Predicting Response to Stepped-Care Cognitive Behavioral Therapy for Insomnia (CBT-I) Using Pre-Treatment Heart Rate Variability (HRV) in Cancer Patients

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Abstract

Predicting Response to Stepped-Care Cognitive Behavioral Therapy for Insomnia (CBT-I) Using Pre-Treatment Heart Rate Variability (HRV) in Cancer Patients

James Garneau

Objective: This longitudinal study examined whether high frequency heart-rate variability (HF-HRV) and HF-HRV reactivity to stress moderates response to cognitive behavioural therapy for insomnia (CBT-I) within a stepped-care framework in cancer patients with comorbid insomnia.
Methods: 177 participants (86.3% female; M_{age}=55.3, SD=10.4) were randomized to receive either stepped-care or standard CBT-I and were followed for 12 months following treatment. HRV measures were assessed at pre-treatment during a rest and worry period. Insomnia symptoms were assessed using the Insomnia Severity Index (ISI) and daily sleep diary across five timepoints.
Results: Resting HF-HRV significantly predicted pre-treatment sleep efficiency but not ISI score. No significant time x HF-HRV or CBT-I group x time x HF-HRV interactions were found, indicating that HF-HRV does not predict differential responses to the different CBT-I group. HRV reactivity was not cross-sectionally or longitudinally related to any outcome variables. In exploratory analyses, significant insomnia severity x time x HF-HRV interactions were observed, suggesting that HF-HRV may predict treatment responses differently based on initial insomnia severity.
Conclusion: Although resting HF-HRV was related to initial sleep efficiency, HF-HRV measures did not significantly predict response to either form of CBT-I. Resting HF-HRV may predict certain treatment outcomes when initial insomnia severity is considered, however these results are exploratory and of unclear clinical significance.

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Contribution of Authors

James Garneau: Literature review, conceptualization of research hypotheses, data processing, statistical analyses, & manuscript preparation, and revisions.

Dr. Jean-Philippe Gouin: Supervision and leadership responsibility for the creation and execution of the research project and manuscript, including conceptualization of research hypotheses, statistical analyses & critical review, commentary, and revision of manuscript drafts.

Dr. Josée Savard: Funding acquisition, study design, data collection, project administration.

Dr. Thanh Dang-Vu: Supervision and leadership responsibility including critical review, commentary, and revision of manuscript drafts.

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Introduction

Chronic insomnia is the most prevalent sleep disorder with over 10% of the general population meeting diagnostic criteria[1-3]. It is characterized by difficulty initiating or maintaining sleep resulting in poor sleep quality and significant distress or impairment in daytime functioning lasting at least 3 nights per week over the course of at least 3 months, despite adequate opportunity for sleep[4,5]. Insomnia has been traditionally considered a symptom of comorbid conditions, however an accumulating body of evidence now supports it as a distinct disorder that independently decreases quality of life[6,7], doubles the risk for the onset and recurrence of depression[7], and may increase risk for cardiovascular morbidity and mortality[9-11]. Insomnia is especially prevalent amongst those with a comorbid diagnosis of cancer, where between 30% and 60% of patients will meet diagnostic criteria for insomnia disorder over the course of their cancer care trajectory[12,13]. In cancer survivors, insomnia has been shown to intensify psychological distress, reduce quality of life, and increase morbidity associated with cancer and treatment[14,15]. If inadequately treated, insomnia can become chronic for up to 64% of cancer patients[13].

Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as the first-line treatment for insomnia disorder[16] and cancer-related sleep disturbances[17]. While approximately 70-80% of insomnia patients will observe a decrease in insomnia symptoms following treatment, around 40% of patients will still exhibit significant residual symptoms[18,19], with factors predicting remission rates remaining largely unknown. Although multiple randomized controlled trials (RCTs) have supported the efficacy of CBT-I in cancer patients[20,21] , accessibility to CBT-I is especially limited in this population[22,23]. To address this accessibility issue, a stepped-care approach to CBT-I has been developed wherein patients begin with a low-intensity, web-based, self-administered intervention followed, if needed, by a more intensive face-to-face treatment with a therapist[24]. In a noninferiority trial, no difference in efficacy between standard CBT-I and the novel stepped-care approach was observed, highlighting the usefulness of this approach[24]. Similar to other RCTs in primary insomnia patients[19], including those using standard[25] and web-based[26,27] CBT-I with cancer patients, a remission rate of about 55% was observed in both stepped-care and standard CBT-I at 12-month follow-up[24]. Thus, indicators of treatment response to stepped-care CBT-I also require further exploration.

The “hyperarousal” model of insomnia describes the interplay among physiological, cognitive, and emotional arousal which are believed to contribute to the development and maintenance of insomnia disorder[28,29]. Autonomic nervous system (ANS) activity may reflect current physiological and emotional hyperarousal. A growing body of literature suggests altered ANS activity in insomnia patients, more specifically in the parasympathetically regulated heart rate variability (HRV). Resting HRV represents the fluctuation in time between consecutive heart beats, which can be separated into low and high frequency domains to reflect sympathetic and parasympathetic influences[30]. The high frequency component (HF-HRV) is an indicator of the vagal influences on the sinoatrial node of the heart via myelinated pathways of the vagus nerve originating from the nucleus ambiguus where greater parasympathetic influence on the cardiac pacemaker via the vagal nerve leads to higher HRV. Accordingly, low baseline HF-HRV reflects a weaker parasympathetic influences on the heart that may promote a state of hyperarousal[30-33]. Consistent with the physiological hyperarousal model of insomnia, low HF-

HRV has been associated with greater heart rate, blood pressure, cortisol, and negative emotional responses to stress[3440].

Prior work has found associations between baseline resting HF-HRV with both subjective and objective measures of sleep quality and disturbances. In non-clinical samples, cross-sectional research has shown associations between greater resting diurnal HF-HRV and better subjective sleep quality measured using the Pittsburgh Sleep Quality Index (PSQI) and Jenkins Sleep Problems scale[42,43]. In the same population, the use of objective measures of sleep quality including PSG and actigraphy derived sleep parameters have shown cross-sectional associations between reduced sleep onset latency, fewer nighttime arousals, worse sleep efficiency, and shorter sleep duration with reduced diurnal measures of HRV[44,42]. Objective short sleep duration related to both experimental sleep deprivation and insomnia has been associated with reduced nocturnal HRV, increased resting heart rate, and risk of cardiovascular morbidity, as evidenced in a systematic review[45]. Together, these findings thus suggest a strong link between sleep quality and HRV in the general population.

