Associations between sleep-related heart rate variability and both sleep and symptoms of depression and anxiety: A systematic review

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Associations between sleep-related heart rate variability and both sleep and symptoms of depression and anxiety: a systematic review

Sleep, HRV and psychiatric disorder review

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Abbreviations:

ANS: autonomic nervous system; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; DFA: detrended fluctuation analysis; ECG: electrocardioagraphy; ESS: Epworth Sleepiness Scale; FIRST: Ford insomnia response to stress test; HADS: Hospital Anxiety and Depression Scale; HF: high frequency; HRV: heart rate variability; LF: low frequency; MDD: major depressive disorder; MSE: multiscale entropy; nHF: normalised high frequency; nLF: normalised low frequency; NREM: non-rapid eye movement; OSA: obstructive sleep apnoea; PLMS: periodic limb movement syndrome; pNN50: percent of differences of adjacent R-R intervals greater than 50msec; PNS: parasympathetic nervous system; PSG: polysomnography; PSQI: Pittsburgh Sleep Quality Index; PTSD: post-traumatic stress disorder; REM: rapid-eye movement; RMSSD: root mean square of successive differences between R-R intervals; R-R: R-peak to R-peak intervals; RSA: respiratory sinus arrythmia; SDNN: standard deviation of differences between R-R intervals; SNS: sympathetic nervous system; SWS: slow wave sleep; WASO: wake after sleep onset

Summary
There is a bidirectional relationship between poor sleep and both mood- and anxiety-related disorders, which are among leading global health concerns. Additionally, both disordered sleep and these psychiatric disorders appear to be independently associated with altered autonomic nervous system (ANS) function. We hypothesise that ANS dysregulation during sleep may explain part of the relationship between poor sleep and mood- and anxiety-related disorders. Heart rate variability (HRV) is a frequently used marker of ANS function and gives an indication of ANS input to the heart - in particular, of the relative contributions of sympathetic and parasympathetic activity. A systematic review of PubMed, Scopus and Web of Science yielded 41 studies dealing with sleep, mood- and anxiety-related disorders and sleep-related HRV. Hyperarousal during sleep, reflecting a predominance of sympathetic activation and indicative of ANS dysregulation, may be an important factor in the association between poor sleep and mood-related disorders. Longitudinal studies and mediation analyses are necessary to further understand the potential mediating role of ANS dysregulation on the relationship between poor sleep and mood- and anxiety-related disorders.

Keywords: autonomic nervous system, heart rate variability (HRV), insomnia, sleep, depression, anxiety, PTSD

1. Introduction

Sleep is essential for the functioning of many of the body's systems, including the brain [1]. According to a recent systematic review, between 20-43% of adults report poor quality or insufficient sleep[2]. Mental illness is one of the leading health concerns globally [3], with anxiety and depressive disorders having estimated global prevalences of 3.6% and 4.4%, respectively pre-2020 [4] with estimated increases of 25.6% and 27.6% respectively due to the subsequent Covid-19 pandemic [5]. Both poor sleep and mood- and anxiety-related disorders are independently associated with increased all-cause mortality[6–8].

Sleep and mood- and anxiety-related disorders

Psychiatric disorders have long been linked to sleep abnormalities[9–13] in a bidirectional manner[14]. Poor sleep increases the likelihood of developing mood- and anxiety-related disorders, specifically[15–17]. Almost all patients with major depressive disorder (MDD) report some form of sleep complaint[18]. Depressed patients with comorbid sleep difficulties usually exhibit more severe symptoms, including increased suicidal ideation, and are more resistant to treatment, while resolving sleep issues appears to improve outcomes, including decreasing symptom severity and increasing rate of recovery[19,20]. Furthermore, patients with anxiety disorders, such as generalised anxiety disorder and post-traumatic stress disorder (PTSD), frequently report sleep disturbances and problems initiating sleep[21]. In fact, individuals with PTSD and concurrent sleep difficulties often remain refractory to treatment, while treating sleep issues improves overall symptoms [22,23].

Autonomic nervous system function and heart rate variability

Both poor sleep and mood- and anxiety-related disorders are associated with altered 24h autonomic nervous system (ANS) function[24–26]. The ANS is composed of two branches: the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). Heart rate variability (HRV) has been widely used as a marker of autonomic functioning due to its non-invasive nature. HRV is an index of vagal activation of the heart that has both chronotropic and modulatory effects. The dorsal motor vagal nuclei in the medulla control cardiac chronotropy (i.e., heart rate), while the nucleus ambiguous in the medulla regulates cardiac modulatory effects [27]. High frequency vagal input into the heart is typically modulated by the spontaneous breathing rate and is also known as respiratory sinus arrhythmia (RSA) [27].

The predominant parasympathetic vagal traffic below the diaphragm involves the gut-brain axis and as such falls outside the scope of our review (which is focusing on HRV). It is worth

noting, however, that part of the feedback from the gut-brain axis - associated with disorders such as depression and PTSD [28]- occurs via the vagus nerve. And *vice versa*, stimulation of the vagus nerve is a treatment option for mood and anxiety disorders [28] as well as for inflammatory bowel disease and pro-inflammatory cytokine production [29].

Methods of HRV analysis typically used can collectively be broken down into time-domain, frequency-domain and non-linear analyses, with the former two comprising more traditional and the latter more recent methodologies. Time-domain measures of HRV include root mean square of successive differences between R-peak to R-peak (R-R) intervals (RMSSD), standard deviation of differences between R-R intervals (SDNN) and percent of differences of adjacent R-R intervals greater than 50msec (pNN50).

Frequency domain measures derived from spectral power analysis of R-R intervals, provide an index of cardiac ANS regulation. Cardiac spectral power in the low frequency band (LF; 0.04-0.15Hz) is purported to be due to baroreflex-mediated modulation of the heart[30], while high frequency variability (HF; 0.15–0.4Hz) is typically due to the influence of the spontaneous breathing rate on heart rate, referred to as RSA. While HF cardiac spectral power reflects only parasympathetic activity[31], LF cardiac spectral power reflects contributions from both the sympathetic and parasympathetic branches of the ANS. Given the large parasympathetic influence on LF cardiac spectral power, the physiological relevance of LF/HF ratio has been disputed[32] and should be interpreted with caution.

Furthermore, non-linear HRV measures (including multiscale entropy (MSE), sample entropy (SampEn), and detrended fluctuation analysis (DFA)) give a global indication of the complexity of heart rate dynamics, specifically the beat-to-beat fluctuations in R-R intervals.

Lower complexity in the HRV signal makes the signal more predictable and less healthy, e.g., such as occurs during chronic heart failure[33]. On the other hand, if there is too much randomness or chaos in the HRV signal it is indicative of impeded cooperation in the physiological control systems. Non-linear analyses have begun providing new insights into HRV, but clinical translation has not occurred to date.

Sleep and HRV

There is extensive research looking at the relationship between sleep and 24h HRV[34,35]. In healthy, neurotypical individuals, wakefulness and rapid eye movement (REM) sleep is predominantly associated with LF power[34–36] in the cardiac spectrogram. On the other hand, HF power in the cardiac spectrogram is increased during sleep compared to during wake and this index of parasympathetic dominance increases with increasing sleep depth[35]. Alteration of this pattern of parasympathetic dominance may impair sleep by inducing a state of alertness (hyperarousal) unconducive to sleep[37]. This hyperarousal is commonly regarded as a contributing factor in insomnia models[37]. While the macrostructure of sleep architecture is associated with altered autonomic activation, it is also important to consider the microstructure. Cyclic alternating pattern of arousal during sleep (characterised by regular fluctuations between greater and lesser arousal) within sleep stages is also associated with less parasympathetic input compared to non-cyclic alternating pattern (which represents more stable sleep)[38–40]. Disrupted sleep is associated with an increase in sympathetic tone[13,41]. Burgess et al. (1997) found that short sleep predominantly impacts sympathetic activation (assessed using pre-ejection period) with parasympathetic activation (assessed using RSA) being mediated more by circadian influence[42]. Given that HRV is not a direct measure of ANS function, however, but only provides an indirect index of ANS function, the current evidence is still too varied for any definitive conclusions to be drawn. Despite this, HRV impairment in insomnia is a widely accepted concept [43].

Mood- and anxiety-related disorders and HRV

While greater complexity in 24h and daytime HRV measures appear to be a characteristic of healthy individuals, disorders such as MDD and generalised anxiety-disorder are associated with decreased complexity[24,44,45]. Several studies show lower 24h and daytime resting HRV in patients with depression- and anxiety-related disorders[24,46], although there are discrepant results. In a review of HRV, various psychiatric disorders and psychotropic medications, studies with only non-medicated patients showed that there was a significantly lower long-term (24h) and short-term (5min daytime rest) HRV in patients with mood- and anxiety-related disorders than controls[47]. This lower HRV also seems to be exacerbated by the psychotropic medications used to treat these disorders[47,48]. Other studies, however, showed no correlation between psychiatric symptom severity and HRV[49,50].

Given these established links between (i) sleep and mood- and anxiety-related disorders, (ii) poor sleep and 24h HRV, and (iii) mood- and anxiety-related disorders and 24h HRV, we propose that ANS dysregulation, specifically during sleep, is a critical factor in explaining the relationship between poor sleep and mood- and anxiety-related disorders. On one hand, a sleep-related ANS imbalance, where there is a shift away from the usual physiological patterns of sympathetic and parasympathetic control, may impair sleep[51]. Additionally, individuals with high levels of anxiety or PTSD may experience hypervigilance or a state of vulnerability at night, making falling asleep or staying asleep difficult. This impaired sleep may then exacerbate any symptoms of anxiety or depression experienced during the day[15,52]. While the mechanisms by which impaired sleep worsens symptoms of anxiety and depression are still unclear, some previously proposed pathways include elevated glucocorticoids associated with the stress response[15,52] and altered brain plasticity leading to altered communication between regions of the brain involved in regulating mood[15].

