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Cognitive behavioural therapy for insomnia does not appear to have a substantial impact on early markers of cardiovascular disease: A preliminary randomized controlled trial

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Abstract

According to the World Health Organization, cardiovascular diseases are the leading cause of death in the world. Therefore, early prevention of these diseases is a public health priority. Epidemiological data suggest that insomnia may be a modifiable risk factor for cardiovascular diseases. A randomized controlled trial in a sample of insomnia patients without cardiovascular disease was conducted to investigate the effects of insomnia treatment on early markers of cardiovascular diseases assessed by 24-hr ambulatory blood pressure, heart rate and heart rate variability monitoring, and morning fasting blood samples. Forty-six patients with insomnia disorder were randomized to cognitive behavioural therapy for insomnia (CBT-I; n = 23) or a waitlist control condition (n = 23). Contrary to the hypothesis, intention-to-treat analyses did not show any significant treatment effects on early markers of cardiovascular disease (d = 0.0–0.6) despite successful insomnia treatment (d = 1.3). Potential methodological and conceptual reasons for these negative findings are discussed. Future studies might include larger sample sizes that are at risk of cardiovascular diseases and focus on other cardiovascular markers.

KEYWORDS

cardiovascular risk, CBT-I, insomnia

German Clinical Trials Register, https://www.drks.de, DRKS00007128

1 | INTRODUCTION

According to the World Health Organization, cardiovascular diseases are the leading cause of death in the world (World Health Organization, 2016). Thus, early prevention of these diseases and the identification of modifiable risk factors are public health priorities potentially affecting millions of people worldwide.

Insomnia, defined by difficulties initiating and/or maintaining sleep and daytime consequences, might be an important but hitherto neglected risk factor for cardiovascular diseases. Although insomnia is often viewed as a nuisance symptom, there is meta-analytic evidence from longitudinal epidemiological cohort studies showing that those with night-time insomnia symptoms have a 1.3–1.6 times higher risk of developing cardiovascular diseases than those without insomnia (Li, Zhang, Hou, & Tang, 2014; Sofi et al., 2014). Whether this association can be attributed to confounding factors, especially to sleep apnea, is an open question; however, there is also some evidence suggesting that this might not be the case (Fan et al., 2019). In addition to these epidemiological data, there is evidence from Mendelian randomization analyses in large samples suggesting that the link between insomnia and cardiovascular diseases might be causal in nature (Jansen et al., 2019; Lane et al., 2019). This would have very important healthcare implications because only in the case of a true causal relationship, can the successful treatment of insomnia be assumed to reduce the risk of cardiovascular diseases.

For ethical reasons, it appears to be inappropriate to conduct randomized controlled trials comparing standard insomnia treatment with a non-treated control group to investigate the long-term impact on the incidence of cardiovascular diseases. However, it is possible to investigate the effects of insomnia treatment on early markers of cardiovascular disease such as blood pressure (Law, Morris, & Wald, 2009), heart rate (Jouven et al., 2005; Zhang, Shen, & Qi, 2016), heart rate variability (Lahiri, Kannankeril, & Goldberger, 2008) or blood sample parameters (C-reactive protein [CRP] (Danesh et al., 2004); n-terminal pro-brain natriuretic peptide [NT-proBNP] (Geng, Huang, Song, & Song, 2017); cystatin C (van der Laan et al., 2016)). This approach has been adopted in a few clinical trials, but with mixed outcomes. McGrath et al. (2017) did not find any effects of an online insomnia intervention on systolic blood pressure as measured by a 24-hr ambulatory blood pressure assessment. Jarrin et al. (2016) found that sleep improvements after insomnia treatment (CBT-I) correlated with measures of heart rate variability in an uncontrolled study. However, contrary to the hypothesis, treatment-related improvements in sleep parameters were associated with a reduction in parasympathetic activation and an increase in sympathovagal balance, indicating rather an adverse effect of CBT-I on heart rate variability. Irwin et al. (2014) reported a significant reduction of C-reactive protein (CRP) levels 16 months after CBT-I in a randomized controlled trial. In general, early markers of cardiovascular diseases were only secondary outcomes in two of these three studies (Irwin et al., 2014; Jarrin et al., 2016), and the hypertension trial, although methodologically rigorous, reported comparably small effects of the insomnia treatment on sleep-related outcomes, thus reducing the likelihood of finding significant treatment effects on blood pressure (McGrath et al., 2017).

