (relation d & e; Fig. 1). These models were adjusted for the previous covariates. Fourth, according to the causal diagram from Fig. 1 and the findings of the previous analyses, we performed the causal mediation analyses using 'lme4' and 'mediation'libraries of R to calculate the effect of each causal pathway of the main variables, night resting HR, sleep disturbance and anxiety, on depression severity considering random effects. All analyses were performed using the R software (R Core Team, 2016, 2023).

4. Results

4.1. Descriptive characteristics

The sociodemographic characteristics are illustrated in Table 2. A total of 461 individuals with N 1679 observations were included in the analyses; we excluded participants with missing data. Of 623 participants with MDD, only 566 people had HR measures. Of these 461 reported IDS-SR26 score, GAD and sociodemographic data. The majority, 370 (80.3 %), reported sleep disturbance. Individuals with higher depression severity reported higher anxiety and sleep disturbance compared to others (Table S1). Fig. 2 shows the association between the night resting mean HR, depression, anxiety and sleep disturbance symptoms on the right and the comparisons between groups according to the symptom severity on the left. Night resting mean HR coefficient was correlated to depression severity (IDS-SR26 items) ($\rho = 0.17, p < 0.001$), and anxiety ($\rho = 0.14, p < 0.001$). In the boxplots, we observed that individuals with higher depression and anxiety severity had higher night mean resting HR compared to the other groups with lower severity, however, with a small effect size (Cohen's values were -0.31 and -0.29 , respectively). Similarly, there was an association between night resting HR and self-reported sleep disturbance (sum of the items IDS-SR-4 Items) was observed ($\rho = 0.13, p < 0.001$). Then, we compared the individuals who reported sleep disturbance (items IDS1-IDS4 ≥ 3) with individuals who did not report sleep disturbance (normal sleepers). The boxplot shows that individuals with sleep disturbance had higher night resting HR compared to normal sleepers.

4.2. Associations between night resting HR, sleep disturbance, anxiety and depression severity

Table 3 shows the results of the different mixed regression models not adjusted and adjusted by covariates. We found that the night mean resting HR was significant in all models except the adjusted model with sleep disturbance (model 3 and 4). Regarding the covariates, BMI, smoking status, comorbidities, and alcohol consumption are the most significant in all the models. All of them are dichotomous variables except for BMI, which is numerical. In model 4, the standardized beta coefficients and p-values for these variables are as follows: $\beta = 0.047$ ($\rho = 0.047$), $\beta = 0.065$ ($\rho < 0.001$), $\beta = 0.093$ ($\rho < 0.001$), and $\beta = -0.12$ ($\rho < 0.001$), respectively.

In Table 4, we found a non-significant effect of night resting HR on

Table 2
Baseline, clinical and night resting hear rate (HR) features (N = 461).

Variables	Median or N (%)	IQR	Min	Max
Age median	49	27	18	80
Gender (Female) (N,%)	343 (74.4)			
Depression severity (median)	25	19	0	62
High depression (≥ 22) (N %)	275 (59.7)			
Low depression (<22) (N %)	186 (40.3)			
Anxiety severity (median)	8	9	0	21
High anxiety (≥ 10) (N %)	181 (39.3)			
Low anxiety (<10) (N %)	280 (60.7)			
Sleep disturbance (IDS1-4)	4	3	0	11
High (≥ 3) (N %)	370 (80.3)			
Low (<3) (N %)	91 (19.7)			
Body Mass Index (median)	25.8	7.6	14	71.7
Smoking status (yes) (N, %)	77 (16.7)			
Alcohol habit (yes) (n, %)	325 (70.5)			
Antidepressant (yes) (n, %)	239 (51.8)			
Medical comorbidity (yes) (n, %)	236 (51.2)			
Night resting mHR	65.0	12.8	43.7	96.5
Times	3	3	1	12

Note: The table presents the baseline characteristics of the 461 participants. mHR represents the mean heart rate, while 'Times' indicates the number of observations per participant.