Similarly, nocturnal ANS imbalance may underly sleep impairment (for example, expressed as insomnia) and contribute to mood- and anxiety-related disorders, either independently or in conjunction with the previously proposed pathways. Additionally, the presence of a mood- and anxiety-related disorder may be associated with an ANS imbalance which may then contribute to difficulties with sleep.

Thus, while the bidirectional relationship between sleep and mood- and anxiety-related disorders is commonly reported, potential underlying mechanisms, such as sleep-related ANS dysregulation, warrant further investigation. Therefore this review will focus specifically on sleep-related HRV, as that is where we hypothesise ANS dysregulation will have the greatest effect on sleep quality and therefore on mood- and anxiety-related disorders. The aim of this study is to systematically review the evidence describing the relationships between sleep-related ANS regulation (as measured by HRV) with both sleep and mood- and anxiety-related disorder outcomes.

2. Methods

2.1. Literature search

Prior to conducting the literature search for this systematic review, the aims and methods were registered with PROSPERO (ID: CRD42020179952). Three databases (PubMed, Scopus and Web of Science) were searched for all peer-reviewed studies published prior to 02 April 2022 using the following search terms: “sleep, insomnia, nervous system, autonomic nervous system, ANS, parasympathetic nervous system, PNS, sympathetic nervous system, SNS, hyperarousal, heart rate variability, HRV, mental health, mental illness, mental disease, mental disorder, depression, anxiety, post traumatic stress disorder, PTSD, post-traumatic stress disorder, posttraumatic stress disorder” (Supplementary Table S1). Filters were applied

to each search limiting the results to journal articles written in or translated to English. The reporting was conducted according to the "*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*" (PRISMA) guidelines[53].

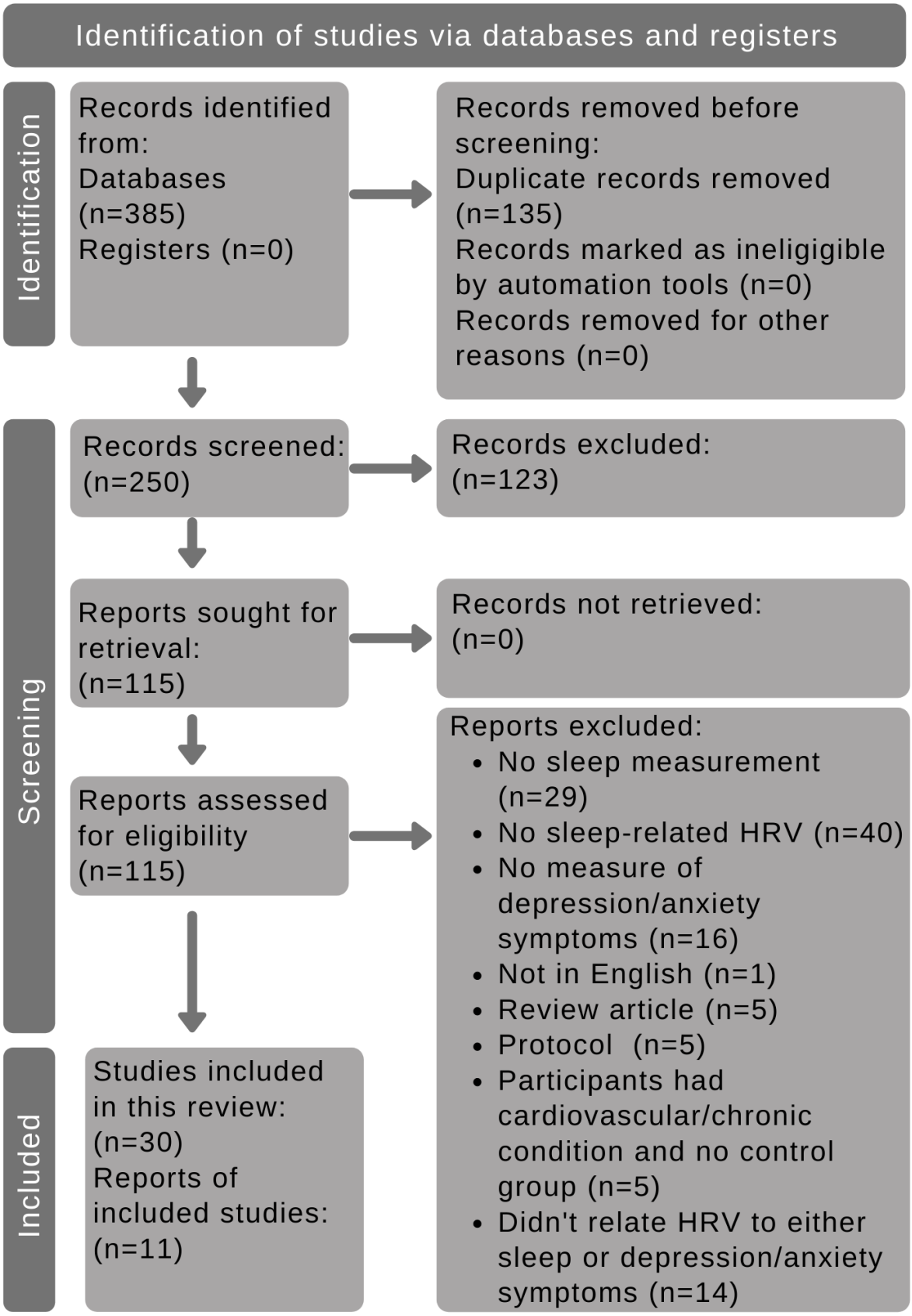

Figure 1: Flow diagram depicting the method of article selection.

2.2. Study selection

Figure 1 depicts the article selection process. The initial database search yielded 372 articles. Following removal of duplicates, two reviewers (AC and PF) independently scanned titles and abstracts of the remaining 251 articles to determine whether they potentially fit the following inclusion criteria: 1) primary research study published in a peer-reviewed journal, 2) participants had no conditions other than diagnosed sleep, mood- or anxiety-related disorders 3) participants were between the ages of 18 and 65 years, 4) at least one sleep quality or duration-related outcome was reported, 5) a measurement of HRV during sleep was provided and 6) anxiety, depression or stress symptom severity outcomes were measured. Control groups from studies comparing individuals with exclusionary conditions (e.g. fibromyalgia) to controls were included provided sleep-related, HRV during sleep and mood-, anxiety- or stress-related measures were conducted. Control groups with scores above clinical cut-offs on questionnaires assessing depression or anxiety symptoms were grouped with diagnosed individuals even though the original study classified them as healthy.

Sleep-related HRV was defined as the inter-beat variability extracted from either the electrocardiogram (ECG) component of polysomnography (PSG) or ambulatory recording (e.g. Polar heart rate monitor) measured during the sleep period. Studies with either or both frequency domain (HF and LF power) and time domain (RMSSD, SDNN, pNN50) measures during sleep were included. Reviews, conference abstracts and case studies were excluded but longitudinal, cohort and cross-sectional studies were included. Any studies which could not be definitively excluded based on their title and abstract were retained for full text screening. Full texts were screened by AC with any queries discussed and resolved with PF, DR and GL. The references of the included studies were manually examined for other potentially relevant studies. Excluded studies with reasons for exclusion are presented in

Figure 1. Where there were queries about the method of the study the authors were contacted to clarify. The bias and quality of the included studies was assessed by AC using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies [54] (Supplementary Table S2).

3. Results

Study characteristics

Table 1 presents the characteristics of all included studies. Participant mean ages range from 19.6±1.8 to 55.6±4.0 years; 36 studies included both men and women[26,49,50,55–87], two and three studies included only women[88,89] or men[62,90,91], respectively.

Table 1: Characteristics of participants and included studies.

Citation	Study design	Population (n)	Method to assign to group	Sleep disorders assessed and method of assessment	Age (y)	Female (%)
Agorastos et al., 2013	CS	PTSD (7) Control (8)	CAPS, SCID	Not reported	26.3±4.0 30.9±10.6	0.0
Alomri et al., 2021	CS	Non-OSA (12) Mild OSA (26) Moderate OSA (16) Severe OSA (20)	PSG, AHI	OSA: PSG	33.7±14.8 37.4±11.5 44.1±12.4 46.5±10.4	36.1
Bassett et al., 2016	CS	Remitted Bipolar Type 1 (29) Recurrent MDD (41) Control (38)	MINI	Not reported	36.9±13.5 42.0±13.1 43.0±9.7	66.7 75.8 45.9
Beilharz et al., 2020	CS	Childhood trauma (22) No childhood trauma (89)	CTQ-SF	Not reported	22.3±4.9 21.7±4.4	68.1 62.9
Bertram et al., 2014	CS	PTSD (56) Control (54)	SCID	Sleep apnoea: self-reported history of diagnosis and usage of a CPAP machine via questionnaires	53.4±11.3 54.5±9.5	0.0 0.0
Brosschot et al., 2007	CS	"Healthy participants" (52)		Not reported	33.8±13.9	75.0
Brupbacher et al., 2021	RCT	Exercise intervention (46) Control (46)	SCID	RLS: validated cut off in the RLS screening questionnaire, sleep apnoea: oxygen desaturation >15 in baseline PSG	46 (37-53) 48 (43-51)	70.0 72.0
Burton et al., 2010	CS	"Healthy participants" (20)		Patient history	36.0±13.2	75.0
Chen et al., 2017	CS	Insomnia (10)	PSG, ISI, FIRST		27.1±6.3	70.0

