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Predicting Heart Rate Variability In Individuals With Insomnia

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PREDICTING HEART RATE VARIABILITY IN INDIVIDUALS WITH INSOMNIA

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Abstract

Predicting Heart Rate Variability in Individuals with Insomnia

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Insomnia is a highly prevalent condition, affecting up to 30% of adults. Research has shown that insomnia may be an independent predictor of heart disease, which is the second leading cause of death in Canada. Heart rate variability (HRV) is a proxy of autonomic activity often used to estimate current heart health. The present study investigated whether sleep disturbance and psychological variables were independently associated with HRV in a highly characterized (n = 140) sample of people with insomnia. Whereas sleep disturbance as assessed by polysomnogram was not found to predict HRV, worry was associated with HRV in rapid eye movement sleep. Results suggest that sleep does not relate to HRV; rather, worry may be important to HRV, though the nature of this association remains unclear. Previous studies showing that sleep and HRV are related may have been due to inadequate assessment of comorbid psychiatric symptoms.

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Introduction

Heart disease is the second leading cause of death among Canadian adults (Statistics Canada, 2007); thus, studies establishing identifiable risk factors are urgently needed. Some studies have shown that insomnia is an independent risk factor for heart disease and myocardial infarction, even in the absence of respiratory pathologies (Schwartz et al., 1999). This association is concerning when we consider that the prevalence rate of insomnia is high - about 30% in the adult population (Buysse, Ancoli-lsrael, Edinger, Lichstein, & Morin, 2006; Roth, 2007). To date, the nature of the association between insomnia and cardiovascular risk is not yet well understood. In light of these startling statistics, there is an urgent need to elucidate this association due to the potentially significant health implications of insomnia for Canadians.

Heart Rate Variability

Heart rate variability (HRV) has gained popularity in the past decade as an informative and easily measured proxy for autonomic activity in the body. It is thought to reflect the heart's ability to adapt to environmental circumstances by detecting and quickly responding to unpredictable stimuli. Therefore, a healthy heart is one that allows for a wide range of variability in response to stimuli, and a potentially unhealthy heart is one that has a decreased ability to adapt its rate of beats in response to environmental circumstance. Although this may seem counter-intuitive, when encountering stress, someone with low HRV and someone with high HRV will experience increased heart rate; however, unlike the low-HRV person, the person with a healthy heart will regulate (i.e., decrease) their heart rate, and greater beat-to-beat variability is observed.

Measures of HRV assess the oscillation of the interval between consecutive heartbeats as well as oscillations between consecutive instantaneous heart rates (Task Force of the European

Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). The potential clinical importance of HRV was revealed in the late 1980's when it was confirmed in several studies that HRV is a strong independent predictor of mortality following acute myocardial infarction (Bigger et al., 1992; Kleiger, Miller, Bigger Jr., & Moss, 1987).

Integration of the measurement of HRV into common clinical practice holds particular promise within the realm of mental health. It is well known that individual variability in response to stressors and homeostatic regulation of arousal in the autonomic nervous system (ANS) plays an important role in mental and physical health (Habib, Gold, & Chrousos, 2001). The ANS is comprised of sympathetic and parasympathetic (vagal) branches, which both exert a regulatory influence on heart rate by influencing the sinoatrial (SA) node, the primary pacemaker for the heart. The sympathetic branch of the ANS increases heart rate by sending an excitatory signal to the SA node. In contrast, the parasympathetic branch of the ANS provides a regulatory balance to the sympathetic branch by exerting an inhibitory effect on the SA node, resulting in decreased heart rate (Appelhans & Luecken, 2006). In someone with a healthy heart, these two branches work together in homeostatic harmony within the ANS to allow the body to respond and adapt quickly and appropriately to stress and environmental stimuli. In terms of heart rate variability, one may think of the branches of the ANS as antagonistic regulators of lengths of time between consecutive heart beats. An increase in heart rate, or decreased length of time between consecutive heart beats, could result from either increased sympathetic activity or a decrease in parasympathetic inhibition of heart rate (known as vagal withdrawal; Appelhans & Luecken, 2006).

Heart rate variability is often used as a proxy for autonomic activity because both the sympathetic and the parasympathetic components of the ANS contribute to the rhythmic

modulation of the heart rate (RR) intervals of the QRS complex (one of the components of a typical electrocardiogram tracing of a complete cardiac cycle) in the electrocardiogram (ECG) at distinct, measurable frequencies. The low frequency (LF) range of heart rate is estimated to be associated with sympathetic activity (0.04-0.15 Hz) while the higher frequency (HF) range with parasympathetic activity (0.15-0.4 Hz), although some have argued that HF activity reflects activity from both the SNS and PNS (Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). The LF/HF ratio is assumed to estimate sympathovagal balance, or the balance between the sympathetic and parasympathetic systems (Lahiri, Kannankeril, & Goldberger, 2008). Many researchers presume that the differences in these frequency ranges allow HRV analysis to estimate the sympathetic and parasympathetic contributions to heart rate and to observe the interplay between these two systems. Unfortunately, the calculation used to compute this ratio relies on external validation with measures of autonomic system activation, often done with laboratory tests involving medications that completely block parasympathetic activity and thus allow for measurement of sympathetic activity. The results of these laboratory tests allow researchers to estimate the distinct frequencies of the heart's activity. Thus, this spectral analytic index is an indirect measure of autonomic tone, rather than a measure of the variability of heart rate, and is consequently not the most accurate method to evaluate the actual variability of heart rate across the recording period. A more accurate alternative measure of variability may be the coefficient of variation (CV) because it corresponds to heart rate variability directly, and does not rely on validation with autonomic system activation. The CV is calculated via a simple equation (the standard deviation of heart rate divided by the mean) and arguably is a more accurate assessment of actual variability of heart rate, which is the main goal of the present study.

As heart rate is not a stationary signal, an unusual variation may indicate a warning of current or impending disease, and may serve as a marker of the state of the ANS that is responsible for regulating cardiac activity. Low HRV has been found to be a risk factor for cardiovascular disease and overall morbidity and mortality (Friedman & Thayer, 1998; Thayer & Brosschot, 2005; Thayer, Smith, Rossy, Sollers, & Friedman, 1998; Yeragani et al., 2002). The decreased rate of oscillations between interbeat intervals found in low HRV is indicative of low parasympathetic activity. As discussed above, the PNS serves to balance the SNS by keeping the sympathoexcitatory neurons under neural control. Low parasympathetic activity results in sympathetic dominance, which can then cause autonomic behaviour that, when sustained over long periods of time, has been hypothesized to be somatically and psychologically pathogenic (Brosschot, Van Dijk, & Thayer, 2007). Low HRV has been linked to psychopathological conditions such as depression, anxiety, post-traumatic stress disorder, and schizophrenia. All of these conditions are associated with a lack of inhibitory neural processes from the PNS, resulting in sympathetic dominance (Friedman & Thayer, 1998; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Low HRV due to a dysfunctional ANS has been hypothesized to be the final pathway between psychopathology and somatic illness, including cardiovascular disease (Brosschot et al., 2007).

Sleep

The autonomic nervous system (ANS) also plays an essential role in the regulation of sleep. Within the sleep-wake cycle, changes in autonomic influences on the cardiovascular, respiratory, and gastrointestinal systems appear in accordance to changes in sleep architecture as seen on the EEG. Day-to-night autonomic changes in the cardiovascular system include a nocturnal reduction in blood pressure, known as the “dipping” phenomenon, which is an

approximate 10% reduction in systolic blood pressure (Sleep Research Society, 2005). This blood pressure "dip" is observed in participants even when they remain supine for 24 hours, indicating that the reduction in blood pressure is not accounted for by inactivity or a change in body position from upright to supine. Blood pressure is typically higher during REM sleep in humans in comparison to non-REM sleep. Abrupt heart decelerations in humans and animals have been observed during tonic REM sleep, a phase during REM when the eyes do not move. Morning awakenings also induce increased heart rate and blood pressure, which is presumed to be activated by the sympathetic nervous system (Sleep Research Society, 2005).

Twenty-four hour HRV studies have shown a nocturnal increase in the standard deviation of RR complex intervals, indicating increased nocturnal HRV (Huikuri et al., 1990). This increased HRV reflects the dominance of parasympathetic tone during sleep in comparison to wakefulness and highlights the influence of the ANS on the heart during sleep. Analysis of nocturnal HRV has also revealed differences between REM and NREM sleep, with increased cardiac vagal tone during NREM than REM sleep (Versace, Mozzato, De Min Tona, Cavallero, & Stegagno, 2003). Because so many autonomic changes occur during the sleep cycle, adapting to these changes via adjusting its rate of beats may present a challenge to a diseased heart. This adaptation challenge is reflected in decreased HRV, which can be easily measured and used as a proxy for heart health.

When discussing nocturnal HRV, it is important to consider sleep as both a physiological and behavioural process. Although sleep architecture changes throughout life from the newborn to the older adult, at all ages, sleep is governed by a set of behavioural and physiological states and stages. The timing of sleep and waking are controlled by the homeostatic process (dependent on the sleep-wake cycle), the independent circadian process, and their interaction.