When comparing individuals diagnosed with an insomnia disorder to matched non-clinical controls, cross-sectional analyses have found significant differences in waking autonomic activity[46-48]. Insomnia in these studies was assessed using either the DSM, ICSD-2, or objective sleep parameters with good sleepers matched based on age, gender, and absence of sleep disorders. Some research has shown reduced waking vagally-mediated HRV[46,47], and increased sympathovagal dominance and heart rate[48] in insomnia patients compared to good sleepers. Furthermore, nocturnal HF-HRV reduction has been observed across all sleep stages when comparing insomnia patients to matched controls[49], with additional evidence demonstrating an increase sympathovagal balance across non-REM and pre-sleep wakefulness in insomnia patients[45,48] and sleep deprived samples[50,51] compared to controls. However, a systematic review of the relationship between autonomic activity and insomnia has reported overall inconclusive evidence for this association[52]. This analysis of 22 studies examining both nocturnal and diurnal HRV parameters in insomnia patients has reported that nearly half of the evidence describes nonsignificant differences in autonomic functioning associated with the disorder. Thus, the notion that HRV is impaired in insomnia patients currently lacks consensus, which the present study aims to explore.

Additional research conducted using various clinical populations with co-occurring sleep disturbances suggests an association between low HF-HRV and insomnia. Research exploring the relationship between major depression, sleep disturbances, and HF-HRV found comparable resting HF-HRV between insomnia patients and those with major depression when PSQI scores were equally low[47]. Increased insomnia and decreased sleep duration were also associated with lower mood during the following day only for those with lower resting HF-HRV, supporting the notion that low parasympathetic nervous system activity is related to poorer emotional regulation[54]. In a study of individuals diagnosed with panic disorder, lower resting HF-HRV was associated with more self-reported sleep disturbances[55]. Furthermore, individual differences in vulnerability to sleep disturbances may be further exacerbated by exposure to acute and chronic stress in both insomnia patients and good sleepers[56-61]. In response to a laboratory stressor, low HF-HRV has been related to worse scores on the PSQI[56]. To summarize, although there exists conflicting evidence regarding the relationship between insomnia and HRV, numerous studies

have indeed found evidence supporting an association between poor sleep and reduced autonomic activity in various clinical and non-clinical populations across the sleep-wake cycle.

In addition to resting HF-HRV, HRV reactivity may also be associated with insomnia. HRV reactivity is defined here as HF-HRV change in response to stress from baseline, where higher reactivity indicates greater reduction following stress. In one longitudinal study, higher initial HRV reactivity was associated with larger stress-related increases in PSQI over time[57]. Although there exists ongoing debate in the literature concerning the theoretical interpretation of greater HRV reactivity as either an adaptive physiological stress response[32] or indicative of poor emotional regulation[33], greater HRV reactivity has been additionally associated with reduced sleep quality in children[62,63] and adults with depression[64]. One study examining the relationship between parasympathetic functioning and sleep disturbances in 93 women with metastatic breast cancer[65] found a negative correlation between HF-HRV reactivity and sleep efficiency, as well as associations between low baseline HF-HRV with reduced objective measures of sleep efficiency and lower self-reported sleep time. Thus, there exists a large body of theoretical and empirical evidence supporting the relationship between sleep quality, HF-HRV reactivity, and the added impact of stress in the context of a cancer diagnosis.

With regard to treatment outcomes, researchers have begun to explore the possibility of using baseline resting HRV as a predictor for responses to psychotherapy. Studies have found that higher vagally-mediated HRV predicted significantly greater symptom reduction following CBT for PTSD with comorbid substance use disorder[66], exposure and response prevention in patients with OCD[67], better treatment outcomes following manualized short-term psychodynamic-interpersonal psychotherapy for chronic pain[68], reduced depressive symptoms in patients diagnosed with stress-related depression following an inpatient personalized psychological intervention[69], and lower workplace related distress at follow-up from psychosomatic workplace intervention including both psychodynamic and cognitive behavioral principals[70]. Additionally, higher HF-HRV in-session predicted superior rated therapeutic alliance during CBT for anxiety and depression related disorders[71]. However, there indeed exist a small number of studies reporting contrasting findings where baseline HRV was not found to differentiate responders and non-responders to psychological and pharmacological treatment for major depression[72-74]. Overall, these results suggest that those with lower baseline HF-HRV may respond less well to psychological interventions. However, to our knowledge, the relationship between baseline HF-HRV and treatment outcome following CBT-I has not yet been examined.

The current study thus aims examine the association between baseline HRV and insomnia symptoms over the course of treatment to better understand whether these biomarkers are longitudinally associated with changes in insomnia symptom following stepped-care CBT-I in cancer patients. To examine this research question, changes in insomnia symptoms in response to a stepped-care CBT-I randomized clinical trial was measured using the Insomnia Severity Index (ISI) and sleep efficiency derived from daily sleep diary data collected across five timepoints spanning 12 months of treatment and follow-up. Resting HF-HRV and HF-HRV in response to a worry task were measured initially prior to treatment[24]. We first hypothesized that initial lower resting HF-HRV and higher HRV reactivity would be cross-sectionally associated with pre-treatment insomnia severity. Additionally, we hypothesized that lower HF-HRV and higher HRV reactivity would predict worse outcomes for CBT-I overall. More specifically, under the stepped-

care framework, we hypothesized that those with reduced baseline autonomic functioning would therefore experience less change in insomnia severity in the low-intensity web-based intervention group compared to those given standard CBT-I, with the aim of highlighting a possible sub-group of patients in need of higher intensity intervention.

Methods

Study Design:

Participants first completed pre-intervention assessments of HRV, insomnia severity, and daily sleep diaries. Participants then received either stepped-care or standard CBT-I interventions in the context of a randomized controlled noninferiority trial. All participants completed follow-up assessments of insomnia severity and daily sleep diary at post-treatment and at 3-, 6-, and 12-month follow-ups.

Participants:

177 cancer patients (86.4% female; M_{age} = 55.26, SD = 10.36) with comorbid symptoms of insomnia participated in the study. Participants were included in the study if they met the following criteria: 1) a diagnosis of any type of nonmetastatic cancer in the past 18 months; 2) Insomnia Severity Index (ISI) score ≥ 8 or regular use (≥ 1 night per week) of psychotropic medication as a sleep aid; 3) between the ages of 18 and 75 to avoid age-related cognitive impairments; 4) ability to read and understand French; 5) living within 50km distance of the research center; and 6) access to the Internet.

Participants were excluded from the clinical trial if they met one of the following criteria: 1) life expectancy less than one year; 2) a diagnosis of metastatic cancer; 3) severe comorbid psychiatric disorders that may require other types of intervention; 4) prior psychological treatment for a sleep disorder; 5) severe cognitive impairments (e.g. *Mini-Mental State Examination* [MMSE] score < 24); 6) formal diagnosis of another sleep disorder; and 7) shift work within the past 3 months or expected in the next 12 months. These eligibility criteria were selected to be the most representative of criteria applicable to conventional real-world clinical settings.

