Insomnia and Type 2 Diabetes: Measurements, Impacts and Interventions

By

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Abstract

Insomnia and type 2 diabetes (T2D) are common chronic health conditions in modern life. In the general population, 1 out of 10 are diagnosed with T2D, and 2 out of 10 have complained of insomnia symptoms. Further, more than half of people with T2D report insomnia symptoms. Previous research has shown associations between insomnia symptoms and risk of T2D. These associations could increase also the risk of medical morbidity such as cardiovascular disorders, hypertension, obesity, neuropathic pain, and psychological symptoms such as depression, anxiety, and pain. Although the underlying mechanisms that explain these associations are unknown, there is a need to understand the additive effect of insomnia symptoms on sleep, diabetes and health outcomes.

People with T2D and people with sleep disturbances share several common health issues, including fatigue, low self-care, high sleep variability, poor sleep quality, daytime sleepiness, and severe symptoms of depression, anxiety, and pain. The literature explaining the actual impact of insomnia symptoms on T2D health outcomes is lacking. Because insomnia symptoms are common for people with T2D, it is imperative to understand the health issues in this population to promote preventive strategies and treatment options. In this dissertation, we examined the impact of insomnia symptoms on sleep, diabetes, and health outcomes for people with T2D. In addition, we studied the effectiveness of cognitive behavioral therapy for insomnia on sleep, diabetes, and health outcomes for people with T2D and insomnia symptoms.

In Chapter 2, we compared the average and variability of sleep parameters in people with T2D with and without insomnia symptoms. As a secondary aim, we assessed the relationship between the average and variability of sleep parameters in people with T2D with and without insomnia symptoms. This study assessed between-group differences in the averages and

variability of sleep efficiency and total sleep time for 59 participants with T2D with and without insomnia symptoms. The data suggested poor average sleep efficiency and high sleep efficiency variability in people with T2D and insomnia symptoms compared to people with T2D without insomnia symptoms, with statistical analyses suggesting psychological symptoms may explain the observed differences. For the secondary analysis, we observed a negative relationship between the average sleep efficiency and the variability of sleep efficiency for the entire sample. In addition, we observed a negative relationship between the average total sleep time and the variability of total sleep time for people with T2D and insomnia symptoms. The results indicated the potential effect of insomnia symptoms on regular sleep efficiency, in which improving sleep efficiency may minimize the variation of sleep efficiency or regulating the sleep schedule optimize sleep efficiency for people with T2D without or without insomnia symptoms.

After understanding the possible impact of insomnia on sleep outcomes for people with T2D, insomnia symptoms may also impact diabetes outcomes. In Chapter 3, we compared the diabetes self-care behavior and glycemic control for people with T2D with insomnia symptoms to those without insomnia symptoms. As a secondary aim, we measured the association between diabetes self-care behavior and insomnia severity for all the sample. Sixty participants with T2D were divided into 2 groups based on the presence of insomnia symptoms, using the Insomnia Severity Index with scores >10 indicating the presence of insomnia symptoms. We established a standardized composite score to account for the Diabetic Care Profile domains, which measured diabetes self-care behavior. The total Diabetic Care Profile composite score was significantly lower for people with T2D and insomnia symptoms compared to people with T2D without insomnia symptoms. Stepwise linear regression results showed that a one-point increase in Insomnia Severity Index score significantly predicted decreased standardized Diabetic Care

Profile composite score by 0.03 after controlling for age, symptoms of pain, depression, and anxiety. The data suggested that people with T2D and insomnia symptoms were more likely to engage in less diabetes self-care behavior compared to people with T2D without insomnia symptoms. However, there was no significant between-group difference in the glycemic control, which might be due the small sample size as the effect size for the between-group difference was large.

Whilst suboptimal diabetes self-care behavior is associated with insomnia symptoms in people with T2D, it is imperative to understand the impact of insomnia symptoms on daytime functioning in people with T2D. In Chapter 4, we compared fatigue, daytime sleepiness, and quality of life related to vitality and physical function in people with T2D with and without insomnia symptoms. Insomnia severity index was used to stratify participants into two groups, insomnia group (N=32) and non-insomnia control group (N=28). Daytime functioning including fatigue, quality of life related vitality, and physical function were worse in people with both T2D and insomnia symptoms compared to people with T2D without insomnia symptoms. Depression symptoms may have independently contributed to daytime functioning outcomes in people with T2D and insomnia symptoms.

In previous chapters, we found evidence for the negative impact of insomnia symptoms on people with T2D, specifically on sleep efficiency, diabetes self-care, and fatigue severity. Thus, it is imperative to identify effective and safe insomnia intervention(s) to help people with T2D with insomnia symptoms optimize their sleep, diabetes, and health outcomes. In Chapter 5, we established a protocol study to be utilized in Chapter 6 and Chapter 7 based on resources and available funds. In Chapter 6, we examined the effect of cognitive behavioral therapy for insomnia (CBT-I) on insomnia severity in people with T2D and insomnia symptoms. The

secondary aim was to explore the effect of CBT-I on other sleep outcomes and concomitant symptoms. Twenty-eight participants with T2D were randomly assigned to the CBT-I group (n=14) or the health education (HE) group (n=14). The data suggested a positive effect of CBT-I on insomnia symptoms, sleep quality, sleep self-efficacy, sleep latency, sleep efficiency, wake after sleep onset, and number of awakenings. In addition, participants in the CBT-I group showed improvements in the severity of depression and anxiety symptoms. Although the HE group received the same amount of face-to-face attention, there were no significant changes in the sleep outcomes or concomitant symptoms for the HE group. These results suggest the importance of using CBT-I with people with T2D and insomnia symptoms to improve sleep and psychological outcomes.

We were also interested in the effect of CBT-I on T2D and health outcomes. Thus, in Chapter 7, we explored the effect of 6 CBT-I sessions on glycemic control, diabetes self-care behavior, and fatigue. Similar to Chapter 6, we randomized 28 participants with T2D and insomnia symptoms to the CBT-I group (n=14) or the health education group (HE; n=14). CBT-I participants showed significantly greater improvements in glycemic control, diabetes self-care behavior, and fatigue. We also found that participants in the CBT-I group experienced a clinically meaningful change in glycemic control (i.e., a difference > 5%). In addition, CBT-I positively impacted diabetes self-care behavior and fatigue. The results suggested improving insomnia symptoms may have positively impacted diabetes health outcomes.

In Chapter 8, we summarized our findings, and we discussed possible mechanisms and future directions for research. In summary, this dissertation project has shown the negative impact of insomnia symptoms on sleep, diabetes, and health outcomes, which improved following CBT-I. Our findings showed worse average sleep efficiency and more variability of

sleep efficiency for people with T2D and insomnia symptoms compared to people with T2D without insomnia symptoms. The data also showed a negative relationship between the average sleep efficiency and the variability of sleep efficiency, which suggested improving average sleep efficiency may minimize sleep efficiency variation and vice versa. Because of these findings, clinicians may want to consider screening for insomnia symptoms in people T2D to optimize sleep efficiency. For our other findings, we found poor diabetes self-care behavior and daytime functioning in people with T2D and insomnia symptoms, in which psychological symptoms might be a contributing factor in this difference. Identifying factors that affect diabetes self-care behavior and daytime functioning in this project may encourage diabetes clinicians to screen for insomnia symptoms with people who have suboptimal diabetes self-care behavior and potentially refer them to sleep specialists. However, future research using a larger sample size of people with T2D is needed to identify the causality relationship between insomnia symptoms and diabetes health outcomes. Finally, this dissertation highlighted the effectiveness of CBT-I on sleep, diabetes, and health outcomes. The data suggested clinical meaningful changes in several sleep and diabetes outcomes. The findings showed improvements in psychological symptoms, which might contribute to blood glucose regulation. However, there is a need to understand the long-term effect of CBT-I on sleep, diabetes, and health outcomes for people with T2D.

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Chapter 1: Introduction

1.1. TYPE 2 DIABETES

Type 2 diabetes (T2D) is one form of diabetes mellitus and is called non-insulin-dependent diabetes mellitus or adult-onset diabetes [1]. T2D causes abnormal amounts of glucose in the blood stream due to insulin resistance or insulin deficiency [2, 3]. More than 90% of the people diagnosed with diabetes mellitus are diagnosed with T2D [2, 3]. In 2013, the number of people with diabetes worldwide increased to 382 million; this number is expected to double by 2035 [4]. Annually, the United states government spends $174 billion for health care, directly or indirectly due to diabetes [5]. In addition, around a quarter million deaths in the United States every year as result of diabetes complications [5]. The rate of death is higher in people with diabetes compared to people without diabetes [6]. Therefore, diabetes researchers might consider contributing factors to reduce the occurrence of diabetes, short and long-time complications of diabetes, and mortality rate.

1.2. INSOMNIA

There are several classification systems for insomnia, which complicates the definition [7, 8]. For example, 8 to 10% of the general population suffers from chronic insomnia, while 20 to 30% report symptoms of insomnia [9, 10]. Insomnia has three main components: chronicity, type, and subtype. Chronicity refers to two stages, acute and chronic (Differed by life stressors versus the hyperarousal) [11]. Type refers to the cause of insomnia including idiopathic insomnia, psychophysiological insomnia, paradoxical insomnia, inadequate sleep hygiene, and insomnia comorbid with medical or psychiatric disorders [11]. Subtype refers to the phenotype of insomnia including initial, middle, late, or mixed insomnia [11].

In clarifying the insomnia phenotypes, Spielman's 3 factors model illustrates that insomnia is perpetuated by sleep extension, which makes people with insomnia lose alignment between sleep opportunity (time in bed and time out of bed) and sleep ability (actual time of sleep) [12]. In addition, the factors are associated with development of insomnia: the long-term effect of the predisposing factors (i.e. the biological triggers in our body such as hormone changes); precipitating factors (i.e. stressors related to life events) that may lead to frustration and worry; and long-term effects that may lead to sleep effort and sleep extension (perpetuating factor) [12]. Therefore, insomnia symptoms are characterized as one or more of following symptoms: difficulty in falling asleep (Initial Insomnia) and/or maintaining sleep (Middle Insomnia) and/or waking up too early (Terminal Insomnia) at least 3 nights/week for past 3 months, which impacts daytime functioning [13].

Insomnia is associated with serious health issues and long-term complications including cardiovascular diseases, hypertension, psychological disorders, and diabetes [14-16]. Previous studies have shown that people with chronic insomnia are at higher risk of having car accidents and experiencing drowsiness [17, 18]. People in modern life are triggered by many stressors, which may perpetuate hyperarousal and sleep effort during a night of sleep [19, 20]. Long-term stressors may have negative impacts on health for different populations [21-23]. However, every chronic health issue or disease has unique characteristic and differential diagnosis. Thus, it important to understand the additive effect of insomnia symptoms on a single population to understand the negative impact.

1.3. INSOMNIA SYMPTOMS AND TYPE 2 DIABETES

Epidemically, both insomnia symptoms and incidence of T2D have been increased dramatically worldwide [24]. It has been suggested that there is a bidirectional relationship between insomnia and T2D [25], which might explain the dramatic increases in the number of T2D and insomnia symptoms worldwide. From 2002 to 2012, the prevalence of T2D increased by 6.8% [26], while the insomnia symptoms increased by 8.0% [27]. Generally, diabetes was the most prevalent comorbidity in people with chronic insomnia (21.13-50%) [28, 29]. In addition, insomnia symptoms have been reported in 50% and 31.3% of people with and without T2D, respectively [30]. For each insomnia symptom among people with T2D, 8–17% reported difficulty falling asleep, 23–40% complained of difficulty staying asleep, and 26–43% had difficulty both in initiating and maintaining sleep [30]. Despite the research on the prevalence of these conditions, the underlying mechanisms that might explain this relationship are unknown.

1.3.1. Possible mechanisms

Insomnia has been shown to increase the risk of T2D through several mechanisms. First, physiological studies suggested a linkage between the etiology of insomnia, activation of the hypothalamic pituitary-adrenal (HPA) axis and sympathetic system activation, and metabolic disorders such as T2D [31]. HPA axis activation leads to cortisol production stimulation from the adrenal cortex, which negatively affects glucose tolerance [31]. Second, insomnia is associated with dysregulations of the fronto-limbic system and reductions in hippocampal volume [32]. This dysregulation leads to blood glucose elevation [33] due to dysregulations in HPA axis and the autonomic nervous system, increases in glucocorticoids secretion, alterations in glucose transport function, and hyperactivation of immune-inflammatory substances, all of which can

exacerbate the pathophysiology of T2D [34]. Finally, after long periods, people with poor sleep quality will have insulin exhaustion, facilitated by decreased insulin sensitivity, which leads to T2D [35].

In addition to the directional relation of insomnia toward T2D, diabetes may increase the symptoms of insomnia. Diabetes symptoms such as frequent nighttime urination, hypoglycemia, hyperglycemia, pain and fatigue tend to have a negative impact on sleep [36-40]. People with diabetes and nocturia due to high blood sugar levels may have sleep disturbances [36]. Additionally, extra glucose will draw water from tissues, which leads to dehydration [37], which may prompt people with diabetes to get up several times during the night to get water. People with T2D with hypoglycemia may experience symptoms such as shakiness, dizziness, hunger and sweating [38, 39]. These symptoms may affect initiating sleep or maintaining sleep [38, 39]. Patients with T2D usually are advised to follow a long-term self-management process which might frustrate them, often leading to poor sleep quality [40]. Metabolic changes and endocrine changes lead to elevation in the body mass index (BMI) due hormone alterations, decreased leptin (satiety) and increased ghrelin (hunger), which is associated with the risk of secondary insomnia [40].

Several shared risk factors of insomnia symptoms and T2D could potentially explain this relationship. However, the association between insomnia symptoms and diabetes was significant even after controlling major risk factors (e.g., age, race, gender, BMI, smoking status, alcohol consumption, depression, and sleep apnea) [30, 31, 41]. This association may lead to various health complications and interfere with diabetes health outcomes [30, 41]. In addition, the associations could increase also the risk of medical morbidity such as cardiovascular disorders,

hypertension, obesity, neuropathic pain, and psychological symptoms such as depression, anxiety, and pain [42].

Although the impact of insomnia and T2D on insulin resistance and glucose dysregulation is known, there are no recommendations in the American Diabetes Association guidelines to include screening for insomnia symptoms as a part of T2D management. While the causal effects are under investigation, there is limited evidence comparing the prevalent health complaints in people with T2D with and without insomnia symptoms (Figure 1.1).

1.4. PREVALENT HEALTH COMPLICATIONS

1.4.1. Fatigue

Fatigue is reported in more than 50% of people with T2D [43, 44], and fatigue might be exacerbated due to insomnia symptoms [45]. Fatigue is defined as a self-reported decline in ability to perform physical and/or mental tasks due to one or a combination of physiological, psychological or lifestyle phenomena [46]. The manifestation of fatigue symptoms could be similar in people with T2D or insomnia symptoms. However, the underlying mechanisms due to these comorbidities are different. The lack of glucose due the T2D pathophysiology affects body's capability to generate energy from blood cells [46]. The fatigue related to insomnia symptoms are generally due to psychological factors such as mental exhaustion due to inadequate sleep [47]. Although the severity of fatigue symptoms elevates depending on the severity of insomnia or T2D symptoms, there is limited research identifying the cumulative effects of both comorbidities on the severity of fatigue or multidimensional fatigue symptoms.

Several risk factors could mediate the relationship between the severity of fatigue and the presence of insomnia or T2D symptoms. Park et al. showed that people with T2D and A1C levels >7% are at high risk of fatigue due to diabetes symptoms, depression, and diabetes distress, but they found no relationship exists between glucose control and fatigue in people with A1C levels ≤7% [48]. On the other hand, people with insomnia commonly suffer from psychological symptoms which might indirectly worsen fatigue symptoms [49]. Unsurprisingly, previous research found increased fatigue symptoms in people with severe insomnia symptoms because of the diagnostic criteria for insomnia that requires the presence of daytime dysfunctions [50]. Additionally, previous research has agreed that common psychological symptoms have a negative impact on people diabetes and sleep outcomes [51]. In addition, because the prevalence of sleep apnea is high in people with T2D [52], it is expected the severity of fatigue could be a consequence of sleep apnea [53]. Further, insomnia symptoms could be reported by people with severe sleep apnea due to frequent awakening during the nights [53]. However, inadequate information about the role of associated risk factors related to insomnia symptoms and T2D such as age, gender, sleep apnea, depression, anxiety, and pain on fatigue severity for people with T2D. Therefore, it is imperative to account for risk factors related to the severity of fatigue in people with T2D and insomnia symptoms in future studies.

1.4.2. Self-care behavior

Diabetes self-care behavior (DSCB) is essential in maintaining or attaining glycemic control [54-56]. DSCB covers several different factors including maintaining a healthy diet, self-monitoring of blood glucose, use of medications, regular physical activity, foot care, healthy coping and risk reduction [57, 58]. Because of the nature of these factors, DSCB is a very

important aspect of T2D care for better lifestyle and health status. Due to the importance of better lifestyle behavior for prevention and treatment aspects, negative factors on diabetes behavior need to be determined to develop additional intervention strategies [59].

Optimal DSCB might be affected by the presence of insomnia symptoms. Since fatigue is a common complaint among people with T2D and may affect the ability to perform DSCB [46, 48, 60], it is imperative to control for fatigue severity to better understand the effect of other contributing factors related to suboptimal DSCB. In addition to the fatigue symptoms, other psychological symptoms might negatively impact optimal DSCB. Poor sleep quality is associated with poor glycemic control [61], a worse attitude toward activities required for optimal management of diabetes, decreased positive attitude toward feeling able to manage diabetes, lower self-reported adherence to good self-care behaviors, and decreased adherence to good diet choices [62]. However, there is still limited evidence of the impact of insomnia symptoms on optimal DSCB while controlling for common extraneous variables such as age, depression and anxiety.

Although the impact of different sleep disorders on the health of people with T2D has been investigated previously [63, 64], no studies have investigated the impact of insomnia symptoms on DSCB for people with T2D. In has been shown that people with T2D with poor sleep quality or excessive daytime sleepiness show decreased adherence to DSCB [62]. This has suggested that psychosocial and mental factors are needed to optimize DSCB. However, these studies had some limitations such as excluding people who had severe daytime sleepiness, the absence of a comparison group, and the inability to identify people with severe insomnia symptoms. These factors limited our understanding regarding the impact of insomnia symptoms on DSCB. A recent literature review recommended investigating the effect of insomnia

characteristics (e.g., initiating asleep, maintaining asleep, nonrestorative sleep) on DSCB to help future research establish effective interventions that target each of the insomnia characteristics [65]. In people with T2D, worse self-care and control problems are highly reported in those who have extensive daytime sleepiness compared to those without [62]. Evidence of the association between insomnia symptoms and DSCB is in its early stages; therefore, investigating the impact of insomnia symptoms on DSCB will help future studies to establish new treatments addressing that issue for people with T2D. Subsequently, the effect of an intervention on DSCB can be evaluated.

DSCB is comprised of several domains that were poorly investigated in people with T2D and insomnia symptoms. The psychological symptoms associated with insomnia might contribute to some DSCB domains such as food choice, physical activity and adherence to medication [66]. Maintaining a physically active lifestyle is important in the prevention of diabetes [65]. Additionally, higher levels of insomnia symptoms were a significant predictor of lower number of steps after controlling for age, BMI, self-reported health, and education (p = 0.026) [65]. However, we were unable to determine the full extent of the impact of insomnia symptoms on all domains related to DSCB in people with T2D and insomnia symptoms including understanding management of practice, support, control problems, social and personal factor, positive attitude, negative attitude, care ability, importance of care, self-care adherence, diet adherence, long-term care benefits, exercise barriers, and glucose monitoring barriers [67]. There is a lack of information on the effect of insomnia symptoms on compliance with activities required for optimal DSCB for people with T2D. It remains uncertain whether insomnia symptoms or diabetes symptoms acts as barriers to effective DSCB. Therefore, understanding

other negative factors impacting DSCB may increase our awareness in future research, clinical evaluation or health management.