Sleep need and intensity is regulated by the homeostatic process according to the amount of time spent awake or asleep. The circadian process functions according to the 24-hour day and regulates the appropriate timing of sleep and wakefulness on an individual basis. The function of sleep is not fully understood; however, the leading hypotheses are that sleep is restorative for brain metabolism, and that it plays a key role in synaptic plasticity and memory consolidation (Sleep Research Society, 2005).

The American Academy of Sleep Medicine divides sleep into two broad types: Rapid Eye Movement (REM) sleep and non-Rapid Eye Movement (NREM) sleep. NREM sleep is further divided into stages N1, N2, and N3 sleep. Stage N3 is where the deepest sleep occurs and is often referred to as delta or slow-wave sleep. Sleep proceeds in cycles of REM and NREM, typically in the order N1-N2-N3-N2-REM. Deep (N3) sleep is found in greater amounts earlier in the sleep cycle, while the proportion of REM sleep increases later in the cycle with the highest proportion just before natural awakening. In humans, a full sleep cycle lasts from 90-110 minutes on average, and most humans experience this cycle 3-4 times per night.

Breathing plays an important role in the distinct states of wakefulness and sleep. The depth, rate, and regularity of breathing change in characteristic patterns across stages of sleep and waking. Importantly, these changes are mediated by connections between the central neurons that generate and modulate the respiratory rhythm and neurons involved in the generation and maintenance of sleep-wake states. Under some conditions, such as obstructive sleep apnea, breathing can become disrupted to the point that it no longer serves its main function to the organism (to ensure pulmonary gas exchange that adequately meets the continual metabolic needs of the organism). When this breathing disruption occurs, sleep may also be interrupted, and a vicious cycle emerges in which the need for sleep and the need for breathing

compete with one another. Therefore, in any study of sleep, it is essential to assess for breathing pathologies that could affect sleep and related variables.

Insomnia

Insomnia, defined as the difficulty with initiation, maintenance, and duration or quality of sleep resulting in impairment of daytime functioning, has been suggested to be an independent risk factor for heart disease and cardiovascular mortality even in the absence of respiratory pathology such as sleep apnea-hypopnea syndrome (Schwartz et al., 1999). However, more recent large prospective epidemiological studies have failed to replicate these results, showing that symptoms of insomnia do not predict cardiovascular mortality in the absence of other non-respiratory pathology (Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002; Phillips & Mannino, 2005, 2007). One of these prospective studies indicated that difficulty falling asleep, waking up repeatedly, and awakening tired and fatigued predicted a slightly elevated risk for cardiovascular disease but not hypertension, while endorsement of difficulty falling asleep or waking repeatedly predicted increased risk for hypertension (Phillips & Mannino, 2007). Unfortunately, it is difficult to compare the results of these studies; all used varying definitions of insomnia and nonspecific insomnia parameter variables as predictors. The definition of insomnia clearly affects its impact in these investigations, and there is a need for a standardized method for defining and evaluating symptoms of insomnia to be consistently used in research. For example, these studies did not assess and exclude occult sleep disorders such as apnea or periodic limb movement disorder, so the "insomnia" evaluated in many of the studies actually may be an occult sleep disorder other than insomnia.

It remains unclear as to why, in some investigations, individuals with insomnia might have an increased risk for cardiovascular disease. In the past decade, there has been a surge of

interest in investigating HRV in individuals with insomnia as a method of evaluating cardiovascular health (e.g. Bonnet & Arand, 1998; Bonnet & Arand, 1996; Busek, Vanková, Opavský, Salinger, & Nevsímalová, 2005; Fang, Huang, Yang, & Tsai, 2008; Hall et al., 2004; Jurysta et al., 2009). To date, the results of these investigations have been mixed. In a frequently cited paper, Bonnet and Arand (1998) matched individuals with psychophysiological insomnia (individuals who display elevated heart rate, body temperature, and whole body metabolic rate) and no other sleep or psychiatric disorders with individuals with normal sleep for a 36-hour laboratory sleep study. Individuals with insomnia displayed significantly lower overall HRV compared with controls across all stages of sleep (Bonnet & Arand, 1998). The authors postulated that insomnia is associated with chronic sympathetic hyperactivity indicated by the increase in sympathovagal balance (decreased HRV) in the insomnia group. Moreover, they added that since increased sympathetic activity is related to many risk factors for coronary heart disease (e.g. increases in circulating triglycerides and cholesterol), this insomnia/sympathetic NS connection could be contributing to the increased risk for cardiovascular mortality in individuals with insomnia. This theory is supported by recent research investigating a sample of individuals with chronic fatigue syndrome (CFS) that found that HRV parameters were the best predictors of subjective sleep measures (Burton, Rahman, Kadota, Lloyd, & Vollmer-Conna, 2010). The authors of this paper purport that this finding suggests a pervasive state of nocturnal sympathetic hyperarousal in individuals with CFS. Bonnet and Arand's theory might suggest that it is this state of sympathetic hyperarousal that leads to increased cardiovascular mortality.

To date, there is no consensus in the literature surrounding the links between insomnia, HRV, and cardiovascular risk. More recent studies have failed to replicate Bonnet and Arand's

results (Fang et al., 2008; Jurysta et al., 2009). An analysis of HRV in healthy controls and subjectively reported insomnia (i.e. insomnia was not objectively confirmed via sleep EEG or prospective sleep diary) found partial support for Bonnet and Arand's hypothesis; a lower standard deviation of RR's (SDNN; the standard deviation of normal-to-normal heart rate intervals, which reflects overall HRV) and reduced parasympathetic activity was found in the insomnia group (Spiegelhalder et al., 2011). The results of this trial could not confirm alterations in sympathovagal balance and parasympathetic nocturnal activity in individuals with subjectively reported insomnia. The authors suggest that these changes in HRV might be specific to individuals with objective insomnia, as a subset of subjects with objective insomnia exhibited these changes in this study. In the sleep literature, evidence exists to indicate that a distinction can be made between objective and subjective insomnia (Krystal, Edinger, Wohlgemuth, & Marsh, 2002; Spiegelhalder et al., 2011). Objective insomnia can be corroborated by PSG sleep data, specifically by sleep EEG data in the alpha, sigma and beta frequency ranges. Conversely, subjectively defined insomnia differs from objective insomnia in terms of conventionally derived PSG sleep and wake time measures but not via spectral amplitude measures (Krystal et al., 2002). The International Classification of Sleep Disorders refers to this phenomenon as "paradoxical insomnia" or sleep-state misperception. Interestingly, studies have shown that individuals with subjective insomnia actually exhibit normal average total sleep time and sleep efficiencies (Edinger et al., 2000). These findings indicate that a thorough study evaluating the effects of insomnia on cardiovascular health should take measurement of both subjective and objective insomnia into consideration.

The association between sleep and cardiovascular risk has also been investigated through studies involving sleep deprivation. These investigations have shown that healthy young

subjects deprived of sleep exhibit amplified parasympathetic activity during subsequent recovery sleep (Holmes, Burgess, & Dawson, 2002) and increased sympathetic activity during the day as indicated by HRV spectral analysis, a technique often used to identify sympathetic and parasympathetic influence on heart rate (Zhong et al., 2005). In a recent study of HRV in women during 40-hour prolonged wakefulness, it was found that the wakefulness group exhibited a significantly higher sympathovagal balance (Anders et al., 2010). Although these studies provide evidence that HRV is influenced by sleep (or lack of sleep), it is yet unclear whether cardiac autonomic regulation is affected by insomnia in the absence of experimental sleep deprivation. Interestingly, it has been shown that experimental sleep deprivation does not produce the same symptoms of insomnia that chronic insomnia sufferers experience (Bonnet & Arand, 1996). Participants with normal sleep who were yoked to the EEG recordings of chronic insomnia sufferers for one week exhibited changes characteristic of mild sleep deprivation rather than insomnia. As described above, some individuals with subjectively reported insomnia have normal mean total sleep times. Thus, sleep deprivation does not necessarily produce the same symptoms as insomnia sufferers. Consequently, using sleep deprivation data for information about heart rate variability and cardiovascular risk may be misleading. There remains a need to investigate HRV in a carefully screened insomnia sample rather than a sample that had solely undergone sleep deprivation, a state not typically applicable to insomnia.

Measurement of Sleep

As indicated above by the inconsistent results of studies investigating sleep using varying sleep indices, the measures used to assess sleep are vitally important. To address this problem, a team of insomnia experts published a paper in 2006 outlining the worldwide expert consensus on recommendations for assessment and reporting standards in insomnia research studies (Buysse et

al., 2006). The authors discuss the benefits and limitations of commonly employed measures for recording sleep variables: the sleep diary and polysomnography (PSG).

1. Sleep Diaries

A sleep diary, completed by the participant upon rising, provides a measure of a subjective daily report of sleep and sleep disturbance to provide an estimate of the night's sleep. The recommended consensus was for a one to two week sleep diary that should include measures of the following: 1) time going to bed, 2) time awakening, 3) time arising out of bed, 4) sleep onset latency (SOL; how many minutes it takes to fall asleep starting from the moment of intention to fall asleep), 5) number of awakenings (NWAK; number of awakenings excluding the final awakening before the final arising), 6) wake after sleep onset (WASO; total amount of time awake during the night excluding SOL and terminal wakefulness (TWASO; amount of awake time between the final awakening and the time getting out of bed)), 7) total sleep time (TST; actual time slept, calculated by: time in bed (TIB) – SOL – WASO – TWASO), 8) sleep efficiency (SE; percent of time in bed spent asleep, calculated by TST/TIB x 100) 9) sleep quality (SQ; a subjective measure of the quality of sleep defined by response on an ordinal or visual response scale), 10) timing/duration of naps or daytime sleep episodes. Research supports that tracking sleep over several consecutive nights via prospective monitoring better captures night-to-night variability that characterizes the sleep of chronic insomnia than PSG (Wohlgemuth, Edinger, Fins, & Sullivan, 1999). Thus, the sleep diary provides a more representative sample of an individual's sleep than only one or two nights of PSG or a one-time questionnaire.