Participants were recruited between April 2014 and September 2017 from the radio-oncology department of the CHU de Québec-Université Laval, direct referrals, advertisements in hospitals, and via other sleep-related studies conducted by the research team. A detailed description of the recruitment process can be found in the parent study[24]. Of the eligible participants, 250 provided informed consent and completed a battery of self-report scales including the ISI, a two-week daily sleep diary, and a clinical interview. After the exclusion and attrition of 73 participants at this stage, 177 individuals were randomized and received treatment. The study was approved by the ethics committee of the CHU de Québec-Université Laval (#2012-1071).

Procedure:

Prior to randomization (T1), participants completed the ISI followed by a two-week daily sleep diary. Once these data were received via post, participants were asked to present to the laboratory for the heart rate data collection. Participants were instructed to refrain from

exercising or consuming caffeine for at least two hours before the assessment. A heart monitor was fitted around the chest at the base of the sternum and the participant's resting baseline heart rate was recorded continuously for five minutes while remaining seated after being instructed to close their eyes and breathe normally. Next, participants engaged in a five-minute worry induction task based on Hofmann and colleagues' protocol[75]. Here, participants were explained the concept of worry and instructed to list their most prevalent worries and worry about the most intense one during a five-minute heart rate recording. Specifically, participants received the following instructions:

"Worry is a chain of negative thoughts about something that can have negative consequences for you in the future. Typically, people worry about something that hasn't happened yet but that could happen in the future, and that is negative. Can you make a list of the things you tend to worry about? Of all worries you mentioned, which do you worry about most often and most intensely about? During the next 5 minutes, I would like you to worry about (the topic they tend to worry about most often and most intensely). *Please close your eyes and try to worry for the complete 5 minutes. If you realize your attention starts wandering off, try to refocus on your worries."*

Following the completion of the pre-intervention assessment, participants were randomly assigned to either standard care CBT-I (StanCBT-I; n = 59) or stepped-care CBT-I (StepCBT-I; n = 118) using group allocation ratio of 1:2. The StanCBT-I group received a manualized six-session face-to-face intervention. The StepCBT-I group was further stratified based on pre-screening ISI score such that participants with more severe insomnia prior to the study (ISI ≥ 15; n = 53) received the same initial treatment as the StanCBT-I group, while those with less severe insomnia prior to the study (ISI ≥ 8, but < 15; n = 65) received an interactive web-based CBT-I. After the first step in both StepCBT-I groups, unremitted participants (n = 29) were offered the second step, which consisted of up to three biweekly individual face-to-face booster sessions of CBT-I with a clinician.

All participants completed follow-up data post-treatment (T2) and at 3-, 6-, and 12-month follow-ups (T3-T5). Specifically, participants repeated the 14-day sleep diary, and the ISI after the 6-week treatment period (post step-one; T2) as well as at 3- (post step-two; T3), 6- (T4) and 12- (T5) month follow-ups. A detailed consort flow chart depicting treatment group allocation, dropout, and trial exclusion at each time point can be found in the parent study[24]. Of the 177 participants, one participant was removed from the analyses following treatment allocation for missing data across all study variables and the sample characteristics were computed using 176 participants. 31 participants (17.6%) had either missing or corrupted resting heart rate data, and an additional 9 participants (22.7%) had missing or corrupted heart rate data during the worry condition. These participants were removed from the relevant statistical analyses. The number of participants included in the final results consisted of 145 (82.4%) and 136 (77.3%) for analyses of resting HF-HRV and HF-HRV reactivity respectively.

Intervention:

The CBT-I protocol followed a manualized six-week multimodal intervention comprised of psychoeducation on sleep, circadian rhythms and sleep hygiene, followed by implementing strategies such as stimulus control, sleep restriction, and cognitive restructuring aimed at

changing psychological and behavioral factors that perpetuate insomnia[76]. The content of CBT-I was the same in both the StanCBT-I and StepCBT-I groups. A detailed description of the web-based intervention is available in the parent study[24].

Measures:

The Insomnia Severity Index (ISI)

The ISI[77] is a brief self-report questionnaire that evaluates an individual's perceived insomnia severity in the prior two-week interval. The ISI comprises seven items assessing 1) difficulties falling asleep, 2) difficulties staying asleep, 3) difficulties with premature awakenings, 4) satisfaction of sleep quality, 5) impairment of daytime functioning due to sleep problems, 6) noticeability of impairments by others, and 7) distress or worry caused by sleep difficulties. Each item is rated on a 0-4 Likert scale for a total score ranging from 0 to 28, where a higher score represents more severity. A score of 15 represents the clinical cut-off of insomnia disorder, whereas scores ranging from 8 to 14 represent clinically subthreshold insomnia symptoms and are still indicative of impairment. The ISI has been empirically validated for use with cancer patients and has demonstrated sensitivity to change over the course of treatment[20]. The Cronbach's alpha was 0.739[24].

Sleep Diary

Daily sleep diaries provide consecutive subjective estimates of sleep parameters including bedtime, nocturnal awakenings, sleep onset latency, and rise time over the course of time. Sleep diaries were completed daily for two-weeks at each timepoint. Sleep efficiency was used as the primary sleep diary variable in the analyses, calculated as the ratio of total sleep time to total time spent in bed according to the recommendations proposed by Buysse and colleagues[78]. Total time spent in bed was calculated as the total time between getting into bed at night for the first time and getting out of bed in the morning for the last time. Total sleep time was calculated as the total time in bed minus sleep onset latency (i.e., time to sleep after lights out), nocturnal awakenings (i.e., total time spent awake during the night, and early morning awakening (i.e., time between waking up and getting out of bed in the morning).

Heart Rate Variability (HRV)

To collect HRV intervals, participants were fitted with a chest belt hardwired with a digital inter-beat interval recorder Polar RS800CX (Polar Electro Oy; Finland: Kempele). The recorder used a sampling rate of 1000 samples per second to measure the interval between successive R-spikes of consecutive QRS complexes. Recording artifacts were manually detected and corrected by using the CardioEdit software (Brain Body Center, University of Illinois at Chicago, 2007). Artifact correction was performed using integer arithmetic (i.e., adding, dividing, or averaging heartbeat intervals to correct missed or erroneous R-spike detections). Corrupted files without at least 60-second clean recording were removed from further analysis. Average HF-HRV for each participant was calculated from the edited inter-beat intervals using the CardioBatch software (Brain Body Center, University of Illinois at Chicago, 2007). This software program implements the moving polynomial method proposed by Porges and colleagues[79] using a 0.12–0.40 Hz bandpass filter applied to the heart rate time series to extract the variance between inter-beat intervals. This method provides an assessment of vagally mediated HF-HRV[80]. HF-HRV reactivity was then calculated as the difference between the average baseline HF-HRV and the average HF-HRV during the worry task[81]. Here, higher HF-

HRV reactivity depicts greater vagal withdrawal, denoted by greater decreases in HF-HRV from the baseline to the worried condition[82,83].