1.4.3. Sleep variability

Intraindividual night-to-night sleep variability (i.e. variation in sleep/wake patterns) is common in modern life. With increasing economic and social demands, people are commonly required to have irregular work schedules that might interfere with maintaining a consistent sleep schedule [68]. In addition, people with detrimental sleep behaviors often try to compensate for a night with too little sleep by trying to get extra hours of sleep, which may lead to a temporary improvement [69, 70]. Unfortunately, this "wrong" sleep behavior could also lead to poor sleep quality on following nights, and it may eventually impair the person's ability to fall asleep because of too much sleep recovery [69, 70]. Beyond the consequences of behavioral and environmental factors on regular sleep schedules, the mismatching between circadian system and sleep homeostasis due to an irregular sleep-wake schedule might contribute to various health problems [71].

Prolonged sleep variabilities have been associated with frustration and distress in people with chronic insomnia [72, 73]. Previous studies have confirmed that people with insomnia have more short-term sleep variability than people without insomnia using sleep diaries and polysomnography [74-77]. Additionally, older adults with insomnia had more sleep variability in wakefulness after sleep onset and sleep efficiency using objective measures [74]. Therefore, measuring sleep variability is recommended due to the importance of sleep variability in sleep patterns for people with insomnia [78, 79]. Although previous studies have shown high sleep variability in adults and older adults with insomnia [80], we were not able to determine if

the comorbidities played a role in this variability. Therefore, the additional effect of insomnia symptoms on the sleep variability of people with T2D is uncertain.

With prevalent sleep disturbances in people with T2D [81], sleep variability could be sustained in people with T2D. Previous studies found high sleep variability was associated with T2D [71, 82-84]. Various T2D symptoms explained the variation in sleep parameters including frequency nocturnal urination, hyperglycemia-related food consumption, hypoglycemia symptoms, obesity, pain and fatigue [85]. These symptoms are considered common sleep disturbances in people with T2D. However, we are limited in determining the additive effect of the T2D symptoms and insomnia symptoms on sleep variability. Therefore, it is important to compare sleep variability in people with T2D with and without insomnia symptoms. Understanding sleep variability in people with T2D with and without insomnia symptoms might add information for future intervention and prevention strategies.

In addition to the importance of measuring sleep variability in people with T2D, presenting the mean values alongside sleep variability might demonstrate additional useful findings. For example, people with low sleep variabilities typically do not have good sleep quality compared to people with high sleep variabilities. This means that people with low sleep variabilities who had poor sleep for the majority of nights would likely demonstrate low sleep variability yet would demonstrate a poor average sleep quality for the measured nights. Thus, it is imperative to present both values to improve our understanding of the effect of insomnia symptoms on T2D sleep outcomes in relation between averages and sleep variabilities.

Subjective and objective measures of sleep are important for clinical and research applications in insomnia symptoms [86]. Sleep diaries and actigraphy are useful tools in

measuring sleep parameters subjectively and objectively, respectively [87]. The sleep parameters measured with these tools can include sleep efficiency, sleep latency, total sleep time, and wake after sleep onset [88]. Due to the discrepancy between subjective and objective measures, including both types of measures simultaneously to capture sleep parameters may be needed [82]. One benefit of using subjective and objective measures is that sleep perception of people with T2D or insomnia symptoms might be affected as consequences of dysregulation of circadian rhythm [89, 90]. Other benefits include the difficulty of reporting the actual duration of sleep latency, total sleep time, and wake after sleep onset. Sleep diaries define sleep based on individuals' best estimation which might incur difficulties in recalling information, whereas actigraphy is less sensitive in detecting the duration of sleep latency and high in detecting wake after sleep onset [88]. Despite mentioned limitations above, both measures are reliable in assessing multiple nights of sleep-wake pattern and sleep efficiency, which is necessary to evaluate the sleep variability [91].

1.4.4. Other factors

Some risk factors may attribute to increasing severity of insomnia symptoms and diabetes complications such as age, sex, sleep apnea, and symptoms of depression and anxiety [92]. These risk factors should be considered for future research in insomnia and T2D.

The most significant demographics predictors of insomnia symptoms and T2D are age and sex [9]. Older adults and being female commonly reported insomnia symptoms. In a contrast, men are twice as likely to have T2D compared to women [93]; however, females are more likely to have complications related to T2D [94]. A study showed men with T2D and insomnia had worse glycemic control compared to women with T2D [95]. Generally, it has been

suggested that the prevalence of sleep disturbances increases as we age, which might be due to increasing the risk of various health problems [96]. This might also explain the increasing risk of insomnia symptoms in older adults with T2D.

Sleep apnea is a common sleep disorder is people with T2D, which is characterized by repetitive episodes of the upper airway collapsing during sleep, resulting in recurrent hypoxia, reduced total sleep time, and increased number of awakenings. In addition, insomnia symptoms co-exist with sleep apnea [97] due to hyperarousal which plays role in the pathophysiology of insomnia, specifically the HPA axis activation [97]. People with treated sleep apnea usually complain of inconvenient therapies, such as passive airway pressure machines that might add frustration and stress to sleep. Therefore, sleep disruption due to frequent hyperarousal may increase fatigue and daytime sleepiness [97]. A systematic review suggested that people with untreated sleep apnea and insomnia symptoms are more likely to have cognitive, emotional, psychological, and physiological complaints than people with sleep apnea only [97]. It has been suggested that people with sleep apnea and insomnia symptoms only received attention regarding their sleep apnea, meaning their insomnia symptoms were not concordantly treated [97]. However, there is limited information about the combined intervention of insomnia and sleep apnea for people with T2D. Due to the prevalence of sleep disturbances, insomnia symptoms, sleep apnea, and the associated daytime dysfunctions on people with T2D, understanding the effect of treating of both insomnia symptoms and sleep apnea on T2D health outcomes might be warranted.

Psychological symptoms include depression and anxiety are commonly reported in people with insomnia symptoms and T2D. People with insomnia are more likely to have depression and anxiety symptoms compared to people without insomnia [98]. It has been

suggested that episodes of insomnia led to increased stress, which exacerbated the severity of depression and anxiety symptoms. In addition, daytime ruminations (e.g., worries, stress related to past failures, or thinking about future responsibilities) might be indirectly associated with inducing insomnia through depression and anxiety [98].

1.5. INTERVENTIONS

1.5.1. Pharmacological

Pharmacological approaches for treating insomnia have potentially serious side effects. Several studies have shown an association between sleeping pill prescriptions and mortality in different populations [99-104]. Different sleep medications were associated with fall risks [105], motor vehicle accidents [106], and suicidality [107]. Individuals with insomnia who use benzodiazepines or non-benzodiazepines are at a higher risk of developing T2D due to potential changes in insulin secretion and sensitivity [108, 109]. It is a widely held view that sleep apnea is a prevalent sleep disorder in people with T2D [110]. One possible explanation for the prevalence of sleep apnea is that hypnotics are respiratory suppressants that might contribute to vital health issues for this population [111]. Weinstock et al. showed insulin sensitivity improved in people with severe sleep apnea after receiving sleep hygiene, dietary counseling, and Passive Airway Pressure support, which suggests the metabolic function in people with T2D might be improved by a sleep promotion program [5]. Thus, it is important to identify safe and effective non-pharmacological treatments for people with T2D and insomnia symptoms.

1.5.2. Behavioral

Comorbidities, such as diabetes, are associated with a set of psychological and behavioral challenges; therefore, patients need to change their behavior as part of a new lifestyle of self-care [112]. The American Academy of Sleep Medicine recommends psychological and behavioral interventions such as CBT-I [113] as a first line effective treatment for people with insomnia [114-119]. CBT-I is designed to change sleep habits as well as correct misconceptions about sleep and insomnia [120]. In meta-analyses, CBT-I has been shown to produce clinically meaningful improvements in sleep outcomes [121], which suggests benefits from using CBT-I as a first line intervention. Additionally, sleep measures, such as a sleep diary, showed minimal to large effect size for sleep onset latency, total sleep time, wake after sleep onset, total wake time, time in bed, early morning awakening, and sleep efficiency [122-124]. One study hypothesized that the improvements in sleep outcomes are due to the effect of CBT-I has toward people's perception of sleep patterns [125, 126].

The Cognitive Behavioral Therapy (CBT) framework addresses the following factors associated with chronic disease: psychological problems, such as mood disorder and fatigue, and an active self-management approach with health care providers [112]. Additionally, chronic disease can be managed by general cognitive practices through a problem-focused and psychologically sensitive manner [112]. Although the effect of CBT was demonstrated in people with somatic illnesses [127-129], the effect of CBT-I on people with T2D is still limited. CBT focuses on the thinking style and thought-challenging process as playing the central role in our emotional and psychological wellbeing [130]. The most common form of CBT that was applied in the diabetes population was designed for treating depression, with mixed results [131-134]. The combination of CBT for depression and diabetes education is effective in improving

depression and glycemic control compared to antidepressants in people with T2D [132]. In addition, the combination of CBT and diabetes management care may improve diabetes self-care and quality of life compared to the diabetes care only [135]. A program-based-telephone delivered CBT combined with observed an walking program was not effective in improving either glycemic control nor physical activity and depressive symptoms [133]. CBT for stress was used for anxiety and diabetes control, which had a significant positive effect on the anxiety and stress levels but not on glycosylated hemoglobin [134].

CBT-I may improve negative sleep discrepancy and sleep variability. One study suggested this improvement might be due to the improvement in insomnia severity. [136] Older adults with insomnia showed improvement in both Actigraph and sleep diary outcomes after behavioral interventions, but the changes in subjective and objective measurements did not correlate within individuals [137]. Lund et al. (2012) showed CBT-I decreased the negative sleep discrepancy (polysomnography vs. sleep diary) in sleep latency but the not number of awakenings after sleep onset or total sleep time [120].

The effect of the CBT-I on people with T2D is unknown. Compared to other populations, people with T2D might suffer from sleep disturbances due to diabetes symptoms such as frequent nocturnal urination, hyperglycemia-related food consumption, hypoglycemia, insulin resistance, obesity, pain and fatigue; thus, knowing the benefits of CBT-I on people with diabetes may add significantly contribute to the literature and help clinicians to be confident in referring people with T2D and insomnia symptoms to use this type of intervention.

It has been suggested stress management could improve T2D progression[66]. However, limited research has focused on the benefit of improving psychological symptoms on glycemic

control for people with T2D. Risk factors related to T2D could be reversible in people with insomnia [29], which supports the need for better management of both comorbidities in order to avoid the negative consequences.

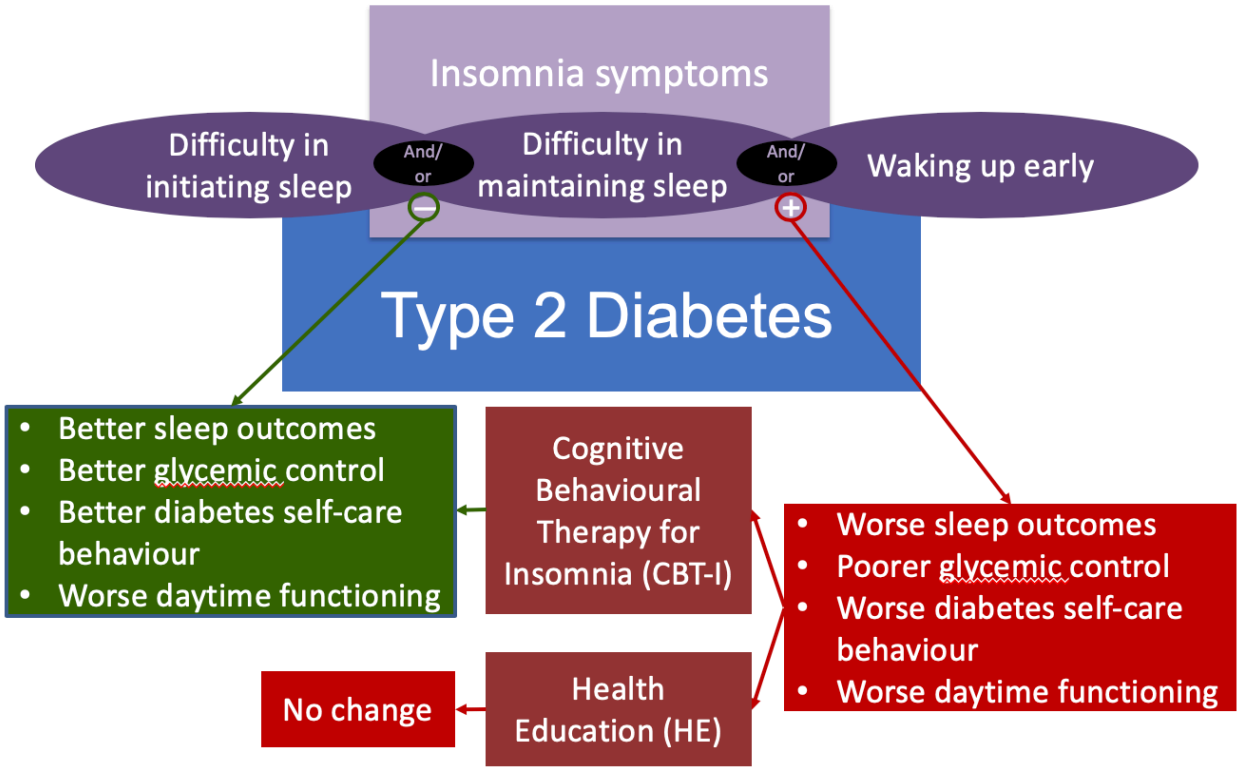


Figure 1.1. The dissertation model

1.6. SPECIFIC AIMS

Insomnia is a common sleep disorder, with three main symptoms: difficulty in initiating sleep, difficulty in maintaining sleep, and/or waking up early without ability to return to sleep [138]. Insomnia can contribute to metabolic dysfunction, which can lead to type 2 diabetes (T2D) [31]. Diabetes self-care behavior (DSCB) is important in attaining and maintaining glycemic control, which worsens as a result of fatigue [62]. People with insomnia usually suffer

from fatigue and daytime sleepiness [47, 139], which negatively influences quality of life [50]. However, the additive effect of insomnia symptoms on diabetes outcomes and health status in people with T2D is unknown. Therefore, it is imperative to investigate the contributing factor that affects DSCB and health outcomes to help individuals with diabetes reach their goals [140].

Assessing sleep using central tendency and variability is important clinically and practically for people with insomnia. People with insomnia have higher night-to-night sleep variability compared to healthy individuals [80]. Compared to other populations, people with T2D might suffer from sleep disturbances due to diabetes symptoms such as frequency nocturnal urination, hyperglycemia, insulin resistance, obesity, pain and fatigue, which might influence the sleep variability [141]. The nature of insomnia is not representable only using mean values, as the reduction in the sleep variability values is a predictor for insomnia and depression recovery [80]. Therefore, understanding the sleep variability in people with T2D with or without insomnia symptoms may improve our understanding to add complementary evidence for future studies.

An effective treatment for people with insomnia is Cognitive Behavioral Therapy for Insomnia (CBT-I) [121]. CBT-I is superior to sleep medications in terms of cost and long-term benefits [142]. Although there is currently limited evidence about the effect of CBT-I on people with T2D, CBT-I is a potentially effective intervention given insomnia's relationship with glucose metabolism. The overall purpose of this study is to investigate the impact of both insomnia symptoms and CBT-I on people with T2D (Figure 1.1). Our central hypotheses are that people with T2D and insomnia symptoms will have worse sleep, diabetes measures and self-reported outcomes compared to people with T2D only, which might be improved following CBT-I.

- **Main objective of aim 1: To compare sleep, diabetes, and health outcomes in people with T2D with and without insomnia symptoms.**

Aim 1.A: to compare the averages of sleep parameters in people with T2D with and without insomnia symptoms, and to compare the variability of sleep parameters in people with T2D with and without insomnia symptoms.

We hypothesized that people with T2D and insomnia symptoms will have worse average total sleep time (H1.A.1) and average sleep efficiency (H1.A.2), and worse variability total sleep time (H1.A.3) and variability sleep efficiency (H1.A.4).

Aim 1.B: to compare glycemic control and diabetes self-care behavior (DSCB) in people with T2D with insomnia symptoms and without insomnia symptoms.

We hypothesized that people with T2D and insomnia symptoms will have worse glycemic control and DSCB composite scores (H1.B.1) compared to people with T2D only. Our secondary aim was to examine the association of insomnia symptoms with the DSCB composite scores among people with T2D.

Aim 1.C: to compare fatigue and daytime sleepiness in people with T2D with and without insomnia symptoms.

We hypothesized that people with T2D and insomnia symptoms would have worse fatigue severity (1.C.1) and daytime sleepiness symptoms (1.C.2) compared to people with T2D without insomnia symptoms.

- **Main objective of aim 2: To investigate the effect of 6-sessions of CBT-I on insomnia severity, sleep outcomes and concomitant symptoms in people with T2D with insomnia symptoms.**

We hypothesized that the CBT-I group will have less severe insomnia symptoms (measured by Insomnia Severity Index) (H2.1), sleep quality (measured by Pittsburgh Sleep Quality Index) (H2.2), daytime sleepiness (measured by Epworth Daytime Sleepiness Scale) (H2.3), sleep latency (H2.4), total sleep time (H2.5), wake after sleep onset (H2.6), and sleep efficiency (H2.7) (measured by Actigraph and sleep diary) compared to the health education control group.

- **Main objective of aim 3: To explore the effect of 6-sessions of CBT-I on fatigue, glycemic control and diabetes self-care behavior (DSCB) in people with T2D and insomnia symptoms.**

We hypothesized that the CBT-I group will have improved glycemic control (by HbA1c Kit) (H3.1), DSCB (measured by Diabetes Care Profile composite score) (H3.2), and fatigue (measured by the Fatigue Severity Scale) (H3.3) compared to the health education control group.

Chapter 2: Sleep Efficiency and Total Sleep Time in People with Type 2 Diabetes with and without Insomnia Symptoms

ABSTRACT

Introduction: There is increasing awareness of the high prevalence of insomnia symptoms in people with type 2 diabetes (T2D). Past studies have demonstrated the importance of measuring sleep parameters using measures of central tendency and measures of variability. In addition, subjective and objective methods have different constructs due to the discrepancies between the two approaches. Therefore, this study aimed to compare the averages of sleep parameters in people with T2D with and without insomnia symptoms, and to compare the variability of sleep parameters in people with T2D with and without insomnia symptoms.

Method: This study assessed the between-group differences in the averages and variability of sleep efficiency (SE) and total sleep time (TST) for 59 participants with T2D with and without insomnia symptoms. Actigraph measurements and sleep diaries were used to assess the sleep parameters in averages and variability which calculated by Coefficient of variation across 7 nights. Mann Whitney U tests were utilized to compare the group-differences in the outcomes. Validated instruments were used to assess the symptoms of depression, anxiety, and pain as covariates.

Results: Objective SE was found to be statistically lower in average (85.98±4.29) and higher in variability (5.88±2.57) for patients with T2D and insomnia symptoms, compared to people with T2D only (90.23±6.44 and 3.82±2.05, respectively). The subjective average and variability of SE was also worse in people with T2D and insomnia symptoms, with symptoms of depression, anxiety, and pain potentially playing a role in this difference. TST was not significantly differ between groups in averages or variability after controlling for age and symptoms of depression, anxiety, and pain.

Conclusions: Future studies are needed to investigate the underlying mechanisms of worsen averages and variability of SE in people with T2D and insomnia symptoms. In addition, prompting the associated risk factors with insomnia symptoms in people with T2D might be warned.

Keywords: Variation, Diabetes, sleep disturbance, insomnia, night-to-night measurements

2.1. INTRODUCTION

Sleep disturbances, especially insomnia, are commonly reported in people with type 2 diabetes (T2D) [41, 143]. The association between insomnia symptoms and T2D may reflect possible bidirectional relationships through the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, appetite-controlling hormones, and glucose metabolism. A preliminary study showed that people with insomnia have increased in the activation of HPA axis which cause high cortisol production [144]. Increasing the cortisol level during poor night of sleep associated with glucose production from the liver side [145]. Another possible mechanism that there were a U-shape association between short and long sleep duration in people with poor glycemic control [40]. Since the mechanisms underlying this association remain unclear, understanding the additive effect of insomnia symptoms on sleep parameters in people with T2D is needed.