		Good sleeper: high vulnerability to insomnia (10) Good sleeper: low vulnerability to insomnia (10)		Semi-structured interview, questionnaires	26.0±4.0 26.9±5.8	80.0 50.0
Cosgrave et al., 2021	CS	Poor sleepers (23) Good sleepers (20)	ISI, PSQI	Not reported	23.7±3.5 22.7±3.2	60.9 55.0
Dennis et al., 2014	CS	PTSD (105) Control (120)	CAPS	Not reported	30.8±5.3 28.0±5.5	45.7 53.3
Dennis et al., 2017	CS	PTSD (93) Control (104)	CAPS	Not reported	28.9±5.6	51.0
De Zambotti et al., 2011	CS	Insomnia (8) Control (8)	PSQI, AIS, ISI	Questionnaires, semi-structured interviews, actigraphy, sleep diaries	23.3±2.4 23.3±3.2	50.0 62.5
Eddie et al., 2020	CS	MDD (39) Insomnia (14) Control (20)	HAM-D, ISI, BDI-II	Questionnaires, patient history	28.1±9.2 32.14±9.1 31.5±14.6	69.2 85.7 75.0
Farina et al., 2014	CS	Insomnia (85) Control (55)	ICSD-2, SCID	Neurologic and psychiatric evaluation	53.2±13.6 54.2±13.9	44.7 41.8
Fatt et al., 2020	CS	"Healthy participants" (24)	Clinician assessment	Patient history	35.4±12.0	75.0
Furutani et al., 2011	CS	High chronic stress (6) Low chronic stress (5)	Stress response questionnaire	Not reported	20.3±0.5	63.6
Hall et al., 2004	CS	Stress exposure (31) Control (28)	Random assignment	Insomnia: patient history	19.6±1.8	49.0
Hall et al., 2013	CS	European American (160) African American (119) Chinese American (53)	Race	Sleep apnoea: patient history, PSG	51.2±2.2 51.0±2.2 51.7±2.2	100.0 100.0 100.0
Idiaquez et al., 2014	CS	Mild OSA (23) Severe OSA (35)	PSG, AHI	OSA: PSG	41.2±8.8 48.9±8.5	8.7 8.6
Israel et al., 2012	CS	Insomnia (54) Control (22)	DSM criteria for self-report data, SCID	Clinical interviews, patient history	34.6±9.7 26.5±7.3	55.6 86.4
Jarrin et al., 2018	CS	Insomnia: objectively short sleep (46) Insomnia: nearly normal sleep (134)	ICSD, SCID, ISI, PSG	Clinical interviews	51.6±10.8 49.3±11.5	52.2 66.4
Kobayashi et al., 2014	CS	PTSD (20) Resilient (18)	SCID, CAPS	Sleep breathing and movement disorders: PSG	24.0±5.6 21.7±3.7	75.0 61.1
Kobayashi et al., 2016	CS	PTSD (38) Resilient (33)	SCID, CAPS	Sleep apnoea: PSG	22.5±4.7 22.7±3.8	65.8 51.5
Kwon et al., 2019	CS	MDD (30) Control (30)	Interview with certified psychiatrist	Sleep breathing disorders: PSG	50.5±14.5 50.0±17.5	50.0 50.0
Leistedt et al., 2011	CS	Unmedicated MDD in depressive episode (25) Control (20)	DSM-IV-TR criteria	PSG, patient history	39.0±19.6 36.0±25.5	0.0 0.0
Mellman et al., 2004	Longitudinal	PTSD (9) Control (10)	SCID, CAPS	Sleep apnoea: PSG	37.1±10.8	31.6
Migliorini et al., 2015	Longitudinal	Bipolar patients during depressive episode (15) Bipolar patients during non-depressed episode (15)	Previous diagnosis of bipolar disorder (I or II), QUIDS	Not reported	Not reported	Not reported
Nishith et al., 2003	Cohort	PTSD (6)	CAPS	PSG, patient history	30.7±9.8	100.0
Orr et al., 2000	CS	"Healthy participants" (15)	Bowel symptom frequency	Patient history	36.2±2.3	86.7

			questionnaire, PSQI, BDI			
Ottaviani, Medea, et al., 2015	CS	Healthy males (19) Healthy females (23)	Sex	Not reported	26.9±5.9 26.5±9.5	0.0 100.0
Ottaviani, Shahabi, et al., 2015	CS	MDD (18) Control (18)	SCID or MINI	Not reported	38.4±12.1 30.1±10.5	66.7 61.1
Rissling et al., 2016	CS	PTSD (97) Control (114)	CAPS	Not reported	28.1±5.5 30.5±5.4	48.3 52.0
Saad et al., 2020	CS	Depressed (25) Control (31)	Medical history, BDI	Sleep apnoea: PSG	33.8±12.2 37.2±12.4	84.0 58.1
Simor et al., 2014	CS	Nightmare (19) Control (21)	Dream Quality Questionnaire, Hungarian version of the Van Dream Anxiety Scale, 7-point Likert scale on nightmare frequency	Not reported	20.9±1.6 21.6±1.5	47.4 47.6
Spiegelhalder et al., 2011	CS	Insomnia (58) Control (46)	DSM-IV criteria	Clinical interview, patient history	39.5±11.8 37.3±11.4	62.1 58.7
Tan et al., 2019	CS	Younger (22) Older (23)	Age at time of study	Not reported	55.6±4.0 67.4±5.2	64.0 61.0
Ulmer et al., 2018	CS CS	Poor sleepers (31) Good sleepers (53) PTSD veterans (29) Control veterans (33)	PSQI CAPS, SCID	OSA, RLS and PMLS: clinical interview, PSG	40.9±17.2 35.2±14.3 31.0±8.7 33.0±7.4	54.8 47.2 12.9
Woodward et al., 2009	CS	PTSD (22) PD (13) PTSD + PD (11) Control (13)	CAPS, SCID	PSG, patient history	42.2 ±12.8 42.1±11.0 42.0 ±13.9 39.6±10.8	Not reported
Wu et al., 2015	CS	PLMS OSA (30) Non-PLMS OSA (30)	PSG	PSG, patient history	54.9±12.8 45.5±15.3	23.3 40.0
Yang et al., 2011	CS	MDD (52) Primary insomnia (47) Healthy control (88)	Interview with psychiatrist based on DSM-IV criteria	Not reported	42.7±10.2 43.9±10.4 41.6±11.7	61.5 66.0 62.5

Data are presented as mean ±SD or percentage. AHI=apnoea hypopnoea index; AIS=Athens Insomnia Scale; BDI=Beck Depression Inventory; BMI=Body mass index; CAPS=Clinician-administered PTSD Scale; CPAP=Continuous positive airway pressure; CS=Cross-sectional; CTQ-SF=Childhood Trauma Questionnaire Short Form; DSM-IV-TR= Diagnostic and Statistical Manual of Mental Disorders, 4th edition (text revision); FIRST=Ford Insomnia Response to Stress Test; ISCD-2=International Classification of Sleep Disorders–second edition; ISI=Insomnia Severity Index; MDD=Major depressive disorder; MINI=Mini-international Neuropsychiatric Interview; OSA=Obstructive sleep apnoea; PD=Panic disorder; PLMS=Periodic limb movement syndrome; PSG=Polysomnography; PSQI=Pittsburgh Sleep Quality Index; PTSD=Post-traumatic stress disorder; QUIDS= Quick Inventory of Depressive Symptomology; SCID=Structured Clinical Interview for DSM-IV.

Included studies reported sleep outcomes, mood- and anxiety-related outcomes and sleep-related HRV in various populations. For ease of understanding, we present the data first for apparently healthy participants (to indicate normative values and associations), then for

participants with defined sleep disorders, and lastly for participants with diagnosed anxiety-mood-related disorders.

Healthy participants

Six studies report on sleep-related HRV and outcomes in healthy participants [67,78,80,81,86,89] (Supplementary Table S3). Two studies measured HRV during various sleep stages and observed that sleep-related HRV varies according to individual sleep stages with greater markers of parasympathetic activity during non-rapid eye movement (NREM) compared to REM sleep[81] and wake[86] indicated by higher HF power (p<0.001) and lower LF/HF (p<0.001) ratios [81]. HF power values were also lower during REM compared to wake (p<0.050)[81,86]. Another study showed that this varied further by ethnic group such that European Americans had higher normalized LF power and LF/HF ratios and lower normalized HF values (i.e. indicative of less parasympathetic activity) during NREM Stage 2 and REM sleep than the African- and Chinese American groups[89].

Poorer sleep quality (β=0.31, 95% confidence intervals (CI): 0.18, 0.44, p<0.001), younger age (β=-0.06, 95% CI: -0.10, -0.001, p=0.012) and lower sleep-related HRV (β=-0.02, 95% CI: -0.04, -0.01, p=0.011) were predictors of more severe psychological symptoms[78], while higher trait worry and rumination were predictors of lower HRV[67]. Lower sleep-related HRV correlates with subjective severity of sleep difficulties (β =-0.47, p=0.005)[80] while higher indices of vagal activity during sleep are linked to better subjective sleep quality[80,86] (β =0.43, p=0.007)[80].

Participants with sleep-related disorders

Insomnia

Ten studies reported on sleep-related HRV in participants with and without insomnia [50,71–73,76,79,83,85,92]. Five of these studies found differences in sleep-related HRV measures between insomnia and control groups[50,69,71,76,85]. Participants with significantly shorter sleep duration or lower sleep quality had lower overall sleep-related HRV[69,71,85] and markers of parasympathetic activity[69,71,85] than controls. Time domain measures (RMSSD[69], SDNN[69,71] and pNN50[69]) during sleep were lower in insomnia groups than controls, and participants with insomnia also showed lower HF power [69] and higher LF power [50,69] and LF/HF ratios[50,85] during sleep compared to controls[50,69]. Furthermore, participants with objective insomnia (measured by PSG) had lower HF power and higher LF/HF ratios during sleep than those with subjective insomnia[76]. Spiegelhalder et al. (2011) observed a trend towards lower sleep-related RMSSD, pNN50 and HF power values in insomnia participants compared to controls, which reached statistical significance when limited to only participants with insomnia and objectively-measured short sleep (RMSSD: p=0.046; pNN50: p=0.024; HF: p=0.037)[71]. Cosgrave et al., 2021 showed similar results, with differences in SDNN only significant when comparing participants with objectively short sleep to controls[85]. Jarrin et al. (2018) found sleep-related HRV differences in objectively-measured short sleepers even after adjusting for covariates (including depressive symptoms) compared to participants with nearly normal objectively-measured sleep duration, but who had subjective insomnia[76]. One study found that during sleep, patients with insomnia also showed diminished MSE[69]. Collectively these findings suggest that short-sleepers and individuals with insomnia, characterised by objectively measured sleep, versus those with insomnia with near-normal objectively measured sleep and control participants, have lower HRV measures, except for measures more typically associated with sympathetic activation, which show higher values in the former group.