Statistical Analysis:

Descriptive Statistics

Descriptive statistics of participant demographics, study measures, medication use, cancer characteristics, and treatment information were computed using IBM SPSS Statistics Version 28.0 and derived from self-report questionnaires at T1 from 176 participants. No significant differences were found between the reported sample characteristics for those with missing HRV data, all p's > 0.09.

Main Analyses

Linear mixed-effects models examined associations between baseline HF-HRV and HF-HRV reactivity, and insomnia severity and sleep efficiency. Linear mixed-effects modelling accounts for individual differences in initial insomnia severity and treatment response by allowing each individual's intercept and time effects to vary freely as random effects. The remaining predictors in each model were included as fixed effects to detect group-level trends. Spearman's Rho correlations were used to quantify the effect size of cross-sectional relationships due to nonnormality of the data. Correlation coefficients were interpreted based on Cohen's guidelines[84].

Separate models were constructed for all analyses using either baseline resting HF-HRV or HF-HRV reactivity to predict change in either ISI score or sleep efficiency across T1-T5. Models with HF-HRV reactivity included resting HF-HRV as covariates. The intercept and time were also included as random effects. Model 1 assessed the cross-sectional relationship between both HRV parameters and insomnia severity or sleep efficiency at T1. Model 2 evaluated the effects both HRV parameters on treatment response over time (T1-T5) across treatment group using a time by HRV interaction. Model 3 expanded on Model 2 by including a 3-way interaction between treatment group, HRV and time in the analysis to examine the effect of standard versus either stepped-care intervention on the association between HRV and insomnia symptom severity over time. The treatment group predictors were referenced to the standard CBT-I control group.

Exploratory Analyses

The first set of exploratory analyses were conducted to evaluate if there are specific components of sleep efficiency associated with baseline resting HF-HRV at T1 and across all five timepoints. Linear mixed-effects modelling was used to examine the cross-sectional and longitudinal relationships between baseline HF-HRV and sleep diary measures of 1) sleep onset latency, 2) total sleep time, 3) total wake after sleep, and 4) early morning awakenings. A second set of exploratory analyses were conducted to explore the role of pre-treatment insomnia severity on the association between baseline resting HF-HRV and changes in sleep outcomes across treatment. A dichotomous initial ISI grouping variable was created separating participants into having either clinical or subthreshold insomnia symptoms at baseline using a score of 15 as the cut-off[77]. Linear mixed-effects models examined whether the interaction between initial insomnia severity and HRV predicted longitudinally change in ISI or sleep efficiency across all five timepoints.

Results

Main Analyses

Table 1 describes the sample demographics and descriptive statistics. Linear mixed-effects regression models first evaluated associations between the pretreatment HRV measures and both insomnia severity and sleep efficiency at baseline (Models 1; Table 2). Baseline resting HF-HRV was positively associated with sleep efficiency. A statistically significant small correlation was observed (r_s = 0.201, p = 0.016) such that higher baseline HF-HRV was associated with better initial sleep efficiency. No such relationship was found with initial insomnia severity in Model 1 (r_s=-0.086, p = 0.302). HF-HRV reactivity was not significant associated with either initial sleep efficiency (r_s= -0.087, p=0.314) or insomnia severity (r_s = 0.024, p=0.778) (Models 1; Table 3).

Next, linear mixed-effects models assessed changes in insomnia severity and sleep efficiency across all five timepoints, irrespective of the type of treatment received. The interaction effects between baseline HF-HRV and time (Models 2; Table 2) and HF-HRV reactivity and time (Models 2; Table 3) did not significantly predict either sleep efficiency or insomnia severity over time. Additional linear mixed-effects models tested whether HRV measures moderated treatment responses to specific treatment groups. None of the three-way interactions between time, treatment groups and either pretreatment resting HF-HRV (Models 3; Table 2) or HF-HRV reactivity (Models 3; Table 3) significantly predicted sleep efficiency or insomnia severity over time. These results indicate that the relationship between the HRV measures and response to CBT-I does not differ based on the type of CBT-I received.

Exploratory Analyses

Given the association between resting HF-HRV and sleep efficiency at baseline, exploratory analyses were conducted to evaluated which specific components of the sleep diary were associated with baseline HF-HRV. We examined the cross-sectional relationship between baseline resting HF-HRV and initial sleep onset latency, total sleep time, wake after sleep onset, and early morning awakening over time at T1 (Models A; Appendix A). A small but statistically significant negative correlation was found between baseline HF-HRV and sleep onset latency (r_s = -0.165, p = 0.047). No other sleep diary parameters were significantly related to HF-HRV.

Given that participants with more severe initial symptoms experience a larger change in sleep symptoms following CBT-I, additional exploratory analyses explore the effect of the participant's initial insomnia severity score on the association between initial resting HF-HRV and changes in sleep outcomes (Table 4). A grouping variable was included separating the sample into those with initial subthreshold (ISI < 15) or clinical (ISI ≥ 15) insomnia. We found a statistically significant three-way interaction effect when predicting insomnia severity (Model A; Table 4) and a marginally significant interaction effect when predicting sleep efficiency (Model 2; Table 4). As illustrated in Figure 1 (left), among individuals with clinical insomnia, lower pre-treatment HF-HRV was associated with a larger decrease in ISI over time compared to those with higher pre-treatment HF-HRV. This association between HF-HRV and change in ISI was inversed and attenuated among participants with subthreshold insomnia at baseline. Figure 1 (right) illustrates a similar relationship where lower pre-treatment HF-HRV in the clinical group may be associated with a larger increase in sleep efficiency over time compared to those with

higher baseline HF-HRV. This association appears again to be attenuated and inversed for those in the initially subthreshold group.

Table 1. Sociodemographic, psychological, and health characteristics of the sample at baseline.