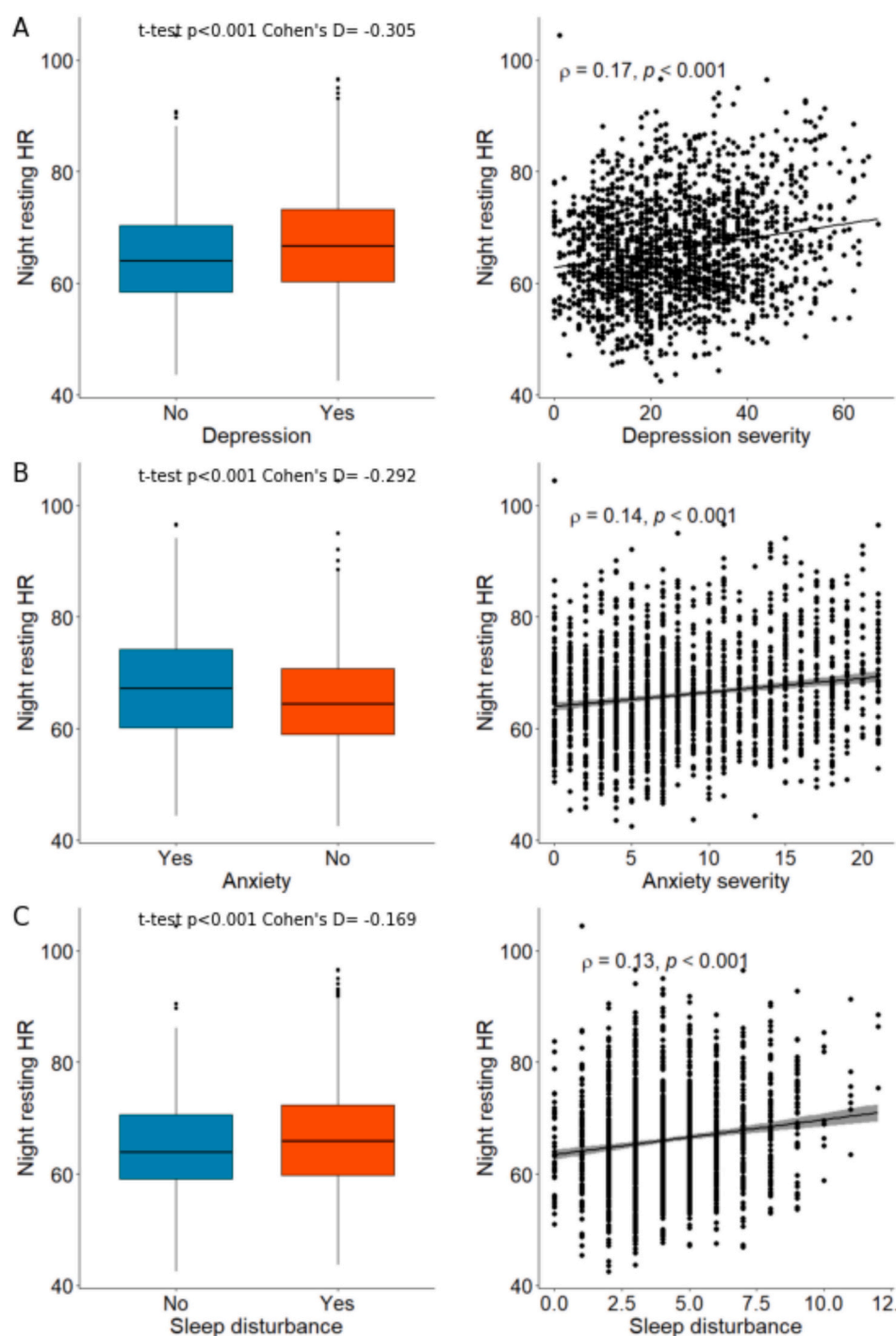


Fig. 2. The scatter plots show the relation between the clinical variables and night resting mean heart rate (HR) on the right side, while the boxplots on the left show the comparison between the groups with different clinical severity.