The current study was specifically designed to evaluate the effects of insomnia treatment on early markers of cardiovascular diseases. A randomized controlled trial was carried out to test the effects of cognitive behavioural therapy for insomnia (CBT-I), the first-line treatment for insomnia (Qaseem, Kansagara, Forciea, Cooke, & Denberg, 2016; Riemann et al., 2017), on several cardiovascular markers. To minimize the potential effect of confounding comorbidities on trial outcomes, only patients with insomnia disorder without comorbid health conditions were recruited (Morin et al., 2015; Riemann et al., 2015). The primary hypothesis was that CBT-I would lead to a significant reduction of the average systolic blood pressure as measured by 24-hr ambulatory assessments at post-treatment. Systolic blood pressure has been selected as a primary outcome because of its reliable association with both insomnia (Meng, Zheng, & Hui, 2013) and cardiovascular diseases (Law et al., 2009). Secondary outcomes included the average 24-hr diastolic blood pressure, night-time and daytime blood pressure measures, 24-hr, night-time and daytime heart rate and heart rate variability measures, as well as early cardiovascular markers from blood samples (CRP, NT-proBNP and cystatin C). As several authors reported that only insomnia with objective short sleep duration is associated with cardiovascular outcomes (Bathgate, Edinger, Wyatt, & Krystal, 2016; Vgontzas, Liao, Bixler, Chrousos, & Vela-Bueno, 2009), exploratory analyses were carried out to investigate treatment effects in this subgroup, although these analyses did not form part of the initial study design.

2 | MATERIAL AND METHODS

2.1 | Procedure

The study flow chart of the randomized clinical trial is presented in Figure 1. The screening procedure involved a clinical interview and physical examination by an experienced psychiatrist specialized in sleep medicine, two nights of polysomnography in a sleep laboratory, and a blood test (blood cell count, and liver, renal and thyroid functioning) that was collected in the morning after the first sleep laboratory night. Afterwards, all patients completed the baseline assessments (T0), which first included a 24-hr ambulatory blood pressure, heart rate and heart rate variability monitoring, morning fasting blood and urine samples of early markers of cardiovascular diseases, and then a 1-week sleep diary and the following questionnaires: the Insomnia Severity Index (ISI; Bastien, Vallières, & Morin, 2001), Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), Multidimensional Fatigue Inventory (MFI; Smets, Garssen, Bonke, & de Haes, 1995), Epworth Sleepiness Scale (ESS; Johns, 1991), Glasgow Sleep Effort Scale (GSES; Broomfield & Espie, 2005), brief version of the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS-16; Morin, Vallières, & Ivers, 2007), Pre-Sleep Arousal Scale (PSAS; Nicassio, Mendlowitz, Fussell, & Petras, 1985), Beck Depression