2. Polysomnography

The PSG is a multi-parametric test used as an objective measure of the biophysiological changes that occur during sleep. The PSG monitors many body functions, including brain (EEG), eye movement (EOG), muscle movement (EMG), heart activity (ECG, pulse oximetry), and respiratory function. PSG monitoring is often used to evaluate and quantify sleep pathologies such as apnea or periodic leg movement syndrome. However, the authors argue that PSG cannot serve as the sole outcome measure in clinical trials studying insomnia because participants with insomnia who have PSG-identified sleep disturbance are only a subset of people meeting the diagnostic criteria for insomnia (i.e., a set of self-reported symptoms) (American Psychiatric Association, 2000).

Methodological concerns also surround the use of the PSG; for example, it is only feasible in most cases to conduct PSG monitoring for one to three nights, which, as discussed above, may be insufficient to adequately capture the features of insomnia. Conditioned arousal is another concern with overnight PSG monitoring in sleep laboratories; because the participants are often conditioned to experience insomnia in their own bedrooms, they often sleep quite well in a laboratory setting where they are not conditioned to be aroused by the new surroundings. There is also evidence for a reverse first-night effect wherein sleep is worsened the first night, providing an overly negative impression of the patient's sleep. The following night, there would be increased pressure for REM sleep and/or increased pressure for delta sleep, and this night would provide another skewed view of the patient's typical sleep pattern. Again, this sleep sample is not representative of the individual's normal sleep experience. Expert consensus on PSG monitoring from this paper is that PSG monitoring cannot be considered the "gold standard" quantitative measure of insomnia against which other measures are judged and validated (Buysse et al., 2006). Still, when evaluating nocturnal HRV in addition to sleep

variables, PSG monitoring captures objective sleep measures that coincide in time with HRV measurements. Therefore, there is some advantage to using PSG to monitor sleep variables in addition to using sleep logs while concomitantly evaluating HRV.

Possible Candidates for Prediction of HRV in Insomnia

With a carefully screened sample of individuals with insomnia, what factors might be important to include in an investigation of the relationship between insomnia and cardiovascular risk? Certainly, with such a sample, there are many possible factors that can be examined; several important candidates are considered in the following paragraphs.

1) Age: Prevalence rates of insomnia have been shown to increase with age in most, but not all, epidemiological studies (Morin, LeBlanc, Daley, Gregoire, & Mérette, 2006; Morphy, Dunn, Lewis, Boardman, & Croft, 2007; Ohayon, 2002). One of the reasons for this increased prevalence is the increase in the rate of sleep-disordered breathing with age (Shahar et al., 2001). Additionally, chronic health problems are more common among older populations, and insomnia has been shown to be associated with chronic health issues (Buysse, 2004). Age is also an important factor when considering HRV. Studies have shown that there is an increased risk of cardiovascular disease with age independent of sleep (Jousilahti, Vartiainen, Tuomilehto, & Puska, 1999). It has also been found that HRV decreases linearly with age in both males and females (Bonnemeier et al., 2003; Umetani, Singer, McCraty, & Atkinson, 1998). Clearly, when studying insomnia and HRV, it is important to consider the effects of age.

2. Sex: Sex has also been shown to be a factor for both insomnia and HRV. Between menses and menopause, the risk for insomnia and depression is higher for women than for men (Krishnan & Collop, 2006). However, some researchers have argued that this difference can be explained by the increased rates of psychiatric illness in woman (specifically depression and

anxiety) and their association with insomnia (Voderholzer, Al-Shajlawi, Weske, Feige, & Riemann, 2003). Since this relationship remains unclear, it is important to consider sex differences in studies of insomnia. Differences due to sex have also been found in studies of HRV. Among newborns, boys have lower HRV than girls (Nagy, Orvos, Bárdos, & Molnár, 2000), and this difference has been found in several studies to be maintained throughout life (Antelmi et al., 2004; Bonnemeier et al., 2003). Research has not yet been able to explain why these differences in HRV exist between males and females; however, it is evident that sex plays a role in HRV and therefore should be considered in any HRV analysis.

3. Cognitive Arousal: Cognitive arousal might also be an important candidate to include in an investigation of HRV and sleep. As discussed above, the sympathetic and parasympathetic components of the ANS respond to environmental stimuli or stressors and contribute separately to modulate heart rate intervals (Rajendra, Paul, Kannathal, Lim, & Suri, 2006). When the sympathetic nervous system (SNS) is activated by a stressor, heart rate, blood pressure and cardiac output are increased and large muscular arteries and bronchioles are dilated, resulting in a physiological state of arousal (Curtis & O'Keefe, 2002). Worry has also been found to contribute to symptoms of insomnia, particularly the onset of insomnia and maintenance of the disorder (Brosschot et al., 2007). These findings are relevant to Harvey's cognitive model of insomnia, which implicates anxiety and distress as important factors that contribute to insomnia (Harvey, Tang, & Browning, 2005). Clearly, cognitive arousal is an important consideration when examining the relationship between insomnia and cardiovascular risk.

Study Rationale

There is mixed evidence for whether HRV relates to insomnia. Many of the existing trials that have investigated the link between insomnia and HRV have been epidemiological,

using few non-validated sleep items that are not necessarily indicative of primary insomnia (e.g. Phillips & Mannino, 2007) and may reflect occult sleep disorders, particularly breathing-relate sleep disorders. Few studies have used clinical samples to investigate this link (e.g. Spiegelhalder et al., 2001; Jurysta et al., 2009; Fang et al., 2008). The existing clinical studies have screened and excluded all comorbidity, which is not representative of a typical insomnia population. In fact, insomnia has been shown to be highly comorbid with many other medical and psychiatric disorders (Stewart et al., 2006; Taylor et al., 2007). Exclusion of comorbidity in studies evaluating the effects of insomnia on cardiovascular health would contribute little to this body of literature. In addition, the commonly used indices of HRV may not be most informative for examining the actual variation of heart rate across the night due to the amount of estimation rather than direct calculations involved in their measurement. Arguably, the HRV parameter chosen for this study (the coefficient of variation) is the best method to calculate actual variability in heart rate data rather than the most commonly used LF/HF ratio method, which relies on additional validation with measures of the degree of autonomic system activation. Findings from the present study will contribute to the literature by clarifying the link between insomnia and HRV in a large, well-characterized, representative experimental sample of individuals with insomnia with a measure of HRV that does not rely on estimation and additional validation.

Primary Hypothesis

Sleep disturbance as assessed by total wake time during the night will significantly predict HRV in a linear multiple regression equation above and beyond other variables (e.g., depression, anxiety, and worry) thought to be associated with HRV.

Method

Participants

Data for this study were collected by Dr. Colleen Carney and colleagues during the operation of the parent study, known as the Pickwick trial. Participants recruited for this trial were either outpatients seeking insomnia treatment or research volunteers participating in ongoing insomnia trials at two medical centers (Duke University Medical Center, Durham, NC and Rush Medical Center, Chicago, IL). Eligible participants were recruited into a larger diagnostic study (N = 163). To be included in this study, participants had to: be 18 years of age or older, fluent in English, mentally competent to provide informed consent, not currently hospitalized, not have a significant cognitive impairment, and had not been previously evaluated by any of the diagnostic study clinicians at the recruitment site. Individuals with clinically significant sleep apnea were excluded using the following criteria: apnea/hypopnea index score (AHI) ≥ 15, or AHI ≥ 5 on either of two overnight screening polysomnograms (PSG) with an accompanying self-reported Epworth sleepiness scale score ≥ 10. To exclude individuals with periodic limb movement (PLM) disorder, participants with a PLM arousal index (PLMAI) > 5 on either of two PSG nights were excluded. Participants whose primary diagnosis was restless leg syndrome or a circadian disorder were excluded. Considering these exclusions, the final sample consisted of 140 participants with insomnia.

Procedures

Participants were either individuals interested in insomnia treatment or research volunteers already participating in an ongoing insomnia trial. Interested participants initially contacted one of the two study sites. Lab coordinators conducted initial phone screens with all

potential participants to assess for basic entry criteria; eligible participants were scheduled for an in-lab screening procedure. The Mini Mental Status Exam was administered to assess competence to provide informed consent, which was gathered from all participants prior to any study activities. During the in-lab screen, participants were evaluated by trained Graduate level mental health professionals for current and past psychiatric disorders with the Structured Interview for Psychiatric Disorders for Diagnostic and Statistical Manual of Mental Disorders IV: Research Version. In addition, participants underwent a thorough medical exam by a physician to assess for physical disorders such as diabetes or cardiac disorders. Data from the medical exam was used to establish if participants had a current cardiac disorder or history of cardiac disorders. Next, participants were asked to record elements of their sleep over the following two weeks using electronic sleep logs. Objective measures of sleep were assessed during two consecutive nights of polysomnographic (PSG) monitoring. Participants who met criteria for insomnia after these procedures and did not satisfy the aforementioned exclusion criteria were asked to complete a battery of psychological questionnaires (described below).