High sleep variability, defined as irregular night-to-night sleep parameters due to a misalignment between sleep-wake timing and the circadian system [146], is a common source of distress in people with chronic insomnia [72, 73]. For example, people with insomnia often compensate for a night of too little sleep by trying to get extra sleep duration the following night. While this may lead to a temporary improvement in sleep efficiency [69, 70], such detrimental sleep behavior may imbalance regular sleep drive and cause difficulty falling asleep and impair sleep duration and efficiency on subsequent nights [69, 70]. Sleep duration and sleep efficiency are important sleep parameters that reflect the overall sleep quality, in which variation in these sleep parameters may affect the sleep quality [147, 148]. Although night to night sleep variability is common sleep behavior in modern life because of increasing economic and social demands [68] and previous research showed that insomnia severity is not correlated with the sleep

variability [80], there is a lack of evidence about the night to night sleep variability in people with T2D and insomnia symptoms.

The averages and variabilities of sleep measures are indicators of the individual's sleep–wake rhythm [149, 150]. Using both values to understand sleep behavior will help for full interpretation. [149-151]. In general, low variability and high average for sleep efficiency would reflect better quality sleep. However, low variability of SE does not represent poor or normal sleep quality in all cases. For instance, a person presented with poor or normal SE in all 7 nights of a week will show low variation in the measured SE, as their SE is consistently poor or normal. Therefore, understanding the association between both averages and sleep variability of sleep parameters may provide a clear insight into current research for people with T2D [71].

Subjective and objective measures of sleep are important for assessing insomnia symptoms in clinical and research applications. Sleep diaries and actigraphy are useful tools to subjectively and objectively measure sleep parameters, respectively, including SE and TST [88]. Due to the discrepancies between subjective and objective measures, capturing both types of measurements simultaneously may be needed to measure sleep parameters [82]. Sleep diaries measure sleep parameters based on the individual's best estimation, which may be affected by recall bias, whereas actigraphy is less sensitive in detecting the time taken for falling asleep and fail to detect waking after sleep onset [88]. In addition, psychological symptoms might play a role in the subjective sleep measures for people with insomnia [152]. Despite these limitations, both measures are reliable in assessing the sleep-wake pattern across multiple nights and provide an indication of the response of TST and SE to treatment, which is key to capturing sleep variability empirically [91].

Several shared health issues commonly existing in people with T2D with sleep disturbances include sleep apnea, depression, anxiety, and pain [153-155]. Previous studies have shown the negative impact of these health conditions on sleep parameters (average and variability) [70, 156]. Older adults with insomnia have a high variation in sleep and reported morning pain, which might because of the psychological symptoms [157]. In multiracial study, severity of sleep apnea episodes was associated with more fragmentation in sleep, and high variation in sleep duration was associated with stress and depression [158]. It has been suggested to consider accounting for severity psychological issues in sleep variability studies [82]. With the prevalent insomnia symptoms in people with T2D, it is imperative to consider the shared health issues in this population to promote preventive strategies and treatment options.

Persistent sleep variability may result in poor sleep quality in people with T2D [159]. **In addition, various T2D symptoms may explain the variation in sleep parameters including frequency nocturnal urination, hyperglycemia-related food consumption, hypoglycemia symptoms, obesity, pain and distress [85]. These symptoms are considered common sleep disturbances in people with T2D. However, there is a need to understand the additive effects of insomnia symptoms on sleep parameters in people with T2D.** However, it is unclear if insomnia symptoms are associated with sleep variability in people with T2D. The purpose of this study was to compare the averages of sleep parameters in people with T2D with and without insomnia symptoms, and to compare the variability of sleep parameters in people with T2D with and without insomnia symptoms. Secondarily, we assessed the association between the average and variability of sleep parameters in people with T2D with and without insomnia symptoms.

2.2. MATERIALS AND METHODS

2.2.1. Design and Participants

This cross-sectional study enrolled 60 participants with self-reported T2D. Part of this project that compared the diabetes outcomes was published elsewhere [160]. We used a number of recruitment sources between November 10, 2018 and April 15, 2019, including a research participant registry, a diabetes clinic, advertisements at a university research center, and flyers distributed in the community. The study was approved by the institutional review board at University of Kansas Medical Center (IRB # STUDY00142985). Written informed consent was obtained from all participants during the first study visit.

2.1.2. Screening procedure

All participants underwent phone and in-person screening sessions to ensure that they meet the eligibility criteria. Individuals were included if they: 1) self-reported T2D, which was confirmed by reviewing participants' medication list during the in-person screening session; 2) were 40-75 years old; 3) were able to understand and follow verbal commands in English; and 4) were able to attend the study visits and complete the testing procedures. Individuals were excluded if they: 1) were at risk of untreated sleep apnea or restless leg syndrome using Stop Bang and restless leg syndrome diagnostic algorithm, respectively; 2) reported being pregnant; 3) reported consuming ≥15 drinks/week for men and ≥8 drinks/week for women; 4) self-reported a diagnosis of neurological diseases, bipolar disorder, seizure disorder, chronic fatigue syndrome, or rheumatic diseases, being on dialysis, blindness, or trans-femoral amputation; 5) reported performing shift-work; 6) scored ≥ 7 out of 10 on the Brief Pain Inventory; 7) scored ≥ 21 on the Beck Depression Inventory; and 8) scored ≥ 15 on the Generalized Anxiety Disorder 7-

item scale. The exclusion criteria were established to minimize the external influence of common health issues on sleep quality in people with T2D.

2.1.3. Group allocation

All participants were stratified based on the Insomnia Severity Index. Participants who scored >10 on Insomnia Severity Index were included in the T2D and insomnia group (T2D+Insomnia), while participants who scored ≤10 were included in the T2D only group (T2D only). Including only patients with insomnia symptoms above the cut-off score of 10 provided optimal sensitivity (97.2%) and specificity (100%) for the detection of insomnia on clinical sample [161]. Additionally, we confirmed that the self-reported symptoms of difficulty falling asleep, maintaining sleep, or waking up too early were present for at least 3 nights/week for the past 3 months in participants in the T2D+Insomnia group. Previous research showed that ISI is not correlated with the sleep variability [80].

2.1.4. Measures

Objective sleep parameters: Sleep efficiency (SE) and total sleep time (TST) were tested using an Actigraph device (Model wGT3X-BT, ActiGraph Corp, Pensacola, FL) as previously described [88]. The Actigraph device is a 3-axis accelerometer that has been validated in people with insomnia. It objectively differentiates people with poor sleep quality from people with good sleep quality [162]. The Actigraph device is a small, non-invasive device that records limb movements using electrical impulses at 30-100 Hertz frequencies. Participants were instructed to wear the Actigraph device on their non-dominant wrist all day for 8 consecutive days and 7

nights, including weekend nights, to capture habitual sleep patterns. The participants were requested to temporary remove the device if submerged in water for more than 30 minutes (i.e., bathing or swimming). A blinded trained assessor scored the Actigraph data using ActiLife software (version 6.11.8, ActiGraph Corp, Pensacola, FL). By using the Cole-Kripke algorithm, which has been validated for adult populations [163], sleep parameters such as SE and TST were objectively assessed. Additionally, the blinded assessor used the sleep diary to obtain a better estimation of the time in bed and time out of bed and removed invalid sleep periods compared to the Actigraphy data. Invalid wear time was defined as wearing the Actigraph device less than 400 minutes per day.

Subjective sleep parameters: Participants were asked to complete a sleep diary to provide best estimation of time in bed, time out of bed, and the duration of sleep latency, wake after sleep onset and early morning awaking. The provided information on the sleep diary was used to calculate the TST and SE. The TST was calculated as (total time in bed - the duration of sleep latency - wake after sleep onset - early morning awaking). Then, the SE was calculated as (TST/total time in bed) x 100.

Possible covariates: Information about the age, sex, body mass index, education, and ethnicity were collected at the assessment session. current passive airway pressure machine usage, and severity of symptoms of pain, depression, and anxiety) were measured. Participants were asked if they are using a passive airway pressure machine through a yes/no question (“Do you use any type of a passive airway pressure machine?”). Pain severity symptoms were measured using the Brief Pain Inventory, which is a validated and reliable measure commonly used to assess pain in diabetic peripheral neuropathy [164]. High Brief Pain Inventory scores indicate severe pain symptoms. Depression symptoms were measured using the Beck Depression

Inventory, which was shown to have high reliability and good validity. The Beck Depression Inventory consists of 21 self-reported items rated on a three-point Likert scale, with scores ≥ 21 indicating severe depression symptoms [165]. The Generalized Anxiety Scale contains 7 items added up to a total score ranging from 0 to 21, with higher scores indicating severe anxiety symptoms. The Generalized Anxiety Scale has been shown to be highly sensitive and specific for the detection of anxiety symptoms, and correlates with other anxiety scales [166].

2.1.5. Power Analysis

All sample size calculations were performed in the PASS 14.0 software using a linear mixed model for continuous outcomes. Based on a previous study investigated sleep variability in people with chronic insomnia, Cohen's d effect sizes for SL, TST, and SE were 0.59, 0.71, and 0.78, respectively [74]. Our sample size calculations are conservatively based on the minimum of above-mentioned effect sizes. Specifically, we have chosen a Cohen's d of 0.59, corresponding to a change of ± 2/3 SD from the mean [124]. To account for the possibility of correlation between 7 repeated measurements (corresponding to 7 nights of sleep), we used a mixed model with a compound symmetry covariance structure (correlation of 0.5 between any pair of measurements) to conduct the sample size calculations. The results of this calculations indicated that 28 subjects in each group are needed to detect a significant difference in sleep variability between groups at the 0.05 significance level with a power of 0.85.

2.1.6. Data Synthesis and Statistical Analysis

All data analyses were performed using SPSS 23.0 for Mac (Chicago, IL). Descriptive statistics included means and standard deviations for continuous variables, while frequencies

were used to describe categorical variables. Descriptive measures of time in bed with mean SE were established as visual circular data using the R statistical package. All sleep parameters (TST and SE) were presented as averages and variabilities of 7 nights. The coefficient of variation was calculated using the following equation: Coefficient of variation = (standard deviation/mean) ×100% to analyze within-subject variability of nighttime sleep across 7 nights. This calculation provides a percentage value, with higher number suggesting higher sleep variability [167].

For demographics and clinical variables, Chi square and independent sample *t*-test analyses were used to assess differences between groups in categorical and continuous variables, respectively. For the main analysis, Mann Whitney U tests were utilized to compare the group-differences in the average and variability of sleep parameters (SE and TST). In performing the exploratory analyses, the complex relationship between insomnia and T2D might be necessary to control for a number of factors by adjusting for covariates to investigate the differences between groups in the sleep parameters. However, due to the small sample size and the fact that the covariates were not included in the power calculation, these complex relationships can only be investigated in an exploratory manner. The decision was made in an exploratory manner because of the significant differences between the groups in age, depression symptoms, anxiety symptoms, and pain symptoms. Thus, to control for age, and symptoms of depression, anxiety and pain, multivariable general linear model was used to examine the differences between groups in sleep parameter averages and sleep variability. Group (ß= T2D+Insomnia group - T2D only group) was included as an independent variable with sleep parameters as dependent variables. For the secondary aim, multiple linear regression tests and scatterplots were utilized to assess the

association between averages and variability values for both groups. All tests were conducted at alpha level of 0.05.

2.3. RESULTS

2.3.1. Descriptive

Fifty-nine participants were recruited and included in the final analysis. The participants' flow diagram is shown in Figure 2.1. Demographics and clinical variables of participants in both groups are summarized in Table 2.1. Participants in both groups were similar in all demographics, except age (p=0.02). Mean Insomnia Severity Index score was 4.64±3.15 in the T2D group and 16.00±3.08 in the T2D+Insomnia group (p<0.001). Participants in the T2D+Insomnia group reported more severe symptoms of depression (11.00±5.91) and anxiety (7.41±4.71) compared to participants in the T2D only group (4.79±4.77 and 2.93±4.00, p<0.001, respectively). Severity of pain was significantly higher in participants in the T2D+Insomnia group (3.27±2.10) compared to participants in the T2D only group (1.55±1.67). Distribution of subjective and objective measure of time in bed with mean SE as a magnitude in both groups are shown in Figure 2.2.

2.3.2. Differences in Sleep Parameters Between Groups

As shown in Table 2.2, people in the T2D+Insomnia group had significant lower averages of objective SE (85.98±4.29) compared to people in the T2D only group (90.23±6.44). For subjective measures, people in the T2D+Insomnia group had lower averages of SE

(85.75±8.70) compared to people in the T2D only group (92.61±5.33). For TST, the subjective average was lower in T2D+Insomnia patients (420.04±72.34) compared to T2D only (474.52±71.43), while no significant between-group difference was observed in the averages of objective TST.

Objective measures demonstrate significantly higher variability in SE for T2D+Insomnia group (5.88±2.57) compared to the T2D only group (3.82±2.05). For subjective measure, people in the T2D+Insomnia group had higher variability in SE (11.13±9.02) compared to people in the T2D only group (4.99±4.63). For TST, the subjective variability was higher (22.71±16.59) in T2D+Insomnia patients compared to T2D only (13.43±8.03), while no significant between-group difference was observed in the variability of objective TST.

2.3.3. Multivariable Generalized Linear Model

Table 2.3 presents the between-group differences in objective averages of sleep parameters after controlling for covariates. After controlling for age, pain severity, depression severity, and anxiety severity, objective measure showed a significantly lower averages of SE (ß=-4.63, p=0.01) in T2D+Insomnia group compared to the T2D only group. However, between-group differences in averages of objective TST measure were not significant when age, pain severity, depression severity, and anxiety severity are incorporated in the model.

Table 2.3 presents the between-group differences in subjective averages of sleep parameters after controlling for covariates. Subjective measure showed significant lower averages of SE (ß=-6.43, p=0.008) in T2D+Insomnia group compared to the T2D only group when adding age only as a covariate. There were no significant group differences in subjective

averages of SE after controlling for pain severity, depression severity, and anxiety severity. In addition, no significant group differences were observed in averages of subjective TST after controlling all covariates.

A significant between-group differences was observed in objective variability of SE (ß=1.98, p=0.03) when controlling for age and pain severity (Table 2.3). People in T2D+Insomnia group showed higher variability of objective SE compared to people in the T2D only group. People in T2D+Insomnia showed significant increase in variability of subjective SE (ß=4.93, p=.04) after controlling for age only. Controlling for age, pain severity, depression severity, and anxiety severity yielded no significant between-group differences in variability in all sleep parameters using objective or subjective measures.

2.3.4. Multiple linear regression

As shown in Figure 2.3, people in T2D+Insomnia group showed a significant relationship between average and variability of objective SE (R^2=0.20, p=0.01). In addition, a significant relationship between average and variability of objective TST was shown in T2D+Insomnia group (R^2=0.21, p=0.009). For subjective measure, significant relationships between average and variability of SE (R^2=0.68, p<0.001) and TST (R^2=0.37, p=0.001) were found in the T2D+Insomnia group.

People in the T2D only group showed significant relationships between average and variability in objective SE (R^2=0.43, p<0.001) and in subjective SE (R^2=0.35, p=0.002). There were no significant relationships between average and variability in objective TST or average and variability in subjective TST.

2.4. DISCUSSION

The aim of this study was to compare the averages and variabilities of sleep parameters SE and TST in people with T2D with and without insomnia symptoms using objective and subjective measurements. Among key findings of our study is the detection of lower averages and higher variability of SE in individuals with T2D and insomnia symptoms compared to patients with T2D only using both subjective and objective measures. Psychological symptoms, including pain, depression, and anxiety, were found to play a role in the differences between groups in variability of SE for subjective and objective measures. Additionally, subjective measures showed that people with T2D and insomnia symptoms had lower averages TST and higher variability in TST compared to those with T2D only. No differences in these measures were observed after controlling for the age of the participants. Subjective and objective sleep measures suggest that patients with T2D and insomnia symptoms exhibit worse averages compared to patients with T2D only.

Understanding the variability in sleep parameters through analysis of the average scores may provide important insight into sleep patterns in people with T2D and insomnia symptoms. Consistent with the findings of our work, a study by Buysee et al. in older adults with insomnia demonstrated high variability in SE and TST assessed using subjective approaches, but not in TST measured objectively, possibly reflecting the fact that people with insomnia commonly underestimate sleep duration [74]. Additionally, the authors reported worse average scores in subjective measures of sleep parameters, but not the objective measures. Possibly, more nights of measurements may introduce more variability in sleep parameters. Alternatively, people with T2D may have misperceptions about their sleep, which may increase the variation in subjectively

quantified sleep parameters. Buysse et al. showed no difference between groups in the number of comorbidities, which may explain the consistency of their study with our results in average values and SE variability [74]. However, our study targeted a population with T2D who commonly reported several sleep disturbances, such as nocturia, which may increase the variability in sleep parameters. Our results contrast those of a multi-racial research study which found higher correlations between self-reported sleep duration and Actigraph measures [168]. Interestingly, measures of variability in sleep parameters, except for subjective measures of SE and TST, failed to demonstrate any differences between participants with and without clinical insomnia [168]. Possible reasons for the inconsistency in the findings include recall bias and imprecision of self-reported sleep duration. Additionally, the authors measured SE and TST over 4 to 5 nights, which may also explain the difference in findings.

Our study supports the importance of measuring both the variations and averages in sleep parameters. For example, we found no differences between groups in the variability of TST measured using Actigraph. However, we found differences in mean scores, which may explain the consistently worse sleep outcomes across most of the measured nights of sleep in people with T2D and insomnia symptoms. Overall, the variability SE is higher in people with T2D and insomnia symptoms, which may explain the inconsistency of poor SE across all measured nights. This may suggest several nights of sleep recovery are needed for people with insomnia symptoms to compensate for previous nights of poor sleep. Additionally, whether measured using subjective or objective approaches, higher averages of SE and TST associated with lower variability in SE and TST in participants with and without insomnia symptoms. These findings indicate the importance of improving the SE and TST in order to decrease the variation in sleep patterns in people with T2D.

Psychological domains, aging, and advanced sleep technology may explain the different observations between objective and subjective sleep measures. Previous research found discrepancies between subjective and objective sleep measurements due to psychological factors and Actigraph sensitivity [169]. The discrepancy between objective and subjective measures were reported by several studies summarized in a recent review [82]. In this summary of sleep studies, the authors noted that failure to control for potential confounders was a main limitation in sleep research [82]. We found no differences between groups in averages and variability of subjective TST after controlling for covariates. Under- and overestimations of sleep duration in subjective reporting are influenced by objective sleep quality and psychological factors affecting individuals with sleep disorders [169]. While our power calculations did not account for covariates which need to be considered in future research, no changes were observed in average of SE in objective measures after controlling for age and symptoms of pain, depression, or anxiety. These factors are commonly associated with both T2D and insomnia, with the additive effect of insomnia symptoms resulting in worse sleep parameters.

Our findings demonstrate that the psychological symptoms, including depression and anxiety, play a role in the variability in SE measured using objective and subjective approaches. We found that both subjective and objective variability in SE was no longer significantly different between groups when the statistical model incorporates psychological symptoms, but not age or pain severity measured objectively. Previously published work found that the subjective SE corresponds to the objective assessment and is influenced by psychosocial factors [170]. This may explain the worse subjectively measured SE in patients with T2D and insomnia symptoms, observed even after controlling for age. However, when adding severity of symptoms of pain, depression, or anxiety, no differences were noted between groups. No other significant

differences were found in variability of SL and TST measured objectively after controlling for covariates. T2D risk factors, such as age, hyperglycemia, and depression, contribute by increasing sleep disturbances, which may explain the lack of differences between groups in averages and variabilities of SE and TST. Despite the known greater variability of sleep in individuals with T2D compared to healthy subjects, further research is needed to investigate the complex relationship between psychological factors and variability in sleep parameters in people with T2D and insomnia symptoms.