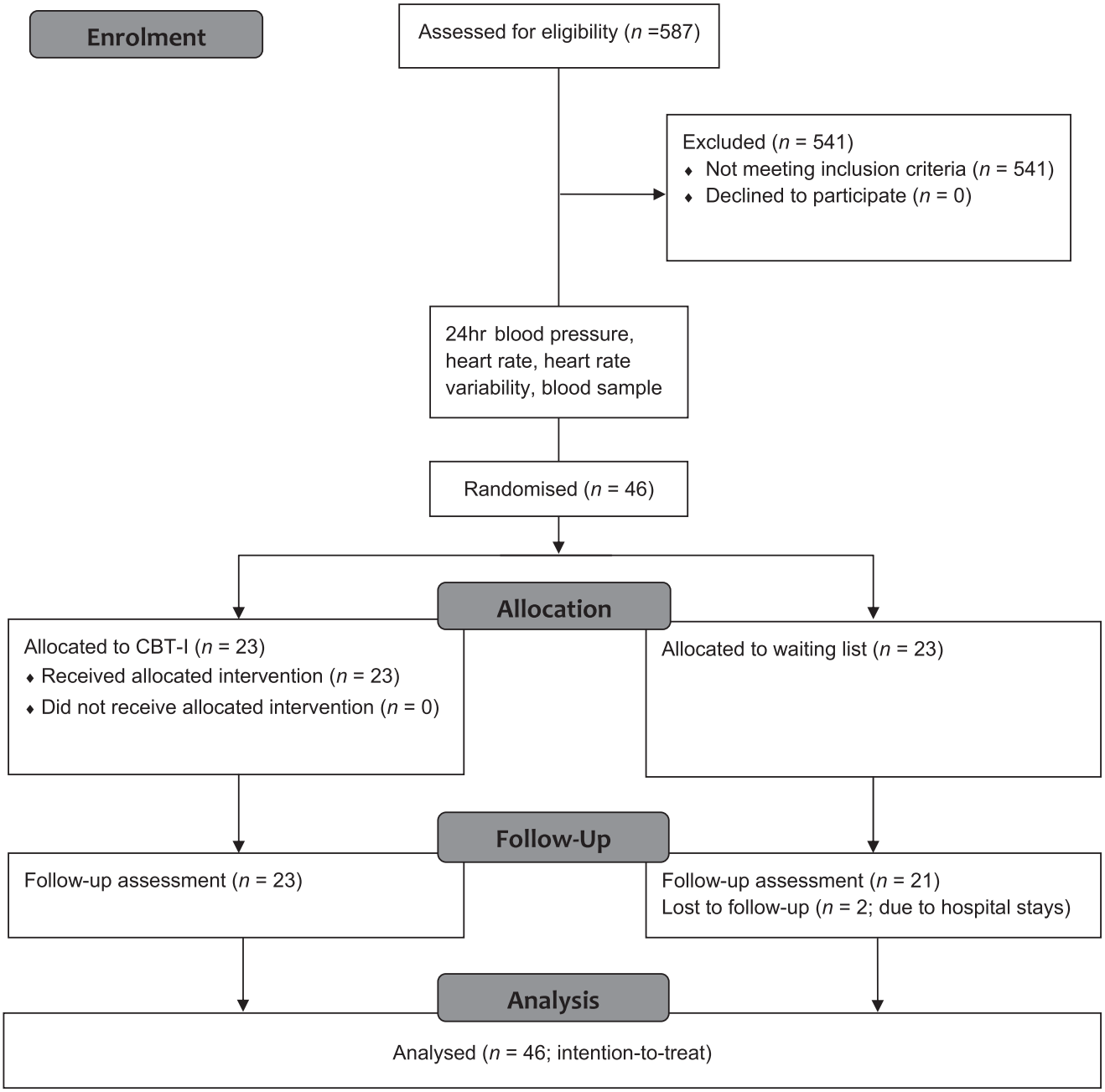

FIGURE 1 Study flow chart of the randomized controlled trial

Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), Medical Outcomes Study 36-item short-form health survey 36 (SF-36; Ware & Sherbourne, 1992), and Frost Multidimensional Perfectionism Scale (FMPS; Frost, Marten, Lahart, & Rosenblate, 1990). After completion of T0, patients were randomized using age-, gender- and ISI-stratified randomization. Patients were first assigned to one of eight possible combinations of covariates (lower vs. higher age, men vs. women, lower vs. higher ISI scores). Simple randomization was then performed within each block using sealed opaque envelopes. The post-treatment/post-waiting list assessment (T1) was conducted as soon as possible after the completion of the treatment/the 8-week waiting list condition, including the same measurements as at T0 in the same order. For ethical reasons, patients in the waiting list control condition received CBT-I after T1. Thus, no follow-up data were collected. Non-abusive use of caffeine and alcohol was allowed during study participation.

2.2 | Participants

Between March 2015 and July 2017, 46 patients diagnosed with insomnia disorder according to DSM-5 criteria participated in this study. All patients were referred to the outpatient sleep clinic at the

Department of Psychiatry and Psychotherapy at the Medical Center – University of Freiburg, Germany, by a medical specialist or primary care provider. In our sleep clinic, the diagnosis of insomnia disorder was made by a board-certified psychiatrist with a specialization in sleep medicine. Only patients with an age between 18 and 65 years were included. Exclusion criteria were any other comorbid psychiatric or sleep disorder, intake of medication affecting sleep in the 2 weeks before or during study participation (stable long-term antihypertensive or thyroid medication was allowed if the patient's medical history did not suggest clinically significant effects on sleep), a sleep apnea index >5/hr, a periodic leg movements during sleep with arousal index >5/hr, night shift work, suicidality, previous treatment with CBT-I, heart failure NYHA II-IV, heart transplants, acute infectious diseases, end-stage renal disease and cancer. The study was conducted in accordance with the Declaration of Helsinki and was registered in the German Clinical Trials Register (https://www.drks.de/drks_web/; DRKS00007128). The study protocol was approved by the Institutional Review Board of the University Medical Centre Freiburg. Written informed consent was obtained from all patients prior to any examination.

2.3 | Polysomnography

As part of the screening procedure, all patients underwent two consecutive nights of polysomnography (PSG) sleep monitoring. On the days prior to these nights they had to refrain from caffeine and alcohol. Sleep was recorded for 8 hr from 22:09 hr ± 20 min until 6:09 hr ± 20 min adjusted to individual habitual bedtimes. The first night was used as an adaptation and screening night and the second night for the assessment of sleep parameters. All recordings included electroencephalogram (EEG) (C3-A2; C4-A1), electrooculography (EOG) (horizontal and vertical) and electromyography (EMG) (submental) and were scored visually by experienced raters according to the American Academy of Sleep Medicine (AASM) criteria (Silber et al., 2007). All patients were screened for apneas and periodic leg movements by monitoring abdominal and thoracic effort, nasal airflow, oximetry, and bilateral tibialis anterior EMG. Sleep recordings were evaluated for the following parameters: total sleep time (TST); sleep onset latency, defined as time from lights out until sleep onset (defined as the first epoch of stage 2); wake after sleep onset (WASO), defined as the difference between sleep period time (SPT; time from sleep onset until final awakening) and TST; number of awakenings; sleep efficiency (ratio of TST to time in bed); arousal index (per hour); sleep apnea index (per hour); periodic leg movements during sleep with arousal index (per hour); and stages 1, 2 and slow wave sleep (SWS) and rapid eye movement sleep (REM) as percentages of SPT.

2.4 | Blood pressure

Ambulatory 24-hr systolic and diastolic blood pressure were measured at T0 and T1 on a working day using the custo screen 400 device (custo med GmbH; https://www.customed.de/), including a blood pressure cuff, a Holter Ambulatory Blood Pressure Measurement (ABPM) recorder and a three-electrode ECG transmitter with an electrode belt placed around the chest according to the manufacturer's recommendations. Recordings started and ended at 20:00 hours, with hourly blood pressure assessments between 22:00 and 06:00 hours (night-time) and half-hourly assessments before and after this period (daytime). Patients were instructed to remove the device for showering and exercise, and missing blood pressure data for the hourly and half-hourly time slots were imputed by averaging neighbouring non-missing data points. All blood pressure data were inspected visually for artefacts or outliers but none were identified.