Looking at the relationships between sleep and sleep-related HRV measures, the LF/HF ratio was positively correlated with objectively measured wake after sleep onset (WASO) (r=0.40; p=0.037) in both insomnia and control participants[72]. Furthermore, daytime sleepiness (ESS scores) negatively correlated with awake and sleep measures of RMSSD (r=−0.446, p=0.015; r=−0.362, p=0.054, respectively) and HF power (r=−0.488, p=0.007; r=−0.402, p=0.031, respectively) and positively with the LF/HF ratio (r=0.353, p=0.061; r=0.399, p=0.032, respectively) only in participants with insomnia [69]. Additionally, one study found sex-linked differences in sleep-related HRV with females (both those with insomnia controls) having lower time domain HRV values compared to males (SDNN $F(97,1)=15.38$, $p<0.001$, β(female)=-12.39); RMSSD ($F(97,1)=6.21$, p=0.014, β(female)=-7.56; and pNN50 ($F(97,1)=12.48$, $p<0.001$, β(female)=-7.08)[71].

Other sleep disorders

Three studies reported on sleep-related HRV and depression/anxiety-related symptoms in participants with obstructive sleep apnoea (OSA)[74,75,87] and one reported on participants with frequent nightmares[77]. In participants with severe OSA, one study reported the sleep-related cardiac spectral power values were mostly in the LF band and reduced in the HF band. There was no association between depressive symptoms and markers of sleep-related ANS function[75]. The log LF/HF ratio was associated with respiratory arousal index (β=0.36; p<0.001) with significantly higher log LF/HF ratios in the severe OSA group than in the non-OSA group[87].

Despite no significant differences in sleep duration or sleep architecture in OSA participants with and without periodic limb movement syndrome (PLMS), the OSA participants with

PLMS had lower sleep-related HRV measures, with lower RMSSD (p=0.032), SDNN (p=0.028), HF (p=0.047) and normalised HF (nHF) (p=0.004) and higher normalised LF (nLF) (p=0.003) and LF/HF ratios (p=0.018) than those without PLMS. After adjusting for age, the presence of PLMS in participants with OSA was still independently associated with sleep-related RMSSD (β=-20.16; 95% CI: -39.90, -0.42, p=0.046), nHF (β=-0.09; 95% CI: -0.16, -0.02, p=0.013) and the LF/HF ratio (β=0.54; 95% CI: 0.04, 1.03, p=0.036). After adjusting for sex, PLMS in participants with OSA was also still independently associated with sleep-related nLF (β=0.09; 95% CI: 0.02, 0.16, p=0.008). There was no significant difference in Hospital Anxiety and Depression Scale (HADS) scores between the two groups[74], so the authors did not investigate the influence of this variable on HRV.

In participants suffering from recurrent nightmares, RMSSD (p=0.002), HF power (p=0.004) and LF power (p=0.006) values were reduced during non-transitory NREM periods compared to controls. Additionally, HRV measures in the nightmare group were similar before and after REM periods, whereas controls had greater RMSSD, HF and LF power values after REM periods compared to before REM sleep[77].

Sleep and sleep-related HRV in participants with mood-, anxiety- and stress-related disorders

Mood-related disorders

Eight studies reported on participants with major depressive disorder (MDD) and one study reported on participants diagnosed with bipolar disorder who were experiencing a depressive episode (Supplementary Table S3). Of these studies, three found that MDD groups reported higher PSQI scores[69,90,93]. Sleep-related time domain measures (RMSSD[66,69,93],

SDNN[57,61,93] and pNN50[69,93]) and HF power[57,69,93] were all lower in MDD compared to control participants. Sleep-related LF power[69,93] and LF/HF ratios[57,93] were higher in participants with MDD than control participants. Basset et al. (2016) found that even after adjusting for covariates (age, sex, PSQI, waking at night and medications) in an extended multivariate model, the presence of depression was still a significant predictor of decreased sleep-related RMSSD (β=-21.86, 95% CI: -32.12, -11.60, $p<0.05$) and SDNN (β=-20.88, 95% CI: -36.73, -5.03, $p<0.05$) compared to controls. Sleep-related HF power was significantly lower in participants with MDD than controls after adjusting for age, sex, PSQI and waking at night, but was no longer significant after accounting for medications[93].

Yang et al. (2011) and Ottaviani et al. (2015) found lower HRV during both wake and sleep in participants with MDD compared to controls while Kwon et al. (2019) only found lower HRV during wake in MDD than control participants in time and frequency domain measures[57]. Saad et al. (2020) found there was a group-sleep stage interaction with the difference in sleep-related HRV between the MDD and control groups widening with increasing sleep depth such that the difference in HRV between groups was greater in NREM Stage 3 than in Stages 1 or 2 (data not shown), although they found no differences during wake. Brupbacher et al. (2021) found no differences in time or frequency domain HRV measures across any sleep stage in participants with MDD after either a bout of aerobic exercise or reading magazines[84].

Non-linear measures (MSE[69], DFA alpha-1[57] and SampEn[90]) of sleep-related HRV were also lower in MDD groups during sleep compared to controls. A stepwise regression analysis showed the DFA alpha-1 correlated with Beck Depression Inventory (BDI) scores ($r=0.36$, $p=0.005$) and accounted for 12.9% of the variance in BDI scores. The effect size of

this association, however, was small[57]. Leistedt et al. (2011) found sleep-related SampEn (MDD: median 15.4; range 6.9–19.8 compared to control: 17.6; 13.8–19.4; $p<0.04$) was associated with HADS score in participants with MDD ($r=-0.40$; $p=0.05$)[90]. Yang et al (2011) found that PSQI score correlated with LF/HF ratio ($r=0.345$, $p=0.057$), RMSSD ($r=-0.404$, $p=0.024$), pNN50 ($r=-0.359$, $p=0.047$) and HF power ($r=-0.376$, $p=0.037$) during wake in the MDD group, with no similar observations among the controls.

Anxiety-related disorders

Eight studies reported on participants with PTSD (Supplementary Table S4) while no studies reported on HRV and sleep in any other diagnosed anxiety-related disorders. All the studies which used PSQI found significantly higher scores in PTSD groups than controls[56,59,60,62]. Mellman et al. (2004) found an interaction effect between PTSD group and sleep stage on ANS function[58]. Time-in-bed nHF power was lower in participants with PTSD than controls ($p<0.05$)[55], as were SDNN, log HF power and log LF power, and none of these measures varied by current comorbid MDD status[56]. Participants with PTSD had higher heart rates during sleep than controls in multiple studies, even after adjusting for age ($p=0.017$), combat exposure ($p=0.003$), sleep and activity ($p<0.05$)[60,62,91]. One model showed a significant interaction between PTSD symptom severity and interval (sleep, rest or activity periods) for HF power ($p=0.028$, Cohen's $d=0.12$) where more severe PTSD symptoms predicted lower HF values during sleep only[65].

While Ulmer et al. (2018) found no overall difference in sleep-related HF power between groups after adjusting for covariates, the participants with PTSD had lower HF power during NREM ($p=0.047$), specifically during the first and fourth NREM cycle, but not during REM ($p=0.16$) sleep. This diminished HF power in participants with PTSD during NREM sleep

remained significant after adjusting for age, sex, apnoea hypopnea index, and BDI-II scores (excluding the sleep questions). Based on this, the authors proposed that PTSD status may mediate the NREM-REM differences in HRV, although this interaction did not reach significance ($p=0.074$)[59]. Agorastos et al. (2013) found positive correlations between clinician-administered PTSD scale scores and heart rate, LF/HF ratio (all $p<0.01$) and DFA alpha ($p<0.05$). Depression severity was also positively correlated with the LF/HF ratio and daytime DFA[91].

In another study, the PTSD-resilient group's (those exposed to trauma but who did not develop PTSD), total sleep time was correlated with nHF power ($r=0.75$, $p=0.001$) and LF/HF ratios ($r=-0.64$, $p=0.008$) during time-in-bed but this relationship was absent in the PTSD group[55]. Another study found heart rate ($r=0.332$, $p<0.05$) and RSA magnitude ($r=-0.333$, $p<0.05$) during sleep were both correlated with PSQI scores in both the PTSD and control groups. Their final model accounted for 37% of the variance in PSQI scores (adjusted $R^2=0.371$, $p<0.001$) and included RSA magnitude and Beck Anxiety Inventory (BAI) scores as significant predictors of sleep quality (RSA: $\beta=-0.28$, $p<0.05$; BAI: $\beta=0.41$, $p<0.01$)[60].

One study reported on "healthy participants" who had clinically significant scores on questionnaires assessing symptoms of anxiety[82]. These participants showed that worry duration correlated with lower sleep-related HRV and that lower sleep-related HRV correlated with poorer sleep quality[82].

Stress-related exposure

Sleep and sleep-related HRV data describing participants with stress-related exposure was reported in three studies (Supplementary Table S4). Two of these studies used participants

where cases and controls both reported questionnaire scores suggesting the presence of clinical levels of anxiety[68,70] whereas Furutani et al. (2011) included participants who were chronically stressed and healthy controls. In the acute stress study by Hall et al. (2004) this stress exposure was in the form of being told they would have to prepare and present a speech in the morning while control groups were told they would be asked to read a magazine. HF was consistently higher in the control group during REM ($p<0.01$) and across all NREM periods ($p<0.02$) while the stress group showed higher LF/HF ratios than controls during NREM ($p<0.05$). The LF/HF ratio during NREM was negatively correlated with sleep maintenance ($r=-0.43$, $p<0.01$)[70].

Meanwhile, in another study, the high chronic stress group had higher LF/HF ratio before sleep onset compared to during sleep (all $p<0.01$), whereas in the low chronic stress group there were no differences between LF/HF ratios measured before or after sleep onset. In the high and low chronic stress groups, both the HF power ($p=0.03$) and LF power values ($p=0.04$) showed significant time effects when comparing pre-, during and post-sleep onset[63], such that HF power increased and LF power decreased as the participants transitioned from wake to sleep.