Several limitations of this study need to be considered in the interpretation of data and in developing future research. Although this study was powered based on the published characteristics of the general population, there is a need to modify the calculations for the diabetic population by taking into account common external variables. There is currently no recommendation on the optimal number of nights that should be assessed to measure sleep parameters in people with T2D and insomnia symptoms. We measured the variability across 7 nights of sleep, but a different presentation would be expected if more nights were included to capture habitual sleep patterns. Greater night-to-night variability was previously shown to require more measured nights to estimate sleep quality accurately [70, 171]. We were not able to determine normal sleep variability in T2D population, which would have been helpful in guiding future work to identify a cut-off score of sleep variability that would predict poor sleep quality. Despite its high sensitivity and specificity, the ISI does not correlate with the sleep variability [80], suggesting that using insomnia diagnostic criteria may result in inconsistent results. Although this study focused on people with T2D, including healthy participants as a third group would help in distinguishing the sleep patterns in T2D population. Screening for the sleep apnea using gold stander measurements such as polysomnography may help in rolling out serious

extraneous variables which might add extra variation to the sleep parameters. Finally, our study did not control for concomitant medications (types or numbers), and we recommend that future studies collect a medication list, due to the potential effect of medications on sleep variability.

In conclusion, this study observed high SE variability and poor SE in people with T2D and insomnia symptoms compared to T2D only group, with statistical analyses suggesting that psychological symptoms may explain the observed difference. There were different observations between objective and subjective measurements of sleep duration, which may reflect the nature of Actigraph and sleep diary measurements. People with T2D and insomnia symptoms had worse symptoms of depression, anxiety, and pain compared to people without insomnia symptoms. Our findings indicate that further research is warranted to investigate the complex relationship between the variability in sleep and psychological factors in people with T2D and insomnia symptoms. In addition, using SE variability rather than TST variability might give important methodological implementations to investigate the association between night to night sleep variability and diabetes outcomes for future studies in people with T2D and insomnia symptoms. Longitudinal deign may help in elucidating the impact of sleep variation on psychological domains and diabetes outcomes for people with T2D.

Table 2.1. Comparison of demographics and clinical variables between T2D with and without insomnia symptoms using independent sample t-test and Chi-square

	T2D only (mean±SD) (n=28)	**T2D+Insomnia (mean±SD) (n=32)**	***p*-value**
Age	64.79±6.50	60.28±7.83	0.02
Gender, Female, n (%)	13 (46.42)	19 (59.37)	0.44
Body Mass Index	35.57±7.90	32.54±5.26	0.08
Education, n (%)			0.42
8 grades or less	0 (0)	1 (3.12)	
High school	5 (17.85)	6 (18.75)	
Some college	11 (39.28)	6 (18.75)	
College graduate	7 (25)	11 (34.37)	
Graduate degree	5 (17.85)	8 (25)	
Ethnicity, n (%)			0.28
White	21 (75)	23 (71.87)	
Black	5 (17.85)	3 (9.37)	
Other	2 (7.14)	6 (18.75)	
Insomnia severity index	4.64±3.15	16.00±3.08	<0.001
Brief Pain Inventory	1.55±1.67	3.27±2.10	0.001
Beck Depression Inventory	4.79±4.77	11.00±5.91	<0.001
Generalized Anxiety Scale	2.93±4.00	7.41±4.71	<0.001
Using passive airway pressure, n (%)			0.74
Never	18 (64.28)	20 (62.5)	
Current	9 (32.14)	12 (37.5)	

Note: T2D: Type 2 diabetes

Table 2.2. Comparison of sleep variabilities and averages in SE and TST between T2D with and without insomnia symptoms using Mann-Whitney U test

			T2D only (mean±SD) (n=28)	**T2D+Insomnia (mean±SD) (n=31)**	***p*-value**
Actigraph	**Average of**	**SE (%)**	90.23±6.44	85.98±4.29	0.005
		TST (min)	415.22±73.70	425.28±63.03	0.58
	Coefficient of Variance of	**SE**	3.82±2.05	5.88±2.57	0.002
		TST	13.77±7.21	17.18±9.47	0.13
Sleep Diary	**Average of**	**SE (%)**	92.61±5.33	85.75±8.70	0.001
		TST (min)	474.52±71.43	420.04±72.34	0.006
	Coefficient of Variance of	**SE**	4.99±4.63	11.13±9.02	0.002
		TST	13.43±8.03	22.71±16.59	0.004

Note: T2D: Type 2 diabetes; SE: Sleep Efficiency; TST: Total Sleep Time; min: Minutes

Table 2.3. Multivariable linear regression examining the association of groups with objective and subjective means of sleep parameters and sleep parameters variability

			Model	R^2	Adjusted R^2	ß	*p*-value
Actigraph	**Average of**	**SE (%)**	**1**	0.14	0.11	-4.31	0.005
			2	0.14	0.09	-4.47	0.008
			3	0.14	0.06	-4.63	0.01
		TST (min)	**1**	0.001	-0.03	3.62	0.85
			2	0.02	-0.02	13.05	0.53
			3	0.04	-0.05	21.49	0.35
	Coefficient of Variance of	**SE**	**1**	0.11	0.08	2.19	0.01
			2	0.12	0.07	1.98	0.03
			3	0.12	0.04	1.87	0.06
		TST	**1**	0.03	0.003	3.15	0.18
			2	0.05	0.008	2.01	0.43
			3	0.21	0.14	0.14	0.95
Sleep dairy	**Average of**	**SE (%)**	**1**	0.15	0.11	-6.43	0.008
			2	0.21	0.15	-4.59	0.07
			3	0.27	0.18	-3.06	0.25
		TST (min)	**1**	0.13	0.09	-35.69	0.11
			2	0.14	0.08	-29.18	0.23
			3	0.17	0.08	-17.70	0.49
	Coefficient of Variance of	**SE**	**1**	0.13	0.10	4.93	0.04
			2	0.18	0.13	3.19	0.21
			3	0.26	0.17	1.39	0.60
		TST	**1**	0.19	0.15	4.92	0.24
			2	0.19	0.14	4.22	0.37
			3	0.21	0.12	3.11	0.53

Note: SE: Sleep Efficiency; TST: Total Sleep Time

Model 1: Control for age

Model 2: Control for age and pain severity

Model 3: Control for age, pain severity, depression severity, anxiety severity

T2D only as reference group

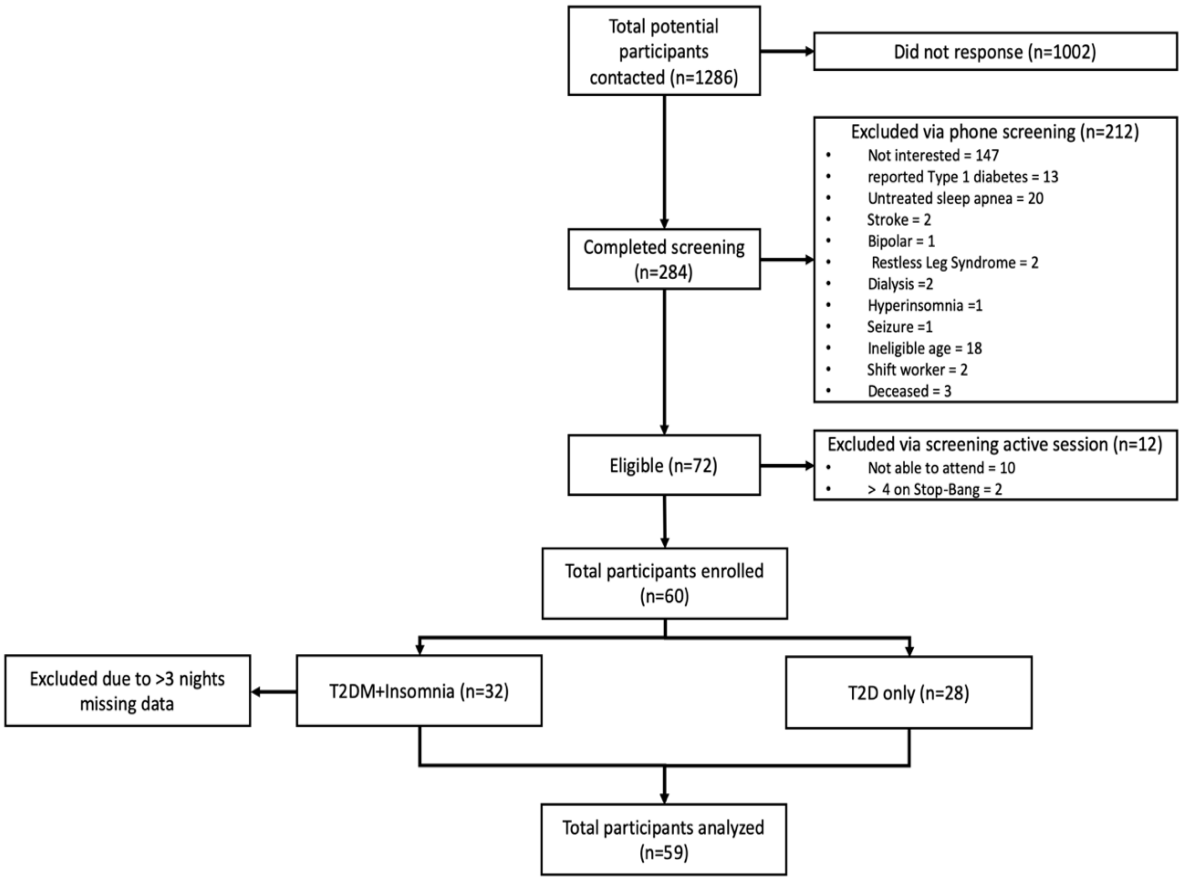
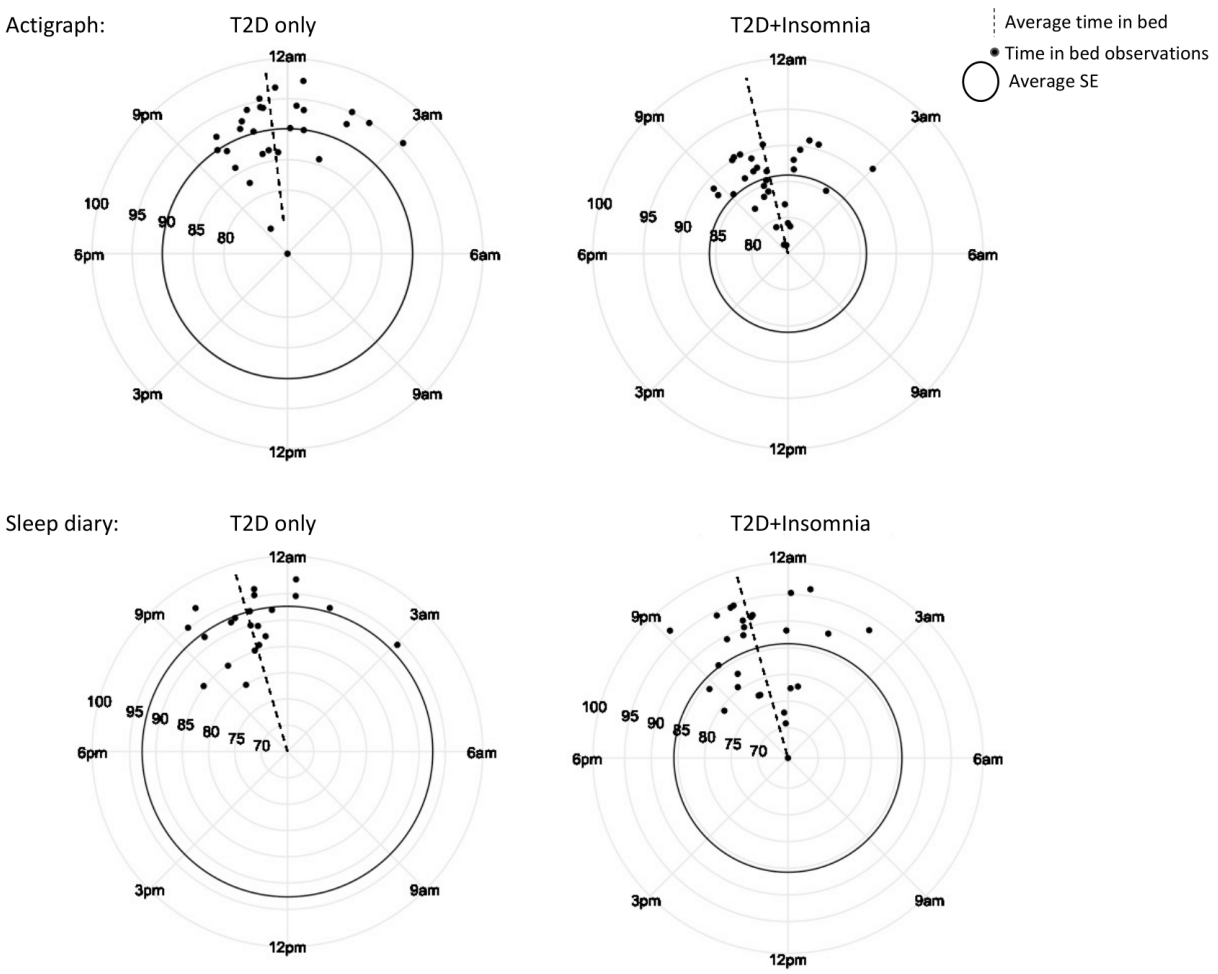
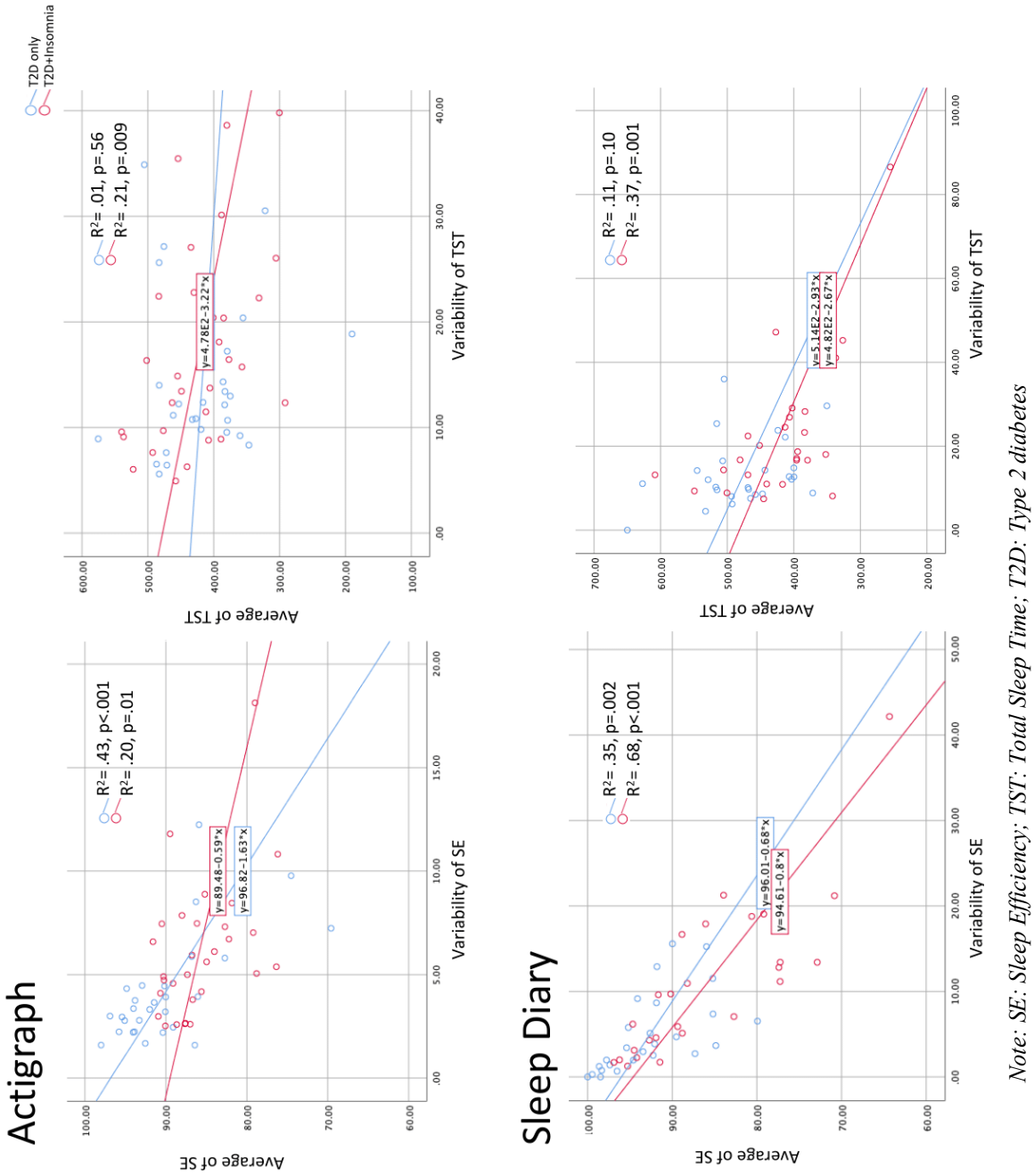


Figure 2.1. Participant recruitment process and flowsheet



Note: SE: Sleep Efficiency; T2D: Type 2 diabetes

Figure 2.2. Descriptive of means of time in bed distribution with sleep efficiency as a magnitude for both groups using Actigraph and sleep diary



Note: SE: Sleep Efficiency; TST: Total Sleep Time; T2D: Type 2 diabetes

Figure 2.3. Graphs to visualize the relationship between sleep variability and average of SE and TST for both groups using Actigraph and sleep diary.

Chapter 3: A Comparison of Diabetes Self-Care Behavior in People with Type 2 Diabetes with and without Insomnia Symptoms

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ABSTRACT

Introduction: Individuals with type 2 diabetes (T2D) are advised to undertake diabetes self-care behavior (DSCB) in order to avoid complications of T2D. However, comorbidities, such as insomnia symptoms which are commonly reported in people with T2D, may limit the ability to engage in DSCB. Insomnia and the common sequalae accompanying insomnia such as pain, depression, and anxiety may negatively influence the performance of DSCB. Therefore, this study aimed to compare the DSCB of people with T2D with and without insomnia symptoms.

Methods: Sixty participants with T2D were divided into 2 groups based on the presence of insomnia symptoms: T2D only group and T2D+insomnia group. Insomnia symptoms were identified using the Insomnia Severity Index (ISI). DSCB was assessed using the Diabetic Care Profile (DCP). A standardized composite score was established to account for all of the DCP domains. Chi square and independent sample *t*-tests were used to assess between-group differences in categorical and continuous variables, respectively. Stepwise linear regression analysis used the ISI score to predict standardized DCP composite score, while controlling for covariates.

Results: Significant between-group differences were found in age, symptoms of pain, depression, and anxiety. The total DCP composite score was significantly lower in the T2D+insomnia group compared to the T2D only group (-0.30±0.46 vs 0.36±0.48, respectively, $p<.001$) with large effect size (g=1.40). Stepwise linear regression results showed that a 1-point increase in ISI score significantly predicted a .03-point decrease in standardized DCP composite score, after controlling for age, symptoms of pain, depression, and anxiety ($\beta= -0.03$, $p=.04$).

Conclusions: The data suggest that people with T2D and insomnia symptoms had worse scores on the majority of the DSCB domains and a worse DCP composite score compared to people with T2D only. The data suggest a negative association between insomnia severity and DSCB among people with T2D. Further research using a larger sample size and more rigorous research design is required to examine the causal relationship between insomnia symptoms and DSCB.

Keywords: Type 2 diabetes, insomnia, self-care, diabetes self-care behavior, composite score, Diabetic Care Profile

3.1. INTRODUCTION

The current American Diabetes Association Standards of Medical Care recommends people with type 2 diabetes (T2D) to perform lifestyle management to optimize glycemic control and prevent complications [172]. Lifestyle management is a fundamental aspect of diabetes self-care behavior (DSCB) activities [172], which include: Understanding the disease better, receiving support from friends and family, controlling glucose level, self-addressing social and personal barriers, improving attitudes toward diabetes, adhering to healthy diet and exercise routines, considering long-term care, and addressing barriers to monitoring glucose [173, 174]. Improved DSCB has been associated with optimal glycemic control [175] and has predicted glycemic control due to its relationship with daytime activities that are essential for successful management of T2D [176]. Thus, understanding factors, such as sleep disturbances, that may influence DSCB might help people with T2D by aiding in improving diabetes outcomes and in preventing long-term complications.

