The Effect of Cognitive Behavioral Therapy for Insomnia in People with Type 2 Diabetes Mellitus, Pilot RCT Part II: Diabetes Health Outcomes

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Abstract

Background: Previous studies have shown the negative impact of sleep disturbances, specifically insomnia symptoms, on glucose metabolism for people with type 2 diabetes (T2D). People with insomnia symptoms are at risk of poor glycemic control and suboptimal diabetes self-care behavior (DSCB). Investigating the impact of a safe and effective intervention for individuals with T2D and insomnia symptoms on diabetes health outcomes is needed. Therefore, the aim of this exploratory study is to examine the effect of Cognitive Behavioral Therapy for Insomnia (CBT-I) on glycemic control, DSCB, and fatigue.

Methods: Twenty-eight participants with T2D and insomnia symptoms after passing an eligibility criteria at a medical research center were randomly assigned to CBT-I (n=14) or Health Education (HE; n=14). The CBT-I and HE groups received 6 weekly one-hour sessions. This Randomized Controlled Trial (RCT) will be using a non-inferiority framework to test the effectiveness of CBT-I. Validated assessments were administered at baseline and post-intervention to assess glycemic control, DSCB, and fatigue. A Wilcoxon signed-rank test was utilized to compare within-group changes from baseline to post-intervention. A Mann-Whitney test was utilized to measure the between-group differences. Linear regression was used to assess the association between blood glucose level and number of days in the CBT-I group.

Results: The recruitment duration was from October 2018 to May 2019. A total of 13 participants completed the interventions in each group and included in the final analysis. No adverse events due to being a part of this RCT were reported. CBT-I participants showed significantly greater improvement in glycemic control, DSCB, and fatigue. There significant association between the number of days in the CBT-I intervention with blood glucose level before bedtime (B=-0.56, *p*=.009) and after awakening in the morning (B=-0.57, *p*=.007).

Conclusions: This study demonstrated a clinically meaningful effect of CBT-I on glycemic control in people with T2D and insomnia symptoms. Also, CBT-I positively impacted daytime functioning, including DSCB and fatigue. Future research is needed to investigate the long-term effect of CBT-I on laboratory tests of glycemic control and to understand the underlying mechanisms of any improvements.

Trial registration: Clinical Trials Registry (NCT03713996). Registered 22 October 2018, https://clinicaltrials.gov/ct2/show/NCT03713996

Introduction

A systematic review and meta-analysis of epidemiological studies found an association between sleep disturbances and poor diabetes health outcomes in people with type 2 diabetes (T2D) [1]. Specifically, a high prevalence of sleep disturbances among people with T2D were associated with poor glycemic control as measured by glycated haemoglobin (HbA1c) and low adherence to optimal diabetes self-care behavior (DSCB) [1, 2]. A recent study found that people with T2D and insomnia symptoms had worse scores in several health domains related to DSCB compared to people with T2D without insomnia symptoms [3]. Additionally, increases in insomnia severity were associated with suboptimal DSCB among people with T2D [3]. It is possible that sleep disturbances lead to fatigue and physical inactivity, which then contributes to poor diabetes health outcomes [4].

Previous studies have shown insomnia symptoms are common among people with T2D [5, 6], and other studies have shown insomnia symptoms to be a mortality risk, even after controlling for comorbidities [7, 8]. The increased mortality risk in people with insomnia might be due to inflammation, which is also associated with cardiovascular diseases [9]. Therefore, while the mechanisms underlying the relationship between T2D and insomnia symptoms are not well understood [10, 11], there is a need to identify an effective treatment for insomnia symptoms to improve T2D health outcomes.

The American Academy of Sleep Medicine recommends treating insomnia symptoms using Cognitive Behavioral Therapy for Insomnia (CBT-I) [12]. CBT-I has been shown to have a superior treatment effect when compared to sleep medications [13], which is significant since these medications can possibly lead to negative side effects [14] or metabolic alterations [15, 16]. Further, a recent study supported the need to investigate the effect of CBT-I on people with T2D due to the harmful side effects of pharmacological treatments and the limited evidence of effectiveness [17].