Note: All the observations were included in the plots.

anxiety. In Table 5, we observed that night resting HR and anxiety had a significant effect on sleep disturbance.

Table S2 compares the models from Table 3 to explore which model provides a better fit for the data. First, we compared the first two models: adjusted model 1 with only HR and adjusted model 2 with anxiety and HR. The results showed the most significant model was model 2 with anxiety ($p < 0.001$). We also compared the models with the sleep disturbance (model 1) with (model 3) to observe if this model provided a significantly better fit to the data than model 1. The results showed that model 3 with sleep disturbance provided a better fit to model 1. Last, we

compared the adjusted model containing sleep disturbance, anxiety, and night resting HR with all previous models (lower AIC); we observed that the final model demonstrated a better fit than the other models. Thus, the night mean resting HR, sleep disturbance, and anxiety showed an increasing effect on depression severity.

The additional linear mixed models including the night resting HR computed during the 2-week prior, including the weekends, the IDS-SR26 completion time, showed that the previous associations were maintained (Please see Table S3).

Table 3

Mixed regression models of night resting heart rate (HR) and Time of assessment on depression severity (IDS-SR26), alone and accompanied by the explanatory variables anxiety and sleep disturbance, and non-adjusted and adjusted by other covariates*.

Features	Model 1				Adjusted Model*	
	Bstd	95 % CI	p-value	βstd	95 % CI	p-value
Night Resting mHR	0.10	0.07–0.22	<0.001	0.06	0.01–0.16	0.025
Time	−0.03	−0.11–0.01	0.020	−0.03	−0.11–0.01	0.021
R2 marginal	0.010			0.187		
R2 conditional	0.779			0.786		
AIC	12,742			12,652		
BIC	12,770			12,717		
Model 2						
Features	Bstd	95 % CI	p-value	βstd	95 % CI	p-value
Night Resting mHR	0.06	0.04–0.15	0.001	0.04	0.00–0.11	0.040
Anxiety	0.59	1.34–1.49	<0.001	0.57	1.29–1.45	<0.001
Time	−0.02	−0.08–0.00	0.070	−0.04	−0.08–0.00	0.055
R2 marginal	0.463			0.544		
R2 conditional	0.819			0.834		
AIC	11,818			11,775		
BIC	11,852			11,846		
Model 3						
Features	Bstd	95 % CI	p-value	βstd	95 % CI	p-value
Night Resting mHR	0.08	0.05–0.19	0.001	0.04	−0.01–0.13	0.076
Sleep disturbance	0.24	1.27–1.71	<0.001	0.23	1.23–1.66	<0.001
Time	−0.02	−0.10– −0.00	0.044	−0.02	−0.10 – 0.01	0.054
R2 marginal	0.079			0.255		
R2 conditional	0.768			0.781		
AIC	12,581			12,497		
BIC	12,614			12,568		
Model 4						
Features	B	95 % CI	p-value	Bstd	95 % CI	p-value
Night Resting mHR	0.05	0.03–0.13	0.003	0.03	−0.01–0.10	0.089
Sleep disturbance	0.14	0.72–1.08	<0.001	0.14	0.64–1.04	<0.001
Anxiety	0.56	1.26–1.41	<0.001	0.54	1.21–1.37	<0.001
Time	−0.02	−0.08–0.01	0.108	−0.02	−0.08– −0.00	0.091
R2 marginal	0.515			0.581		
R2 conditional	0.824			0.839		
AIC	11,732			11,695		
BIC	11,770			11,772		

* Note: Models on the left include night mean resting HR and anxiety and/or sleep disturbance (continuous score) as indicated. Adjusted models on the right include all the previous variables and covariates (age, gender, smoking status, antidepressant medication, and medical comorbidity). Night resting HR was calculated 2 weeks (excluding weekend) prior the IDS-SR26 completion.

Table 4

Mixed regression model of anxiety and wave of assessment on night resting heart rate (HR), non-adjusted and adjusted by covariates*.