2.5 | Heart rate and heart rate variability

Epochs of 30 s length were extracted from the ECG to analyse heart rate and heart rate variability. After applying a high-pass filter at 4.5 Hz, a peak detection algorithm was used to identify QRS complexes. Occasional ectopic beats were automatically identified and replaced with the linearly interpolated RR interval (RRI) data. Epochs with body movements or accumulated artefacts of more than 10 s were discarded from the analysis. For evaluating heart rate variability, both time and frequency domain methods were applied. In the time domain, the standard deviation of RRIs (SDNN) was computed for each epoch, reflecting overall heart rate variability. Frequency domain measures based on the fast Fourier transform (FFT) algorithm were applied on the RRI time series resampled to a regular sampling rate of 1 Hz. The whole RRI time series was filtered in two frequency bands: low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.4 Hz) using FFT. Subsequently, mean absolute values were computed for successive 30-s epochs. The LF/HF ratio was computed as a marker for sympathovagal balance. Epoch-wise heart rate, LF/HF and SDNN data were inspected visually for artefacts or outliers but none were identified.

2.6 | Blood sample

A routine fasting blood sample was taken in the morning at T0 and T1. CRP, NT-proBNP and cystatin C levels were determined by the Institute of Clinical Chemistry and Laboratory Medicine of the Medical Center – University of Freiburg, Germany, within the clinical routine. NT-proBNP levels below 50 pg/ml are not precisely determined within this clinical routine and were, thus, set to 50 pg/ml.

2.7 | Cognitive behavioural therapy for insomnia

The CBT-I intervention was provided by the first (12 patients) and last authors (11 patients) and consisted of eight weekly individual

sessions lasting 50 min each. The treatment comprised sleep hygiene education, relaxation training, sleep restriction therapy, stimulus control therapy and cognitive therapy. Sleep hygiene education involved general information about sleep and insomnia, including the so-called "sleep hygiene rules" about health practices (e.g., exercise, caffeine and alcohol use) and environmental factors (e.g., light, noise and temperature) that may promote or interfere with sleep. Relaxation therapy included progressive muscle relaxation and autogenic training. Sleep restriction therapy was based on continuous sleep diary data. The initial sleep window was generated using the average total sleep time of 7 days of sleep diary data. The window was positioned according to patient preference. The minimum time in bed was 4 hr. On a weekly basis, time in bed was either increased by 30 min when sleep efficiency was >90% or decreased by 30 min when sleep efficiency was <80% and remained the same when sleep efficiency was 80%–90%. Stimulus control therapy was used as described in Bootzin (1972). Cognitive elements included cognitive restructuring, constructive worry and paradoxical intention.

2.8 | Statistical analysis

All analyses were carried out using the statistical software package R (http://www.R-project.org/). Descriptive presentation of the data includes mean values and standard deviations. Data were analysed using an intention-to-treat approach. Missing data at T1 were imputed using the last-observation-carried-forward method. Treatment effects were analysed using two-way ANOVAs with the between-subject factor group (treatment vs. waiting list), the within-subject factor time (T0 vs. T1), and the group × time interaction. The primary outcome was the mean 24-hr systolic blood pressure. The level of significance was set at $p < .05$ (two-tailed). Exploratory analyses were carried out to investigate treatment effects in those with objective short sleep duration. To be consistent with the data from the Penn State Cohort (e.g., Vgontzas et al., 2009), insomnia with objective short duration was defined as a polysomnographically determined total sleep time of <6 hr on the first sleep laboratory night. For the exploratory analyses, insomnia patients without objective short sleep duration were removed from the treatment group and the same analyses were conducted as described above for the primary analyses.

3 | RESULTS

3.1 | Sample characteristics and treatment efficacy

The study sample included 46 patients with insomnia disorder (29 women, 17 men; CBT-I group: 14 women, 9 men; waiting list control group: 15 women, 8 men) with an age of 41.0 ± 14.5 years (CBT-I group: 40.8 ± 14.0 years; waiting list control group: 41.2 ± 15.1 years). Missing data at T1 was imputed for two patients of the waiting list control group who could not be assessed at T1 as they were admitted to hospital. One patient had an accident not related to daytime fatigue/tiredness and the other patient suffered from severe back pain involving intake of analgesic medication.

TABLE 1 Baseline data (second night of polysomnography)

Variable	Second night, treatment group	Second night, waiting list control group
TST (min)	397.8 ± 40.9	409.8 ± 34.6
SOL (min)	19.9 ± 12.0	19.0 ± 12.1
WASO (min)	43.7 ± 27.4	45.7 ± 29.4
NOA	25.7 ± 8.0	26.2 ± 6.3
SE (%)	83.0 ± 8.6	85.4 ± 7.2
Arousal index (hr^{-1})	13.7 ± 4.7	15.5 ± 6.8
Apnea index (hr^{-1})	0.4 ± 0.5	0.2 ± 0.6
PLMS index (hr^{-1})	0.7 ± 1.7	0.5 ± 0.8
Stage 1 (% SPT)	7.9 ± 3.3	7.5 ± 3.2
Stage 2 (% SPT)	53.3 ± 8.4	54.7 ± 7.0
SWS (% SPT)	10.6 ± 8.1	9.8 ± 8.3
REM (% SPT)	18.3 ± 5.4	18.0 ± 4.9

Note: Results depict means ± standard deviations.