Finally, participants exposed to childhood trauma also reported poorer quality sleep, based on PSQI scores ($p<0.001$)[68], compared to controls. Whilst the trauma group showed only a trend towards lower sleep-related HRV, when this group was split and analysed based on the type of trauma experienced, the physical abuse subgroup showed significantly lower HF power values than controls in the early hours of the night[68].

Risk of bias

There was considerable bias in many of the included studies (Supplementary Table S2). Potential confounders such as age (which ranged widely in these studies), sex and comorbidities were not considered in many of the HRV analyses [50,55,57,63,68,73,75,77,79–81,88,94]. Additionally, most studies did not adequately describe the study participants in sufficient detail, making it difficult to compare populations and thus limiting the generalisability of the results[50,56,60,61,63,68,71,73–75,77,81,82,88,90,91,93,94].

4. Discussion

This review found that 29 of the 35 studies assessed reported lower HRV during sleep (as measured using time-domain, frequency-domain or non-linear methods) in participants with both mood- and anxiety-related disorders and sleep disorders compared to participants without these disorders. This suggests that sleep-related ANS dysfunction may be a common but independent factor to both sets of disorders, and may be an underlying reason for the frequent co-occurrence of these conditions, especially given that in healthy individuals, both poor sleep and lower sleep-related HRV are predictors of more severe psychological symptoms[78]. This review is unable to categorically show that ANS dysregulation plays a role in the relationship between sleep and mood/anxiety-related symptoms, given a) the heterogeneity of the sleep, HRV and mood- and anxiety-related disorder symptom measures, b) that the majority of the included studies were cross-sectional in design, c) that many did not control for known confounders, including 3 studies where participants were taking psychotropic medications, 6 studies where the authors did not state whether or not participants were taking psychotropic medications and 15 studies which did not report excluding participants with comorbid sleep disorders and d) that there are at present no mediation analyses of sleep, HRV and mood- and anxiety-related symptoms. Despite this, we

did find that the presence of mood-, anxiety- or sleep-related disorders was associated with reduced sleep-related HRV and altered indices of sympathovagal modulation. This relationship appears limited to objectively-measured shorter, poorer quality or more disordered sleep in sleep-related disorder populations.

We considered the relationships between depressive- and anxiety-related symptoms and sleep-related HRV in populations with sleep disorders such as insomnia, OSA etc. Specifically, results from seven studies showed that objectively-measured short, poor quality or more severely disordered sleep (e.g. more severe OSA) may be associated with ANS dysregulation [50,71,74–76,85,87]. Meanwhile, insomnia groups with significantly higher subjective measures of poor sleep (PSQI and/or ISI scores) unanimously reported more severe depressive or anxiety-related symptoms but the majority showed no differences in measures of HRV[69,71–73,79]. Given the limited sample sizes of these studies, they may have been underpowered to detect HRV differences. Seven of the nine studies where participants with insomnia had objectively-measured shorter, poorer quality or more severely disordered sleep than controls showed they had lower HRV compared to controls. This suggests that objective measures of quality or disordered sleep may be necessary for the categorisation of insomnia that manifests with detectable changes in HRV.

Given the complexity of the physiology underlying psychiatric disorders and insomnia it may also be that those studies that include insomnia groups with significantly higher subjective measures of poor sleep exhibit a scenario where other factors, such as psychological factors (e.g. rumination) [17], either a) compound subtle alterations in ANS regulation which the studies were underpowered to detect or b) are the predominant drivers of the observed

relationship between poor sleep and mood- and anxiety-related disorders (as proposed in our model in Figure 2 by the arrows which bypass sleep-related ANS dysregulation).

Participants with MDD, PTSD, and acute stress all had lower sleep-related markers of PNS activity[55–57,69,70,93] and overall HRV[57,61,66,69,93] compared to controls. All participants diagnosed with a mood disorder showed some evidence of lower overall HRV, and time-domain HRV measures remained significant even after adjusting for medication usage. These differences widened with increasing sleep depth[61] such that differences in HRV between MDD-diagnosed individuals and controls were greater in Stage 3 NREM than in Stage 1 NREM sleep. There was a significant interaction between PTSD symptom severity and interval (sleep, rest or activity periods) for HF power where more severe PTSD symptoms predicted lower HF power values during sleep only[65]. This finding specifically highlights the association between symptom severity and sleep-related HRV dysregulation. In the stress-related studies sleep-stage specific ANS dysregulation was found with differences in sympathovagal modulation in chronically high-stressed participants during NREM sleep and negatively correlated with sleep maintenance. Collectively, these results suggest that these lower HRV values during sleep (and during NREM sleep specifically), indicative of sleep-related hyperarousal, are linked to more severe symptoms of anxiety (including stress) and depression as well as the presence of sleep disorders and, by extension, poor sleep quality.

We also considered sleep parameters in participants with mood- and anxiety-related disorders and lower sleep-related HRV. In individuals diagnosed with or self-reporting MDD- and PTSD, lower sleep-related HRV measures were associated with poorer self-reported sleep quality[56,59,60,69,82,90,93], whereas controls had higher sleep-related HRV. Measures of

hyperarousal also negatively correlated with sleep quality[62,70,82] although this relationship was absent in some PTSD-diagnosed participants[55]. None of the included studies focused on the potential mediation relationship between sleep, sleep-related HRV and mood- and anxiety-related disorders and few studies controlled for the effect of poor sleep and depressive- or anxiety-related symptoms on HRV. There were clear differences, however, in sleep-related indices of ANS regulation between healthy participants and those with sleep or mood- and anxiety-related disorders. The healthy participants displayed markers of more parasympathetic activity/less sympathetic activity during sleep than the disordered groups. Additionally, many of these differences were sleep stage specific in the participants diagnosed with depression- or anxiety-related disorders. This supports our hypothesis that ANS dysregulation may influence the observed relationship between sleep and mood- and anxiety-related disorders and suggests that it may be sleep stage specific.

Based on this, we propose that ANS dysregulation during sleep may influence the apparent bidirectional relationship between poor quality or disordered sleep and mood- or anxiety-related disorders (see Figure 2). Robust studies are required to test this hypothesis. Since parasympathetic input usually predominates during sleep[35], indices of parasympathetic input are positively correlated with good sleep quality and lower HRV during sleep predicts increased severity of sleep difficulties in apparently healthy individuals [78]. Thus, attenuation of parasympathetic activity at night, potentially contributing to a state of hyperarousal, is likely unconducive to good quality sleep. This is in line with the current literature which accepts hyperarousal as a factor in insomnia[95,96] and that there may in fact be a continuum of ANS dysfunction which parallels the range in sleep complaint severity. Additionally, this continuum of dysfunction may be as a result of a “natural continuum of basal arousal levels” making some individuals more prone to hyperarousal than others[95,96]

and thus more prone to insomnia. If an individual does develop hyperarousal leading to poor quality sleep, this would then potentially exacerbate any depressive/anxiety-related symptoms. Alternatively, we found both depression- and anxiety-related disorders to be associated with lower overall sleep-related HRV and, specifically, sleep-related parasympathetic modulation. This may push an individual into a state of hyperarousal which then impacts on sleep and leads to the development of co-morbid insomnia. This also concurs with other literature which proposes a hyperarousal subtype of PTSD[97] and that hyperarousal may also present in anxiety[98], stress[99], depression[98], and insomnia[95]. This in turn may also explain why some patients experience sleep disturbances and others do not[100].

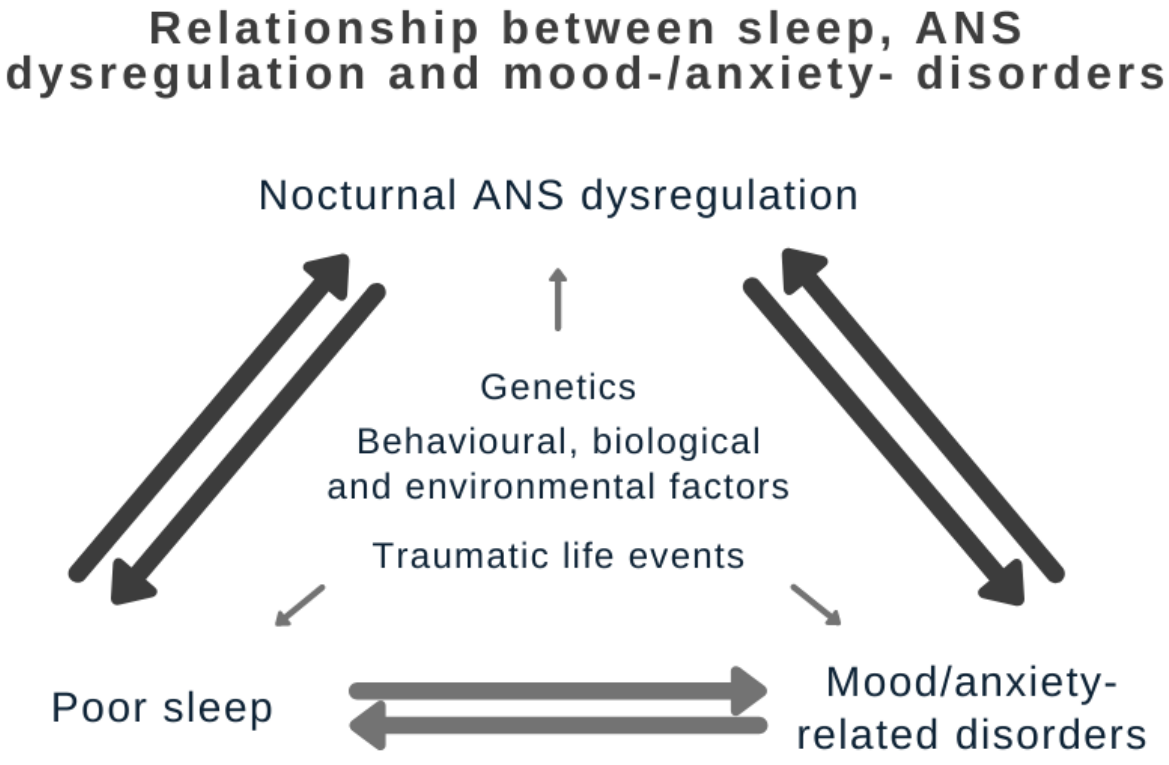

Figure 2: Diagram depicting the proposed relationship between sleep, autonomic nervous system (ANS) dysregulation and mood- and anxiety-related disorders. The arrows indicate the direction of the relationships such that ANS dysregulation can be either a contributing causal factor to

and / or a consequence of poor sleep and mood- and anxiety-related disorders. Light grey arrows indicate established relationships which are not the focus of this review.