Features	Model 1				Adjusted Model*	
	βstd	95 % CI	p-value	βstd	95 % CI	p-value
Anxiety	0.04	0.01–0.13	0.028	0.02	−0.02–0.10	0.225
Time	0.03	0.01–0.07	0.017	0.03	0.01–0.07	0.017
R2 marginal	0.002			0.117		
R2 conditional	0.839			0.841		
AIC	11052			11000		
BIC	11079			11066		

Note: Covariates are age, gender, smoking status, antidepressant medication, and medical comorbidity.

* Adjusted model by the following covariates: age, gender, smoking status, antidepressant medication, and medical comorbidity.

4.3. Identification of causal mediation mechanism

According to our hypothesis and based on the findings observed in the previous steps, we executed two mediation models to explore the role of sleep disturbance between night resting HR and depression severity and between anxiety and depression severity (Fig. 3).

In the first mediation model, the total effect of night resting HR on depression was $\beta = 0.010$ ($p = 0.016$). This total effect was composed by the direct effect that was equal to $\beta = 0.064$ ($p = 0.074$) and the indirect effect that was $\beta = 0.025$ ($p = 0.014$).

In the second model, the total effect of anxiety on depression severity was $\beta = 1.386$ ($p < 0.001$), the direct effect was $\beta = 1.294$ ($p < 0.001$) and the indirect effect was $\beta = 0.09$ ($p < 0.001$), being a 7 % of the total effect.

5. Discussion

To the best of our knowledge, this is the first study that explored how night resting HR, sleep disturbance, and anxiety symptoms are interrelated, as well as the mediating pathways through which they contribute to depression severity among individuals with a history of recurrent MDD (Correia et al., 2023). The findings are in line with our hypothesis; night resting HR was associated with depression severity through sleep disturbance. The association found between increased night resting HR and depression severity confirmed the findings observed in our prior study (Siddi et al., 2023), where depression severity was assessed with a different tool (Patient Health Questionnaire 8 items) every 2 weeks; and the association between depression severity and sleep disturbance features collected passively using the Fitbit (Zhang et al., 2021).

Table 5
Mixed regression model of night resting HR, anxiety and time of assessment on sleep disturbance (IDS-SR 1–4), non-adjusted and adjusted by covariates*.

Features	Model 1			Adjusted Model*		
	Bstd	95 % CI	p-value	βstd	95 % CI	p-value
Night Resting Mhr	0.11	0.01–0.04	<0.001	0.07	0.00–0.03	0.018
Time	–0.02	–0.02–0.00	0.071	–0.03	–0.02–0.00	0.150
R2 marginal	0.012			0.079		
R2 conditional	0.597			0.603		
AIC	7030			7024		
BIC	7058			7089		
Model 2						
Features	Bstd	95 % CI	p-value	Bstd	95 % CI	p-value
Anxiety	0.29	0.09–0.13	<0.001	0.28	0.09–0.13	<0.001
Time	–0.01	–0.02–0.01	0.456	–0.02	–0.02–0.01	0.318
R2 marginal	0.086			0.144		
R2 conditional	0.591			0.600		
AIC	6921			6921		
BIC	6949			6987		
Model 3						
Features	Bstd	95 % CI	p-value	βstd	95 % CI	p-value
Night Resting Mhr	0.08	0.01–0.03	0.006	0.06	0.00–0.03	0.036
Anxiety	0.28	0.09–0.13	<0.001	0.28	0.09–0.12	<0.001
Time	–0.02	–0.02–0.01	0.454	–0.02	–0.02–0.00	0.267
R2 marginal	0.096			0.147		
R2 conditional	0.593			0.601		
AIC	6924			6927		
BIC	6957			6998		

Note: Covariates are age, gender, smoking status, antidepressant medication, medical comorbidity. AIC = Akaike information criterion; BIC = Bayesian information criterion.

* Adjusted model by the covariates age, gender, smoking status, antidepressant medication, medical comorbidity.