Abbreviations: NOA, number of awakenings; PLMS, periodic leg movements during sleep; REM, rapid eye movement sleep; SE, sleep efficacy; SOL, sleep onset latency; SPT, sleep period time; SWS, slow wave sleep; TST, total sleep time; WASO, wake after sleep onset.

Polysomnographic data of the sample are presented in Table 1 and Table S1. Eleven patients in the CBT-I group were assigned to the group with objective short sleep duration. On average, the patients in the CBT-I group attended 7.3 ± 1.3 treatment sessions in 8.9 ± 3.0 weeks; the average duration between T0 and T1 was 12.7 ± 4.8 weeks. T0 and T1 data for subjective sleep-related and psychopathology-related outcomes are presented in Table 2 and Table S2, illustrating a high treatment efficacy ($d = -1.3$) comparable to meta-analytical data of CBT-I effects (Ballesio et al., 2018; van Straten et al., 2018).

3.2 | Blood pressure

Blood pressure data are presented in Table 3. There was no significant group × time interaction effect for mean 24-hr systolic or diastolic blood pressure. Likewise, there was no significant group × time interaction effect on night-time systolic or diastolic blood pressure or on daytime systolic or diastolic blood pressure. In addition, exploratory correlational analyses did not show any significant associations between improvement in ISI scores and changes in 24-hr, night-time or daytime systolic or diastolic blood pressure levels between T0 and T1 (all $p > .2$). This pattern of results suggests that CBT-I, at a dose effective for insomnia, had no detectable effects on blood pressure. Figure 2 presents group data for each time slot. The

TABLE 2 Psychometric data

	Treatment		Control		Treatment × Time		Effect size
Questionnaire	Pre	Post	Pre	Post	*F*	*p*	*d*
ISI	15.4 ± 4.3	6.5 ± 3.8	14.5 ± 5.0	13.0 ± 4.7	35.51	.000	−1.3
SD-TST (hr)	5.9 ± 1.4	6.3 ± 1.4	5.7 ± 1.1	6.2 ± 1.3	0.10	.757	−0.1
SD-TIB (hr)	8.1 ± 0.9	7.1 ± 1.1	7.9 ± 0.8	8.0 ± 0.9	8.98	.005	−0.8
MFI	50.1 ± 11.4	39.1 ± 11.5	55.3 ± 14.7	53.1 ± 18.0	7.86	.007	−0.8
BDI	6.5 ± 5.4	3.2 ± 4.0	9.7 ± 4.3	8.8 ± 5.0	4.58	.038	−0.6
STAI (state)	37.9 ± 7.9	32.6 ± 7.9	43.4 ± 10.0	41.3 ± 10.6	2.09	.155	−0.4
STAI (trait)	39.5 ± 8.0	34.0 ± 8.2	43.5 ± 8.6	42.1 ± 9.2	6.34	.016	−0.4

Note: Results depict means ± standard deviations.

Abbreviations: BDI, Beck Depression Inventory; ISI, Insomnia Severity Index; MFI, Multidimensional Fatigue Inventory; SD-TIB, sleep diary – time in bed; SD-TST, sleep diary – total sleep time; STAI (state), State-Trait Anxiety Inventory (state); STAI (trait), State-Trait Anxiety Inventory (trait).

TABLE 3 Blood pressure data (mm Hg)

	Treatment		Control		Treatment × Time		Effect size
Variable	Pre	Post	Pre	Post	*F*	*p*	*D*
Mean 24-hr systolic blood pressure	124 ± 11	124 ± 13	126 ± 11	125 ± 11	0.20	.654	0.1
Mean 24-hr diastolic blood pressure	83 ± 7	83 ± 9	84 ± 5	83 ± 7	0.99	.325	0.3
Night-time systolic blood pressure	113 ± 12	113 ± 13	115 ± 13	116 ± 13	0.13	.725	0.1
Night-time diastolic blood pressure	74 ± 8	73 ± 8	75 ± 7	75 ± 8	0.04	.846	−0.1
Daytime systolic blood pressure	127 ± 12	127 ± 14	129 ± 11	128 ± 12	0.36	.553	0.2
Daytime diastolic blood pressure	85 ± 8	85 ± 9	87 ± 5	85 ± 8	1.10	.301	0.3

Note: Results depict means ± standard deviations.

exploratory analyses for treatment effects in those with objective short sleep duration also did not show any significant group × time interaction effect for 24-hr, night-time or daytime diastolic blood pressure (all $p > .1$).