The heart rate signal was obtained during PSG recordings on both nights of the overnight sleep study. Short-term epochs of 30 seconds in length were extracted from the ECG to analyze HRV. Epochs were chosen according to EEG sleep staging (assigned by trained raters and sleep experts Dr. Colleen Carney and Dr. Andrew Krystal, inter-rater reliability data available) to guarantee stationarity of the signal for spectral analysis. All 30-second epochs were visually inspected for artifacts or inaccurate detections, which were excluded to minimize error in HRV calculations. This step is necessary for the accuracy of the data; for example, if a participant were to turn over in bed, the rater would see an obscuring of heart data in that particular corresponding epoch, which contaminates the heart data. This step is also recommended by the

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, who are the leaders on HRV analysis (Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). The consequence of this procedure is that sample size is often decreased due to exclusion of participants whose ECG signal was excessively disrupted during the night, leaving an insufficient amount of data from which the computer program can calculate the coefficient of variation. It is also possible that the ECG leads from which the signal is derived were not properly positioned or came loose early, leaving no data to de-artifact. Thus, at this stage of the procedure, sample size was decreased.

After the raw HRV data was de-artifacted for each participant, it was analyzed in a program called DECODE, written in Visual Basic by colleagues at Duke University. This program calculated the coefficient of variation for each participant (the standard deviation of heart rate divided by the mean) for both NREM and REM sleep stages and across the entire night.

To assess for variables that are associated with HRV to include in the regression analyses, Spearman's correlations were run on several variables of interest that have been shown in previous studies to be related to heart rate or HRV. Among the variables included in this analysis were age, sex, expressed/suppressed anger (as assessed by the STAXI-II), anxiety as assessed by the BAI, depression as assessed by the BDI, cognitive arousal/worry as assessed by the PSWQ, and total wake time after sleep onset (WASO) and sleep onset latency (SOL) as assessed via both two-week sleep logs and PSG monitoring.

Information gathered from the correlational and t-test analyses were used to inform the primary hierarchical multiple regression analyses of the study. The number of predictors in

proportion to the sample size is an important factor in regression equations; therefore, due to the small sample size in this study, the number of predictors was kept to a minimum. The psychological variables with the highest correlation to HRV were entered into the analyses in step 1 of the regression models. The sleep disturbance variable that produced the model that accounted for the most variability in HRV was entered in the second step. The same regression model was replicated to predict NREM and REM HRV from both nights 1 and 2.

Measures

Mini-Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975): was administered to all participants to identify and exclude individuals with cognitive deficits that rendered them unable to give informed consent or to fully participate in the treatment process. The MMSE is widely used in assessment of cognitive impairment and has demonstrated good reliability and validity data (Mitrushina & Satz, 1991; Tombaugh & McIntyre, 1992). Individuals who obtained an MMSE < 24, the recommended cutoff score to indicate possible cognitive impairment, were excluded from the study (Kukull et al., 1994).

Structured Interview for Psychiatric Disorders for Diagnostic and Statistical Manual of Mental Disorders IV: Research Version (SCID-IV-TR; First et al., 2002): was used to screen participants for prior psychiatric conditions and comorbid Axis I psychiatric status.

Duke Structured Interview for Sleep Disorders (DSISD; Edinger et al., 2004): was administered to participants to discern various types of sleep disorders. It is a commonly used clinician-administered measure that assesses for various sleep disorders such as breathing pathology (e.g. apnea), leg movement disorders (e.g. periodic limb movement disorder) and parasomnias.

Sleep Logs: Subjective sleep estimates were obtained using a time-stamped, specifically programmed handheld computer. The Palm-Pilot® style electronic device contained an interactive program that automated the collection of subjective sleep data. Each morning upon rising, participants were asked to record information in the electronic sleep log, including bedtime, SOL, NWAK, TWT, and rising time. In addition, the program asked participants to rate the quality of their sleep and how rested they feel upon arising on a 10-point Likert scale. Participants were asked to record sleep log information in their handheld device for a two-week pre-interview assessment phase of the study. Estimates of TST, SOL, WASO, and SE were calculated from the electronic recordings.

Polysomnography (PSG): was employed to objectively assess sleep. Because previous HRV studies may have neglected occult sleep disorders, it is important to objectively check for undiagnosed leg or breathing pathology. All study participants completed two consecutive nights of polysomnographic (PSG) monitoring in the sleep laboratories of their respective study sites. The PSG monitoring montage included two channels of EEG, one chin EMG channel, two channels of EOG, one channel of airflow, two channels of respiratory effort, one channel of pulse oximetry, two channels of anterior tibialis EMG, and one channel of body position monitoring. The PSG also includes an electrocardiogram (ECG) signal, which is the present study's main measure of heart rate. All PSG recording devices were placed by trained certified technicians just prior to the participant's reported usual bedtime. Experienced sleep technicians scored all PSG records at computer reader stations using standard scoring criteria. Apneas and hypopneas were identified in the records using standard methods, and an apnea/hypopnea index (AHI) was calculated for each participant. Standard criteria were also used to identify periodic

limb movements and periodic limb movement-related arousals, and a movement-arousal index (PLMAI) was calculated.

Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988): was used to assess participants' level of anxiety. Carney and colleagues evaluated the utility of the BAI in an insomnia population. Their results indicated that the BAI includes nine items that contribute variance that is attributable to insomnia rather than to the construct of interest. Due to these important item limitations in the BAI, a modified version of the BAI was used wherein the non-discriminatory items identified by Carney et al. were excluded.

Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961): was used to assess depression. As with the BAI, it has been found that the BDI contains several items that do not discriminate between individuals with insomnia with and without depression (Carney, Ulmer, Edinger, Krystal, & Knauss, 2009). Items that did not discriminate between depressed and non-depressed insomnia patients (e.g., insomnia, irritability, decreased concentration, fatigue) overlap significantly with the daytime symptoms of insomnia (e.g., Edinger et al., 2004). The present analysis employed the BDI-II with the exclusion of the aforementioned non-discriminatory items that contribute unique variance attributable to insomnia rather than depression.

Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990): was used to assess cognitive arousal, that is, worry. The PSWQ is a commonly used and well-validated measure to assess the tendency to worry in adult populations (Brown, Antony, & Barlow, 1992).

State-Trait Anger Expression Inventory (STAXI-II; Spielberger, Sydeman, Owen, & Marsh, 1999): was used to assess anger expression and anger suppression. The STAXI-II

measures the intensity of anger as an emotional state (state anger) and the personality disposition to experience angry feelings (trait anger). Subscales from this measure were extracted to measure anger suppression and expression.

Heart Rate Variability: was calculated from continuous heart rate data collected during the overnight PSG. There are many ways to measure variations in heart rate, but to date, there are no universally accepted indices. The 1996 report by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology states that the method selected should correspond with the aim of the study (Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). The most commonly employed methods for measuring HRV include time and frequency domain methods, although there are other more complicated and thus less frequently utilized techniques as well.

The simplest method for measuring HRV uses time domain measures; with this method, using a continuous ECG recording, either the heart rate at any point in time or the intervals between successive normal complexes are determined. Simple time-domain variables can then be calculated, including the mean normal-to-normal (NN) interval, the mean heart rate, and the difference between the longest to shortest NN interval, etc. Statistical time-domain measures can be calculated from a series of instantaneous heart rates or cycle intervals, usually recorded over a longer period of time (traditionally 24 hours). Using this method, the simplest variable to calculate is the standard deviation of the NN interval (SDNN), which is mathematically equal to total power (variance) of spectral analysis, a frequency domain method to assess HRV explained below. Importantly, as the period of monitoring decreases, SDNN estimates shorter and shorter cycle lengths, and is thus dependent on the length of recording period. It is inappropriate in

practice to compare SDNN or other time-domain measures obtained from recordings of different durations (Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). Because the parent study did not employ uniform recording lengths for each participant, this method was not chosen to capture HRV.

Geometrical time-domain methods present RR intervals in geometric patterns from which a simple formula is used to judge the HRV based on the pattern. This method is highly insensitive to artifacts and ectopic beats (Rajendra et al., 2006) and is most accurate when heart rate is monitored over a 24 hour period (Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). Because the parent study only monitored heart rate overnight, this method was not used as a measure of HRV. All time-domain analyses lack the ability to discriminate between sympathetic and parasympathetic contributions of HRV.

Other analyses of HRV are conducted based on the spectrum of frequencies (oscillations) of the heart rate variability signal. Frequency domain analyses use various spectral methods to identify and measure the principal rhythmic fluctuations that characterize the RR interval time series. Power spectral density (PSD) analysis provides the basic information for how power (i.e. variance) distributes as a function of frequency (Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996). Short-term recordings are typically 2 to 5 minutes, and long-term recordings can be up to 24 hours.