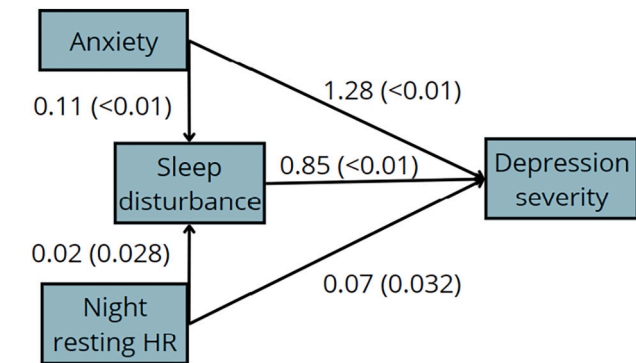


Fig. 3. Causal diagrams on the mediation role of sleep disturbance between night resting HR or anxiety and depression severity.

Heightened anxiety levels often perceive everyday situations as stressful, leading to a more frequent release of adrenaline and other stress hormones, consequently increasing HR (Kim et al., 2018; Steimer, 2002). However, in the present study, a direct association between anxiety levels and night resting HR was not observed. Night resting HR might depend on individual variation in stress susceptibility, resilience and reactivity (Halaris, 2016).

Despite the lack of a direct association between anxiety and night resting HR, anxiety did contribute to the amplification of depressive severity and sleep disturbance. The association between anxiety and depression severity was partially mediated by sleep disturbance (6 %). This means that both anxiety and sleep disturbance have a direct increasing effect on depression severity. People who suffer from both MDD and elevated levels of anxiety often can have a lower their ability to either fall asleep initially or maintain uninterrupted sleep (Cox and Olatunji, 2016; Nutt et al., 2008). The presence of significant anxiety symptoms and sleep disturbance generally predicts worse of depression severity (da Estrela et al., 2021; Jansson-Fröjmark and Lindblom, 2008; Kalin, 2020). Various studies demonstrated that patients with anxious MDD were more likely to be severely depressed and to have more

suicidal ideation (Fava et al., 2004; Kessler et al., 2015).

These findings underscore the intertwined relationship between anxiety, sleep disturbance, and depression severity, providing a foundation to explore how physiological markers, such as night resting HR, may contribute to this complex interaction.

In this study, the association between night resting HR and depression severity was mediated by sleep disturbance. Previous studies have demonstrated that changes in HR across sleep may be a physiological marker of depression severity in a sample with MDD and sleep disturbance (da Estrela et al., 2021; Saad et al., 2019, 2020). Increased night resting HR is linked with an altered balance of the ANS clinically manifested as increased HR and cardiac output. It is associated with reduced melatonin secretion (Sewerynek, 2002; Simko et al., 2016), responsible for circadian variability and the sleep quality (Pandi-Perumal et al., 2020). Thus, elevated night resting HR may indicate a set of physiological changes, which lead to sleep disturbance including challenges initiating sleep or maintaining uninterrupted sleep, which in turn impede sleep quality. This suggests that the physiological manifestation of increased night resting HR may contribute to the complexities of sleep patterns observed in individuals grappling with depressive symptoms. These disruptions in sleep, in turn, may exacerbate the depression symptoms (Cox and Olatunji, 2016; Fang et al., 2019), perpetuate the course of depression, or increase the risk of recurrence of MDD (Baglioni et al., 2011).

Understanding these connections is crucial for developing targeted interventions and comprehensive approaches to addressing sleep-related challenges in the context of depression. In conclusion, there are intricate associations among anxiety, sleep complaints, and increased night HR in MDD. Recognizing and addressing these interconnections is vital for providing comprehensive care and improving the overall well-being of individuals affected by MDD. An integrated approach that addresses all three components is often the most effective way to manage the condition.

5.1. Strengths and limitations

This study includes objective and subjective measures and are collected over months. Moreover, it includes data collected from

clinically relevant sample in their natural environment. We controlled our models for multiple variables known to impact HR, sleep and depression anxiety, including gender, BMI, alcohol smoking and antidepressant medication, however there may still have been incomplete control of these covariates leading to residual confounding - for example, we did not take account of antidepressant doses, and other medications and/or physical illnesses were not included in our models. Finally, although we report a causal mediation between night resting HR, sleep disturbance, anxiety with depression severity, this type of analysis precluding inferences of directionality among the associations observed such as depressive symptoms may have preceded night resting HR irregularities and sleep disturbance.