CBT-I is a potentially efficacious intervention for people with T2D as it may address altered metabolism. CBT-I modules may interrupt the physiological mechanisms such as hypothalamic pituitary-adrenal (HPA) axis activation [10, 11], which may be one link between insomnia symptoms and T2D. For example, it has been shown that an association between sleep homeostasis and glucose regulation could be adjusted using sleep restrictions and stimulus control therapies [18]. In addition, ancillary modules in CBT-I, such as relaxation techniques and sleep hygiene, could play a role in reducing stress and nocturia episodes (i.e., the number of bathroom visits per night) [19–21].

The objective of this study was to explore the effect of 6 sessions of CBT-I on HbA1c, DSCB and fatigue. We hypothesized participants in the CBT-I group would have greater improvements in HbA1c, DSCB, and fatigue compared to participants in the health education (HE) group. We anticipated an improvement in sleep and concomitant outcomes (Part I of the intervention trial)[22] will positively impact people with T2D and health outcomes (Part II of the intervention trial) because of the relationship between insomnia symptoms and poor diabetes-related health outcomes.

Methods

Participants and Materials

The procedures and interventions for this project were described in a published protocol report [23]. This intervention trial was described according to the CONSORT 2010 guideline [24]. Prior to being enrolled in the study, potential participants were screened according to eligibility criteria, which are presented in Table 1.

Table 1
The inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Ages between 40 to 75 years	Self-reported neurological diseases (e.g. Alzheimer's disease, Parkinson's disease, Traumatic Brain Injury, Stroke, Multiple Sclerosis)
Self-reported diagnosis of type 2 diabetes	Self-reported untreated sleep disorders as well as: - Scored > 4 on Stop-Bang score - Failed to pass Restless Leg Syndrome Diagnostic Index
Scored > 10 on Insomnia Severity Index and self-reported symptoms of insomnia at least 3 nights/week for the past 3 months	Scored ≥ 7 on Brief Pain Inventory
Able to travel to the University of Kansas Medical Center to attend 6 sessions	Scored ≥ 21 on Beck Depression Scale
Able to understand and follow verbal commands in English	Scored ≥ 15 on Generalized Anxiety Disorder-7
	Self-reported following medical issues: Chronic Fatigue Syndrome, Fibromyalgia, Bipolar, Seizure Disorders and Rheumatic Diseases, Dialysis, blindness, trans-femoral amputation, speech deficits, or significant auditory impairment
	Performed night shift work
	Heavy alcohol drinker (≥ 15 alcohol drinks per week for men and ≥ 8 alcohol drinks per week for women)
	Reported being pregnant

Study Design

This RCT had an allocation ratio of 1:1, and utilized a superiority framework to test the effectiveness of the CBT-I. Participants were randomly assigned to either the CBT-I group (n = 14) or the HE group (n = 14). We used age to stratify participants into either the older (63–75 years) or the younger (40–62 years) age group. This study was registered in the Clinical Trials Registry (NCT03713996) [25]. This study was approved by the Institutional Review Board and the Human Subjects Committee of the University of Kansas Medical Center. All participants signed a written informed consent before the assessment visit. Data collections and provided interventions were taken place at the University of Kansas Medical Center.

Outcomes

All participants completed outcome measures at baseline, and all participants completed the same outcome measures one week after completing the intervention. The primary outcome, insomnia severity, was included in the RCT Part I in which the power calculation was established and its preliminary data was published elsewhere [22].