Characteristic		Total sample (N=176)
Age - *M* (*SD*)	(Years)	55.26 (10.36)
Sex - % (n)	Female	86.4% (152)
Body Mass Index - *M* (*SD*)	(kg/m^2)	26.23 (4.98)
Highest level of education - % (n)	Secondary school	33.0% (58)
	College[1]	11.4% (20)
	University	47.7% (84)
	Other	8.0% (14)
Marital Status - % (n)	Married/common law	65.3% (115)
	Separated/divorced	13.1% (23)
	Single	17.0% (30)
	Widowed	4.0% (7)
Occupation - % (n)	Working full/part time	14.2% (25)
	Sick leave	50.6% (89)
	Retirement	29.0% (51)
	Other	6.3% (11)
Annual Household Income - % (n)	< $40,000	16.4% (29)
	$40,001 – $80,000	38.1% (67)
	$80,001 – $120,000	21.6% (38)
	>$120,000	17.0% (30)
	Unsure/Prefer not to answer	6.8% (12)
Use of psychotropic medication - % (n)	Yes	47.2% (83)
Cancer diagnosis	Breast	76.7% (135)
	Prostate	6.3% (11)
	Gynecological	4.5% (8)
	Other	12.2% (22)
Time Since Cancer Diagnosis - *M* (*SD*)	(Months)	9.2 (9.5)
Cancer T-Stage - % (n)	0	5.7% (10)
	I	17.1% (30)
	II	9.7% (17)
	III	4.0% (7)
	IV	1.1% (2)

	Unknown/unavailable	62.5% (110)
Past Cancer Treatment	Surgery	87.5% (154)
	Radiation therapy	88.1% (155)
	Chemotherapy	51.1% (90)
	Hormonotherapy	48.9% (86)
	Other	31.8% (56)
Current Cancer Treatment	Radiation therapy	0% (0)
	Chemotherapy	9.7% (17)
	Hormonotherapy	46.6% (82)
	Other	12.5% (22)
Resting HF-HRV - *M* (*SD*)	$\ln(ms^2)$	5.28 (1.46)
Missing Resting HRV - % (n)		17.6 % (31)
HF-HRV during worry task - *M* (*SD*)	$\ln(ms^2)$	4.99 (1.56)[2]
Missing Worry HRV - % (n)		19.3% (34)
HF-HRV Reactivity[3] - *M* (*SD*)	$\ln(ms^2)$	0.26 (0.60)
Missing HF-HRV Reactivity - % (n)		22.7% (40)
Insomnia Severity Index - *M* (*SD*)	Total Score	15.33 (4.11)
Insomnia Severity Index - % (n)	No clinical significance (0–7)	2.3% (4)
	Subthreshold insomnia (8–14)	40.9% (72)
	Moderate insomnia (15–21)	51.7% (91)
	Severe insomnia (22–28)	5.1% (9)
Sleep Efficiency - *M* (*SD*)	(%)	78.29 (9.22)
Other Sleep Diary Parameters - *M* (*SD*)	Total Time in Bed (hours)	8.88 (0.97)
	Total Sleep Time (hours)	6.95 (1.06)
	Sleep Onset Latency (min)	33.70 (23.98)
	Nocturnal awakening (min)	47.59 (30.80)
	Early morning awakening (min)	34.71 (28.78)

Note. % represents a valid percentage. All reported sample characteristics were measured prior to treatment at T1. [1]In Quebec, college refers to the first level of post-secondary education which precedes university. [2]HF-HRV was significantly reduced after the worry tasked compared to at rest. [3]HF-HRV reactivity was computed as the difference between resting HF-HRV and HF-HRV following the worry task.

Table 2. Resting HF-HRV Longitudinal Mixed Effect Models Predicting Insomnia Severity and Sleep Efficiency Across T1 – T5 (n=145).

	Insomnia Severity (ISI)			Sleep Efficiency		
Fixed Effects	Model 1 β (t-statistic; p-value)	Model 2 β (t-statistic; p-value)	Model 3 β (t-statistic; p-value)	Model 1 β (t-statistic; p-value)	Model 2 β (t-statistic; p-value)	Model 3 β (t-statistic; p-value)
Intercept	14.01 (14.34; <0.001)***	15.64 (9.92; <0.001)***	14.14 (5.83; <0.001)***	74.10 (33.80; <0.001)***	72.18 (26.50; <0.001)***	72.06 (15.08; <0.001)***
Time	-1.79 (-14.72; <0.001)***	-2.35 (-5.29; <0.001)***	-1.73 (-2.24; 0.0257)*	1.98 (12.16; <0.001)***	2.66 (4.48; <0.001)***	1.68 (1.53; 0.128)
HF-HRV	-0.034 (-0.20; 0.84)	-0.34 (-1.19; 0.237)	-0.16 (-0.35; 0.727)	0.92 (2.34; 0.021)*	1.27 (2.57; 0.0112)*	1.72 (1.94; 0.054)[t]
HF-HRV X Time		0.11 (1.31; 0.189)	0.015 (0.10; 0.917)		-0.13 (-1.19; 0.236)	-0.010 (-0.05; 0.960)
Stepped-Care Web Group			0.95 (0.26; 0.793)			6.17 (0.87; 0.387)
Stepped-Care Professional Group			2.66 (0.77; 0.440)			-4.79 (-0.71; 0.482)
Time X Stepped-Care Web			-0.053 (-0.05; 0.962)			0.50 (0.31; 0.754)
Time X Stepped-Care Professional			-1.57 (-1.46; 0.149)			2.31 (1.52; 0.128)
HF-HRV X Stepped-Care Web			-0.28 (-0.42; 0.673)			-1.51 (-1.18; 0.240)
HF-HRV X Stepped-Care Professional			-0.017 (-0.03; 0.979)			-0.02 (-0.01; 0.989)
Time X HF-HRV X Stepped-Care Web			0.034 (0.17; 0.866)			-0.04 (-0.13; 0.897)
Time X HF-HRV X Stepped-Care Professional			0.18 (0.91; 0.366)			-0.28 (-0.98; 0.326)

Note. t < .10; *p<.05; **p<.01; ***p<.001; HF-HRV = Resting High Frequency Heart Rate Variability; Both Stepped-Care Web and Stepped Care Professional groups were referenced to the Standard CBT-I Group.

Table 3. HF-HRV Reactivity Longitudinal Mixed Effect Models Predicting Insomnia Severity and Sleep Efficiency Across T1 – T5 (n=136).