The heart rate data collected from the parent study is best suited for analysis of HRV via the coefficient of variation (calculated by the standard deviation of heart rate divided by the mean), one of the two most commonly employed frequency domain analyses. This measure is simple to compute and intuitively simpler to understand; because we are interested in the

"variability" of heart rate, the coefficient of variation is a well-established, direct measure of variability. The other most popular method of measuring HRV, the ratio of LF power to HF power, relies on validation with measures of the degree of autonomic system activation. Therefore, this measure could actually reflect autonomic "tone" without being an indicator of the "variability" of heart rate. In addition, because this method includes a measure of power in the ultra-low frequency range, it relies on the data being stationary over a relatively long segment to yield a statistically viable estimate. For the parent study, HRV data is available during all sleep stages, requiring a measure of HRV that can be calculated using a shorter segment of stationary data. The coefficient of variation was chosen as the method used to calculate HRV because it was most appropriate and parsimonious for the requirements of the study (Krystal et al., 2002).

Statistical Analyses

All analyses were conducted using SPSS for windows version 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (i.e. mean, standard deviation, range, skewness, and kurtosis) were calculated for the variables of interest. Variables that violated the assumption of normality were transformed using a log transformation and re-checked for normality. Spearman's correlations were conducted among HRV variables and all other key variables, which were used to inform the regressions. A non-parametric test for correlations is used in sleep and HRV research (e.g. Hall et al., 1998; Hall et al., 2004) because even after transformations there is a tendency for several variables to deviate slightly from normality (see variables with an asterisk in Table 2). Though these variables were transformed using a log transformation and re-checked for normality, many of the variables, though within normal range (|2| and |7| for skewness and

kurtosis, respectively), violated the more conservative Kolmogorov-Smirnov test of normality. A visual inspection of these variables indicated approximately normal distributions.

Independent samples t-tests were conducted to test for simple group comparisons. Hierarchical linear multiple regression was used to explore the relative contribution of psychological covariates to HRV variables (REM HRV CV night 1, NREM HRV CV night 1, REM HRV CV night 2, NREM HRV CV night 2, and total mean HRV night 1 and night 2). Post hoc power analyses were conducted for all tests using an online effect size calculator and G* Power (Faul, Erdfelder, Lang, & Buchner, 2006, 2009). The critical alpha for these tests was set a priori at $\alpha = .05$. These tests were exploratory, and thus a statistical adjustment was not applied to account for the number of tests conducted.

Results

Preliminary Analyses

Assumption of Normality. Prior to conducting the primary analyses, the data were screened for violations of the normality assumption. An inspection of the heart rate coefficients of variability (CV) for REM and non-REM sleep for nights one and two revealed that three of four distributions were approximately normal, with skewness and kurtosis values within the normal ranges of |2| and |7|, respectively (West, Finch, & Curran, 1995). The coefficient of variability for REM night one did not fall within these parameters and was transformed using a log transformation. The distribution was re-checked to ensure that the distribution approximated normal.

Further investigations of normality were conducted on the remaining predictor and covariate variables. Many of these variables also violated the assumption of normality and so

were transformed via a log transformation and re-examined. The transformed variables are indicated with an asterisk in Table 2; raw data before transformation is displayed for ease of comparison.

Participant demographic characteristics are displayed in Table 1. Characteristics of the variables of interest are displayed in Table 2.

Table 1

Participant Demographics

Variables	Proportion (%)	n
Sex		
Female	70.3	45
Male	25.0	16
Ethnicity		
Caucasian	65.6	40
African American	26.2	16
American Indian	1.6	1
Asian American	1.6	1
Other	4.9	3

Table 2

Descriptive Characteristics of Study Variables

Variables	Mean	SD	Minimum	Maximum	Range
Outcome					
REM CV 1*	.066	.027	.029	.130	.101
NREM CV 1	.057	.021	.020	.112	.092
REM CV 2	.067	.026	.022	.123	.101
NREM CV 2	.063	.023	.034	.115	.081
Predictor					
BAI total*	18.83	13.43	0.0	35.0	35.0
BDI total*	15.26	12.22	0.0	56.0	56.0
Trait Anger	18.13	5.67	10.0	35.0	25.0
Anger Suppression	17.0	5.70	3.0	30.0	27.0
Diary mean SOL* (minutes)	47.11	37.11	9.44	143.67	134.22
Diary mean TWT* (minutes)	120.43	66.91	30.39	326.31	295.92
PSG SOL night 1* (minutes)	42.73	50.65	0.0	210.5	210.5
PSG TWT night 1* (minutes)	55.4	45.34	4.0	207.0	203.0
PSG SOL night 2* (minutes)	30.25	27.26	2.5	120.00	117.5
PSG TWT night 2* (minutes)	43.12	32.76	6.0	152.5	146.5
PSWQ	46.57	19.4	10.0	86.0	76.0
Age	49.50	13.47	18.0	81.0	63.0

Note. Variables with an asterisk (*) were transformed via a log transformation to satisfy the assumption of normality. CV = Coefficient of Variation, BAI = Beck Anxiety inventory, BDI = Beck Depression Inventory, SOL = Sleep Onset Latency, TWT = Total Wake Time, PSG = Polysomnogram, PSWQ = Penn State Worry Questionnaire.

Correlations

Before conducting the main regression analyses, Spearman's correlations were calculated for the variables of interest to assess for relationships between variables that might inform the regressions. The Penn State Worry Questionnaire (PSWQ) score emerged as having a significant association with the heart rate coefficients of variability. Depression as assessed by the BDI was found to be significantly associated with NREM HRV during night 1, and therefore was also chosen to be included as a psychological predictor in the main regression analyses. Correlations are displayed in Tables 3-6.

Table 3

Correlations between REM HRV Coefficient of Variability Night 1 and Predictors

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. REM CV night 1	1.00											
2. Age	.01 p = .95	1.00										
3. BDI	-.07 p = .67	.23 p = .15	1.00									
4. BAI	.07 p = .71	-.13 p = .41	.48* p = .00	1.00								
5. PSWQ	.32* p = .05	-.11 p = .48	.52* p = .00	.56* p = .00	1.00							
6. Trait Anger	.04 p = .84	.06 p = .69	.12 p = .47	.14 p = .39	.48* p = .00	1.00						
7. Anger Expression	-.08 p = .65	.12 p = .45	.65* p = .00	.36* p = 03	.60* p = .00	.50* p = .00	1.00					
8. Anger Suppression	-.11 p = .53	.07 p = .66	.63* p = .00	.38* p = .01	.59* p = .00	.42* p = .01	.99* p = .00	1.00				
9. Mean log TWT	-.28 p = .10	.27 p = .09	.14 p = .39	.05 p = .74	-.21 p = .19	-.10 p = .54	.09 p = .60	.040 p = .81	1.00			
10. Mean log SOL	.08 p = .63	.13 p = .40	.27 p = .09	.30 p = .06	.22 p = .16	.28 p = .08	.12 p = .45	.07 p = .67	.17 p = .28	1.00		
11. PSG SOL night 1	.06 p = .76	.15 p = .37	.15 p = .39	.17 p = .30	.21 p = .21	.17 p = .31	.29 p = .09	.24 p = .16	.14 p = .40	.28 p = .09	1.00	
12. PSG TWT night 1	-.05 p = .79	.41* p = .01	.03 p = .85	-.01 p = .94	-.22 p = .18	.06 p = .74	.05 p = .76	-.02 p = .93	.33* p = .04	.20 p = .22	0.00 p = .99	1.00

Note. * indicates that correlation is significant at the 0.05 level (2-tailed).

Table 4

Correlations between NREM HRV Coefficient of Variability Night 1 and Predictors

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. NREM CV night 1	1.00											
2. Age	-.19 p = .25	1.00										
3. BDI	-.32* p = .05	.23 p = .15	1.00									
4. BAI	-.10 p = .55	-.13 p = .41	.48* p = .00	1.00								
5. PSWQ	-.07 p = .70	-.11 p = .48	.52* p = .00	.56* p = .00	1.00							
6. Trait Anger	-.09 p = .61	.06 p = .69	.12 p = .47	.14 p = .39	.48* p = .00	1.00						
7. Anger Expression	-.22 p = .19	.12 p = .45	.65* p = .00	.36* p = .03	.60* p = .00	.50* p = .00	1.00					
8. Anger Suppression	-.24 p = .15	.07 p = .66	.63* p = .00	.38* p = .01	.59* p = .00	.42* p = .01	.99* p = .00	1.00				
9. Mean log TWT	-.23 p = .16	.18 p = .09	.14 p = .39	.05 p = .74	-.21 p = .19	-.10 p = .54	.09 p = .60	.04 p = .81	1.00			
10. Mean log SOL	-.01 p = .93	.13 p = .40	.27 p = .09	.30 p = .06	.22 p = .16	.28 p = .08	.12 p = .45	.07 p = .67	.17 p = .28	1.00		
11. PSG SOL night 1	-.05 p = .78	.15 p = .37	.15 p = .39	.17 p = .30	.21 p = .21	.17 p = .31	.29 p = 09	.24 p = .16	.14 p = .40	.28 p = .09	1.00	
12. PSG TWT night 1	.08 p = .64	.41* p = .01	.03 p = .85	-.01 p = .93	-.22 p = .18	.05 p = .74	.05 p = .76	-.02 p = .93	.33* p = .04	.20 p = .22	0.00 p = .99	1.00

Note. * indicates that correlation is significant at the 0.05 level (2-tailed).