3.3 | Heart rate and heart rate variability

One patient in the treatment group had to be excluded from the heart rate and heart rate variability analysis. The patient took off the electrocardiography belt early in the evening at T0 and refused to wear it again at T1. For three additional patients, two of whom were in the treatment group and one in the control group, the last-observation-carried-forward method had to be used because of device handling errors or technical problems with the electrocardiography belt at T1. Heart rate and heart rate variability data are presented in Table 4. There was no significant group × time interaction effect for mean 24-hr heart rate, LF/HF or SDNN. Likewise, there were no significant group × time interaction effects on night-time heart rate, LF/HF or SDNN or on daytime heart rate, LF/HF or SDNN. In addition, exploratory correlational analyses did not show any significant associations between improvement in ISI scores and changes in 24-hr, night-time or daytime HR, LF/HF or SDNN between T0 and T1 (all $p > .2$). This pattern of results suggests that CBT-I had no detectable effects on heart rate and heart rate variability in this sample. The exploratory analyses for treatment effects in those with objective short sleep duration also did not show any significant group × time interaction effect for 24-hr, night-time or daytime heart rate, LF/HF or SDNN (all $p > .1$).

3.4 | Blood test

Due to errors in blood sampling and analysis, there were two missing datasets for CRP at T0. These two patients, who both formed part of the intervention group, were excluded from the analysis. In addition, the last-observation-carried-forward method was used for one patient in the control group with missing data at T1, as well as for two patients in the intervention group and one patient in the control group with CRP levels >10 mg/L at T1. CRP data are presented in Table 5. There was no significant group × time interaction effect on CRP levels and no significant correlation between improvement in ISI scores and changes in CRP levels between T0 and T1 ($r = -.06$; $p = .722$).

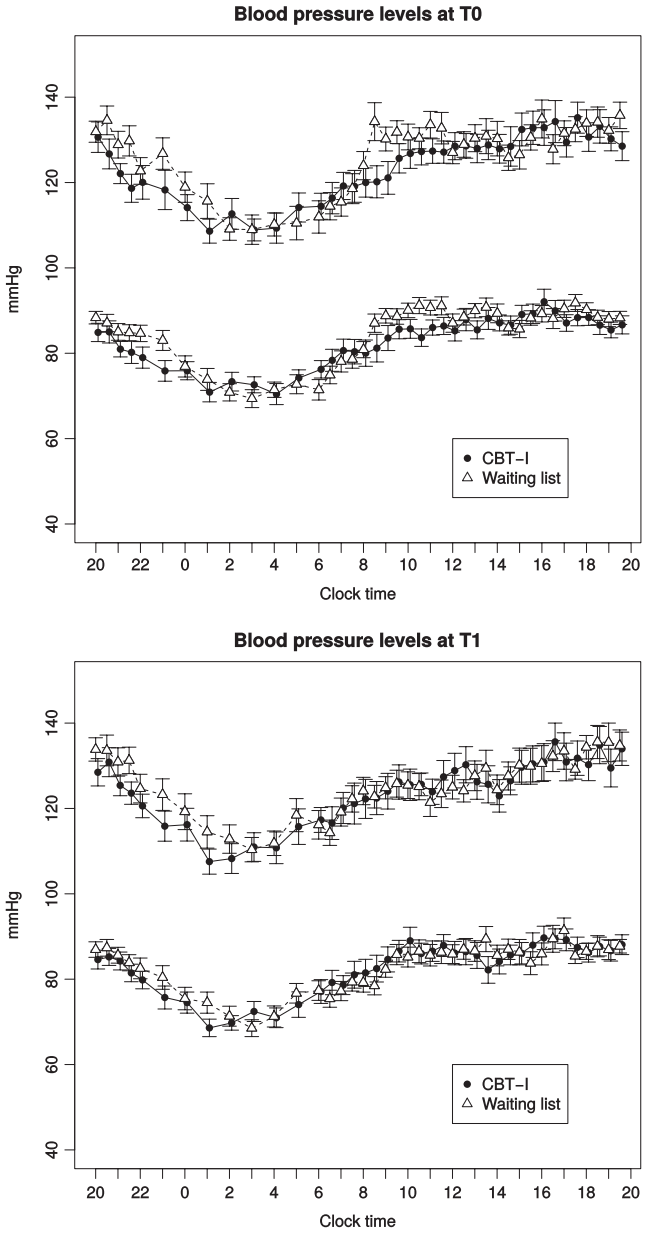

FIGURE 2 Group data for systolic (top) and diastolic (bottom) blood pressure for each time slot

There was one missing dataset for NT-proBNP at T0, and this patient was excluded from the intervention group. The last-observation-carried-forward method was used for one patient from the control group with missing data at T1. NT-proBNP data are presented in Table 5. There was no significant group × time interaction effect on NT-proBNP levels and no significant correlation between improvement in ISI scores and changes in NT-proBNP levels between T0 and T1 ($r = -.18$; $p = .239$).

There were two missing datasets for cystatin C at T0, one in the intervention group and one in the control group, and these patients were excluded. The last-observation-carried-forward method was used for one additional patient in the control group with missing data at T1. Cystatin C data are presented in Table 5. There was no significant group × time interaction effect on cystatin C levels and no significant correlation between improvement in ISI scores and changes in cystatin C levels between T0 and T1 ($r = -.06$; $p = .723$).