	Insomnia Severity (ISI)			Sleep Efficiency		
Fixed Effects	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
	β (t-statistic; p-value)	β (t-statistic; p-value)	β (t-statistic; p-value)	β (t-statistic; p-value)	β (t-statistic; p-value)	β (t-statistic; p-value)
Intercept	13.93 (14.08; <0.001)***	15.68 (10.48; <0.001)***	14.15 (5.79; 0.001)***	74.34 (33.15; <0.001)***	72.48 (24.81; <0.001)***	71.52 (15.19; <0.001)***
Time	-1.76 (-13.96; <0.001)***	-2.44 (-5.42; <0.001)***	-1.77 (-2.28; 0.0232)*	2.04 (11.15; <0.001)***	2.68 (4.09; <0.001)***	1.79 (1.58; 0.115)
HF-HRV	-0.03 (-0.16; 0.871)	-0.38 (-1.38; 0.171)	-0.20 (-0.43; 0.665)	0.82 (2.04; 0.0437)*	1.22 (2.25; 0.0260)*	1.71 (1.96; 0.0527)[t]
HF-HRVr	0.016 (0.04; 0.970)	0.44 (0.63; 0.528)	1.40 (1.27; 0.207)	-0.81 (-0.80; 0.424)	-1.66 (-1.24; 0.218)	1.86 (0.87; 0.386)
HF-HRV X Time		0.14 (1.64; 0.102)	0.03 (0.23; 0.819)		-0.14 (-1.12; 0.263)	-0.020 (-0.09; 0.927)
HF-HRVr X Time		-0.17 (-0.80; 0.427)	-0.46 (-1.31; 0.191)		0.31 (0.98; 0.310)	-0.059 (-0.12; 0.908)
Stepped-Care Web Group			1.23 (0.34; 0.734)			6.99 (0.99; 0.323)
Stepped-Care Professional Group			-1.48 (-1.36; 0.174)			-3.07 (-0.45; 0.650)
Time X Stepped-Care Web			-0.23 (-0.20; 0.842)			0.44 (0.27; 0.789)
Time X Stepped-Care Professional			-1.48 (-1.36; 0.174)			2.02 (1.28; 0.201)
HF-HRVr X Stepped-Care Web			-1.04 (-0.68; 0.498)			-6.34 (-2.17; 0.0319)*
HF-HRVr X Stepped-Care Professional			-1.74 (-0.93; 0.355)			-3.67 (-1.01; 0.313)
Time X HF-HRVr X Stepped-Care Web			0.30 (0.62; 0.537)			0.77 (1.09; 0.277)
Time X HF-HRVr X Stepped-Care Professional			0.67 (1.12; 0.265)			0.16 (0.18; 0.857)
HF-HRV X Stepped-Care Web			-0.32 (-0.48; 0.635)			-1.33 (-1.03; 0.304)
HF-HRV X Stepped-Care Professional			0.14 (0.21; 0.833)			-0.41 (-0.32; 0.748)
Time X HF-HRV X Stepped-Care Web			0.066 (0.32; 0.752)			-0.079 (-0.26; 0.795)
Time X HF-HRV X Stepped-Care Professional			0.16 (0.76; 0.500)			-0.21 (-0.71; 0.478)

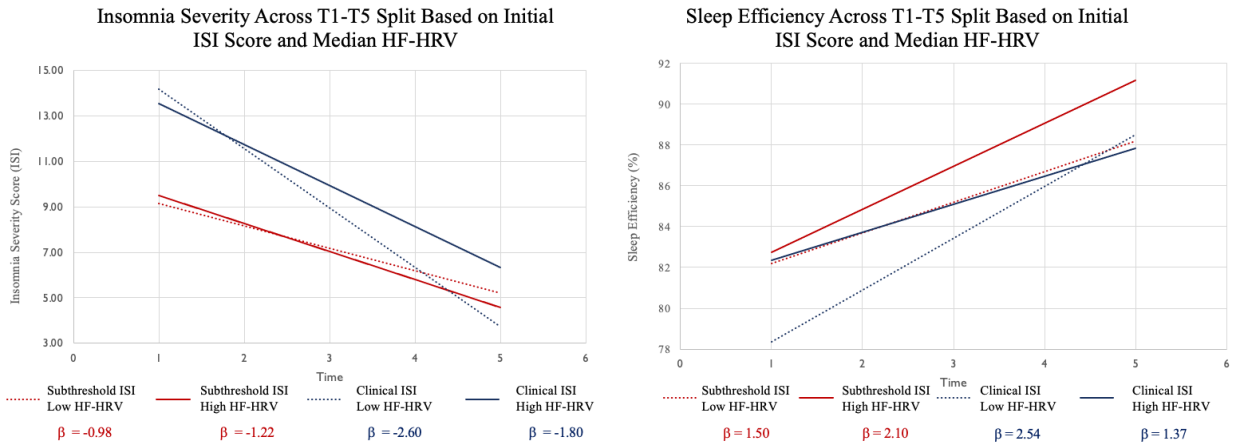
Note. t < .10; *p<.05; **p<.01; ***p<.001; HF-HRV = Pre-Treatment Resting High Frequency Heart Rate Variability; HF-HRVr = Pre-Treatment High Frequency Heart Rate Variability Reactivity; Both Stepped-Care Web and Stepped Care Professional groups were referenced to the Standard CBT-I Group.

Table 4. Exploratory Longitudinal Mixed Effect Models Using Initial Insomnia Severity to Predict Sleep Outcomes Across T1 – T5 (n = 145).

	Insomnia Severity (ISI)	Sleep Efficiency
Fixed Effects	Model 1	Model 2
	β (t-statistic; p-value)	β (t-statistic; p-value)
Intercept	19.39 (10.94; <0.001)***	67.07 (18.13; <0.001)***
Time	-3.51 (-6.37; <0.001)***	3.72 (4.58; <0.001)
HF-HRV	-0.55 (1.68; <0.0961)^{t}	2.12 (3.09; 0.0024)**
HF-HRV X Time	0.23 (2.22; 0.0270)*	-0.31 (-2.10; 0.0363)*
ISI <15	-9.96 (-3.57; <0.001)***	12.67 (2.18; 0.0311)*
TimeX ISI < 15	2.93 (3.38; <0.001)***	-2.56 (-2.00; 0.0459)*
HF-HRV X ISI < 15	0.77 (1.53; 0.129)	-2.08 (-1.96; 0.0518)^{t}
Time X HF-HRV X ISI < 15	-0.33 (-2.09; 0.0370)*	0.045 (1.92; 0.0549)^{t}

Note. t < .10; *p<.05; **p<.01; ***p<.001; HF-HRV = Resting High Frequency Heart Rate Variability; ISI < 15 = Group with Subclinical Pre-Treatment Insomnia Severity; ISI ≥ 15 = Group with Clinical Pre-Treatment Insomnia Severity. The ISI < 15 group was referenced to the ISI ≥ 15 group.

Figure 1. Graphic representations of the relationships between both sleep efficiency (left) and ISI score (right) with resting HF-HRV over time contrasting clinical and subthreshold groups at baseline.



Note. The x-axis represents the five timepoints, beginning at T1; A median split was used to separate participants into either High or Low HF-HRV groups for illustration; HIGH RSA denotes participants above the median HF-HRV of the sample; LOW RSA denotes participants below the median HF-HRV of the sample; Clinical ISI group indicates baseline ISI >= 15; Subthreshold ISI group indicates baseline ISI < 15; Unstandardized simple slopes were derived for each subgroup for illustrative purposes reported as β.