Diabetes control measurement

A point-of-care instrument was used to assess HbA1c using a disposable finger stick HbA1c kit (A1CNow + test kit; Bayer Healthcare, Tarrytown, NY). This instrument measures the level of glycosylated hemoglobin via immunoassay, reflecting average glucose blood levels over the past 6 to 12 weeks [26]. During a previous diabetes management program, the A1CNow + provided accuracy and precision when performing a point-of-care, and a 0.05 reduction in HbA1c is considered clinically meaningful [27]. In addition, random blood glucose (RBG) levels were assessed by a glucose meter (FreeStyle Flash, Contour® Bayer Healthcare, Diagnostic Division, Tarrytown, NY). Participants were not asked to follow dietary restrictions prior to the RBG test. During the intervention, participants in the CBT-I group were asked to record their blood glucose level on their own right before bedtime and after awakening in the morning throughout the study period (i.e., 7 days/nights per week for 7 weeks).

Diabetes self-care behavior (DSCB)

Self-care was assessed using the Diabetes Care Profile (DCP), which is a validated survey that measures 13 psychosocial and educational factors [28, 29]. The 13 domains are associated with the management of diabetes, including understanding management of practice, support, control problems, social and personal factors, positive attitude, negative attitude, care ability, importance of care, self-care adherence, diet adherence, long-term care benefits, exercise barriers, and glucose monitoring barriers [29]. A standardized total DCP composite score was established to present all 13 domains that were scored according to the Fitzgerald et al. scoring criteria [29]. Next, each participant's domain score was standardized using z-scores, and then averaged to create a standardized total DCP composite score. High scores on the DCP composite score indicate better DSCB.

Fatigue severity

Daily fatigue was measured using the Fatigue Severity Scale (FSS) that consists of 9 items developed to assess disabling fatigue on daily life. The FSS has been shown to be valid and reliable [30]. Each item was measured on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). Mean item response for the completed FSS items was used for analysis.

Interventions

All participants in the CBT-I group and HE group attended 6 sessions that were scheduled consistently one session per week with the CBT-I provider. Neither the CBT-I provider nor the participants were blinded in this study. The protocol paper describes session by session of both interventions [23].

Cognitive Behavioral Therapy for Insomnia

Five main therapeutic techniques were provided during the 6-session including sleep restriction therapy, stimulus control therapy, sleep hygiene, relaxation techniques, and cognitive therapy. In order to monitor nightly sleep changes and issues, the CBT-I provider reviewed the sleep diary for each session. In addition, calculates of sleep changes were made to prescribe the sleep schedules for the following week.

Health Education

Five main health education materials were introduced during the 6-session including brief sleep hygiene, foot care, diabetes classifications, healthy diet, and physical activity. During the HE sessions, we provided informal face to face interview to

engage the participants into the conversations. Participants' comprehensive and experiences about the provided materials were facilitated through open questions.

Statistical analysis

All data analyses were performed using SPSS 23.0 for Mac (Chicago, IL) and R (https://www.R-project.org/) [31]. Descriptive statistics included means and standard deviations for the assessed variables. We used Shapiro–Wilk tests to assess the normality of residuals during model development. For the main analysis, we used Mann-Whitney U tests to examine the between-group differences of the CBT-I and HE groups in HbA1c, RBG, DSCB, and fatigue change scores. We also used Wilcoxon signed-rank tests to compare within-group changes for both groups. Effect sizes were calculated using Cohen's *d* [32]. We calculated absolute percentage changes in all outcomes to graph the between-group differences. For secondary purpose, we used linear regression analyses to predict blood glucose levels (before bedtime and after awakening in the morning) based on 49 days across the course of the study including 6 weeks CBT-I and post-assessment. For all analyses, the alpha level was set at .05.

Results

The consort of this intervention trial shows a total of 28 participants enrolled in the study, and 26 participants completed the study (Fig. 1). There were no baseline differences between groups in demographics including age, sex, ethnicity, and education ($p > .05$) [22]. In addition, there were no significant between-group differences in the baseline assessments of HbA1c, RBG, DCP composite score, or FSS (Table 2).

Table 2
Comparison of clinical variables within and between groups.