Sleep disturbances have been shown to prevent people with T2D from engaging in optimal DSCB. Several barriers related to psychological or physiological factors, such as sleep disturbances, might prevent people with T2D from engaging in optimal DSCB [62, 177, 178]. Common daily symptoms, such as depression, anxiety, and pain, that are associated with both T2D and poor sleep quality may exacerbate the difficulties to adhere with optimal DSCB [34, 179]. Taken together, poor sleep quality and these common daily symptoms can yield a vicious cycle that decreases the daytime functioning of people with T2D [180, 181]. Previous research has shown the relationship of domains in DSCB with sleep disturbances [62, 65, 182]. These studies suggested the associated risk factors with sleep disturbances including low physical activity, fatigue, depression may result in low adherence to optimal DSCB and poor glycemic

control. Since the majority of these studies agreed that DSCB and sleep quality predict glycemic control, understanding the effect of a specific sleep disturbance on the DSCB domains is warranted.

Insomnia symptoms are commonly reported in people with T2D [183], and insomnia symptoms are characterized as one or more of following symptoms: Difficulty in falling asleep, maintaining sleep, and/or waking up too early at least 3 nights/week for past 3 months, which impacts daytime functioning [184]. Despite the advancing research on T2D pathophysiology, current research often focuses on barriers that might affect good DSCB [62, 65, 177, 178, 182, 185]. However, previous studies relied on global sleep quality measurements to define sleep disturbances. There is a lack of information on the effect of insomnia symptoms on adherence with activities required for optimal DSCB in people with T2D. It remains uncertain if insomnia symptoms act as barriers to engage in better DSCB. In our preliminary findings, it has been shown that improving insomnia symptoms using non-pharmacological intervention showed positive effect of glycemic control [186]. Therefore, understanding the effect of insomnia symptoms on the DSCB domains is warranted.

Since DSCB is an important aspect of T2D care, understanding negative factors related to DSCB may increase our understanding of T2D care in future research, clinical evaluation and health management. Therefore, in this study, the primary aim was to examine the DSCB domains among people with T2D with insomnia symptoms compared to those without insomnia symptoms. We hypothesized that people with T2D and insomnia symptoms will have worse DSCB domains of understanding of their disorder, friends and family support, controlling problems, social and personal barriers, attitudes toward diabetes, diet and exercise adherence, long-term care, and monitoring barriers compared with people with T2D only. Our secondary

aim was to examine the association of insomnia symptoms with the DSCB composite scores among people with T2D. The results of this paper may help in determining the impact of insomnia symptoms on people with T2D to help effective clinical assessment and treatment development in T2D population.

3.2. METHODS

3.2.1. Research Design

The design of this study was cross-sectional on people with T2D with and without insomnia symptoms. Participants with T2D were stratified to two groups, with insomnia symptoms (T2D+insomnia) and without insomnia symptoms (T2D only). A cut-off score of >10 on insomnia severity index (ISI) was used to stratify participants, and this cut-off score provided optimal sensitivity (97.2%) and specificity (100%) for the detection of insomnia in a clinical sample [161].

3.2.2. Participants

A total of 60 participants with self-reported T2D were recruited at the University of Kansas Medical Center (KUMC) as well as through flyers in the community around KUMC. The Frontiers registry at KUMC was used to communicate with the potential participants during the daytime via phone calls and emails [187]. The recruitment period was between November 2018 and April 2019. The study was approved by the Institutional Review Board at KUMC. Written informed consent was obtained for each participant prior to their inclusion in the study.

3.2.3. Procedures

All participants were enrolled in this study after being screened for meeting the inclusion criteria during a phone and in-person screening session. Individuals were included if they: 1) Self-reported T2D, which was confirmed by reviewing participants' medication list during the in-person screening session; 2) were 40-75 years old; 3) were able to understand and follow verbal commands in English; and 4) were able to attend and finish the testing procedure. Individuals were excluded if they: 1) Reported untreated sleep apnea or scored > 4 on Stop-Bang questionnaire; 2) were at risk of the Restless Leg Syndrome (RLS) according to the RLS Diagnostic Index [188]; 3) reported being pregnant; 4) reported consuming ≥15 alcoholic drinks/week for men and ≥8 alcoholic drinks/week for women; 5) self-reported neurological diseases (e.g., Multiple Sclerosis, Alzheimer's disease, Parkinson's disease, Traumatic Brain Injury, and Stroke), bipolar disorder, seizure disorder, chronic fatigue syndrome, rheumatic diseases, being on dialysis, blindness, or trans-femoral amputation; 6) reported working at night; 7) scored ≥ 7 out of 10 on the Brief Pain Inventory (BPI); 8) scored ≥ 21 on the Beck Depression Inventory (BDI); or 9) scored ≥ 15 on the Generalized Anxiety Disorder 7-item (GAD-7) scale. A description of the clinical features for the excluded participants is provided in Figure 3.1.

Participants were divided into either the T2D+insomnia group or the T2D only group, based on their ISI score. Participants in the T2D+insomnia group scored >10 on ISI, with self-reported symptoms of difficulty falling asleep, maintaining sleep, or waking up too early at least 3 nights/week for the past 3 months. Participants who scored ≤ 10 on ISI were assigned to the T2D only group. The ISI is a self-report measure designed to evaluate the nature, severity, and impact of insomnia [161].

3.2.4. Measures

Demographic variables: Age, sex, ethnicity, and education were gathered at the first assessment session.

Clinical Variables: Body Mass Index (BMI) was calculated using the NIH National Heart, Lung, and Blood Institute website (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm). *Random blood glucose level:* Glucose level was measured by a glucose meter (FreeStyle Flash, Contour® (Bayer Healthcare, Diagnostic Division, Tarrytown, NY)). *Glycemic control (HbA1c)* was tested using A1CNow+ testing Kit (TMS Company) which provides percent of glycated hemoglobin A1c levels in the capillaries (fingerstick). *Passive Airway Pressure (PAP) utilization:* Determining whether participants were using a PAP machine was obtained by asking a yes/no question (e.g., "Do you use a PAP machine?").

Pain severity symptoms: Daily pain symptoms was measured using the four item BPI, which has demonstrated strong evidence of reliability and validity in assessing painful diabetic peripheral neuropathy[164]. We averaged the four items to represent the daily severity scale of the BPI.

Depression severity symptoms: Depression symptoms were measured using the 21-item BDI, with scores ≥21 indicating severe depression symptoms. The BDI has demonstrated strong evidence of reliability and validity [189, 190].

Anxiety severity symptoms: The GAD-7 contains 7 items where the total score ranged from 0 to 21, with higher scores indicating severe anxiety symptoms. The GAD-7 has been

shown to be highly sensitive and specific for the detection of anxiety symptoms, and it is correlated with other anxiety scales [166].

Diabetes Self-Care Behavior (DSCB): The Diabetic Care Profile (DCP) was used to assess DSCB. The DCP is a validated instrument that measures psychosocial and educational factors associated with the management of diabetes [67, 191]. It has been shown that the DCP has demonstrated evidence of validity based on internal structure and relations to other variables in diverse samples of people with diabetes [191]. In addition, poor diabetes outcomes, such as poor glycemic control, were associated with poor scores in DCP domains [191-193]. The DCP consists of 13 domains, including understanding management of practice, support, control problems, social and personal factor, positive attitude, negative attitude, care ability, importance of care, self-care adherence, diet adherence, long-term care benefits, exercise barriers, and glucose monitoring barriers [67]. Detailed description of questions and number of items of each domain on DCP are provided in Table 3.1. To create the standardized DCP composite score, each domain of the DCP was scored according to the scoring rules provided by Fitzgerald et al [67]. Next, each participant's domain score was standardized using z-scores. Support needs, support received, and support Attitudes were averaged together for the subscale titled support. We then averaged the 13 standardized domain scores to create a standardized DCP composite score.

3.2.5. Statistical Analysis

All data analyses were performed using SPSS 23.0 for Mac (Chicago, IL) and R (https://www.R-project.org/) [194]. Descriptive statistics included means and standard deviations

for continuous variables and frequencies for categorical variables. Chi square and independent sample *t*-test analyses were used to assess for between-group differences in categorical and continuous variables, respectively. The Mann-Whitney U test was utilized for between-group differences in non-normally distributed data. A stepwise linear regression analysis with two models was utilized with the ISI score as the independent variable and total DCP composite score as the dependent variable. Covariates were determined based on the demographics and clinical variables that were statistically significant differ between groups. Hedges' g (g) was used to calculate the effect size between groups, in which small effect equals 0.2, medium effect equals 0.5, and large effect equals 0.8. All tests were conducted at an alpha level of 0.05.

3.3. RESULTS

Sixty participants were recruited and included in the final analysis. The flowchart is shown in Figure 3.1. DCP data from one participant in T2D+insomnia group was excluded because more than 50% of the items were not completed. Participants' demographics and clinical variables of both groups are summarized in Table 3.2. Participants in both groups were similar in all demographics except age (p=0.02), where the T2D+insomnia group was approximately 65 years old and the T2D only group was approximately 60 years old. The mean score of the ISI was 16.00±3.08 in the T2D+insomnia group and 4.64±3.15 in the T2D only group (p<0.001). Participants in the T2D+insomnia group reported higher symptoms of depression (11.00±5.91) and anxiety (7.41±4.71) compared to participants in the T2D only (4.79±4.77 and 2.93±4.00, respectively). Severity of pain was significantly higher in people with T2D+insomnia group (3.27±2.10) compared to participants in T2D only group (1.55±1.67). There were no significant

between-group differences in random glucose level and glycemic control (p=0.08 and p=0.58, respectively). The mean duration of self-reported T2D diagnosis was 16.50±10.35 years in the T2D+insomnia group versus 14.23±12.00 years in the T2D only group (p=0.44).

The total standardized DCP composite score was significantly lower in the T2D+insomnia group compared to the T2D only group (-0.30±0.46 vs 0.36±0.48, respectively, p<.001; g=1.40; Table 3.3). In addition, participants in the T2D+insomnia group scored significantly lower on 10 out of 13 domains of the DCP, including understanding management of practice, support, control problems, social and personal factor, positive and negative attitudes, care ability, self-care adherence, diet adherence, log-term care benefits, and exercise barriers compared to participants in T2D only group, which all indicate poor outcomes (Table 3.3). The effect sizes of all the significantly differed DSCB domains ranged from 0.51 to 1.40, which indicate moderate to large effect sizes. The stepwise linear regression analysis of potential predictors of standardized DCP composite score for all participants is presented in Table 3.4. The final model of the stepwise linear regression results showed that a 1-point increase in ISI significantly predicted a .03-point decrease in standardized DCP composite score in people with T2D, even after controlling for age, pain, depression, and anxiety (β= -0.03, p=.04).

3.4. DISCUSSION

This is the first study comparing domains of DSCB in people with T2D with and without insomnia symptoms. Despite the small sample size, our findings showed that participants with T2D and insomnia symptoms had a lower total DCP composite score and worse scores on 11 out of 13 DSCB domains, compared to participants with T2D only. These findings suggested a

negative relationship between insomnia symptoms and DSCB in people with T2D. People with T2D and insomnia symptoms showed more severe symptoms of pain, depression and anxiety compared to participants with T2D without insomnia symptoms. After controlling for age and psychological symptoms, decreased ISI scores significantly predicted greater DCP composite scores for the sample. These results may indicate the importance of screening insomnia symptoms in people with T2D for better DSCB outcomes.

Several potential explanations may illustrate the association between insomnia symptoms and DSCB. The 10 DSCB domains that were worse in people with T2D and insomnia symptoms compared to people with T2D only were understanding management of practice, support, control problems, social and personal factors, positive attitude, negative attitude, care ability, diet adherence, self-care adherence, log-term care benefits, and exercise barriers. These domains required complex actions related to psychosocial, judgmental, educational, and emotional distress aspects [195]. Generally, people with T2D required more effort for diabetes education in order to be able to perform optimal self-care, diet adherence, and long-term benefits, in which extra effort may eventually increase diabetes distress [195]. Our findings indicated that the effects of insomnia symptoms may contribute in diabetes-related distress and may eventually affect domains that are important in DSCB for people with T2D. In addition, insomnia symptoms are associated with declining initial learning and consolidation of treatment plans [196], which could be a factor in suboptimal DSCB. Also, another study has shown the effect of sleep disturbances on mood and cognition function [197], and cognitive declines on self-care [198]. However, it was difficult to determine whether low scores of domains on DSCB related to educational aspects were due to learning issues or cognitive difficulties related to sleep disturbances [199]. This is consistent with a previous study which found that people with

insomnia have impaired psychological wellbeing outcomes, which may further complicate T2D management [195]. In addition, our data suggested that people with T2D and insomnia symptoms tended to receive less support from family and friends, which is consistent with an 8-year longitudinal study found that a lack of friend and family support were predictors of sleep disturbances in middle-aged adults [200]. Our findings were consistent with previous studies that suggested an association between poor sleep quality and positive attitude, control problems [62], and high burdens of self-care in people with T2D [182]. In a longitudinal study, sleep quality was a strong prediction of poor self-care for 64 older adult patients with T2D [177]. Also, recent study suggested improving sleep quality may help to increase diabetes self-care management among people with T2D [201]. Overall, future research needs to investigate the underlying mechanisms that cause suboptimal DSCB in people with T2D and insomnia.

Psychological factors such as depression and anxiety have been associated with DSCB in people with T2D [202, 203]. We found that people with T2D and insomnia symptoms had worse symptoms of depression and anxiety than those with T2D only. It might be that the combination of psychological issues along with insomnia symptoms explains relationship between insomnia symptoms and suboptimal DSCB. Although we excluded people with severe symptoms of depression and anxiety, we did observe changes in the magnitude of the regression coefficient for insomnia symptoms when covariates were added, but ISI still significantly predicted the total DCP composite score. Our findings supported the association between negative psychological wellbeing and social outcomes with insomnia that has been found in previous studies [204, 205], and this association may exacerbate poor adherence to DSCB. Future studies are needed to evaluate the complex relationship between DSCB and insomnia symptoms in T2D with and without severe symptoms of psychological health.

Contrary to the domains of DSCB previously mentioned, we found no between-group differences in the glucose monitoring barriers and importance of care domains. People with T2D and insomnia symptoms had lower scores in these domains but did not reach the significant level. Glucose monitoring is important diabetes daily routines to control hyperglycemia or hypoglycemia for optimal glycemic control [206]. However, based on a systematic surveillance of 247 studies showed that routine home glucose monitoring is not needed in patients with T2D [207]. In addition, our study suggested that insomnia symptoms might not have an additional effect on barriers related to glucose monitoring such as financial, environmental, or psychological barriers. Additionally, our work suggested that no effects of insomnia symptoms on participants' knowledge of the importance of diabetes care, which includes managing blood sugar, weight, diet, medicine, exercise and stress in people with T2D. Although both groups had enough knowledge of diabetes care, insomnia symptoms showed evidence of deteriorating other domains related to DSCB. To our knowledge, there is limited research investigating the glucose monitoring barriers importance of care domains in people with T2D and sleep disturbances, which made difficulties in comparing our findings with previous studies.

Insomnia symptoms and DSCB may be associated due to different potential mechanisms. A meta-analysis regarding glycemic control in people with T2D and sleep disturbances showed between-study heterogeneity [208]. They concluded that the presence of comorbidities, diabetes medications, untreated other sleep disorders, unreported depression, and sample size may have contributed to the between-study heterogeneity. With the reported information, it is possible that we did not find between-group differences in glycemic control or glucose level due to the low sample size and less sensitive blood measures. However, we did find severe insomnia symptoms predicted low adherence to DSCB in people with T2D after controlling for covariates. It has been

suggested that the association between insomnia symptoms and glycemic control may have resulted from changes in physiological pathways which led to metabolic changes. These changes may eventually deteriorate DSCB and increase the risk of poor glycemic control [209]. In addition, exploring the efficacy of a sleep behavioral intervention combined with diabetes education to address the insomnia symptoms and improve DSCB in people with T2D is needed.

Although this is the first study to compare multiple domains of DSCB in T2D with and without insomnia symptoms, some limitations of this study should be mentioned. Although we used a sensitive and valid screening instrument to screen for clinical insomnia in community sittings, conducting clinical interviews to ascertain the diagnosis and duration of symptoms is a gold standard criterion to diagnose people with insomnia. Measuring glycemic control using HbA1c kits is less sensitive than laboratory blood tests. We recommend future studies use more sensitive measures of glycemic control and include other common diabetes lab outcomes to identify any between-group differences. We measured DSCB subjectively, since there are no standardized objective measures that could be used to assess self-care in this population. It could be beneficial to develop an objective measure to capture activities related to DSCB such as physical activity, diet, sleep quality, medication adherence, and glucose monitoring. Finally, future studies with larger sample sizes and more rigorous designs are needed to overcome the limitations associated with low sample sizes and to minimize the impact of extraneous variables.

In conclusion, this study found that individuals with T2D and insomnia symptoms showed lower total DCP composite scores and worse scores on the majority of DSCB domains when compared to those with T2D only. These findings suggested a negative relationship between insomnia symptoms and DSCB in people with T2D. After controlling for age and psychological symptoms, decreased ISI scores were associated with positive DCP composite

scores in this population. Thus, the data suggested that T2D and insomnia symptoms were associated with worse DSCB compared to the DSCB of those with T2D only. Further research is required using a longitudinal design to examine the causality relationship between insomnia symptoms and DSCB on a larger sample size. In addition, we recommend future work explore the association between DSCB and insomnia symptoms in people with T2D with and without psychological symptoms to help in establishing interdisciplinary interventions for this population.

Table 3.1. Description of DCP domains questions and number of items

Domain	Number of items	Questions about the…
understanding management of practice	13	…understanding of role factors related to diabetes such as, stress, diet, exercise, medication, foot-care, and blood sugar.
Support (needs, received, and attitudes)	18	…need and help from family and friends such as, planning meal, taking medication, getting enough exercise, caring of feet, and handling feeling about diabetes
Control problems	19	…number of symptoms of hyper and hypoglycemia (during past month), and frequency of causes that blood sugar become too high or too low (during past year) such as infection, upset or angary, wrong medication or food.
Social and personal factor	13	…feelings that diabetes keeps from performing daily activities (during past year) and avoids from social and personal aspects such as having enough money, meeting family responsibilities, having good relationship, being active, and eating as much food as wanted.
positive attitude	5	…satisfaction with life such as ability and willingness to do anything.
negative attitude	6	…feeling about diabetes such as being afraid, unhappy, and depressed, or dissatisfied with life because of diabetes.
care ability	4	…ability to control common aspects for diabetes care such as blood sugar, weight, diet, medicine, exercise and stress
importance of care	4	…knowing the importance of common aspects for diabetes care such as blood sugar, weight, diet, medicine, exercise and stress
self-care adherence	4	…blood sugar and weight were in good control, duties (diet, medicine, exercise) done for diabetes control, and feelings (fear, worry, anger) handled well
diet adherence	4	…meal plan, food quantity, and food exchange lists
long-term care benefits	5	…best possible care of eye, kidney, foot, hardening of the arteries, and heart
exercise barriers	5	…trouble getting enough exercise because of effort, useless, hatred, and health
glucose monitoring barriers	11	…don't testing sugar as often as have been told because of keeping forget, not right place or time, costing a lot, running out of materials, and hurting fingers

Table 3.2. Comparison of demographics and clinical variables between T2D with and without insomnia symptoms.