Table 5

Correlations between REM HRV Coefficient of Variability Night 2 and Predictors

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. REM CV night 2	1.00											
2. Age	-.03 p = .88	1.00										
3. BDI	.30 p = .10	.23 p = .15	1.00									
4. BAI	.26 p = .16	-.13 p = .41	.48* p = .00	1.00								
5. PSWQ	.42* p = .02	-.11 p = .48	.42* p = .00	.56* p = .00	1.00							
6. Trait Anger	.06 p = .76	.06 p = .69	.12 p = .47	.14 p = .39	.48* p = .00	1.00						
7. Anger Expression	.35 p = .07	.12 p = .45	.65* p = .00	.36* p = .03	.60* p = .00	.50* p = .00	1.00					
8. Anger Suppression	.32 p = .08	.07 p = .66	.63* p = .00	.38* p = .01	.59* p = .00	.42* p = .01	1.00* p = .00	1.00				
9. Mean log TWT	-.20 p = .28	.18 p = .27	.28 p = .07	.26 p = .09	.02 p = .89	.10 p = .55	.13 p = .43	.08 p = .60	1.00			
10. Mean log SOL	.01 p = .95	.13 p = .40	.27 p = .09	.30 p = .06	.22 p = .16	.28 p = .08	.12 p = .45	.07 p = .67	.67* p = .00	1.00		
11. PSG SOL night 2	.26 p = .19	.30 p = .09	.25 p = .16	0.00 p = .98	.10 p = .58	-.14 p = .45	.08 p = .68	.04 p = .85	.19 p = .29	.16 p = .38	1.00	
12. PSG TWT night 2	-.06 p = .81	-.08 p = .72	.06 p = .70	-.21 p = .32	-.15 p = .48	-.33 p = .12	-.19 p = .38	-.19 p = .38	-.22 p = .29	-.19 p = .38	.12 p = .67	1.00

Note. * indicates that correlation is significant at the 0.05 level (2-tailed).

Table 6

Correlations between NREM HRV Coefficient of Variability Night 2 and Predictors

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. NREM CV night 2	1.00											
2. Age	-.08 p = .65	1.00										
3. BDI	-.11 p = .54	.23 p = .15	1.00									
4. BAI	-.12 p = .51	-.13 p = .41	.48* p = .00	1.00								
5. PSWQ	-.05 p = .78	-.11 p = .48	.52* p = .00	.56* p = .00	1.00							
6. Trait Anger	-.10 p = .57	.06 p = .69	.12 p = .47	.14 p = .38	.48* p = .00	1.00						
7. Anger Expression	.03 p = .86	.12 p = .45	.65* p = .00	.36* p = .03	.60* p = .00	.50* p = .00	1.00					
8. Anger Suppression	.02 p = .93	.07 p = .66	.63* p = .00	.38* p = .01	.59* p = .00	.42* p = .01	1.00* p = .00	1.00				
9. Mean log TWT	-.08 p = .66	.18 p = .27	.28 p = .07	.26* p = .09	.02 p = .89	.10 p = .55	.13 p = .43	.08 p = .60	1.000			
10. Mean log SOL	.03 p = .87	.13 p = .40	.27 p = .09	.30 p = .06	.22 p = .16	.28* p = .08	.12 p = .45	.07 p = .67	.67* p = .00	1.000		
11. PSG SOL night 2	.27 p = .14	.30 p = .16	.25 p = .16	0.00 p = .98	.10 p = .58	-.14 p = .45	.08 p = .68	.04 p = .85	.19 p = .29	.16 p = .38	1.000	
12. PSG TWT night 2	.20 p = .40	-.08 p = .78	.06 p = .78	-.21 p = .32	-.15 p = .48	-.34 p = .12	-.19 p = .38	-.19 p = .38	-.22 p = .30	-.19 p = .38	.11 p = .67	1.000

Note. * indicates that correlation is significant at the 0.05 level (2-tailed).

T-Tests

In order to assess for group differences, some preliminary t-tests were conducted on different groupings of the heart rate coefficient of variation variables.

Independent samples t-tests were conducted to compare all HRV coefficients of variability variables between males and females. The results of Levene's test revealed that equal variances could be assumed. The t-test analyses revealed no significant difference in mean HRV coefficients of variability across REM and NREM sleep stages for either night 1 or night 2 (see Table 7). Males and females were also compared on their mean HRV coefficients of variability for all of night one and two (combined REM and NREM sleep). Again, these tests revealed no difference in HRV between males and females.

An independent samples t-test was run to test for mean HRV coefficients of variability differences between participants with a lifetime diagnosis of major depressive disorder (MDD) and participants with no history of MDD. For each of the HRV coefficients of variability and for mean HRV across both nights, no mean differences were found (see Table 8).

The same independent samples t-tests were also run to compare participants diagnosed with any current anxiety disorder to participants with no anxiety disorder diagnosis. A difference was found for REM CV night 2 between current anxiety disorder (M = .088 SD = .020) and no current anxiety disorder (M = .062, SD = .026; $t(30) = -2.686$, $p = .01$, $d = 1.09$). No other group differences were found (see Table 9). Because of this significant result for anxiety groups during REM night 2, anxiety as assessed by the BAI was included in the regression analyses as a potentially important psychological predictor of HRV.

To compare mean HRV for participants having used sleep medications within the past month (as determined by the study physician during the physical examination) and participants

having used no sleep medications within the past month, another independent samples t-test was conducted. No group differences were found for any of the main HRV variables or for the mean HRV CV for nights 1 or 2 with combined REM and NREM sleep (results are displayed in Table 10).

A final set of independent samples t-tests were conducted to test for mean differences on all HRV variables for participants diagnosed with either a cardiac disorder or no cardiac disorder diagnosis as assessed during the physical exam by the study physician. Conditions that qualified as "cardiac disorders" were: high blood pressure, high cholesterol, heart valve problems, heart palpitations, any previous myocardial infarction, angina, chest pain, stroke, or blood clots. No group differences were found on any of the HRV variables or on mean HRV across sleep conditions for night 1 and 2 (results displayed in Table 11).

Table 7

Mean Heart Rate Variability Coefficients of Variability for Males and Females

	Gender				*t*	df	*p*	*d*
	Females		Males					
	M	SD	M	SD				
REM HRV CV night 1	.071	.027	.064	.029	.763	34	.45	.260
NREM HRV CV night 1	.059	.022	.056	.017	.384	36	.70	.151
REM HRV CV night 2	.066	.026	.072	.019	-.551	29	.59	-.258
NREM HRV CV night 2	.059	.021	.069	.019	-1.37	32	.18	-.504
Total mean HRV CV night 1	.065	.023	.061	.021	.541	34	.59	.184
Total mean HRV CV night 2	.063	.021	.071	.023	-.941	32	.35	-.382

Note. *d* = Cohen's *d*, a measure of effect size.

Table 8

Mean Heart Rate Variability Coefficients for Participants with a Lifetime Diagnosis of Major Depressive Disorder vs. No Diagnosis

	Lifetime MDD Diagnosis				*t*	df	*p*	*d*
	Yes		No					
	M	SD	M	SD				
REM HRV CV night 1	.064	.021	.074	.034	1.06	21.63	.30	-.381
NREM HRV CV night 1	.054	.018	.064	.022	1.71	37	.10	-.454
REM HRV CV night 2	.065	.023	.074	.031	.977	30	.34	-.359
NREM HRV CV night 2	.060	.024	.068	.020	1.041	33	.31	-.384
Total mean HRV CV night 1	.059	.018	.070	.027	1.38	22.32	.18	-.513
Total mean HRV CV night 2	.063	.022	.071	.023	1.08	33	.29	-.390

Note. *d* = Cohen's *d*, a measure of effect size.

Table 9

Mean Heart Rate Variability Coefficients for Participants with a Current Anxiety Disorder Diagnosis vs. No Diagnosis

	Current Anxiety Disorder				*t*	df	*p*	*d*
	Yes		No					
	M	SD	M	SD				
REM HRV CV night 1	.079	.026	.064	.027	-1.559	35	.13	.577
NREM HRV CV night 1	.064	.014	.056	.023	-1.091	37	.28	.388
REM HRV CV night 2	.088	.020	.062	.026	-2.686	30	.01*	1.094
NREM HRV CV night 2	.066	.020	.062	.023	-.461	33	.65	.185
Total mean HRV CV night 1	.072	.018	.061	.023	-1.371	35	.18	.518
Total mean HRV CV night 2	.075	.018	.063	.023	-1.483	33	.15	.568

Note. *d* = Cohen's *d*, a measure of effect size.
* indicates significance at $p < .05$.

Table 10

Mean Heart Rate Variability Coefficients for Participants With a Current Cardiac Disorder vs. No Cardiac Disorder

	Current Cardiac Disorder				*t*	df	*p*	*d*
	Yes		No					
	M	SD	M	SD				
REM HRV CV night 1	.072	.032	.067	.026	-.500	35	.62	.187
NREM HRV CV night 1	.058	.024	.058	.019	-.048	37	.96	0
REM HRV CV night 2	.077	.024	.065	.028	-1.187	30	.25	.461
NREM HRV CV night 2	.066	.020	.062	.023	-.443	33	.66	.186
Total mean HRV CV night 1	.065	.028	.063	.020	-.249	35	.80	.041
Total mean HRV CV night 2	.072	.019	.064	.024	-1.04	33	.31	.365

Note. *d* = Cohen's *d*, a measure of effect size.