Discussion

The goal of this study was to examine if resting HF-HRV and HRV reactivity were associated with pre-treatment insomnia symptoms, and subsequent symptom reduction following standard or stepped-care CBT-I. Lower resting HF-HRV was significantly associated with poorer sleep efficiency at pre-treatment, but not with self-reported insomnia severity. Contrary to our hypotheses, there was no statistically significant association between the HF-HRV parameters and insomnia symptom reduction following CBT-I. Moreover, there was no significant association between HF-HRV and treatment response to the stepped-care web, stepped-care professional, or standard CBT-I groups over time. Similarly, HRV reactivity was not associated with sleep efficiency or insomnia severity at pre-treatment or follow-up. In exploratory analyses, we found that initial insomnia severity possibly moderates the association between HF-HRV and sleep outcomes over treatment follow-up. Overall, our findings suggest that although HF-HRV was associated with pre-treatment sleep efficiency, but it was not related to responses to CBT-I.

Resting HF-HRV and Baseline Insomnia

Consistent with our hypothesis, there was a significant relationship between lower diurnal resting HF-HRV and poorer self-reported sleep efficiency at pre-treatment, in line with previous research finding the same association in patients with breast cancer[65] and insomnia patients[53]. Sleep efficiency is derived from daily sleep diary entries providing subjective estimates of sleep parameters including bedtime, nocturnal awakenings, sleep onset latency, and rise time. Exploratory analyses on the sleep diary components found that sleep onset latency may be driving the relationship between lower HF-HRV and poorer sleep efficiency at baseline. One interpretation of these findings is that increased diurnal autonomic arousal reduces the ability to initially fall asleep leading to reduced sleep efficiency. Previous findings suggest that higher resting diurnal HF-HRV is associated with shorter PSG derived sleep onset latency, fewer nighttime awakenings, and subsequently higher self-reported sleep quality, while no significant associations were observed for other sleep parameters[42].

Contrary to our hypothesis, however, there was no significant relationship between resting HF-HRV and self-reported ISI score. This finding is consistent with another study that found no association between resting HF-HRV and ISI score in good sleepers[56]. In contrast to the sleep efficiency measure, the ISI evaluates both insomnia symptoms as well as consequences of insomnia including the degree of distress caused by sleep difficulties during the day[77]. Perceived daytime impairment and distress measured by the ISI may be more strongly related to cognitive hyperarousal than with physiological hyperarousal. Previous research suggests that pre-sleep cognitive arousal exhibits a stronger relationship with daytime impairment measured by the ISI than pre-sleep somatic arousal measured using the Pre-Sleep Arousal Scale (PSAS)[85]. Moreover, additional research has found that PSG derived total sleep time was only related to the somatic subset of the PSAS in both insomnia patients and good sleepers, whereas the ISI was only related to the cognitive subset of the PSAS in insomnia patients[86]. Thus, HRV reductions seen in insomnia may be more related to nighttime insomnia symptoms rather than its perceived impact on daytime impairment.

The clinical profile of insomnia disorder has been proposed to vary based on PSG derived TST, distinguishing between those with normal sleep duration similar to good sleepers, and those

with objective short sleep duration (OSSD), often defined as having less than 6 hours of total sleep[87]. Although individuals with both phenotypes report daytime impairment and sleep-related distress that may be reflected in ISI scores, OSSD has additionally been associated with reductions in nocturnal vagally-mediated HRV[88,89], as well as increased risk of hypertension, diabetes, cardiovascular morbidity, and mortality[90,9-11]. According to Harvey's cognitive model of insomnia[91], excessive sleep-related worry can perpetuate cognitive and somatic hyperarousal in a vicious cycle leading to real sleep deficits. Thus, one interpretation of the current findings is that sleep-related distress reflected in the ISI may not be related to reduced HRV per se, but the sleep deficits associated with insomnia may relate to impairment in cardiometabolic functioning.

HRV and Treatment Outcomes

Contrary to our hypotheses, we did not find a significant relationship between pretreatment HF-HRV or HRV reactivity and insomnia symptoms in response to CBT-I over time, nor did we find significant between-group differences in treatment outcome. Given that remission rates were consistent with previous RCTs across stepped-care groups[24], one explanation for these findings is that individual differences in parasympathetic functioning may not moderate the efficacy of CBT-I in this population. Under the theoretical framework where the parasympathetic nervous system plays a vital role in managing autonomic arousal affecting the expression and control of emotions[92], numerous studies have reported positive associations between pre-treatment HRV and response to various cognitive-behavioral and psychodynamic interventions treating a wide array of psychopathology involving emotional dysregulation[66-70]. However, there exists contrasting evidence that baseline vagally-mediated HRV may not predict response to psychological treatment for major depression[72-74] despite the disorder's well documented relationship to blunted HRV[93]. Although emotional regulation difficulties are considered to be a significant component of insomnia[94], the current research did not find conclusive evidence linking baseline HF-HRV to changes in insomnia severity over the course of CBT-I. As mentioned, the initial relationship found between resting HF-HRV and sleep efficiency could in part be due to sleep deficits accrued by chronic insomnia. It has been theorized that individuals with the OSSD phenotype may respond better to treatments targeting physiological hyperarousal, whereas insomnia patients with normative sleep may benefit more from cognitive-emotional based treatments like CBT-I[87]. Maybe medication and psychological treatments with an emphasis on relaxation training may reduce physiological hyperarousal[95-97] and thus may be more related to baseline HRV than CBT-I.

HRV Reactivity and Baseline Insomnia

There was no significant association found between HF-HRV reactivity to the worry task and pre-treatment sleep efficiency or ISI score. To date, few studies have examined the association between HRV reactivity to stress and sleep quality in insomnia. In good sleepers, higher initial HRV reactivity has been positively associated with increased stress-related changes in PSQI scores[57,64], increased actigraphy derived sleep disturbances[62,63], and lower sleep efficiency in women with breast cancer[65]. However, research examining physiological stress reactivity differences between insomnia patients and good sleepers has found no significant differences in HF-HRV and salivary cortisol reactivity to laboratory stressors[98,99], including no relationship between change in salivary cortisol and PSG measures of sleep[99,100]. Furthermore, low HF-HRV during a worry task was solely found to be related with stress-induced increases in ISI and not baseline ISI score in university students[56]. Our results thus suggest that HRV

reactivity to stress may not be cross-sectionally associated with self-reported sleep disturbances and distress in cancer patients with insomnia.