	T2D only (mean±SD) (n=59)	**T2D+insomnia (mean±SD) (n=59)**	***p*-value**	**Effect Size**
Age	64.79±6.50	60.28±7.83	.02	g=0.62
Gender, Female, n (%)	13 (46.42)	19 (59.37)	.44	OR=1.68
BMI	35.57±7.90	32.54±5.26	.08	g=0.46
Education, n (%) 8 grades or less High school Some college College graduate Graduate degree	 0 (0) 5 (17.85) 11 (39.28) 7 (25) 5 (17.85)	 1 (3.12) 6 (18.75) 6 (18.75) 11 (34.37) 8 (25)	.42	OR=1.11
Ethnicity, n (%) White Black Other	 21 (75) 5 (17.85) 2 (7.14)	 23 (71.87) 3 (9.37) 6 (18.74)	.28	OR=1.08
ISI total	4.64±3.15	16.00±3.08	<.001	g=3.65
BPI	1.55±1.67	3.27±2.10	.001	g=0.90
BDI	4.79±4.77	11.00±5.91	<.001	g=1.15
GAD-7	2.93±4.00	7.41±4.71	<.001	g=1.02
Using PAP, n (%) Never Current	 18 (64.28) 9 (32.14)	 20 (62.5) 12 (37.5)	.74	OR=1.2
Random glucose level	134.96±26.67	162.09±78.88	.08	g=0.45
HbA1c, %	6.77±1.03	6.92±0.96	.58	g=0.15
Diabetes Duration	14.23±12.00	16.50±10.35	.44	g=0.20

Note: g: Hedges' g; OR: odds ratio; T2D: Type 2 diabetes; BMI: Body mass index; ISI: Insomnia Severity Index; BPI: Brief Pain Inventory; BDI: Beck Depression Inventory; GAD-7: Generalized Anxiety Scale; PAP: Passive Airway Pressure; HbA1c: glycemic control

Table 3.3. Comparison of DCP 13 domains and composite score between T2D with and without insomnia symptoms

	T2D only (mean±SD) (n=59)	T2D+insomnia (mean±SD) (n=59)	*p*-value	Effect Size	95% Confidence Interval
Control problems	.37±1.01	-.26±.95	.02*	0.64	(0.08 to 1.16)
Social and personal Factors	.61±.86	-.34±.89	<.001*	1.08	(0.49 to 1.4)
Exercise barriers	.39±.1.00	-.37±.86	.003*	0.81	(0.27 to 1.25)
Monitoring barriers	.08±.82	-.13±1.21	.87**	0.21	(-0.36 to 0.79)
Negative attitude	.38±1.11	-.2±.81	.02**	0.59	(0.07 to 1.08)
Understanding management of practice	.55±.97	-.47±.81	<.001*	1.13	(0.56 to 1.48)
Support	.22±.81	-.15±.61	.04*	0.51	(0.01 to 0.75)
Positive attitude	.26±1.33	-.17±.74	.02**	0.39	(-0.12 to.1.00)
Care ability	.42±1.07	-.35±.82	.002*	0.80	(0.31 to 1.27)
Importance of care	.07±1.28	-.21±.88	.08**	0.26	(-0.28 to 0.85)
Self-care adherence	.63±1.02	-.43±.78	<.001*	1.16	(0.60 to 1.54)
Diet adherence	.44±.89	-.32±1.00	.005*	0.80	(0.24 to 1.28)
Log-term care benefits	.27±.76	-.33±1.20	.02**	0.60	(0.06 to 1.12)
DCP total composite score	.36±.48	-.30±.46	<.001*	1.40	(0.42 to 0.92)

Note: T2D: Type 2 diabetes

**Independent sample t-test*

***Mann-Whitney U test*

Table 3.4. Stepwise linear regression results of the potential predictors of Diabetes Care Profile composite score.

Model	Predictors	β	*t*	*p-value*	
First Model (n= 59)	**ISI**	-0.05	-5.26	<.001	R=0.57 R^2 Change=0.33 *p*<0.001
Final Model (n= 59)	**ISI**	-0.03	-2.11	0.04	R=0.72 R^2 Change=0.20 *p*=0.001
	Age	0.006	0.77	0.44	
	BPI	0.001	0.03	0.98	
	BDI	-0.04	-2.84	0.006	
	GAD-7	-0.01	-0.56	0.58	

Note: ISI: Insomnia Severity Index; BPI: Brief Pain Inventory; BDI: Beck Depression Inventory; GAD-7: Generalized Anxiety Scale

Dependent variable: DCP composite score

First Model: ISI

Final Model: ISI, age, BPI, BDI, and GAD-7 that remained in the final model.

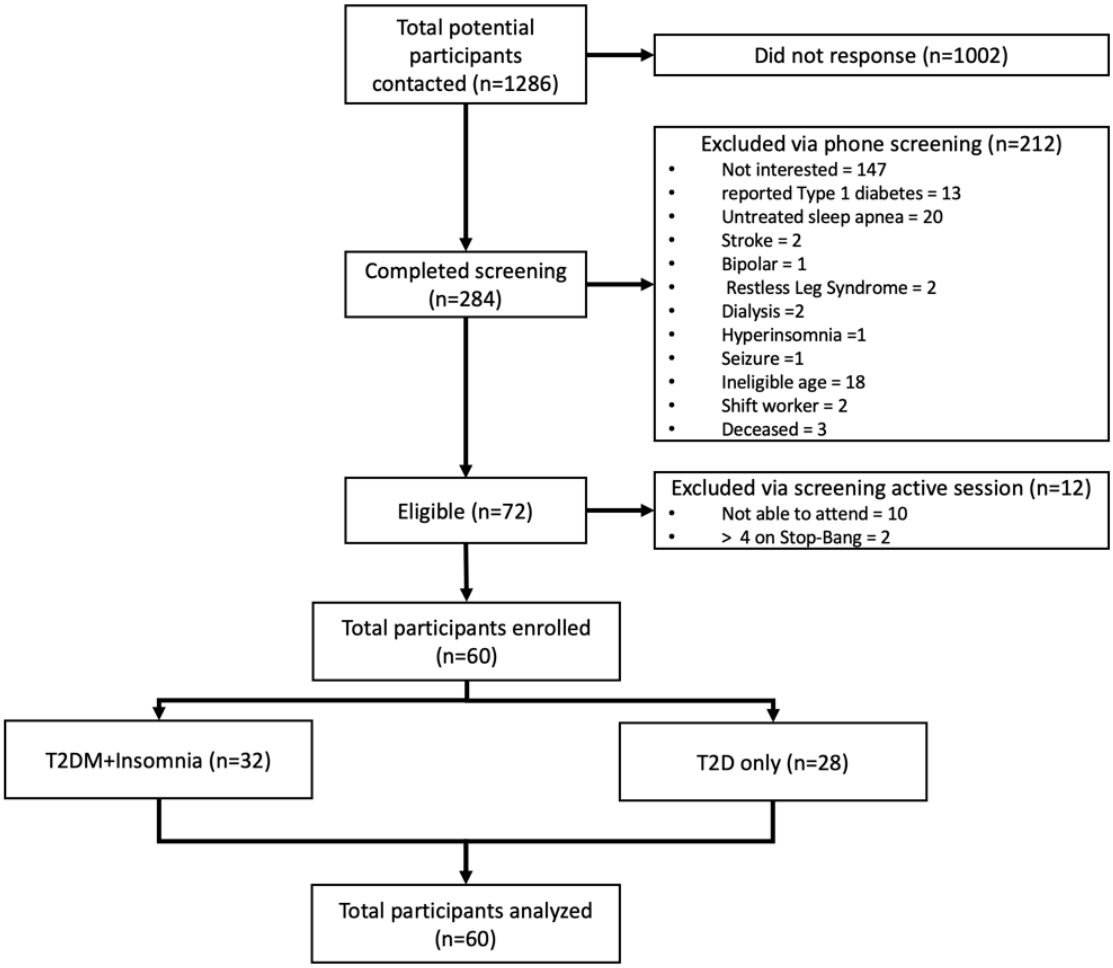

Figure 3.1. Participant recruitment process and flowsheet

Chapter 4: Daytime functioning in People with Type 2 Diabetes and Insomnia Symptoms: A Comparison-Correlational Study

ABSTRACT

Purpose: This study compared fatigue, daytime sleepiness, and quality of life (QoL) related to vitality and physical function in people with type 2 diabetes (T2D) with and without insomnia symptoms.

Methods: This study was a comparison design which used validated instruments to assess common daytime functioning including fatigue severity, daytime sleepiness, and vitality and physical function related to QoL in 60 participants with T2D with and without symptoms of insomnia. Insomnia severity index (ISI) was used to stratify participants into an insomnia (IN) group and non-insomnia control (CN) group. Data on age, gender, education, body mass index, and depression symptoms were collected. Parametric and non-parametric tests for between-group differences in all outcomes were performed. Multiple linear model and partial correlations tests were utilized to examine the relationships between outcomes in the two groups after controlling for age and depression symptoms.

Results: Levels of fatigue severity, and QoL related vitality and physical function were worse in the IN group compared to CN group ($P<.004$). After controlling for age, the IN group had greater fatigue severity ($R^2=0.15$, $p=.003$), and lower QoL related to vitality and physical function ($R^2=0.25$, $p<.001$; and $R^2=0.11$, $p=.004$, respectively). There were no significant differences between the groups in any outcomes after controlling for depression symptoms. There was also no significant between-group difference in daytime sleepiness after controlling for age and depression. However, daytime sleepiness was correlated with ISI in the full sample after controlling for age.

Conclusion: Daytime functioning including fatigue, and QoL related vitality and physical function were worse in people with both T2D and insomnia symptoms compared to people with T2D only. Depression symptoms may have an independent contribution for the daytime functioning, in which future research is needed to investigate the complex relationship between depression, insomnia symptoms and daytime functioning for people with T2D.

Keywords: Type 2 diabetes, insomnia, fatigue, daytime sleepiness, quality of life, daytime functioning

4.1. INTRODUCTION

Sleep disturbances have been associated with impairments such as fatigue and daytime sleepiness in people with type 2 diabetes (T2D) [180, 182]. In addition, hypoglycemia and/or hyperglycemia may exacerbate fatigue, while poor glycemic control has been associated with daytime sleepiness [210, 211]. Sleep disturbances, particularly insomnia symptoms such as difficulty falling asleep, maintaining asleep, and/or waking up too early are associated with suboptimum self-care behavior in those with T2D [160]. Despite the growing prevalence of insomnia symptoms in people with T2D, however, it is not clear whether or to what extent these symptoms exacerbate fatigue and daytime sleepiness.

Both, insomnia and T2D are thought to have a bidirectional relationship in which hypothalamic-pituitary-adrenal (HPA) axis hyperactivation increases cortisol level, which negatively impacts fatigue, daytime sleepiness and depression [212, 213]. Increasing the cortisol level during a poor night of sleep is associated with the risk of hyperglycemia due to liver glucose production [212, 213]. Self-reported daytime functioning has been widely used to collectively describe the constellation of psychological and physical symptoms that includes fatigue, daytime sleepiness, mood disturbance, and QoL [47, 214]. Hyperactivation of the HPA axis due to a poor night of sleep [213] or diabetes related distress [212] can disrupt homeostasis throughout the body and may contribute to the common reports of fatigue, daytime sleepiness and depression observed in people with T2D [213, 215] and with insomnia [213]. However, while the underlying mechanisms of the association of poor daytime functioning with T2D or insomnia symptoms have yet to be tested, there is a need to investigate the additive effect of insomnia symptoms on self-reported fatigue and daytime sleepiness in people with T2D.

Insomnia symptoms and T2D may each influence daytime functioning independently of one another. However, their combined effects in those with both T2D and insomnia remain unclear. Understanding how insomnia symptoms affect daytime functioning in individuals with T2D may help facilitate the design of preventive strategies in diabetes management to optimize care in this population. Therefore, the primary purpose of this study was to compare fatigue, daytime sleepiness, vitality, and physical function in people with T2D with and without insomnia symptoms. Our hypotheses were that people with T2D and insomnia symptoms would have worse fatigue severity, daytime sleepiness symptoms, and QoL related to vitality and physical function compared to people with T2D without insomnia symptoms. Our secondary aim was to investigate the relationship between insomnia symptoms and daytime functioning outcomes in people with T2D after controlling for risk factors of insomnia and T2D such as age and depression symptoms.

4.2. METHODS

4.2.1. Research Design

This study was conducted as part of a larger project investigating the consistency of sleep schedules in people with T2D. Portions of this project have been published elsewhere [160]. This cross-sectional study utilized data from people with T2D only and people with both T2D and insomnia symptoms. Participants were stratified into two groups, those with insomnia (IN) and without insomnia (CN), using a cut-off score of >10 on the insomnia severity index (ISI).

4.2.2. Data Collection Procedures

Participants were recruited through the University of Kansas Medical Center's Frontiers research subject registry [187], Cray Diabetes clinic, and campus advertisements, as well as through flyers distributed to the surrounding community. The study was approved by the University of Kansas Medical Center's Institutional Review Board. Written informed consent was obtained from each participant during the first study visit.

Participants were enrolled in the study following telephone and in-person screening sessions. Individuals were included if they 1) had self-reported T2D; 2) were 40-75 years old; 3) were able to understand English; and 4) were able to attend to and finish the testing procedures. Individuals were excluded if they 1) were at risk of untreated sleep apnea or restless leg syndrome as determined by the Stop Bang and Restless Leg Syndrome Diagnostic Index; 2) reported being pregnant; 3) reported heavy alcohol use (i.e., ≥15 alcohol drinks per week for men and ≥8 for women; 4) had a self-reported history of neurological disease, bipolar disorder, seizure disorder, chronic fatigue syndrome, rheumatic disease, dialysis, blindness, or amputation; 5) currently performed night-shift work; 6) reported severe symptoms of pain, depression and anxiety, as evidenced by a score of ≥7 on the Brief Pain Inventory, ≥21 on the Beck Depression Scale, and ≥15 on the Generalized Anxiety Disorder–7 scale.

Participants were allocated into either the insomnia (IN) group or non-insomnia control group (CN) based on their score on the ISI, with those scoring > 10 allocated to the IN group and those scoring ≤ 10 allocated to the CN group. The ISI is a self-report measure designed to evaluate the nature, severity, and impact of insomnia [161]. Scores on the ISI range from 0 to 28, with higher scores indicating greater insomnia severity [161]. Previous research has shown this instrument to be an excellent screening tool to predict the diagnosis of insomnia [216], and a cut-

off score >10 has been shown to result in high sensitivity (97.2%) and specificity (100%) for the detection of insomnia in a clinical sample [161].

4.2.3. Participants

A total of 60 participants with self-reported T2D participated in the study and were included in the final analysis.

4.2.4. Measures

All measurements, including demographic and clinical variables, fatigue severity, daytime sleepiness symptoms, and QoL related vitality and physical function, were obtained during the course of a single visit.

Demographic and clinical variables: Information regarding age, sex, education and ethnicity was collected during the assessment visit. BMI was calculated via height and weight measurements. Positive Airway Pressure (PAP) machine utilization was determined through the use of a yes/no question (e.g., “Do you use a PAP machine?”).

Daytime functioning: Each participant completed a comprehensive assessment of daytime functioning including *fatigue severity, daytime sleepiness, vitality*, *physical function, and depression symptoms.*

Fatigue severity was measured using the Fatigue Severity Scale (FSS), which is a 9-item questionnaire that has been validated in people with diabetes [44]. The FSS emphasizes the impact of daily functional fatigue accumulation during the past week on subscales of motivation,

exercise, interference with work, family, or social life. These subscales are summed to yield with a score of <4 indicating no fatigue, scores between 4 and 4.9 indicating moderate fatigue, and a score ≥5 indicating severe fatigue [44].

The Short Form-36 vitality (SF 36-vitality) subscale is widely used to measure energy in chronic disease groups [217]. Vitality represents the combination of fatigue and energy. The SF-36-vitality includes four questions, two related to fatigue and two related to energy over the past 4 weeks. These questions represent both positive (energetic) and negative (tired) states. Scoring criteria for SF-36-vitality was used for each item, then summed to range between zero (worse scores) to 100 (optimal scores) [218].

Physical function over the past 4 weeks was measured using the Short Form-36 physical subscale (SF 36-physical function) [218]. This subscale contains ten items rated from zero (very limited ability to perform daily physical activates) to 100 (able to perform all daily activities without limitations).

Daytime sleepiness symptoms were assessed through the Epworth Sleepiness Scale (ESS) which refers to usual lifestyle in recent times. The ESS consists of eight items rated on a 4-point Likert scale, with subjects rating how likely they would be to fall asleep in 8 different states of daily activity [62]. The ESS has demonstrated satisfactory test-retest reliability ($r = .82$) and internal consistency ($\alpha = .88$) [62]. A cutoff score of ≥10 suggests pathological sleepiness [62].

4.2.5. Statistical Analysis

All data analyses were performed using SPSS 23.0 for Mac (Chicago, IL). Descriptive statistics included means and standard deviations, and frequencies were used for continuous

variables and categorical variables, respectively. Skewness and kurtosis tests examined the normality of residuals during model development. Chi-square and independent sample *t*-test analyses were used to assess between-group differences in categorical and continuous variables, respectively. Pearson correlation was utilized to investigate the relationship between daytime functioning outcomes and ISI scores. A multivariate linear model assessed the differences between groups in daytime functioning outcomes after controlling for covariates. Partial Pearson's correlation tests were used to assess the relationship between daytime functioning outcomes and insomnia severity after controlling for demographic variables. Symptoms of depression, as assessed by the Beck Depression Inventory [165], was also included as a covariate. All tests were conducted at an alpha level of 0.05.

4.3. RESULTS

4.3.1. Demographics and clinical variables

Figure 4.1 shows the flowsheet of the study. Demographics and clinical variables for participants in both groups are summarized in Table 4.1. There were no differences between the CN and IN groups in any demographic variables with the exception of age (64.79±6.50 and 60.28±7.83, respectively, p=0.02). The average ISI score was 4.64±3.15 in the CN group and 16.00±3.08 in the IN group (p<0.001). Participants in the CN group reported less depression symptoms compared to participants in the IN group (4.79±4.77 and 11.00±5.91, p<0.001).

4.3.2 Measures of daytime functioning

There were significant between-group differences in FSS (p=0.003), SF 36-vitality (p<0.001) and SF 36-physical function (p=0.004) scores. People in the IN group reporting higher

scores on the FSS (4.29±1.40), and lower scores on the SF 36-vitality (41.77±18.86) and SF 36-physical function (58.55±23.85) compared to the CN group (3.15±1.44, 60.71±13.79, and 78.64±16.77, respectively) (Table 4.2). No significant between-group difference was observed in ESS scores (p=0.09).

Results of the multiple linear model are provided in Table 4.3. After controlling for age, the multivariable linear model showed significantly higher scores for IN group in FSS (ß=1.15, p=.003), and lower scores in SF 36-vitality (ß=-18.87, p<.001) and SF 36-physical function (ß=-16.66, p=.004). However, no significant between-group differences in FSS, SF 36-vitality, and SF 36-physical function were observed when covariates of age and depression symptoms were added to the model (p=.19, p=.07, p=.70, respectively). No significant between-group differences in ESS were noted in any of the models (p>.05).

4.3.3. Relationships between insomnia severity and daytime functioning

In table 4.4, Pearson's correlation showed moderate positive correlations between ISI scores and FSS (r=.34, p=.008) and ESS (r=.35, p=.006), and moderate negative correlation with vitality-SF 36 (r=-.48, p<.001) and physical function-SF 36 (r=-.35, p=.006) after controlling for age. However, no significant correlations between these variables were observed after controlling for symptoms of depression.

4.4. DISCUSSION AND CONCLUSIONS

This project is the first to compare measures of daytime functioning such as fatigue, daytime sleepiness, vitality related QoL, and physical function related QoL in people with T2D with and without insomnia symptoms. Consistent with our hypothesis, we found that people with T2D and insomnia symptoms reported higher fatigue severity, and poor vitality and physical function related to QoL than people with T2D without insomnia symptoms. We also observed moderate correlations between insomnia severity and fatigue severity, daytime sleepiness, and vitality and physical function related QoL across both groups. Depression, rather than age, seemed to mediate these relationships.

High fatigue severity and low QoL are common health complains in people with T2D as well as in people with insomnia. We observed significantly higher fatigue scores in those with T2D and insomnia symptoms than those without insomnia symptoms. This suggests that the combination of T2D and insomnia might aggravate the severity of fatigue or the perception of poorer daytime function in general. Consistent with our findings, a large cohort study of 13,171 adults with T2D, aged 30–75 years, reported that 24.6% of the sample complained of fatigue and 24.2 % reported insomnia symptoms [219]. Likewise, worse scores in QoL related to vitality and physical function were observed in people with T2D and poor sleep quality compared with people with T2D and good sleep quality. Furthermore, there was a moderate negative correlation between sleep quality and QoL related to vitality and physical function. In a different study of 116 participants with T2D, lower physical function related QoL was significantly associated with poor sleep quality [220]. However, these previous studies did not account for depression symptoms as a confounding factor in the relationship between insomnia and daytime functioning in people with T2D.