	CBT-I (mean±SD)		p^a	HE (mean±SD)		p^a	p^b	p^c
	Pre, n = 14	Post, n = 13		Pre, n = 14	Post, n = 13			
HbA1c, %	7.8±2.1	7.3±1.8	.02	6.5±0.6	6.7±0.8	.19	.09	.01
RBG	177.46±110.97	154.70±38.72	.91	137.00±19.16	144.46±30.68	.43	.66	.58
DCP	-0.21±0.53	0.19±0.40	.03	-0.32±0.44	-0.28±0.52	.65	.80	.01
FSS	4.20±1.40	2.79±1.21	.002	4.36±1.44	4.30±1.58	.56	.95	.001

CBT-I: Cognitive Behavioral Therapy for Insomnia; HE: Health Education; A1C: glycemic control; RBG: Random blood glucose; DCP: Diabetes Care Profile composite score; FSS: Fatigue Severity Scale; [a]Comparison of the pre- and post-intervention values using [a]Wilcoxon signed-rank test; [b]Baseline difference between groups; [c]Comparison of between group difference using Mann-Whitney U tests

CBT-I: Cognitive Behavioral Therapy for Insomnia; HE: Health Education

There were significant between-group post-intervention differences in HbA1c ($d = 0.41$, $p = .01$), DCP composite score ($d = 1.01$, $p = .01$), and FSS ($d = 1.07$, $p = .009$; Fig. 2; Table 2). There were significant within-group differences for the CBT-I group in HbA1c ($p = .02$), DCP composite score ($p = .03$), and FSS ($p = .002$), which are also shown in Table 2. However, there were no within-group differences in HbA1c, DCP composite score, or FSS for the HE group.

We noted declines in blood glucose levels before bedtime and after awakening in the morning for the CBT-I group using the R software package (Fig. 3). The linear regression analysis showed significant association between the number of days in the CBT-I intervention with blood glucose level before bedtime (B=-0.56, $p = .009$) and after awakening in the morning (B=-0.57, $p = .007$) (Fig. 3).

Discussion

To our knowledge, this was the first RCT examining the effect of CBT-I on diabetes outcomes and daytime functioning in people with T2D and insomnia symptoms. This study suggested CBT-I was effective in improving HbA1c, DSCB and FSS for people with T2D and insomnia symptoms. Glucose blood levels, both before bedtime and after awakening in the morning, also decreased over the course of the CBT-I intervention.

Diabetes outcomes improved following CBT-I, with a clinically meaningful difference in HbA1c. Clinical improvement in HbA1c may be due to reductions in insomnia severity, which might foster improved DSCB. After the CBT-I intervention, as shown in Fig. 2, there was 0.05% absolute percentage reduction in HbA1c, which suggests a clinically significant change based on the American Diabetes Association statistics [33]. It is recommended that people with T2D maintain HbA1c levels below 6% to reduce their risk of developing microvascular complications, although HbA1c between 6.5% and 7.9% is often considered acceptable by physicians [34]. Interestingly, the HE intervention provided to the control group, which included sleep hygiene, diet, and physical activity, was not sufficient to improve HbA1c. However, the baseline data of HbA1c suggests less room of improvement for people in the HE group, which might future research is needed to consider HbA1c in the power calculation and randomization process. As shown in the initial part of this intervention trial, improving insomnia symptoms following CBT-I may produce reductions in depression and anxiety symptoms that are often associated with daily hyperglycemia [22]. Previous studies have shown the negative influence of the combination of insomnia and depression on an individual's glucose metabolism [35], which could be adjusted using CBT-I [36].

Besides the effect of improving insomnia symptoms on HbA1c, improvements in DSCB could also explain the clinical changes in HbA1c. Our study tracked glucose levels for participants in the CBT-I group, and there was a statistically significant decrease over the course of the intervention. This is entirely observational, however, as we did not monitor glucose before time in bed and after awakening in the morning in the HE group. Regardless, self-monitoring of blood glucose should be done as a part of DSCB when trying to minimize problems related to hyperglycemia. It has been suggested that self-monitoring of blood glucose significantly reduces HbA1c levels for people with poorly controlled T2D [37].