This pattern of results suggests that CBT-I had no detectable effects on blood sample parameters in this sample. The exploratory analysis for treatment effects in those with objective short sleep duration also did not show any significant group × time interaction effect for CRP, NT-proBNP and cystatin C levels ($p > .1$).

4 | DISCUSSION

In the current study sample, no evidence could be found in support of the idea that CBT-I has an effect on early markers of cardiovascular disease, that is, systolic and diastolic blood pressure, heart rate and heart rate variability measures, CRP, NT-proBNP and cystatin C, in patients with insomnia disorder. The data on insomnia severity show that this result emerged despite successful insomnia treatment with an ISI reduction of 8.9 points in the treatment group compared to 1.5 points in the waiting list control group. Therefore, it appears rather unlikely that the absence of a group by time effect on early markers of cardiovascular disease can be attributed to an ineffective therapeutic intervention.

There are a number of potential reasons for these negative findings. First, the study did not focus on individuals at risk of cardiovascular disease or individuals with pathological levels of early markers for cardiovascular disease (e.g., patients with hypertension or elevated CRP levels). These individuals might have had a greater potential for improvement in early markers of cardiovascular disease, and thus, the current study might have been limited by floor and ceiling effects. However, in principle, markers of cardiovascular disease can be changed even when they are in the normal range, at least by pharmacological agents (Thomopoulos, Parati, & Zanchetti, 2017). To the best of our knowledge, there is no evidence suggesting that non-pharmacological interventions show a fundamentally different pattern of results (e.g., with positive effects on increased blood pressure and no effect on normal or decreased blood pressure).

Second, it is conceivable that potential cardioprotective effects of CBT-I manifest themselves only in the long term, and that our study was not able to detect these effects because of a lack of follow-up assessment. Our study, however, was designed to investigate short-term effects of CBT-I on early markers of cardiovascular disease for the ethical reasons described above. Although most studies report that CBT-I effects on subjective sleep-related outcomes are simply sustained at follow-up assessments (Morin, Colecchi, Stone, Sood, & Brink, 1999), knowledge on the time course of psychotherapy effects on physiological outcomes is very limited (Abbott et al., 2014; Gonçalves et al., 2015).

Third, in the current study, patients with insomnia were selected without reference to objective sleep parameters. Although this is in line with diagnostic criteria and improves the ecologic validity of our results, considerable evidence suggests that polysomnographically determined short sleep duration may be a marker of biologic severity

TABLE 4 Heart rate and heart rate variability

	Treatment		Control		Treatment × Time		Effect size
Variable	Pre	Post	Pre	Post	*F*	*p*	*d*
Mean 24-hr HR (bpm)	75 ± 7	77 ± 7	75 ± 9	74 ± 9	2.88	.097	0.5
Mean 24-hr LF/HF	2.1 ± 0.5	2.1 ± 0.5	2.1 ± 0.4	2.1 ± 0.4	2.01	.163	0.4
Mean 24-hr SDNN (ms)	50 ± 17	48 ± 16	51 ± 19	51 ± 17	0.65	.425	−0.2
Night-time HR (bpm)	64 ± 7	66 ± 7	65 ± 11	65 ± 11	0.58	.450	−0.2
Night-time LF/HF	1.8 ± 0.6	1.8 ± 0.5	1.7 ± 0.5	1.8 ± 0.5	0.02	.885	0.0
Night-time SDNN (ms)	55 ± 22	51 ± 22	56 ± 27	54 ± 20	0.38	.541	−0.2
Daytime HR (bpm)	81 ± 8	82 ± 8	80 ± 10	78 ± 9	3.89	.055	0.6
Daytime LF/HF	2.2 ± 0.5	2.3 ± 0.6	2.3 ± 0.4	2.2 ± 0.5	3.31	.076	0.5
Daytime SDNN (ms)	48 ± 16	47 ± 15	49 ± 16	50 ± 15	0.47	.496	−0.2

Note: Results depict means ± standard deviations.

Abbreviations: HF, high frequency; HR, heart rate; LF, low frequency; SDNN, standard deviation of RR intervals.

TABLE 5 Blood test

	Treatment		Control		Treatment × Time		Effect size
Variable	Pre	Post	Pre	Post	*F*	*p*	*d*
CRP (mg/L)	1.0 ± 1.3	1.4 ± 1.6	0.8 ± 0.8	1.0 ± 0.9	0.47	.496	0.2
NT-proBNP (pg/ml)	73 ± 38	78 ± 47	66 ± 34	69 ± 55	0.07	.798	0.1
Cystatin C (mg/L)	0.87 ± 0.10	0.85 ± 0.09	0.83 ± 0.13	0.84 ± 0.13	1.64	.207	−0.4

Note: Results depict means ± standard deviations.