Kohler et al. (2016) proposed a hypothesis by which poor sleep quality and hyperarousal may exacerbate depression- and anxiety-related symptoms. They suggest that activation of the SNS without the corresponding counter-action of the PNS leads to systemic inflammation[101], which itself may be exacerbated by consequent sleep disruption[14]. This, in turn, creates an environment which leaves the brain vulnerable to the development of symptoms of a psychiatric disorder[101]. Thus, ANS dysregulation may influence the relationship between sleep and depression-/anxiety-related disorders.

The limitations of this review are that most of the included studies used observational designs and therefore are unable to demonstrate causality. There were no studies investigating how sleep-related HRV may mediate the relationship between disordered sleep and mood- and anxiety-related disorders, as most just looked at HRV as an outcome in populations diagnosed with or self-reporting disordered sleep or mood- and anxiety-related disorders. Only a few studies in sleep disorder populations accounted for symptoms of anxiety and depression in their analyses of the relationship between sleep quality and HRV[72,76]. Additionally, none of the 41 reviewed studies looked at generalised anxiety-disorder or non-diagnosed anxiety in the general population. Given the high-stress nature of our current society and that hyperarousal is a characteristic of anxiety-related disorders, this appears to be a gap in the literature and an important direction for further research. Additionally, longitudinal studies and mediation analyses are required to further determine the relationship between sleep quality, ANS dysregulation and mood- and anxiety-related disorders. Finally, future research should focus on sleep stage differences as almost all studies which included

PSG found HRV differences only during specific sleep stages or found different patterns of HRV compared to controls during the different sleep stages.

Practice points:

1. People with sleep or mood- and anxiety-related disorders are more likely to exhibit lower sleep-related HRV compared to apparently healthy controls.
2. Altered sleep-related HRV may be one of the underlying mechanisms influencing the development of insomnia and depression.
3. For insomnia populations, objective PSG-derived differences in sleep quality or duration are likely required to detect differences in HRV.

Research agenda:

1. Further research should focus on the link between generalised anxiety disorder or anxiety-related symptoms, HRV and sleep.
2. It should be investigated whether HRV mediates the relationship between poor sleep and mood- and anxiety-related disorders.
3. Longitudinal studies and mediation analyses investigating the relationship between sleep, HRV and mood- and anxiety-related disorders are required to determine what role altered HRV may play in the development of poor sleep or psychiatric disorders.

5. Conclusion

While the current evidence is too varied to conclusively state that ANS dysregulation plays a role in the relationship between disordered sleep and mood- and anxiety-related disorders, we

did find that ANS dysregulation appears to be independently associated with both disordered sleep and mood- and anxiety-related disorders. This variation is likely largely due to methodological differences such as using PSG vs subjective sleep quality assessments as HRV differences may be sleep stage specific and particularly associated with objectively shorter, poorer quality or more disordered sleep. Included studies largely showed lower sleep-related HRV, lower markers of sleep-related parasympathetic activity and altered sleep-related sympathovagal balance in populations with sleep or mood- and anxiety-related disorders versus controls which could be a marker of hyperarousal in these populations. Hyperarousal is widely considered a factor of insomnia and is a characteristic of anxiety-related disorders such as PTSD. This provides common ground between sleep and psychiatric disorders and provides support for the hypothesis that sleep-related ANS dysregulation influences the observed bidirectional relationship between sleep and mood- and anxiety-related disorders. However, longitudinal studies (accounting for confounding factors) and mediation analyses are necessary to further elucidate the relationship between sleep, HRV and mood- and anxiety-related disorders.

References

[1] Institute of Medicine Committee. Sleep disorders and sleep deprivation: an unmet public health problem. In: Colten HR, Altevogt BM, editors. The National Academics Press, 2006. https://doi.org/10.5860/choice.44-5682.

[2] Chattu V, Manzar Md, Kumary S, Burman D, Spence D, Pandi-Perumal S. The Global Problem of Insufficient Sleep and Its Serious Public Health Implications. Healthcare 2018;7:1. https://doi.org/10.3390/healthcare7010001.

[3] Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. The Lancet 2015;386:743–800.

[4] World Health Organization. Depression and other common mental disorders: global health estimates 2017:1–24.

[5] Santomauro DF, Mantilla Herrera AM, Shadid J, Zheng P, Ashbaugh C, Pigott DM, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. The Lancet 2021;398:1700–12. https://doi.org/10.1016/S0140-6736(21)02143-7.

[6] Rod NH, Vahtera J, Westerland H. Sleep Disturbances and Cause-Specific Mortality: Results From the GAZEL Cohort Study. Am J Epidemiol 2011;173:300–9. https://doi.org/10.1016/j.ypsy.2011.07.039.

[7] Harris EC, Barraclough B. Excess mortality of mental disorder. British Journal of Psychiatry 1998;173:11–53. https://doi.org/10.1192/bjp.173.1.11.

[8] Gallicchio L, Kalesan B. Sleep duration and mortality: A systematic review and meta-analysis. J Sleep Res 2009;18:148–58. https://doi.org/10.1111/j.1365-2869.2008.00732.x.

[9] Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: A meta-analytic review. Psychophysiology 2007;44:660–9. https://doi.org/10.1111/j.1469-8986.2007.537.x.

[10] Tkachenko O, Olson EA, Weber M, Preer LA, Gogel H, Killgore WDS. Sleep difficulties are associated with increased symptoms of psychopathology. Exp Brain Res 2014;232:1567–74. https://doi.org/10.1007/s00221-014-3827-y.

[11] Perils ML, Giles DE, Buysse DJ, Tu X, Kupfer DJ. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. J Affect Disord 1997;42:209–12. https://doi.org/10.1016/S0165-0327(96)01411-5.

[12] Geoffroy PA, Hoertel N, Etain B, Bellivier F, Delorme R, Limosin F, et al. Insomnia and hypersomnia in major depressive episode: Prevalence, sociodemographic characteristics and psychiatric comorbidity in a population-based study. J Affect Disord 2018;226:132–41. https://doi.org/10.1016/j.jad.2017.09.032.

[13] Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: Effects on autonomic function, neuroendocrine stress systems and stress responsivity. Sleep Med Rev 2008;12:197–210. https://doi.org/10.1016/j.smrv.2007.07.007.

[14] Fang H, Tu S, Sheng J, Shao A. Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment. J Cell Mol Med 2019;23:2324–32. https://doi.org/10.1111/jcmm.14170.

[15] Meerlo P, Havekes R, Steiger A. Chronically restricted or disrupted sleep as a causal factor in the development of depression. Curr Top Behav Neurosci 2015;25:459–81. https://doi.org/10.1007/7854_2015_367.

[16] Jansson-Fröjmark M, Lindblom K. A bidirectional relationship between anxiety and depression, and insomnia? A prospective study in the general population. J Psychosom Res 2008;64:443–9. https://doi.org/10.1016/j.jpsychores.2007.10.016.

[17] Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of insomnia, depression, and anxiety. Sleep 2005;28:1457–64. https://doi.org/10.1093/sleep/28.11.1457.

[18] Tsuno N, Besset A, Ritchie K. Sleep and depression. Journal of Clinical Psychiatry 2005;66:1254–69. https://doi.org/10.1159/000284520.

[19] Park SC, Kim JM, Jun TY, Lee MS, Kim JB, Jeong SH, et al. Prevalence and clinical correlates of insomnia in depressive disorders: The CRESCEND study. Psychiatry Investig 2013;10:373–81. https://doi.org/10.4306/pi.2013.10.4.373.

[20] Franzen PL, Buysse DJ. Sleep disturbances and depression: Risk relationships for subsequent depression and therapeutic implications. Dialogues Clin Neurosci 2008;10:473–81. https://doi.org/10.31887/dcns.2008.10.4/plfranzen.

[21] Jansson M, Linton SJ. The role of anxiety and depression in the development of insomnia: Cross-sectional and prospective analyses. Psychol Health 2006;21:383–97. https://doi.org/10.1080/14768320500129015.

[22] Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: Secondary symptom or core feature? Sleep Med Rev 2008;12:169–84. https://doi.org/10.1016/j.smrv.2007.08.008.

[23] Gilbert KS, Kark SM, Gehrman P, Bogdanova Y. Sleep Disturbances, TBI and PTSD: Implications for Treatment and Recovery. Clin Psychol Rev 2015;40:195–212. https://doi.org/10.1016/j.cpr.2015.05.008.

[24] Andrew HK, Daniel SQ, Marcus AG, Kim LF, Kerri B, Justine MG, et al. Impact of Depression and Antidepressant Treatment on Heart Rate Variability: A Review and Meta-Analysis. Biol Psychiatry 2010;67:1067–74.

[25] Stein PK, Pu Y. Heart rate variability, sleep and sleep disorders. Sleep Med Rev 2012;16:47–66. https://doi.org/10.1016/j.smrv.2011.02.005.

[26] Bassett D. A literature review of heart rate variability in depressive and bipolar disorders. Aust N Z J Psychiatry 2016;50:511–9. https://doi.org/10.1177/0004867415622689.

[27] Porges SW. The polyvagal theory: New insights into adaptive reactions of the autonomic nervous system. Cleve Clin J Med 2009;76. https://doi.org/10.3949/ccjm.76.s2.17.