There are few physiologic mechanisms that might explain improvements in HbA1c. First, the negative effects of sleep disturbances on metabolism might cause decreased brain glucose utilization, which could lead to hyperglycemia [38]. Reducing sleep disturbances via CBT-I might regulate glucose utilization, which could improve HbA1c. Second, previous studies have suggested a U-shaped relationship between sleep duration with HbA1c levels, where excessively short or long sleep durations have been noted to be associated with higher HbA1c levels. Sleep restriction therapy might lead to improved HbA1c levels by maintaining sleep durations within an optimal range of 7–8 hours. Third, sleep disturbances are associated with appetite hormone dysregulations [38], and these dysregulations could be adjusted through sleep hygiene and stimulus control therapy. Sleep hygiene and stimulus control might help the participants in scheduling meals and acquiring a better understanding of their bodily needs regarding food consumption. Fourth, abnormal HPA axis activation might be normalized as a result of improving insomnia symptoms. This normalization could reduce cortisol secretion during sleep, which has been linked to reduced morning glucose levels. Finally, the associated behavioral mechanisms between sleep and T2D such as impaired decision-making [39] might be disrupted by CBT-I. Effective decision making may assist people with T2D in understanding domains related to diabetes such as food choices, control problems, diabetes distress, and medication adherence.

Although the HE group received the same amount of face-to-face attention, we did not find any significant improvement in the diabetes and daytime functioning outcomes. This reiterated the importance of considering CBT-I as a treatment in diabetes clinics for people with T2D who suffer from insomnia symptoms. Contrary to the positive results of CBT-I on insomnia symptoms, glycemic control, and fatigue for people with T2D, there were no significant improvements in RBG for either group. Several factors might explain these results such as the specificity of interventions, the short-term intervention

or methodological factors. CBT-I is designed to change detrimental beliefs about sleep behavior, which could demonstrate a secondary effect on RBG over time. However, the data from this study suggested blood glucose level could be decreased at nights before bedtime and in the mornings after awakening.

This study has identified the effect of CBT-I on diabetes health outcomes in people with T2D; however, some limitations need to be considered for future research. First, including other highly sensitive glucose metabolism measures on larger sample size, such as homeostatic model assessment and oral glucose tolerance test, may generalize the other effects of CBT-I on diabetes parameters. Second, diabetes management includes interdisciplinary approaches, such as diet, physical activity, and medication adherence, to ensure optimal HbA1c. Future work needs to track daily changes in these activities to better explain the impact of CBT-I on HbA1c. Third, comprehensive functional assessments, including variables such as cognition, motivation and activities of daily living, may help to efficiently identify other results following CBT-I. Finally, although this study demonstrated clinical improvements in HbA1c and DSCB after participants underwent six sessions of CBT-I, future research is needed to measure the sustainability of these improvements for at least three months.

Conclusion

this study reported clinical information about the effectiveness of CBT-I on diabetes health outcomes. CBT-I showed a clinically meaningful effect on HbA1c and significant improvements in optimal DSCB and fatigue in people with T2D and insomnia symptoms. There is still a need to understand the underlying mechanism of these enhancements, and future research is needed to investigate the long-term effect of CBT-I on diabetes blood parameters and to understand the underlying mechanisms of these improvements.

List Of Abbreviations

RCT: Randomized Controlled Trial

T2D: Type 2 diabetes

HPA: hypothalamic pituitary-adrenal

CBT-I: Cognitive behavioral therapy for insomnia

HE: Health education

HbA1c: Glycemic control

RBG: Random blood glucose

DSCB: Diabetes self-care behavior

DCP: Diabetes Care Profile

FSS: Fatigue Severity Scale

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board and the Human Subjects Committee of the University of Kansas Medical Center (IRB # STUDY00142985). All participants signed a written informed consent before the assessment visit.