Abbreviations: CRP, C-reactive protein; NT-proBNP, N-terminal pro brain natriuretic peptide.

of insomnia (Vgontzas, Fernandez-Mendoza, Liao, & Bixler, 2013) and related to hypertension (Vgontzas et al., 2009, 2013), heart rate variability (Spiegelhalder et al., 2011) and inflammatory markers (Fernandez-Mendoza et al., 2017). Against this background, it is conceivable that successful insomnia treatment might have a more pronounced effect on early markers of cardiovascular disease in insomnia patients with objective short sleep duration. This idea did not form part of the initial set of hypotheses as laid out in the study design, but was also pursued. Yet, additional exploratory analyses did not support this idea. However, because the sample size for these analyses was small, future investigations should explore this with greater statistical power. In this context, it has to be admitted that a polysomnographic assessment at T1 would have been informative for a more complete evaluation of the effects of objective short sleep duration on early markers of cardiovascular disease.

Fourth, both at T0 and T1, polysomnographic recordings during the 24-hr blood pressure, heart rate and heart rate variability assessments would have helped to evaluate whether a potential treatment effect on the night-time parameters might have been compromised by a pre- to post-treatment reduction in total sleep time in the CBT-I group due to sleep restriction or stimulus control therapy. Put differently, it is also conceivable that possible negative cardiovascular effects due to sleep restriction therapy mask potentially positive effects of behavioural therapy, resulting in a non-significant change in cardiovascular outcome parameters. Indeed, objective sleep duration appears to be moderately reduced following CBT-I (Mitchell, Bisdounis, Ballesio, Omlin, & Kyle, 2019). Thus, if objective sleep duration is a major factor linking insomnia to cardiovascular disease, CBT-I may fail to improve early markers of cardiovascular disease because of a lack of positive effects on objective sleep duration.

Fifth, the sample size of the current study needs to be discussed. The *a-priori* power analysis was based on the assumption that CBT-I has the potential to produce medium-sized effects on early markers of cardiovascular disease (ANOVA within-between interaction; effect size $f = 0.25$; $\alpha = 0.05$; $1 - \beta = 0.90$; correlation among repeated measures $r = .5$). This was based on the observation that case–control studies in highly selected samples have reported medium-sized differences in physiological measures between patients with insomnia and healthy controls (Spiegelhalder et al., 2015), and that medium effect sizes were reported for antihypertensive drugs (Leucht, Helfer, Gartlehner, & Davis, 2015). However, CBT-I effects on cardiovascular markers might be considerably smaller than this, and our study lacks the power to detect such effects.

Two other limitations of the current investigation have to be acknowledged. First, 16% of the time slots for blood pressure needed to be interpolated, 4% of the epochs for heart rate and heart rate variability analyses did not contain valid data, and 5%–11% of the blood

samples were missing or invalid. This reduces the statistical power of the current analyses. Second, we recruited only patients with insomnia disorder without comorbid health conditions. Although this reduces potential effects of confounding comorbidities on outcome parameters, it also reduces the generalizability of the results for the whole population of patients with insomnia, which often occurs comorbid to other conditions (Vgontzas et al., 2009, 2013).

Finally, our results should be interpreted against the background of previous studies, which have investigated the effect of CBT-I on heart rate variability, blood pressure and inflammatory markers as early markers of cardiovascular disease. Jarrin et al. (2016) found that treatment-related sleep improvements were associated with a reduction in parasympathetic activation, indicating rather an adverse effect of CBT-I on heart rate variability. According to the authors, this might be due to higher levels of stress induced by the surrounding of a sleep laboratory during heart rate variability measurements. Yet our study, in which patients' heart rate variability was measured at home, a much more naturalistic setting than a sleep laboratory, found no effect of CBT-I on heart rate variability. In line with McGrath et al. (2017), we found no effect of CBT-I on blood pressure. Although their results may be at least partly due to a rather modest treatment effect of CBT-I (ISI reduction of 2.8 points in the treatment group), this is rather unlikely for our study (ISI reduction of 8.9 points in the treatment group). This suggests that CBT-I does not appear to have an effect on blood pressure in insomnia patients. With regard to inflammatory risk, our results confirm Irwin et al.'s (2014) finding that CBT-I has no immediate effect on CRP. But Irwin et al.'s (2014) study also demonstrates a long-term effect of CBT-I on CRP. This lends credibility to the hypothesis that CBT-I does have a positive effect on cardiovascular risk factors, but only in the longer term. In light of this, future studies investigating CBT-I as a cardiovascular safeguard should apply a longitudinal design.

In summary, CBT-I had no significant impact on early markers of cardiovascular disease in this randomized controlled trial of insomnia patients without cardiovascular diseases. In light of these preliminary findings, future studies might include larger sample sizes, samples at risk of cardiovascular diseases, longer observational periods and/or other markers of cardiovascular disease. In addition, other evidence-based treatments for insomnia (e.g., pharmacological treatments) might also be investigated for their effects on early markers of cardiovascular disease in future trials.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Conceptualization: AFJ and KS. Formal analysis: AFJ, BF and KS. Investigation: AFJ and KS. Methodology: AFJ, BF and KS. Writing, original draft: AFJ and KS. Writing, review and editing: AFJ, EH, BF, UA, FH, CB, KD, ES, CN, SDK, DR, JB and KS.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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