[28] Breit S, Kupferberg A, Rogler G, Hasler G. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. Front Psychiatry 2018;9. https://doi.org/10.3389/fpsyt.2018.00044.

[29] Wang H, Yu M, Ochani M, Amelia CA, Tanovic M, Susarla S, et al. Nicotinic acetylcholine receptor α7 subunit is an essential regulator of inflammation. Nature 2003;421:384–8. https://doi.org/10.1038/nature01339.

[30] Rahman, Faisal; Pechnik, Sandra; Gross, Daniel; Sewell, LaToya; Goldstein D. LF Power Reflects Baroreflex Function, Not Cardiac Sympathetic Innervation. Clinical Autonomic Research 2011;21:133–41. https://doi.org/10.1007/s10286-010-0098-y.LF.

[31] Shinar Z, Akselrod S, Dagan Y, Baharav A. Autonomic changes during wake-sleep transition: A heart rate variability based approach. Auton Neurosci 2006;130:17–27. https://doi.org/10.1016/j.autneu.2006.04.006.

[32] Billman GE. The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. Front Physiol 2013;4 FEB:1–5. https://doi.org/10.3389/fphys.2013.00026.

[33] Wu GQ, Arzeno NM, Shen LL, Tang DK, Zheng DA, Zhao NQ, et al. Chaotic signatures of heart rate variability and its power spectrum in health, aging and heart failure. PLoS One 2009;4:e4323.

[34] Calandra-Buonaura G, Provini F, Guaraldi P, Plazzi G, Cortelli P. Cardiovascular autonomic dysfunctions and sleep disorders. Sleep Med Rev 2016;26:43–56. https://doi.org/10.1016/j.smrv.2015.05.005.

[35] Miglis MG. Autonomic dysfunction in primary sleep disorders. Sleep Med 2016;19:40–9. https://doi.org/10.1016/j.sleep.2015.10.001.

[36] Vaughn B V., Quint SR, Messenheimer JA, Robertson KR. Heart period variability in sleep. Electroencephalogr Clin Neurophysiol 1995;94:155–62. https://doi.org/10.1016/0013-4694(94)00270-U.

[37] Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, et al. The hyperarousal model of insomnia: A review of the concept and its evidence. Sleep Med Rev 2010;14:19–31. https://doi.org/10.1016/j.smrv.2009.04.002.

[38] Ferini-Strambi L, Bianchi A, Zucconi M, Oldani A, Castronovo V, Smirne S. The impact of cyclic alternating pattern on heart rate variability during sleep in healthy young adults. Clinical Neurophysiology 2000;111:99–101. https://doi.org/10.1016/S1388-2457(99)00212-6.

[39] Bosi M, Milioli G, Riccardi S, Melpignano A, Vaudano AE, Cortelli P, et al. Arousal responses to respiratory events during sleep: the role of pulse wave amplitude. J Sleep Res 2018;27:259–67. https://doi.org/10.1111/jsr.12593.

[40] Halász P, Terzano M, Parrino L, Bódizs R. The nature of arousal in sleep. J Sleep Res 2004;13:1–23. https://doi.org/10.1111/j.1365-2869.2004.00388.x.

[41] Medic G, Wille M, Hemels MEH. Short- and long-term health consequences of sleep disruption. Nat Sci Sleep 2017;9:151–61. https://doi.org/10.2147/NSS.S134864.

[42] Burgess HJ, Trinder J, Kim Y, Luke D. Sleep and circadian influences on cardiac autonomic nervous system activity. Am J Physiol Heart Circ Physiol 1997;273:1761–8. https://doi.org/10.1152/ajpheart.1997.273.4.h1761.

[43] Dodds KL, Miller CB, Kyle SD, Marshall NS, Gordon CJ, Gordon CJ. Heart rate variability in insomnia patients: a critical review of the literature. Sleep Med Rev 2017;33:88–100.

[44] Chalmers JA, Quintana DS, Abbott MJA, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: A meta-analysis. Front Psychiatry 2014;5:1–11. https://doi.org/10.3389/fpsyt.2014.00080.

[45] Kemp AH, Quintana DS, Felmingham KL, Matthews S, Jelinek HF. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: Implications for cardiovascular risk. PLoS One 2012;7:1–8. https://doi.org/10.1371/journal.pone.0030777.

[46] Licht CMM, De Geus EJC, Richard Van DA, Penninx BWJH. Association between anxiety disorders and heart rate variability in the netherlands study of depression and anxiety (NESDA). Psychosom Med 2009;71:508–18. https://doi.org/10.1097/PSY.0b013e3181a292a6.

[47] Alvares GA, Quintana DS, Hickie IB, Guastella AJ. Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: A systematic review and meta-analysis. Journal of Psychiatry and Neuroscience 2016;41:89–104. https://doi.org/10.1503/jpn.140217.

[48] Licht CMM, De Geus EJC, Van Dyck R, Penninx BWJH. Longitudinal evidence for unfavorable effects of antidepressants on heart rate variability. Biol Psychiatry 2010;68:861–8. https://doi.org/10.1016/j.biopsych.2010.06.032.

[49] Kobayashi I, Lavela J, Bell K, Mellman TA. The impact of posttraumatic stress disorder versus resilience on nocturnal autonomic nervous system activity as functions of sleep stage and time of sleep. Physiol Behav 2016;164:11–8. https://doi.org/10.1016/j.physbeh.2016.05.005.

[50] Farina B, Dittoni S, Colicchio S, Testani E, Losurdo A, Gnoni V, et al. Heart Rate and Heart Rate Variability Modification in Chronic Insomnia Patients. Behavioral Sleep Medicine 2014;12:290–306. https://doi.org/10.1080/15402002.2013.801346.

[51] Tobaldini E, Nobili L, Strada S, Casali KR, Braghiroli A, Montano N. Heart rate variability in normal and pathological sleep. Front Physiol 2013;4:1–11. https://doi.org/10.3389/fphys.2013.00294.

[52] Cox RC, Olatunji BO. A systematic review of sleep disturbance in anxiety and related disorders. J Anxiety Disord 2016;37:104–29. https://doi.org/10.1016/j.janxdis.2015.12.001.

[53] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. The BMJ 2021;372:2020–1. https://doi.org/10.1136/bmj.n71.

[54] Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, et al. Checklist for Analytical Cross Sectional Studies. Joanna Briggs Institute Reviewer's Manual 2017:6. https://doi.org/10.17221/96/2009-CJGPB.

[55] Kobayashi I, Lavela J, Mellman TA. Nocturnal Autonomic Balance and Sleep in PTSD and Resilience. J Trauma Stress 2014;27:712–6. https://doi.org/10.1002/jts.

[56] Dennis PA, Watkins LLL, Calhoun PS, Oddone A, Sherwood A, Dennis MF, et al. Posttraumatic stress, heart rate variability, and the mediating role of behavioral health risks. Psychosom Med 2014;76:629–37. https://doi.org/10.1097/PSY.0000000000000110.

[57] Kwon H Bin, Yoon H, Choi SH, Choi JW, Lee YJ, Park KS. Heart rate variability changes in major depressive disorder during sleep: Fractal index correlates with BDI score during REM sleep. Psychiatry Res 2019;271:291–8. https://doi.org/10.1016/j.psychres.2018.11.021.

[58] Mellman TA, Knorr BR, Pigeon WR, Leiter JC, Akay M. Heart rate variability during sleep and the early development of posttraumatic stress disorder. Biol Psychiatry 2004;55:953–6. https://doi.org/10.1016/j.biopsych.2003.12.018.

[59] Ulmer CS, Hall MH, Dennis PA, Beckham JC, Germain A. Posttraumatic stress disorder diagnosis is associated with reduced parasympathetic activity during sleep in US veterans and military service members of the Iraq and Afghanistan wars. Sleep 2018;41. https://doi.org/10.1093/sleep/zsy174.

[60] Woodward SH, Arsenault NJ, Voelker K, Nguyen T, Lynch J, Skultety K, et al. Autonomic Activation During Sleep in Posttraumatic Stress Disorder and Panic: A Mattress Actigraphic Study. Biol Psychiatry 2009;66:41–6. https://doi.org/10.1016/j.biopsych.2009.01.005.

[61] Saad M, Ray LB, Bradley-Garcia M, Palamarchuk IS, Gholamrezaei A, Douglass A, et al. Autonomic modulation of cardiac activity across levels of sleep depth in individuals with depression and sleep complaints. Psychosom Med 2020;82:172–80. https://doi.org/10.1097/PSY.0000000000000766.

[62] Bertram F, Jamison AL, Slightam C, Kim S, Roth HL, Roth WT. Autonomic Arousal During Actigraphically Estimated Waking and Sleep in Male Veterans With PTSD. J Trauma Stress 2014;27:610–7. https://doi.org/10.1002/jts.

[63] Furutani M, Tanaka H, Agari I. Anxiety and heart rate variability before sleep indicate chronic stress in students. Percept Mot Skills 2011;112:138–50. https://doi.org/10.2466/09.13.PMS.112.1.138-150.

[64] Dennis PA, Kimbrel NA, Sherwood A, Calhoun PS, Watkins LLL, Dennis MF, et al. Trauma and autonomic dysregulation: Episodic-versus systemic-negative affect underlying cardiovascular risk in posttraumatic stress disorder. Psychosom Med 2017;79:496–505. https://doi.org/10.1097/PSY.0000000000000438.

[65] Rissling MB, Dennis PA, Watkins LL, Calhoun PS, Dennis MF, Beckham JC, et al. Circadian Contrasts in Heart Rate Variability Associated With Posttraumatic Stress Disorder Symptoms in a Young Adult Cohort. J Trauma Stress 2016;29:415–21. https://doi.org/10.1002/jts.22125.

[66] Ottaviani C, Shahabi L, Tarvainen M, Cook I, Abrams M, Shapiro D. Cognitive, behavioral, and autonomic correlates of mind wandering and perseverative cognition in major depression. Front Neurosci 2015;9. https://doi.org/10.3389/fnins.2014.00433.