Consent to publish

Not applicable

Availability of data and materials

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

Competing interests

The authors whose names are listed in this manuscript have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Nothing to declare.

Author contributions

all Authors read and approved the manuscript. MMA conceptualized the study, researched and analyses the data, wrote the manuscript; AMA, SA, JR, MP, JM, PK, and SC contributed in reviewing and writing the manuscript; MP help in the planning the data analysis and assuring the power analysis. JM help in strengthen the research question and recruitment. JR, JM, PK and CS conceptualized the study.

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Figures

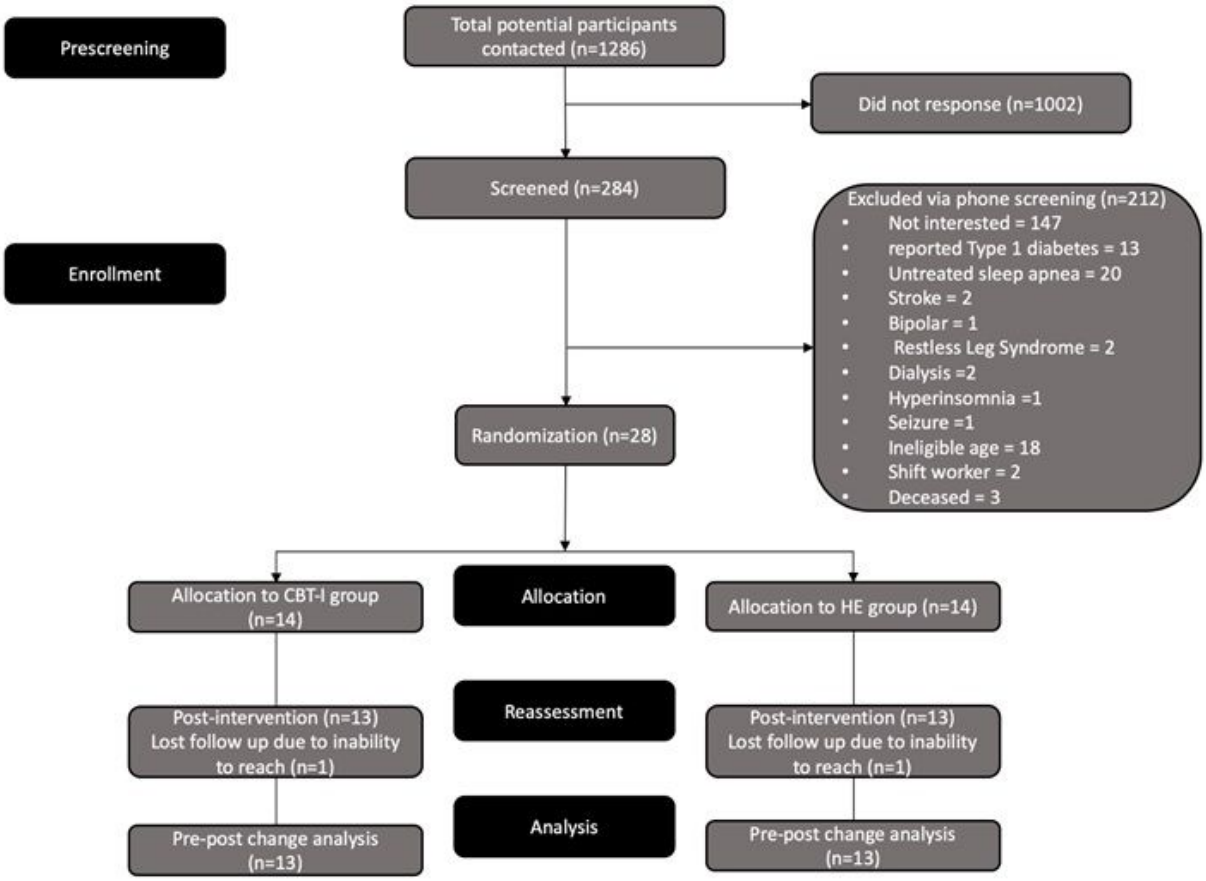

Figure 1

Consort of the study. CBT-I: Cognitive Behavioral Therapy for Insomnia; HE: Health Education