Although we excluded individuals with severe symptoms of depression from our study, we found that symptoms of depression influenced the relationship between insomnia symptoms and daytime functioning in people with T2D. This is in agreement with a previous study of 2024 patients with insomnia which observed that the association between insomnia severity and fatigue was mediated by depression symptoms [221]. Moreover, it has been shown that people with chronic insomnia are often diagnosed with major depression, which might be associated with fatigue symptoms [222]. This data suggests that treating depression symptoms might be beneficial in reducing fatigue in people with insomnia [221]. However, a cross-sectional study of people with T2D showed that depression symptoms were not a predictor of fatigue severity in this population. Rather, sleep quality was found to be the strongest explanatory factor for fatigue [223]. One possible explanation for this inconsistency may be the use of a validated survey for insomnia in the former studies versus screening for sleep disturbances using a subjective sleep quality questionnaire in the latter. Our study employed the ISI, an instrument that is well-validated for insomnia screening, and our data are in agreement with previous studies that utilized ISI to confirm insomnia symptoms. Nevertheless, other methods of diagnosing insomnia, such as comprehensive interviews, might yield different findings. Future studies are still needed to investigate the complex associations between insomnia, fatigue, and depression in people with T2D.

Previous studies have provided conflicting results related to the association between insomnia and daytime sleepiness. It has been suggested that daytime sleepiness is associated with insomnia only in people with T2D with short sleep duration [31]. This is possibly because some people with insomnia symptoms may actually spend long periods of time in bed sleeping, thus reducing the need to nap during the daytime. Similarly, some studies have reported increased

daytime sleepiness in people with T2D [181, 224]. Although our findings suggest a moderate correlation between daytime sleepiness and insomnia severity in this group of individuals with T2D, there were no between-group differences in ESS score and both groups fell below the cut-off score of 10 that has been suggested to reflect excessive daytime sleepiness. Neither did we observe between-group differences in sleep apnea status or BMI, both of which have been associated with daytime sleepiness [225]. This may be due to the fact that we relied on a relatively simple screening to determine the presence of sleep apnea. Use of a more objective measure, such as polysomnography, to identify untreated sleep apnea may help better characterize these relationships in future studies.

Daytime dysfunction is associated with psychological distress in both people with T2D and those with insomnia [180, 226]. When account for depression symptoms in the model, we did not observe significant relationships between daytime functioning and symptoms of depression. A review study challenged the assumption of daytime functioning impairments due to insomnia [47]. The review showed that daytime sleepiness was not increased in people with insomnia; however, impairments in fatigue, mood, and QoL were associated with insomnia. Our data suggest the effects of insomnia, depression, or the combination of both may explain the deterioration of fatigue, and QoL related to vitality and physical function. Indeed, depression symptoms could worsen daytime functioning in people with T2D and insomnia symptoms. Therefore, there is a need to understand the complex relationship between insomnia and depression in people with T2D.

Although this study has identified a potential impact of insomnia symptoms on daytime functioning in people with T2D, there are several limitations that must be considered. Despite the presence of a comparison group, it is not possible to determine causal relationships due to the

cross-sectional nature of the study. Future investigations should consider longitudinal designs to examine causal relationship between insomnia symptoms and poor daytime functioning outcomes in people with T2D. In addition, medications such as antidepressants and hypnotics have a negative effect on fatigue and daytime sleepiness [227], while stimulants have a positive impact on daytime sleepiness [228]. Our work did not account for the use of these medications. However, we did not find any significant difference in the number of medications between groups. Although, our participants visited our lab independently, other comorbidities may influence activity level. Future studies may consider the number of comorbidities to control as a covariate. Finally, comprehensive functional assessments, including variables such as cognition, self-care, and activities of daily living may help in identifying other associations with insomnia and poor daytime symptoms.

In conclusion, this study suggested a negative impact of insomnia symptoms on fatigue and QoL related to vitality and physical function in people with T2D. Depression symptoms may have an independent contribution to the daytime functioning in people with T2D with insomnia symptoms. Diabetes educators may consider including sleep hygiene or cognitive behavioral therapy for insomnia with diabetes education to promote daytime functioning in people with insomnia symptoms. Future research is needed to investigate the complex relationship between depression, insomnia symptoms and daytime functioning in people with T2D.

4.5. IMPLICATIONS/RECOMMENDATIONS

The results of this project provide insight into the negative impact of insomnia symptoms on daytime functioning in people with T2D. Evaluation of insomnia symptoms using a feasible

and sensitive tool such as the ISI may improve the standard of diabetes care. For instance, diabetes self-care behavior requires many daytime activities that could be affected by insomnia symptoms. Therefore, ruling out negative factors that could be barriers to optimizing daytime functioning outcomes may support diabetes health outcomes. In addition, diabetes educators may consider providing sleep hygiene to those who present with high scores on ISI and FSS, and refer those with high risk of sleep disorders. Providing sleep hygiene in diabetes education may offer beneficial suggestions to improve daytime functioning outcomes such as ensuring enough sleep at night, developing routine sleep schedule, avoiding excessive awake time on the bed, and avoiding caffeine for 6 hours before bedtime. In addition, suggestions specific for those with diabetes may include avoiding drinking too much before bedtime in order to minimize bathroom visits at night, scheduling meals at least 4 hours before bedtime, assuring enough physical activity during the day but avoiding vigorous physical activity within 4 hours of bedtime, and encouraging patients with sleep apnea to adhere to the Passive Airway Pressure throughout the night. Finally, preliminary data have shown that cognitive behavioral therapy for insomnia may be a feasible and effective means of improving sleep outcomes and glycemic control for people with T2D [186]. These promising results may encourage diabetes educators and other health care professionals to be consider sleep training in order to optimize diabetes management for their clients.

Table 4.1. Comparison of demographics and clinical variables between participants withT2D with and without insomnia symptoms.

Variables	CN group (mean±SD) (n=28)	IN group (mean±SD) (n=32)	*p*-value
Age	64.79±6.50	60.28±7.83	.02**
Gender, Female, n (%)	13 (46.42)	19 (59.37)	.44*
BMI	35.57±7.90	32.54±5.26	.08**
Education, n (%)			.42**
8 grades or less	0 (0)	1 (3.12)	
High school	5 (17.85)	6 (18.75)	
Some college	11 (39.28)	6 (18.75)	
College graduate	7 (25)	11 (34.37)	
Graduate degree	5 (17.85)	8 (25)	
Ethnicity, n (%)			.28**
White	21 (75)	23 (71.87)	
Black	5 (17.85)	3 (9.37)	
Other	2 (7.14)	6 (18.74)	
ISI	4.64±3.15	16.00±3.08	<.001*
BDI	4.79±4.77	11.00±5.91	<.001*
Using PAP, n (%)			.74**
Never	18 (64.28)	20 (62.5)	
Current	9 (32.14)	12 (37.5)	

Note: T2D: Type 2 diabetes; CN: Control group (no insomnia); IN: insomnia group; BMI: Body Mass Index; ISI: Insomnia Severity Index; BDI: Beck Depression Inventory; PAP: Passive Airway Pressure

**Chi-square test*

***Independent two sample t test*

Table 4.2. Comparison of daytime functioning outcomes between T2D with and without insomnia symptoms.

	CN Group (mean±SD) (n=28)	**IN Group (mean±SD) (n=32)**	***p*-value**	**Effect Size**	**95% Confidence Interval**
FSS	3.15±1.44	4.29±1.40	.003*	0.80	(-1.87 to -.40)
ESS	7.36±5.00	9.75±5.68	.09*	0.44	(-5.17 to .39)
SF 36-Vitality	60.71±13.79	41.77±18.86	<.001*	2.10	(10.24 to 27.63)
SF 36-Physical function	78.64±16.77	58.55±23.85	.004*	0.96	(5.23 to 26.95)

Note: T2D: Type 2 diabetes; FSS: Fatigue Severity Scale; ESS: Epworth Sleepiness Scale

**Independent two sample t-test*

Table 4.3. Multivariable linear regression to investigate relationship between the daytime functioning outcomes (Dependent variables) and group (independent variable) after controlling for age and depression symptoms

	Model	ß	Observed Power	*p*-value	95% Confidence Interval
FSS	**1**	1.15	.86	.003	(.40 to 1.89)
	2	.53	.25	.19	(-.28 to 1.35)
ESS	**1**	1.78	.23	.22	(-1.12 to 4.68)
	2	-.70	.07	.71	(-.44 to -.07)
SF 36-Vitality	**1**	-18.87	.98	<.001	(-27.76 to -9.98))
	2	-8.1	.40	.07	(-1.74 to -.40)
SF 36-Physical function	**1**	-16.66	.84	.004	(-27.81 to -5.50)
	2	-2.09	.06	.70	(-12.80 to 8.62)

Note: FSS: Fatigue Severity Scale; ESS: Epworth Sleepiness Scale; group variable included two categories: Insomnia and no insomnia (reference category)

Model 1: Age was controlled

Model 2: Age and depression symptoms were controlled

Table 4.4. Correlations between daytime functions and insomnia symptoms after controlling for age and depression symptoms.

Outcomes (n=60)	ISI					
	Model 1		Model 2		Model 3	
	r	*p*-value	Partial r	*p*-value	Partial r	*p*-value
FSS	.34	.008	.35	.007	.10	.44
ESS	.35	.006	.31	.02	.16	.21
SF 36-Vitality	-.48	<.001	-.46	<.001	-.20	.13
SF 36-Physical function	-.35	.006	-.34	.01	.02	.90

ISI: Insomnia Severity Index; FSS: Fatigue Severity Scale; ESS: Epworth Sleepiness Scale

Model 1: No covariates

Model 2: Age was controlled

Model 3: depression symptoms was controlled

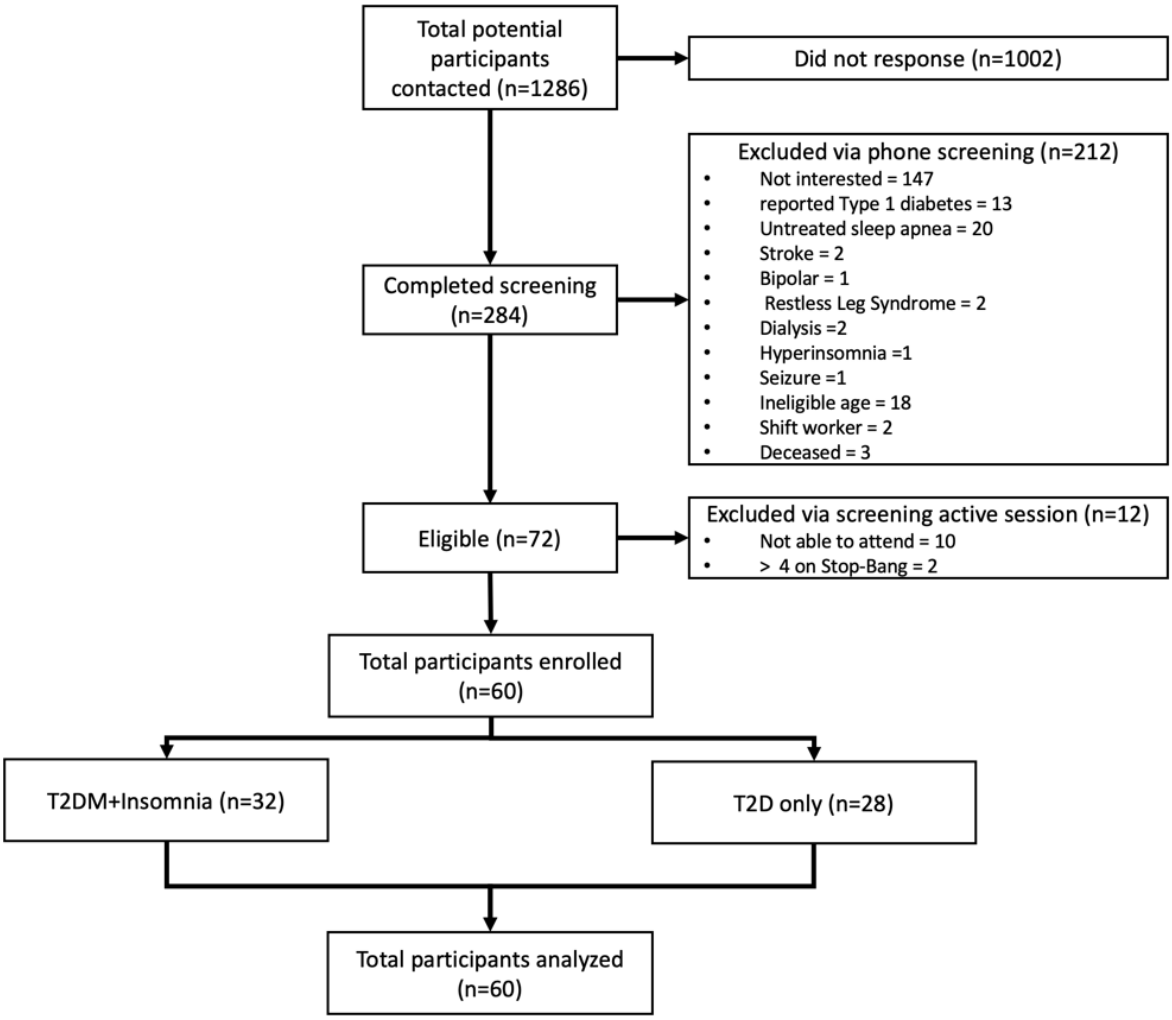

Figure 4.1. Participant recruitment process and flowsheet

Chapter 5: The Effect of Cognitive Behavioral Therapy for Insomnia on Individuals with Type 2 Diabetes and Insomnia Symptoms: A Protocol for a Randomized Controlled Trial

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ABSTRACT

Background: Insomnia symptoms are a common form of sleep difficulties among people with type 2 diabetes (T2D) affecting sleep quality and health outcomes. Several interventional approaches have been used to improve sleep outcomes in people with T2D. Non-pharmacological approaches such as Cognitive Behavioral Therapy for insomnia (CBT-I) show promising results regarding safety and sustainability of improvements, although CBT-I has not been examined in people with T2D. Promoting sleep for people with insomnia and T2D could improve insomnia severity and diabetes outcomes. Thus, the purpose of this study is to establish a protocol for a study to examine the effect of 6 sessions of CBT-I on insomnia severity, sleep variability, and other health-related outcomes in individuals with insomnia symptoms and T2D.

Methods: This randomized controlled trial will use random mixed block size randomization with stratification to assign 28 participants to either a CBT-I group or a Health Education group. Chi-square and independent *t* tests will be used to test for between-group differences at baseline. Independent *t* tests will examine the effect of the CBT-I intervention on change score means for the Insomnia Severity Index, diabetes self-care behaviors, glycemic control, fatigue, sleep quality, and daytime sleepiness. Mixed models will be used to compare the difference in sleep variability between the CBT-I group and the Health Education group. Finally, a completer vs non-completer analysis will be performed. For all analyses, alpha level will be set at 0.05.

Results: This study recruitment began in February 2019 and expected to be competed in September 2019.

Conclusions: The intervention included 6 sessions of CBT-I will provide insight about its effect in improving insomnia symptoms, sleep variability, fatigue, and diabetes outcomes in people

with insomnia symptoms and T2D when compared to control. This study was registered in the Clinical Trials Registry (NCT03713996)

Keywords: Insomnia, Diabetes, Behavioral intervention, Cognitive Behavioral Therapy, CBT, Sleep Variability, Self-Care

5.1. INTRODUCTION:

Type 2 diabetes (T2D) is the predominant form of diabetes mellitus, which results in multiple complications including sleep difficulties [229]. T2D is due to relative insulin deficiency and peripheral insulin resistance [230]. Consequently, T2D causes abnormal amounts of glucose in the bloodstream [231]. Because of this, T2D has been linked to several complications including hyperglycemia, which may also affect multiple organs and systems. As a result, hyperglycemia may lead to sleep disturbances due to associated symptoms including headache, increased thirst, and nocturia [232].

Sleep disturbances have been shown to increase activation of the hypothalamic pituitary-adrenal (HPA) axis [233], which may further exacerbate the management of T2D [31]. During a night of poor sleep, cortisol levels increase due to hyperactivation of the stress system "HPA system", which then leads to an increased glycation level in the blood stream [234]. Because individuals with T2D are particularly susceptible to hyperglycemia, an increased glycation level may be particularly problematic [235]. To illustrate that, increasing the glucose level during a night of sleep in people with T2D may increase the bathroom visits as well as the number of awakenings [236]. Increasing the number of awakenings during a night of sleep is a part of poor sleep quality [237], which may further contribute in activation of the stress system [235]. This might suggest a bidirectional relationship between sleep disturbances and hyperglycemia. Compounding this issue even further, previous research has shown that rates of several sleep disorders including obstructive sleep apnea, insomnia, and restless leg syndrome are increased in people with T2D [30, 41, 220]. After controlling for age and gender, the prevalence of insomnia diagnosis is significantly higher in people with T2D compared to people without T2D [30, 41, 238].

Insomnia is one of the most common sleep disorders in people with T2D as more than half report insomnia symptoms [30, 238]. In one study of people with T2D, 8–17% reported difficulty falling asleep, 23–40% reported difficulty staying asleep, and 26–43% reported difficulty in both initiating and maintaining sleep. In another study of 7239 individuals with T2D, 76.8% of that sample reported experiencing insomnia symptoms regularly. For those 7239 individuals, the three most prevalent insomnia symptoms were nocturia (43.8%), difficulty falling asleep (30.5%), and waking after sleep onset (27.0%) [30, 41].

For adults and older adults diagnosed with clinical insomnia, there are several negative effects of insomnia that are harmful to long term health, such as increases in daytime sleepiness, fall risk, fatigue, and a decline in quality of life [239, 240]. Furthermore, studies have reported that insomnia is associated with hypertension, diabetes, and cardiovascular disease [240-242]. Consequently, insomnia increases the risk of all-cause mortality three fold over a 15 year follow-up period [243].

While individuals with T2D or insomnia are at increased risk of negative health outcomes, there are also unique risks to those who have both T2D and insomnia. People with T2D who experience poor sleep quality or excessive daytime sleepiness show decreased adherence to Diabetes Self-Care Behavior (DSCB) [62]. DCSB is essential in maintaining or attaining glycemic control in people with T2D [56]. Sleep quality and low sleep variability are also important for well-being and a healthy life [148, 244]. Indeed, poor health and quality of life are thought to be associated with poor sleep quality in people with T2D [245-247]. In addition to deficits in sleep quality, high sleep variability is common in people with insomnia [248] and may be even more prominent in people with T2D [84]. Further, it has been found that variability of bedtime and wake time were associated with high level of inflammatory biomarker called TNF-α

in people with and without insomnia [249]. TNF-α is associated with vascular diseases such as atherosclerosis [250].

Pharmacological approaches for treating insomnia have potentially serious side effects on health. Several studies have shown an association between sleeping pill prescriptions and mortality in different populations [99-104]. Different sleep medications were associated with increased risk of fall [105], motor vehicle accidents [106], and suicidality [107]. Individuals with insomnia who use benzodiazepines or non-benzodiazepines are at high risk of developing T2D due to potential changes in insulin secretion and sensitivity [108, 109]. It is a widely held view that sleep apnea is prevalent sleep disorder in people with T2D [110]. A possible explanation of increasing the severity of sleep apnea is that hypnotics are respiratory suppressants that might contribute in vital health issues for this population [111]. Weinstock (2012) showed insulin sensitivity improved in people with severe sleep apnea after receiving sleep hygiene, dietary counseling, and CPAP support, which suggests the metabolic function in people with T2D might be improved by a sleep promotion program [5]. Thus, it is important to identify safe and effective non-pharmacological treatments for people with T2D and insomnia symptoms.

The American Academy of Sleep Medicine recommends Cognitive Behavioral Therapy for Insomnia (CBT-I) as the first line of treatment for people with insomnia [251]. A meta-analysis has shown CBT-I to produce clinically meaningful improvements in sleep outcomes including sleep latency, sleep efficiency, number of awakenings, and total sleep time [121]. Additionally, CBT-I is designed to change sleep habits as well as address misconceptions about sleep and insomnia. CBT-I is superior to sleep medications in terms of cost and long-term benefits [142]. Although there is currently limited evidence about the effect of CBT-I on people with T2D, CBT-I is a potentially effective intervention given insomnia's relationship with

glucose metabolism. In adults with sleep restriction, increasing the total sleep time by a simple low cost intervention was associated with improvements in fasting insulin sensitivity [252].