[67] Ottaviani C, Medea B, Lonigro A, Tarvainen M, Couyoumdjian A. Cognitive rigidity is mirrored by autonomic inflexibility in daily life perseverative cognition. Biol Psychol 2015;107:24–30. https://doi.org/10.1016/j.biopsycho.2015.02.011.

[68] Beilharz JE, Paterson M, Fatt S, Wilson C, Burton A, Cvejic E, et al. The impact of childhood trauma on psychosocial functioning and physical health in a non-clinical community sample of

young adults. Australian and New Zealand Journal of Psychiatry 2020;54:185–94. https://doi.org/10.1177/0004867419881206.

[69] Yang AC, Tsai SJ, Yang CH, Kuo CH, Chen TJ, Hong CJ. Reduced physiologic complexity is associated with poor sleep in patients with major depression and primary insomnia. J Affect Disord 2011;131:179–85. https://doi.org/10.1016/j.jad.2010.11.030.

[70] Hall M, Vasko R, Buysse D, Ombao H, Chen Q, Cashmere JD, et al. Acute Stress Affects Heart Rate Variability during Sleep. Psychosom Med 2004;66:56–62. https://doi.org/10.1097/01.PSY.0000106884.58744.09.

[71] Spiegelhalder K, Fuchs L, Ladwig J, Kyle SD, Nissen C, Voderholzer U, et al. Heart rate and heart rate variability in subjectively reported insomnia. J Sleep Res 2011;20:137–45. https://doi.org/10.1111/j.1365-2869.2010.00863.x.

[72] Chen IY, Jarrin DC, Ivers H, Morin CM. Investigating psychological and physiological responses to the Trier Social Stress Test in young adults with insomnia. Sleep Med 2017;40:11–22. https://doi.org/10.1016/j.sleep.2017.09.011.

[73] De Zambotti M, Covassin N, De Min Tona G, Sarlo M, Stegagno L. Sleep onset and cardiovascular activity in primary insomnia. J Sleep Res 2011;20:318–25. https://doi.org/10.1111/j.1365-2869.2010.00871.x.

[74] Wu MN, Lai CL, Liu CK, Yen CW, Liou LM, Hsieh CF, et al. Basal sympathetic predominance in periodic limb movements in sleep with obstructive sleep apnea. J Sleep Res 2015;24:722–9. https://doi.org/10.1111/jsr.12314.

[75] Idiaquez J, Santos I, Santin J, Del Rio R, Iturriaga R, Del R, et al. Neurobehavioral and autonomic alterations in adults with obstructive sleep apnea. Sleep Med 2014;15:1319–23. https://doi.org/10.1016/j.sleep.2014.05.030.

[76] Jarrin DC, Ivers H, Lamy M, Chen IY, Harvey AG, Morin CM. Cardiovascular autonomic dysfunction in insomnia patients with objective short sleep duration. J Sleep Res 2018;27. https://doi.org/10.1111/jsr.12663.

[77] Simor P, Körmendi J, Horváth K, Gombos F, Ujma PPPP, Bódizs R. Electroencephalographic and autonomic alterations in subjects with frequent nightmares during pre-and post-REM periods. Brain Cogn 2014;91:62–70. https://doi.org/10.1016/j.bandc.2014.08.004.

[78] Tan JPH, Beilharz JE, Vollmer-Conna U, Cvejic E. Heart rate variability as a marker of healthy ageing. Int J Cardiol 2019;275:101–3. https://doi.org/10.1016/j.ijcard.2018.08.005.

[79] Israel B, Buysse DJ, Krafty RT, Begley A, Miewald J, Hall M. Short-Term Stability of Sleep and Heart Rate Variability in Good Sleepers and Patients with Insomnia: For Some Measures, One Night is Enough. Sleep 2012;35:1285–91. https://doi.org/10.5665/sleep.2088.

[80] Burton AR, Rahman K, Kadota Y, Lloyd A, Vollmer-Conna U. Reduced heart rate variability predicts poor sleep quality in a case-control study of chronic fatigue syndrome. Exp Brain Res 2010;204:71–8. https://doi.org/10.1007/s00221-010-2296-1.

[81] Orr WC, Elsenbruch S, Harnish MJ. Autonomic regulation of cardiac function during sleep in patients with irritable bowel syndrome. American Journal of Gastroenterology 2000;95:2865–71. https://doi.org/10.1016/S0002-9270(00)01110-2.

[82] Brosschot JF, Van Dijk E, Thayer JF. Daily worry is related to low heart rate variability during waking and the subsequent nocturnal sleep period. International Journal of Psychophysiology 2007;63:39–47. https://doi.org/10.1016/j.ijpsycho.2006.07.016.

[83] Eddie D, Bentley KH, Bernard R, Yeung A, Nyer M, Pedrelli P, et al. Major depressive disorder and insomnia: Exploring a hypothesis of a common neurological basis using waking and sleep-derived heart rate variability. J Psychiatr Res 2020;123:89–94. https://doi.org/10.1016/j.jpsychires.2020.01.015.

[84] Brupbacher G, Zander-Schellenberg T, Straus D, Porschke H, Infanger D, Gerber M, et al. The acute effects of aerobic exercise on nocturnal and pre-sleep arousal in patients with unipolar depression: Preplanned secondary analysis of a randomized controlled trial. J Clin Med 2021;10. https://doi.org/10.3390/jcm10174028.

[85] Cosgrave J, Phillips J, Haines R, Foster RG, Steinsaltz D, Wulff K. Revisiting nocturnal heart rate and heart rate variability in insomnia: A polysomnography-based comparison of young self-reported good and poor sleepers. J Sleep Res 2021;30:1–12. https://doi.org/10.1111/jsr.13278.

[86] Fatt SJ, Beilharz JE, Joubert M, Wilson C, Lloyd AR, Vollmer-Conna U, et al. Parasympathetic activity is reduced during slow-wave sleep, but not resting wakefulness, in patients with chronic fatigue syndrome. Journal of Clinical Sleep Medicine 2020;16:19–28. https://doi.org/10.5664/JCSM.8114.

[87] Alomri RM, Kennedy GA, Wali SO, Alhejaili F, Robinson SR. Association between nocturnal activity of the sympathetic nervous system and cognitive dysfunction in obstructive sleep apnoea. Sci Rep 2021;11. https://doi.org/10.1038/s41598-021-91329-6.

[88] Nishith P, Duntley SP, Domitrovich PP, Uhles ML, Cook BJ, Stein PK. Effect of cognitive behavioral therapy on heart rate variability during REM sleep in female rape victims with PTSD. J Trauma Stress 2003;16:247–50. https://doi.org/10.1023/A:1023791906879.

[89] Hall MH, Middleton K, Thayer JF, Lewis TT, Kline CE, Matthews KA, et al. Racial differences in heart rate variability during sleep in women: The study of women across the nation sleep study. Psychosom Med 2013;75:783–90. https://doi.org/10.1097/PSY.0b013e3182a7ec5c.

[90] Leistedt SJ-J, Linkowski P, Lanquart J-P, Mietus JE, Davis RB, Goldberger AL, et al. Decreased neuroautonomic complexity in men during an acute major depressive episode: Analysis of heart rate dynamics. Transl Psychiatry 2011. https://doi.org/10.1038/tp.2011.23.

[91] Agorastos A, Boel JA, Heppner PS, Hager T, Moeller-Bertram T, Haji U, et al. Diminished vagal activity and blunted diurnal variation of heart rate dynamics in posttraumatic stress disorder. Stress 2013;16:300–10. https://doi.org/10.3109/10253890.2012.751369.

[92] Thielmann B, Schierholz RS, Böckelmann I. Subjective and objective consequences of stress in subjects with subjectively different sleep quality–a cross–sectional study. Int J Environ Res Public Health 2021;18. https://doi.org/10.3390/ijerph18199990.

[93] Bassett D, Bear N, Nutt D, Hood S, Bassett S, Hans D. Reduced heart rate variability in remitted bipolar disorder and recurrent depression. Australian and New Zealand Journal of Psychiatry 2016;50:793–804. https://doi.org/10.1177/0004867416652734.

[94] Migliorini M, Mariani S, Bertschy G, Kosel M, Bianchi AM. Can home-monitoring of sleep predict depressive episodes in bipolar patients? Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference 2015;2015:2215–8. https://doi.org/10.1109/EMBC.2015.7318831.

[95] Bonnet MH, Arand DL. Hyperarousal and insomnia. Sleep Med Rev 1997;1:97–108. https://doi.org/10.1016/j.smrv.2009.07.003.

[96] Bonnet MH, Arand DL. Hyperarousal and insomnia: State of the science. Sleep Med Rev 2010;14:9–15. https://doi.org/10.1016/j.smrv.2009.09.002.

[97] Weston CSE. Posttraumatic stress disorder: A theoretical model of the hyperarousal subtype. Front Psychiatry 2014;5. https://doi.org/10.3389/fpsyt.2014.00037.

[98] Greaves-Lord K, Ferdinand RF, Sondeijker FEPL, Dietrich A, Oldehinkel AJ, Rosmalen JGM, et al. Testing the tripartite model in young adolescents: Is hyperarousal specific for anxiety and not depression? J Affect Disord 2007;102:55–63. https://doi.org/10.1016/j.jad.2006.12.009.

[99] Goldstein DS. Stress-induced activation of the sympathetic nervous system. Baillieres Clin Endocrinol Metab 1987;1:253–78. https://doi.org/10.1016/S0950-351X(87)80063-0.

[100] Van Wyk M, Thomas KGF, Solms M, Lipinska G. Prominence of hyperarousal symptoms explains variability of sleep disruption in posttraumatic stress disorder. Psychol Trauma 2016;8:688–96. https://doi.org/10.1037/tra0000115.

[101] Köhler O, Krogh J, Mors O, Benros ME. Stress, the Autonomic Nervous System, and the Immune-kynurenine Pathway in the Etiology of Depression. Curr Neuropharmacol 2016;14:732–42. https://doi.org/10.2174/1570159X14666151208113.