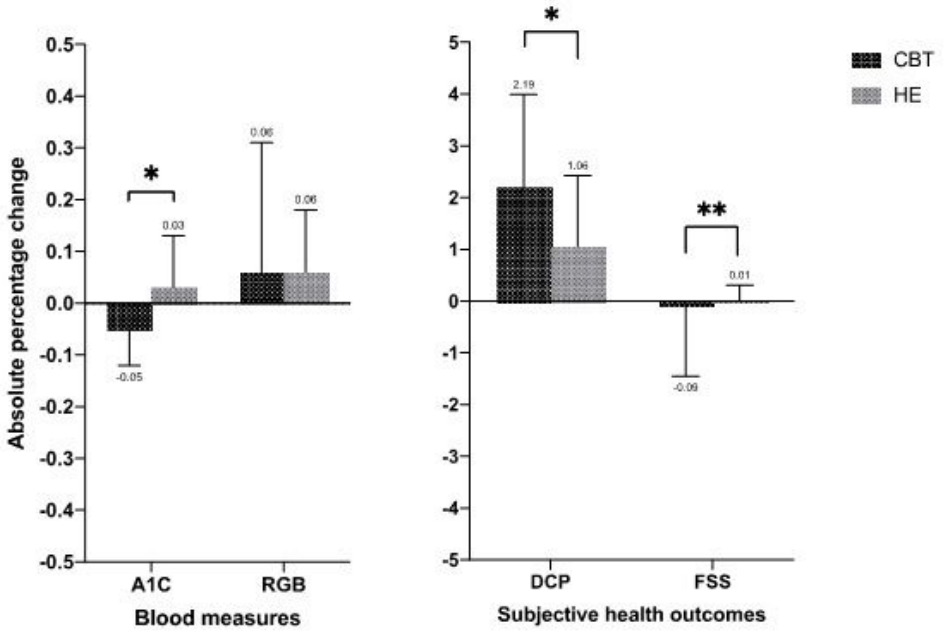

Figure 2

Absolute percentage change of all outcomes for both groups; *p=0.01, **p=0.001

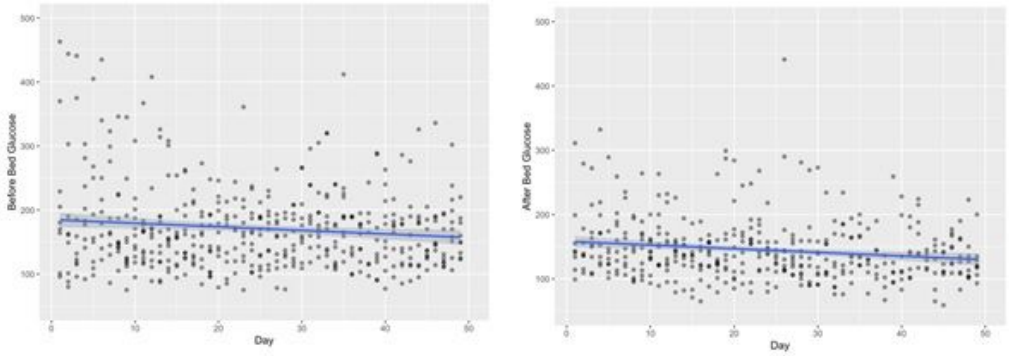

Figure 3

Daily glucose blood levels before bedtime and after awakening in the morning during the CBT-I intervention

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.pdf