Table 11

Percent of Time Spent in REM Sleep Night 1 vs. Night 2

% of Time Spent in REM Sleep				*t*	df	*p*	*d*
Night 1		Night 2					
M	SD	M	SD				
17.7	.08	20.2	.06	-2.267	47	.028	-.357

Note. *d* = Cohen's *d*, a measure of effect size.
* indicates significance at p < .05.

Primary Analyses

Regressions

Hierarchical linear multiple regression analyses were used to examine the predictive value of sleep variables and select psychological variables that were shown to be associated with HRV via the preliminary correlation and independent t-test analyses. To predict each main HRV coefficient of variability (REM night 1, NREM night 1, REM night 2, NREM night 2), psychological variables were entered in the first step of the regression: BDI, BAI, and worry (PSWQ score). Worry was found in the correlation analyses to be most highly associated with HRV variables, particularly with REM HRV. Total wake time after sleep onset as measured by the PSG was entered in step 2 of the regression equation to investigate if sleep problems significantly predict HRV beyond the psychological variables. For all variables in each model, the Tolerance values were >0.10 and the Variance Inflation Factor (VIF) values were <10.0, which excluded multicollinearity. Results from these regression analyses are depicted in Tables 12-15.

A significant regression model emerged using the above variables to predict REM CV night 2; adjusted $R^2 = .41$, $F(4) = 3.367$, $p = .04$ (see Table 14). Regression models predicting REM CV night 1 and NREM CV's nights 2 and 3 failed to reach significance. In all models, sleep disturbance as measured by PSG total wake time after sleep onset (TWT) failed to contribute statistically significant unique variance to each of the four regression models (see Tables 12, 13, and 15.

Table12

Hierarchical Multiple Regression Analyses Predicting Night 1 REM HRV Coefficient of Variability from Worry, Anxiety, Depression, and Sleep Disturbance.

	Model Outcome					
Predictor	ß	*p*	Adjusted R^2	F	ΔF	*p* of model
Step 1			.055	1.63		.21
BAI	-.255	.23				
BDI	-.153	.45				
PSWQ	.434	.04*				
Step 2			.043	1.36	.64 (n.s.)	.27
BAI	-.263	.22				
BDI	-.191	.36				
PSWQ	.458	.04*				
TWT	.143	.43				

Note. * indicates $p < .05$

Table 13

Hierarchical Multiple Regression Analyses Predicting Night 1 NREM HRV Coefficient of Variability from Worry, Anxiety, Depression, and Sleep Disturbance.

	Model Outcome					
Predictor	ß	*p*	Adjusted R^2	F	ΔF	*p* of model
Step 1			.092	2.14		.12
BAI	-.118	.57				
BDI	-.419	.04*				
PSWQ	.246	.23				
Step 2			.112	2.08	1.73 (n.s.)	.11
BAI	-.129	.53				
BDI	.475	.02*				
PSWQ	.290	.16				
TWT	.220	.20				

Note. * indicates $p < .05$

Table 14

Hierarchical Multiple Regression Analyses Predicting Night 2 REM HRV Coefficient of Variability from Worry, Anxiety, Depression, and Sleep Disturbance.

	Model Outcome					
Predictor	ß	p	Adjusted R^2	F	ΔF	*p* of model
Step 1			.409	4.46		.03*
BAI	-.245	.417				
BDI	.414	.126				
PSWQ	.590	.06				
Step 2			.413	3.64	1.08 (n.s.)	.04*
BAI	-.203	.51				
BDI	.469	.09				
PSWQ	.510	.11				
TWT	-.216	.32				

Note. * indicates $p < .05$

Table 15

Hierarchical Multiple Regression Analyses Predicting Night 2 NREM HRV Coefficient of Variability from Worry, Anxiety, Depression, and Sleep Disturbance.

	Model Outcome					
Predictor	ß	p	Adjusted R^2	F	ΔF	*p* of model
Step 1			.068	1.41		.28
BAI	-.660	.07				
BDI	.323	.29				
PSWQ	.198	.57				
Step 2			.005	1.02	.112 (n.s.)	.43
BAI	-.673	.08				
BDI	.300	.35				
PSWQ	.241	.53				
TWT	.087	.74				

Discussion

The expectation that the degree of sleep disruption (i.e., combined sleep diary and overnight PSG total wake time) would be independently associated with HRV was not supported. In both the correlational and hierarchical multiple regression analyses, sleep variables SOL and WASO as assessed by both sleep logs and PSG were not found to be significantly associated with HRV. The results suggest that sleep disturbance actually may not be important to HRV. Perhaps these results are not so surprising given that the evidence for the link between HRV and insomnia has been mixed. Also, in studies showing a link, there have been methodological limitations that cast doubt on whether the effects are actually due to other sleep or psychiatric disorders, such as an anxiety disorder or major depression.

A particular strength of the present study in comparison to previous research is the extensive medical and psychological characterization of participants. Thus, it is possible in this study to conduct some comparisons that may not have been possible in a study that employed extensive exclusion criteria rather than characterization. In the present study, a series of independent samples t-tests were conducted to explore, in a sample of individuals with insomnia, the results of previous studies that have shown that anxiety is associated with heart rate and heart rate variability (e.g. Dishman et al., 2000; Gorman & Sloan, 2000; Licht, Geus, Dyck, & Penninx, 2009). Participants with a current anxiety disorder diagnosis were compared to participants with no anxiety disorder diagnosis on key HRV variables (see Table 9). A significant difference was found between the two groups on REM HRV night 2, indicating that participants with a current anxiety disorder had a significantly higher HRV coefficient of variation. The effect size as calculated by Cohen's $d = 1.09$ indicates that this mean difference carries a large effect (a discussion of effect size and power is found below). This finding is

somewhat counterintuitive, as research has shown that higher HRV is generally indicative of a healthier heart (e.g. Colhoun, Francis, Rubens, Underwood, & Fuller, 2001). Thus, a higher HRV would not be expected in individuals with an anxiety disorder. However, we must bear in mind that this is a sample with no healthy comparison group; as such, both groups may actually exhibit elevated HRV. Also, to date, no normative data exists for HRV during sleep from which to compare the mean HRV coefficients of variation in the sample. Alternatively, it is possible that elevated levels of anxiety are actually beneficial to HRV in an insomnia sample. To date, there is not enough evidence to conclude that anxiety in insomnia leads to a beneficially increased HRV; however, this may be an interesting avenue for future research.

Due to the continuous overnight heart rate monitoring employed in this study, it is also possible to compare HRV between REM and NREM sleep. Some studies only use short monitoring periods; thus, drawing conclusions about differences between stages of sleep may not be possible or valid. An examination of the results of the present study suggests that there may be important differences between REM and NREM sleep and between nights 1 and 2. The only significant regression model was found when the independent variable was night 2 REM HRV (see Table 15). In this model, the combination of anxiety, depression, and worry accounted for 41% of the variance in HRV. Each of the three other regression models predicting HRV from REM night 1 and NREM nights 1 and 2 did not explain more than 11% of the variance in HRV. It is difficult to speculate as to why night 2 REM HRV produced the only significant model when all models included the same combination of predictor variables. A visual inspection of the spread of the HRV key variables did not suggest the influence of an outlier. Interestingly, a post-hoc paired samples t-test on percent of time spent in REM sleep during nights 1 and 2 indicated that significantly more REM sleep occurred during night 2 ($t(47) = -2.267$, $p < .05$).

This increase in time spent in REM sleep is suggestive of 'REM pressure.' REM pressure is a compensatory mechanism that is activated when there has been some REM sleep deprivation the prior night. When there is REM sleep deprivation, pressure for REM sleep increases, and the following night, greater amounts or higher density of REM sleep occurs. REM pressure is relevant in this context when the disruption of spending the first night in a sleep laboratory deprives people of sleep, more specifically REM sleep (Pigeon & Perlis, 2006). Indeed the REM percentage of the first night was below adult normative data (<20%). Consequently, the following night, there was an increased drive for REM sleep. Thus, it is possible that the significant results were found only during the second night because there was more REM sleep during which the autonomic effects of worry could be detected.

Spectral analysis studies of HRV have shown that there are important differences in REM vs. NREM sleep in terms of autonomic activity. Sympathetic modulation is decreased throughout NREM sleep, while SNS modulation actually increases during REM sleep. The converse has been found for parasympathetic modulation of REM and NREM sleep (Baharav et al., 1995; Busek et al., 2005; Vaughn, Quint, Messenheimer, & Robertson, 1995). In the correlational analyses, worry was found to be positively associated with HRV during REM sleep only. In addition, worry was an element of a significant model predicting REM HRV in combination with the other variables (anxiety, depression, and TWT). Though it is true that there is some overlap between variables, it warrants discussion that worry, though it failed to reach significance (p= 0.06) had a fairly large beta value (.6). Due to the small sample size, it is possible that power issues may be hampering this beta weight associated with worry. The beta weights associated with the other variables were much lower. Nonetheless, these findings are consistent with conclusions in the literature that have emphasized worry's importance to HRV

and its interaction with the relative sympathetic dominance of REM vs. NREM sleep. Worry has been postulated to be negatively influential to HRV and, subsequently, cardiovascular health by decreasing HRV during sleep due to withdrawal of parasympathetic inhibitory action, which is normally controlled by the prefrontal cortex (Brosschot et al., 2007). During worry states characterized by vigilance and arousal, priority may be given to these cognitive processes. Thus, inhibition of the SNS from the prefrontal cortex is withdrawn, and sympathetic dominance prevails. Previous research has shown that normal participants were found to have lower HRV that was related to worry and stress during waking and the subsequent sleep period. Worry duration was found to mediate the effects of the stressors. Under sustained periods of time, sympathetic dominance may be pathogenic to the heart, resulting in decreased HRV.