6. Conclusion

In summary, this study reveals that the link between depression severity and night resting HR is mediated by sleep disturbance. This underscores the necessity of accounting for sleep quality when assessing how HR abnormalities relate to depression severity. Prolonged elevation of resting HR during nighttime can disrupt sleep, exacerbating depressive symptoms. Long-term monitoring in real-world setting of these indicators may aid in preventing depression relapse.

CRedit authorship contribution statement

Elena Condominas: Writing – original draft, Software, Methodology, Funding acquisition, Formal analysis, Data curation. **Albert Sanchez-Niubo:** Formal analysis, Data curation. **Joan Domènech-Abella:** Writing – review & editing, Supervision, Conceptualization. **Josep Maria Haro:** Writing – original draft, Formal analysis. **Raquel Bailon:** Writing – original draft, Formal analysis, Data curation. **Iago Giné-Vázquez:** Writing – original draft, Formal analysis, Data curation. **Gemma Riquelme:** Validation, Supervision. **Faith Matcham:** Writing – review & editing, Data curation. **Femke Lamers:** Writing – review & editing, Supervision, Data curation. **Spyridon Kontaxis:** Writing – review & editing. **Estela Laporta:** Writing – review & editing. **Esther Garcia:** Writing – review & editing, Validation, Supervision, Data curation. **Maria Teresa Peñarrubia Maria:** Writing – review & editing. **Katie M. White:** Writing – review & editing. **Carolyn Oetzmann:** Writing – review & editing. **Peter Annas:** Writing – review & editing. **Matthew Hotopf:** Writing – review & editing, Funding acquisition. **Brenda W.J.H. Penninx:** Writing – review & editing. **Vaibhav A. Narayan:** Writing – review & editing. **Amos Folarin:** Writing – review & editing. **Daniel Lightley:** Writing – review & editing. **Nicholas Cummins:** Writing – review & editing. **Yathart Ranjan:** Writing – review & editing. **Giovanni de Girolamo:** Writing – review & editing. **Antonio Preti:** Writing – review & editing. **Sara Simblett:** Writing – review & editing. **Til Wykes:** Writing – review & editing. **Inez Myin-Germeys:** Writing – review & editing. **Richard Dobson:** Writing – review & editing. **Sara Siddi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

Vaibhav A Narayan is employee of Janssen Research and Development LLC. Peter Annas is employed by the pharmaceutical company H. Lundbeck A/S. Josep Maria Haro 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.

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Participants in the CIBER site came from following four clinical communities in Spain: Parc Sanitari Sant Joan de Déu Network services, Institut Català de la Salut, Institut Pere Mata, and Hospital Clínic San Carlos. Participant recruitment in Amsterdam was partially accomplished through Hersenonderzoek.nl, a Dutch online registry that facilitates participant recruitment for neuroscience studies. Hersenonderzoek.nl is funded by ZonMw-Memorabel project no 73305095003, a project in the context of the Dutch Deltaplan Dementie, Gieskes-Strijbis Foundation, the Alzheimer's Society in the Netherlands and Brain Foundation Netherlands. We thank all GLAD Study volunteers for their participation, and gratefully acknowledge the NIHR BioResource, NIHR BioResource centres, NHS Trusts and staff for their contribution. We also acknowledge NIHR BRC, King's College London, South London and Maudsley NHS Trust and King's Health Partners. We thank the National Institute for Health Research, NHS Blood and Transplant, and Health Data Research UK as part of the Digital Innovation Hub Programme. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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Ethical approval has been obtained in London from the Camberwell St Giles Research Ethics Committee REC reference: 17/LO/1154, in London from the CEIC Fundacio Sant Joan de Deu CI: PIC-128-17 and in the Netherlands from the Medische Ethische Toetsingscommissie VUMs METc VUmc registratienummer: 2018.012 – NL63557.029.17.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jad.2025.02.010>.

Data availability

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

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