Exploratory Analyses

Our exploratory analyses examining the moderating effect of the clinical severity of initial ISI score on the association between initial resting HF-HRV and changes in sleep outcomes found significant effects for change in ISI and marginally significant effects for change in sleep efficiency over time. Our findings suggested that those with subthreshold insomnia severity (ISI <15) and higher HF-HRV experienced the most gains in sleep efficiency from CBT-I over time. In contrast, participants with clinically severe insomnia (ISI≥15) and *lower* HF-HRV at baseline underwent the largest change over time in both sleep efficiency and ISI score. There are broadly two distinct conceptualizations of the association between insomnia and low HRV in the literature. As previously described, one body of research describes reduced HRV and other markers of cardiometabolic functioning as a consequence of short sleep duration and deprivation attributed to chronic insomnia[45,90]. Alternatively, reduced pre-sleep HRV has also been conceptualized as a marker of autonomic arousal that predisposes the individual to poor sleep[29,49,53,101]. In line with Harvey's cognitive model for insomnia[91] these two processes may contribute to a self-sustaining loop in a complementary manner, whereby the heightened arousal state exhibited in chronic insomniacs may be exacerbated by daily worry about sleep issues, which could in-turn amplify sleep deficits leading to further dysregulation in the autonomic nervous system. In relation to the current findings, higher baseline HF-HRV for those with subthreshold insomnia may be more associated with better emotional regulation, less anxiety, and reduced risk for stress-related insomnia[32-34,56] presuming a lesser effect of lower-severity insomnia on sleep deficits and deprivation. Accordingly, these individuals may initially possess more psychological and physiological resources attributing to successful treatment outcomes. In contrast, low HF-HRV in those with worse insomnia severity may be primarily reflecting reduced autonomic functioning associated with prolonged sleep deprivation. Accordingly, perhaps these individuals increasingly benefit from the improved sleep consolidation following CBT-I. Alternatively, under the framework where low HF-HRV is viewed as a risk factor for higher emotionality, one group of researchers posits that those with lower pre-treatment HF-HRV may be better suited for cognitive-behavioral strategies that improve emotion regulation[102]. This study found that higher pre-treatment HF-HRV was associated with blunted cognitive-behavioral and acceptance-commitment therapy outcomes for those with anxiety disorders, whereas those with lower HF-HRV experienced heightened gains. In the context of the current study, if low HF-HRV is conceptualized as a risk factor for poorer emotional regulation, individuals with worse insomnia severity and low HF-HRV may be more likely to benefit from CBT-I given the link between enhanced sleep and improved autonomic functioning[103]. Nonetheless, given that these results are exploratory in nature, the results should be interpreted with caution given the lack of a priori hypotheses and methodological limitations.

Strengths/limitations/Future directions

The current study exhibits several notable methodological strengths. The recruitment of participants directly from the clinic setting with broad inclusion criteria increased the ecological validity of the study, where the sample was selected to represent individuals seeking treatment for insomnia in real-world clinical settings. Additionally, the small dropout rate throughout the study minimized the potential for attrition bias. The longitudinal design of this study provided

confidence in the directionality of the relationship between the pretreatment biomarkers and post-treatment symptom severity. Furthermore, this study employed sound measures of insomnia and HF-HRV strengthening the validity of the results. On the other hand, these findings may be less generalizable to the male population given that we had a predominantly female sample (86%), with research showing that women generally have greater HF-HRV than men[104]. Additionally, the elevated mean age of our sample (55.3 years) may introduce confounds that affect HRV, as HF-HRV has been shown to generally decrease with age[105], and can be further reduced following menopause[106]. Thus, these potentially confounding factors may have played a role in reducing the overall validity of the analyses as they were not included as covariates in the regression models. Given these limitations, future research should aim to replicate these findings while accounting for sex and age differences in HRV. Furthermore, since the stepped-care groups were created based on an initial ISI cut-off-score and grouping allocation followed a 1:2 ratio following randomization, this may have reduced the stochastic variability of the sample. This is especially important given that our exploratory analyses found initial ISI score to be a possible moderator of the relationship between HF-HRV and treatment response. Moreover, our exploratory analyses are limited in that they used initial ISI score as both the grouping variable of initial clinical severity as well as an outcome variable. Future research is therefore needed to replicate these exploratory analyses and specifically test these hypotheses to properly understand the clinical significance of these findings. Lastly, future research should begin to examine the effect of alternate biomarkers for autonomic activity and stress response given the association between ANS activation, sleep quality, and psychological treatment response in the literature. Sympathetic activation and salivary cortisol have been linked to reduced sleep quality and insomnia in prior work[107,108] with blood markers of inflammation related to lower sleep duration in good sleepers[109].

Conclusion

In summary, this study suggests that although baseline HF-HRV was associated with pre-treatment sleep efficiency, neither HF-HRV nor HRV reactivity to stress were related to treatment responses to CBT-I. In this stepped-care treatment delivery approach, HF-HRV was not related to treatment responses across the different stepped care CBT-I groups. Therefore, it appears that pre-treatment waking HF-HRV lacks clinical utility as a means to highlight possible sub-groups of cancer patients in need of higher intensity intervention for insomnia.

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Appendices

Appendix A. Exploratory Longitudinal Mixed Effect Models Predicting Additional Sleep Outcome Variables T1 – T5 (n=145).

	Sleep Onset Latency		Total Sleep Time		Wake After Sleep Onset		Early Morning Awakening	
Fixed Effects	Model A β (t-statistic; p-value)	Model B β (t-statistic; p-value)	Model A β (t-statistic; p-value)	Model B β (t-statistic; p-value)	Model A β (t-statistic; p-value)	Model B β (t-statistic; p-value)	Model A β (t-statistic; p-value)	Model B β (t-statistic; p-value)
Intercept	1.53 (18.90; <0.001)***	1.56 (15.62; <0.001)***	2.56 (135.73; <0.001)***	2.56 (118.13; <0.001)***	1.58 (15.27; <0.001)***	1.58 (12.54; <0.001)***	1.38 (10.61; <0.001)***	1.44 (9.47; <0.001)***
Time	-0.049 (-8.30; <0.001)***	-0.060 (-2.78; 0.0056)**	0.0074 (6.80; <0.001)***	0.0074 (1.88; 0.0602)^{t}	-0.065 (-8.81; <0.001)***	-0.066 (-2.48; 0.0134)*	-0.068 (-8.29; <0.001)***	-0.090 (-3.06; <0.0024)**
HF-HRV	-0.027 (-1.85; 0.0660)^{t}	-0.033 (-1.79; 0.0795)^{t}	0.0078 (2.30; 0.0230)*	0.0078 (1.98; 0.0492)*	-0.0037 (-0.20; 0.842)	-0.0046 (-0.20; 0.843)	-0.0013 (-0.05; 0.957)	-0.013 (-0.48; 0.631)
HF-HRV X Time		0.0021 (0.52; 0.602)		~0 (-0.02; 0.988)		~0 (0.06; 0.949)		0.0043 (0.81; 0.420)

Note. t < .10; *p<.05; **p<.01; ***p<.001; HF-HRV = Resting High Frequency Heart Rate Variability.