In the present study, it is possible that the same association between worry and HRV were not found during NREM sleep because NREM reflects relative parasympathetic dominance with which worry does not interact as strongly. Similar results were found in a study evaluating the effect of acute stress (standard speech task paradigm); acute stress was associated with decreased levels of parasympathetic modulation reflected in HRV during REM sleep but also during the night as a whole (Hall et al., 2004). Interestingly, this larger (N = 59) study found that elevated levels of sympathovagal balance (determined by spectral analysis of HRV) during NREM sleep were modestly associated with decreases in sleep maintenance and deep sleep as measured by wakefulness during sleep and automated delta counts, respectively. The present study did not find that sleep variables (including wakefulness during sleep) were significantly associated with HRV. This discrepancy may be a power issue due to the smaller sample size of the current study. It is also a possibility that modest changes in sleep maintenance associated with HRV are more distinct in a normal sample rather than an insomnia sample.

As described above, previous findings suggest that duration of worry is an important factor when considering its bearing on HRV. Longer duration of worry prolongs the sympathetic dominance of the SNS, impacting heart rate and beat-to-beat variability. In the present study, worry duration was not assessed; therefore, it is possible that participants' average worry duration was not long enough to cause a significantly negative effect on HRV. Alternatively, it is possible that in individuals with insomnia, worry in nonpathological amounts may actually be beneficial to HRV. Indeed, the average PSWQ score of participants in the present study was below the commonly used cutoff of 65 for clinically significant worry (Fresco, Mennin, Heimberg, & Turk, 2003). Thus, the present sample exhibited elevated but nonpathological worry. The relationship between worry and HRV is a puzzling one, as other studies outside of insomnia have found that pathological amounts of worry have had a deleterious effect on HRV (i.e. decreased HRV). However, it bears mention that the use of HRV as a proxy measure of heart health has not yet been well-validated. Thus, it is not yet known if HRV should be expected to be the same or different across disorders, ages, and measurement techniques. Consequently, to date, conclusions from studies that utilize HRV should be drawn with caution.

Findings from this study suggest that an association does not exist between sleep disturbance and heart rate variability. Thus, insomnia may not actually have an effect on cardiovascular health. Clinically, this implication is relevant to individuals presenting with insomnia; the sleep disturbance itself does not appear to be harmful to cardiovascular health. Consequently, treatment providers might ease patient fears about the negative health consequences of insomnia. Rather, the evidence herein points to psychological factors such as worry and anxiety that may exert influence on HRV, though it is yet unclear through which mechanisms these factors may be beneficial or harmful in an insomnia population.

Another possible explanation for not finding a sleep-HRV link may relate to potential power problems. Anxiety as assessed by the BAI (nondiscriminatory sleep items removed) was not significantly associated with HRV, though it has been shown to be consistently associated with HRV in the literature (see the Introduction). This finding may be due to lack of power to detect significant effects among these variables. A power calculation conducted on the widely used computer program G*Power (Faul, Erdfelder, Lang, & Buchner, 2006, 2009) indicates that a sample size of n = 112 is necessary to detect a significant effect with a conventional power of .8, alpha level of .05 (two tailed), and correlation coefficient of .26 (found between the BAI and REM HRV night 2). The actual sample size for this comparison was 31; thus, in light of low power, we must interpret this nonsignificant finding cautiously. In addition, no significant differences were found between males and females on any of the HRV CV variables, including total HRV for nights 1 and 2 (see Table 7). A post-hoc power analysis revealed that these analyses may have also been underpowered; the largest effect size was calculated for NREM night 2 (Cohen's d = -.504, a medium effect). With an effect of this magnitude, an alpha level of .05 and power of .8, a sample size of n = 120 is required to detect such an effect. Though the parent Pickwick trial remains the largest, most well-characterized insomnia study to date, in an investigation of heart rate variability, there are many factors that negatively influence sample size. For example, the n for night 2 decreased substantially from the n for night 1, as some participants did not complete the night 2 overnight sleep study. The necessary practice of de-artifacting the ECG data to exclude errors in the heart rate signal also decreased the sample size. Thus, when examining the results of this trial, it is important not only to consider the results of a Fisherian test but also to consider effect sizes. Effect size is often considered to be more informative than *p* values by statisticians in the behavioural sciences because they reflect actual

clinical significance (Kazdin & Bass, 1989). Cohen proposes conventional use of standard effect sizes when reporting scientific results. For a t-test of two independent means, a small but not trivial effect size would be .20, a medium effect size .50, and a large effect size .80 (Cohen, 1992).

There are additional possible caveats to the study's findings. For example, heart rate variability is affected by mechanisms other than those studied in this trial. Activity level has been shown to influence HRV, with increased activity resulting in increased HRV (Levy et al., 1998; Malfatto et al., 1996). Unfortunately, activity level was not assessed in the parent trial and therefore cannot be included in the present study. Though it would be useful to include all of the mechanisms that can affect HRV in this type of study, it is neither feasible nor necessary to include every mechanism in order to evaluate the importance of others.

Another possible limitation of this study is that the chosen measure to depict HRV, the coefficient of variation (CV), has a restricted range (|1|). The mean HRV values assessed in this study across nights and sleep periods was even more restricted, with an average range of .09 (see Table 1). A restriction of range is known to influence correlations, which could bias a regression analysis (Wiseman, 1967). The mean HRV CV data in the present sample (mean = .06 for all CV variables) is the same as that reported in a paper evaluating normal values for HRV in healthy adults (Nunan, Sandercock, & Brodie, 2010), however, it is difficult to know if these norms apply because this sample was not studied overnight and they were not screened for sleep and other disorders. Although the values found in the current sample do not deviate from the norm, it is unclear if they are valid approximations of the population; thus, restricted range of values for HRV may be a limitation of the study. Finally, because HRV was continuously assessed over 8 hours unlike most HRV protocols, which only sample HRV for short five-minute

segments, the sampling rate (i.e. heart rate detection rate) was lower in the present study. However, as it was considered more important to measure HRV over the entire nocturnal period than to have a higher sampling rate in the present study, a lower sampling rate is acceptable.

Implications

This is the largest, most thoroughly assessed insomnia and HRV study to date. The results suggest that worry in an insomnia population might relate to HRV, while symptoms of insomnia do not relate to HRV. The conclusions drawn from the results of this study are potentially important because to date, the body of knowledge surrounding insomnia and cardiovascular risk has been largely from epidemiological studies that include one or two items targeting sleep that do not specifically implicate insomnia over other occult sleep disorders that have known effects on cardiovascular health. The sample of the parent study from which the present study is based is a thoroughly well-classified, large sample of individuals with insomnia with the exclusion of occult sleep disorders (e.g. apnea, hypopnea). It is the best clinical sample to date from which researchers can study insomnia and its implications and associated factors. Thus, results from the present study contribute to the body of literature surrounding insomnia and cardiovascular risk because they are more generalizeable to a true insomnia population. Previous studies of insomnia and HRV have had methodological problems that might partially explain the discrepancies between the present study and those in the literature. As discussed, insomnia is a highly comorbid condition (Stewart et al., 2006; Taylor et al., 2007). Previous studies have often excluded all comorbidity in an attempt to evaluate HRV in insomnia (e.g. Spiegelhalder et al., 2011). Thus, these studies may not be generalizeable to a true insomnia population. Many of the existing HRV and insomnia or sleep studies have also employed varying methods for evaluating HRV, often via spectral analysis, which relies on estimations of

electrical input from the autonomic nervous system. Unfortunately, this method is an indirect way to assess HRV. The measure used to evaluate HRV in the present study, the coefficient of variation, is a direct method of assessing beat-to-beat variation in heart rate. Thus, it is a more accurate picture of true heart rate variability. Finally, another methodological problem of previous studies involves the period of time employed to assess HRV. Some trials have assessed HRV in small segments as opposed to an all-night measurement of HRV (e.g. Fang et al., 2008). An all-night assessment of HRV is obviously a much more accurate depiction of HRV during the night than inferring nocturnal HRV from short segments of measurement. Thus, findings from this study suggest that insomnia and HRV are not related except through possible worry mediation.

Future Directions

The results of this exploratory study stimulate new questions in the field of HRV and insomnia. It was found in the present study that sleep variables do not appear to predict HRV above and beyond psychological variables. In future trials, it would be informative to follow a similarly well-classified sample of insomnia participants and a healthy comparison group longitudinally to evaluate cardiovascular disease later in life. To date, the risk of cardiovascular disease due to insomnia is still unclear. However, the results of this study indicate that it may not be specific indices of sleep disturbance per se that affects cardiovascular health but rather the psychological cognitive processes that often accompany insomnia, such as worry, that result in potentially enhanced or poorer cardiovascular outcomes.

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