5.1.1. Objectives and hypotheses:

The primary objective of this study is to establish a protocol for a study to: 1) Investigate the effect of 6 sessions of CBT-I on insomnia severity in people who have T2D and are experiencing insomnia symptoms. 2) Explore the effect of 6 sessions of CBT-I on sleep variability, fatigue, glycemic control and DSCB in people who have T2D and are experiencing insomnia symptoms. The researchers anticipate that improving the symptoms of insomnia in people with T2D may also help improve sleep variability, fatigue, glycemic control, and DSCB due to the relationship between insomnia symptoms and diabetes health outcomes.

5.1.2. Trial design:

The study design will be a pilot randomized controlled trial (RCT). This study will have an allocation ratio of 1:1, and this RCT will be using a superiority framework to test the effectiveness of the experimental CBT-I intervention. This protocol is in accord with the SPIRIT 2013 statement [253], and the intervention will be described according to the CONSORT 2010 guideline [254].

5.2. METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

5.2.1. Study setting:

This study will be conducted at the University of Kansas Medical Center (KUMC) in the United States. The study sites are also listed on (https://clinicaltrials.gov/ct2/show/NCT03713996?term=diabetes&cond=Cognitive+behavioral+therapy&rank=5).

5.2.2. Eligibility criteria:

The inclusion and exclusion criteria are shown in Table 5.1.

All intervention sessions will be delivered by a trained CBT-I provider. The CBT-I provider is a physical therapist who completed coursework and a Mini-Fellowship in Behavioral Sleep Medicine through the University of Pennsylvania. Ongoing mentorship will be provided by an experienced CBT-I provider.

5.2.3. Interventions:

All participants will receive 6 sessions over the course of 6 weeks of either CBT-I or Health Education (i.e. one session per week for 6 weeks). Sessions will last one hour for both groups to mitigate the impact of social interaction. We chose health education sessions as usual care for people with T2D. Table 5.2 describes each intervention arm with all components. The timeline of each component for the CBT-I and Health Education groups is provided in Figure 5.2 and Figure 5.3.

5.2.3.1. Experimental intervention:

Participants allocated to the CBT-I group will meet with the CBT-I provider weekly for one-hour of CBT-I sessions. CBT-I is designed to address cognitive and behavioral factors that perpetuate insomnia [112]. CBT-I includes several therapeutic components including sleep restriction therapy, stimulus control therapy, sleep hygiene, relaxation techniques, and cognitive therapy. At each session, the CBT-I provider will ask about any new difficulties, explain the outline of the session, calculate the sleep efficiency of the previous 7 nights of sleep, and close the session with assessing any concerns and providing a new sleep diary. At each session, prescribed time in bed and out of bed will be determined based on calculation for sleep efficiency of the weekly sleep diary. Sleep efficiency will be calculated as the ratio of total sleep time and total bedtime multiplied by 100. At each session, if the sleep efficiency is greater than 90%, participants will be given the opportunity to go to bed 15 minutes earlier. If the sleep efficiency is between 85 and 89.9%, participants will be asked to remain on the same sleep schedule as currently prescribed. If the sleep efficiency is less than 85%, participants will be asked to move their bedtime 15 minutes later, although total time in bed will not be less than 6 hours.

During each session, the CBT-I provider will use two sheets: A checklist and a tracking sheet. The checklist will be used for quality assurance and standardization of treatment sessions across participants to assure the participant's compliance with the CBT-I intervention, CBT-I components delivery, updating sleep diary summary, addressing any immediate concerns or problems with participation, discussing motivation and general compliance issues, and self-assessment of provided sessions. The tracking sheet will be used to document treatment sessions

to track the date and time of sessions, new difficulties and adverse events, provided therapies, and prescribed time in bed and out of bed.

The participants will be called one day before each session to confirm their session appointment the following day and to remind the participant bring their completed sleep diary. In addition, a folder will be provided at the first session to keep provided materials together for review. The CBT-I sessions will be audio recorded in order to assess treatment integrity if the subject agrees.

CBTI intervention fidelity will be assessed by one independent CBT-I expert who will use a scoring sheet to assess CBT-I provider's compliance in utilizing the manual to deliver the CBT-I. The CBT-I provider will be scored on 5 scales from 0 (poor) to 6 (excellent) based on their (1) addressing immediate concern, (2) explaining the outline of the session, (3) discussing the sleep diary outcomes, (4) adherence in providing the intervention, and (5) competency in delivering each session.

5.2.3.2.Health Education:

Participants allocated to the health education group will meet with the CBT-I provider weekly for one-hour health education sessions. The health education sessions include several components including brief sleep hygiene, foot care, diabetes classifications, healthy diet, and physical activity. During all sessions, subjects will be encouraged to engage in discussion through open questions about their experience of diabetes and lifestyle as well as their comprehension of the provided materials. Similar to the CBT-I group, session tracking sheets will be used to track new difficulties or concerns and provided educations.

5.2.4. Outcomes:

Insomnia severity is the primary outcome, which can be measured using the Insomnia Severity Index (ISI). Secondary outcomes include sleep variability, fatigue, DSCB, glycemic control, daytime sleepiness, sleep quality, and glucose levels. Sleep variability outcomes will be measured by an Actigraph device (Actigraph wGT3X-BT), which will measure sleep latency, total sleep time, wakefulness after initial sleep onset, and sleep efficiency over the course of 7 nights. Fatigue will be measured using the Fatigue Severity Scale (FSS), which will assess the fatigue in daily life and differentiate between fatigue and clinical depression. DSCB will be measured using the Diabetic Care Profile (DCP). Glycemic control (A1C) will be measured using HbA1c testing kits. Daytime sleepiness will be measured using the Epworth Sleepiness Scale (ESS). Sleep quality will be measured using the Pittsburgh Sleep Quality Index (PSQI). Random glucose levels will be obtained using glucose meters, which measure the amount of glucose in the blood at that time. A detailed description of the outcome measures is explained in the data collection and methods section.

5.2.5. Participant timeline:

All measurements will be performed at baseline and one week after treatment completion (Figure 5.1). Participants who wish to withdraw during the intervention will be asked to complete the reassessment session.

At initial contact with a potential subject, a phone screening interview or diabetes clinic interview will be conducted by a member of the research team to determine whether an individual qualifies to progress to an in-person screening for the study. The phone screening

interview assesses participant eligibility according to age, self-report T2D diagnosis, ISI score, ability to understand English, Stop-Bang score, Restless Leg Syndrome Diagnostic Index, pregnancy status, alcohol use, night shift work, and undiagnosed neurological disorders.

Individuals passing the phone screening will be scheduled for an in-person screening session to assess eligibility according to symptoms of pain, depression, and anxiety. During the in-person screening session, interested participants will be excluded if they**:**

1. Have score ≥ 7 out of 10 on the Brief Pain Inventory (BPI) [255], which indicates severe pain symptoms.
2. Have score ≥ 21 on the Beck Depression Inventory (BDI), which indicates severe depression symptoms [165].
3. Have score ≥ 15 on the Generalized Anxiety Disorder 7-item (GAD-7) scale, which indicate severe symptoms level of anxiety [256].

Subjects will undergo the consent process in a private room at KUMC before completing any of the in-person screening assessments. Individuals passing the in-person screening will then immediately begin baseline assessment.

5.2.6. Sample size:

To detect the effect of CBT-I on people with T2D and symptoms of insomnia, the change in pre-post ISI was used to determine sample size. Pre-post changes using the minimal clinically meaningful difference of 8 points for the ISI in a previous study [257] were used to estimate the effect size. This calculation resulted in 14 participants per group to reject the null hypothesis of equal means when the population mean difference equals 8 with a standard deviation of 7. The

results of this calculations indicated that 28 subjects in both groups to detect the significant difference between groups at 0.05 significant level and power of 0.80.

5.2.7. Recruitment:

Subjects will be recruited from diabetes and sleep clinics at KUMC, university advertisements, community centers in Kansas City, flyers, personal referrals and newsletters, and a registry of patients from KUMC who have signed up to be contacted about potential research opportunities.

5.3. METHODS: ASSIGNMENT OF INTERVENTIONS (FOR CONTROLLED TRIALS)

5.3.1. Allocation sequence generation:

We will use random mixed block size randomization[258] to assign participants to either CBT-I (n=14) or Health Education (n=14) groups. Participants will be stratified by age where 62 years of age is the value that will stratify participants into either the older age group (63-75 years old) or the younger age group (40-62 years old). The reason that we chose age as a blocking variable is that the impact of age on sleep is more pronounced than gender [259] as older adults often have poorer sleep [260] and lower slow wave sleep [261] as compared to young adults.

5.3.2. Allocation concealment mechanism:

Participant allocations will be placed in sealed envelopes. The envelopes are prepared by a research assistant, who withholds this information from the CBT-I provider. After finishing the

baseline assessment, participants will be asked to open the sealed envelope to disclose their group allocation. Microsoft Excel will be used to create the randomization lists.

5.3.3. Allocation implementation:

A computer will be used to generate the random mixed block size randomization sequences. Results of the generator will be concealed from the assessor and CBT-I provider. Participants will be asked to open the sealed enveloped after informed consent and baseline assessment are completed.

5.3.4. Blinding:

The assessor, who is blinded to group allocation, will score the Actigraph data. The assessor will have experience in scoring criteria and will have no involvement in providing the interventions. The CBT-I provider will not be blinded in this project.

5.4. METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

5.4.1. Data collection and methods:

The ISI is a self-report measure designed to evaluate the nature, severity, and impact of insomnia [161]. The ISI is a valid and reliable measure of clinical insomnia and involves of 7 questions, each rated on a 0-4 Likert scale. Total scores range from 0 to 28, with higher scores indicating greater insomnia severity [161]. The internal consistency of ISI was excellent for community sample and clinical sample (Cronbach α of 0.90 and 0.91, respectively). The cut-off

score > 10 in the ISI provided optimal sensitivity and specificity for the detection of insomnia based on ICD-10 (Area Under the Curve = 0.88, 95% Confidence Interval= (0.84, 0.92)) and DSM-5 diagnostic criteria (Area Under the Curve = 0.82, 95% Confidence Interval = (0.78, 0.86)) [262].

The Actigraph device is a small, non-invasive device worn on the non-dominant wrist that records limb movements by electrical impulses, and the Actigraph has been validated for use in people with insomnia [263]. In addition to the Actigraph, we will also use a sleep diary allow for better estimation for the time in bed and time out of bed as well as removing invalid sleep periods that are measured by the Actigraph [264]. The sleep diary will also provide total time spent in bed, total time spent out of bed, time in bed, time out of bed, time lights out, number of awakenings, number of bathroom visits, and blood glucose level before and after sleep time.

The FSS is a 9-item questionnaire that has been validated in people with diabetes [44]. The FSS measures fatigue across five subscales including motivation, exercise, interference with work, family, or social life. These subscales have total scores where a score <4 indicates no fatigue, scores between 4 and 4.9 indicate moderate fatigue, and score >5 indicate severe fatigue [44].

The DCP uses items with 5-point Likert scales to evaluate the frequency of symptoms related to diabetes. The DCP is a validated instrument that measures self-reported diabetes control as well as psychological and social factors associated with the management of diabetes [67, 191].

A1C will be determined using the HbA1c test by a disposable blood finger stick test using (A1cNow+) kit. The A1C indicates the average blood glucose level of people with diabetes

over the previous 2-3 months and represents the current management of diabetes [265]. Every 1% drop in A1C is associated with improved outcomes with no threshold effect [266].

The ESS uses 8 items on a 4-point Likert scale, where the subjects' rate how likely they would be to fall asleep in 8 different states of daily activities. The ESS has demonstrated satisfactory psychometric properties such as test–retest reliability (r = .82) and internal consistency (Cronbach alpha = .88). The cutoff point is ≥ 10 to distinguish between normal from pathological sleepiness [62].

The PSQI is a validated 19-item questionnaire that differentiates between poor sleepers and good sleepers. The PSQI uses 7 items on a 4-point Likert scale, and the PSQI yields a global SQ score that ranges from 0 to 21. Poor sleepers have > 5 scores as a cutoff global PSQI score with sensitivity (89.6%) and specificity (86.5%). In our study, we will use a 3-factor scoring model for the PSQI (Sleep Efficiency, Perceived Sleep Quality, and Daily Disturbances), which has been tested and validated [267]. Sleep duration and sleep efficiency were classified under the Sleep Efficiency factor; subjective sleep quality, sleep latency, and use of sleeping medications were categorized under the Perceived Sleep Quality factor; and the frequency of sleep disturbances and daytime dysfunction were classified under the Daily Disturbances factor.

5.4.2. Data management:

All study-related procedure will be performed at Georgia Holland laboratory in Hemenway Life Sciences Innovation Center on the KUMC campus. All obtained participant records will be kept in locked cabinet inside the Georgia Holland laboratory. Electronic study

data will be saved in the KUMC Research Electronic Data Capture (REDCap) system. For voice records, all tapes will be saved on a secure university-supported network drive.

5.4.3. Statistical methods:

A Chi-square test will be used to compare between-group differences in categorical variables. Independent sample *t* tests will be used to compare differences in continuous between-group demographic characteristics and clinical variables. The effect of the CBT-I intervention will be investigated by calculating within-group change scores for the ISI, DSCB, A1C, fatigue, sleep quality, and daytime sleepiness. Then, independent sample *t* tests will be utilized to investigate the between-group difference in the change score means. Mixed models will be used to compare the difference in sleep variability between the CBT-I group and the Health Education group. A completer vs non-completer analysis will be performed. For all analyses, alpha level will be set at 0.05.

5.4.4. Exploratory analysis:

Post-hoc analysis using type of medications and number of medications will considered to address the potential confounding effects on the outcomes. Univariate linear regression will be used to control for demographic and clinical variables (covariates). The decision to perform these analyses will be made if there are significant differences between the groups at baseline in depression symptoms, anxiety symptoms, pain symptoms, gender, body mass index, or any demographics (other than age) or clinical variables. Those participants who are treated with CPAP will be asked to report their compliance using CPAP during baseline and post intervention

assessments. Subjects who are using CPAP will be given modified sleep diary to check off nights of CPAP compliance during the assessment sessions. An exploratory sub-analysis will be utilized to investigate the difference in insomnia severity between compliance and non-compliance with CPAP. Non-compliance is defined as 1) missing more than 2 nights during the 7 nights period that the participant is wearing the actigraph or 2) using the CPAP for < 4 hours per night during this project.

5.5. METHODS: MONITORING

5.5.1. Data monitoring:

The primary investigator will review the data set at least semi-annually. The primary investigator's evaluation will be focused on the quality of data collection and data management. In addition, the investigators will review data in an on-going manner for accuracy, both as these data are entered into the database and during analysis.

5.5.2. Harms:

During the pre and post assessment sessions, testing will be stopped if the subjects show signs of low blood sugar (< 70 mg/dL), or if signs of dizziness or headache are noted by the assessor or reported by the participant. During assessment sessions, participants also will be instructed to stop the test at any time for a rest break, as often as needed.

There is a risk of skin redness may be associated with wearing the Actigraph for one week. The risks of wearing the Actigraph are nearly the same as wearing a wrist watch. If skin redness or inflammation happened, subjects may remove the Actigraph and immediately report

the symptoms to research personnel. Additionally, a risk of minor electrical shock if the Actigraph is damaged. If damage to the Actigraph occurs, subject will be asked to return it to our lab, and they will be given a replacement.

Initially, participating in a CBT-I intervention may have an increase in sleepiness which may impact participants' fatigue, thinking ability, or functional abilities. It is anticipated that this increase in sleepiness will be temporary and should help participants sleep better in the long-term.

During the in-person screening session, if suicidal intent is identified through either the BDI (question #9 with a '2' or a '3') or verbal statement from the participant, a suicidality protocol will be followed. The suicidality protocol is designed to provide the researcher with contact information for appropriate psychology and psychiatric professionals at KUMC.

5.6. ETHICS AND DISSEMINATION

5.6.1. Research ethics approval:

The study will be performed in accordance with KUMC's Institutional Review Board and Human Subjects Committee. No individuals will be excluded based on sex, race, or ethnicity. Interested participants will be administered a structured screening interview to determine their eligibility for the project.

5.6.2. Consent or assent:

Consent will be obtained in Georgia Holland Health Exercise and Aging Lab (HEAL) on the main campus of KUMC. Participant will be encouraged to ask any questions about the study as much as they need, and members of research study will answer their questions. In addition, participants will be informed if there is any change in the protocol to sign a new consent form.

5.6.3. Confidentiality:

All data will be de-identified and stored on the KUMC research private drive which will be secured and backed up every night. The working dataset will be stored on a password-protected computer in the primary investigator's laboratory, with access restricted to study researchers who actively working with these data. All subject files and documents will be stored in locked cabinet.

5.7. RESULTS

A total of 28 participants with T2D and insomnia symptoms will be recruited from February 2019 until the recruitment is complete. This project is currently open for recruitment. The estimated completion date for the study is September 2019. Our results will describe the changes in insomnia severity, sleep variability, fatigue, glycemic control, and DSCB. We will report our results in tables and figures using SPSS and Graphpad, respectively. Results of this protocol will be found in Chapter 6 and Chapter 7.

5.8. DISCUSSION

Our project will be the first in conducting a randomized control trial using CBT-I for people with T2D. If this study indicates that 6 sessions of CBT-I are effective in improving insomnia symptoms, sleep variability, fatigue, and diabetes outcomes in people with insomnia symptoms and T2D when compared to health education, CBT-I could be implemented as an effective and safe treatment for this population. Therefore, the clinical implications will include patients with insomnia symptoms and T2D who will be seen by a trained CBT-I provider.

Pharmacological interventions for sleep difficulties have shown harmful effects on people with T2D. There is a need to better understand safe intervention benefits in people with T2D. This study will contribute to the management of T2D using behavioral sleep intervention as an effective and safe treatment for people with insomnia symptoms. The results will contribute to the literature by examining the effect of CBT-I on both sleep and diabetes outcomes. This will help in understanding the effectiveness of short duration intervention designed for people with insomnia symptoms.

The study strengths include utilizing important methods for people with T2D such as objective measures, design, and safe intervention. Determining sleep variability using objective and subjective measures will accurately detect sleep improvement after an intervention. Using comparative groups to understand the effect of CBT-I on insomnia symptoms, sleep variability, fatigue, and diabetes health outcomes will add new information to the literature and improve understanding of clinical conditions. Previous studies recommend optimizing the sleep quality and quantity for people with comorbidities. Understanding the effect of CBT-I in people with T2D will expand the generalizability of using this type of interventions.

Some limitations in this protocol might be important to consider in future work. First, we will not confirm the diagnosis of T2D using the current American Diabetes Association guidelines. However, a study showed that the specificity of prevalent self-reported diabetes and incident self-reported diabetes were 84% and 97%, respectively, and sensitivity of 55% and 80% compared to fasting glucose, HbA1c, and/or medication use [268]. In addition, a study suggests that self-report of diabetes is sufficiently accurate [269]. To overcome this limitation, we will review the medication list to confirm T2D diagnosis during the in-person screening visit. Second, we might not able to distinguish the improvement in insomnia severity between controlled diabetes vs uncontrolled diabetes, which might be examined under future sleep behavioral therapy studies. Finally, we will not be able to monitor CPAP compliance during the intervention, but we will follow up with people in the CBT-I group to ensure no issue wearing a CPAP machine every session.

Table 5.1. The inclusion and exclusion criteria.

Inclusion Criteria	**Exclusion Criteria**
Age 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 T2D	Stop-Bang score > 4
Insomnia Severity Index >10 and self-reported symptoms of insomnia at least 3 nights/week for the past 3 months	Failure to pass Restless Leg Syndrome Diagnostic Index
Able to attend 6 sessions	Brief Pain Inventory score ≥ 7
Able to understand and follow verbal commands in English	Beck Depression Scale scores ≥ 21
Able to travel to KUMC	Generalized Anxiety Disorder-7 scores ≥ 15
	Women who are pregnant
	Self-reported following medical issues: Chronic Fatigue Syndrome, Fibromyalgia, Bipolar, Seizure Disorders and Rheumatic Diseases
	Speech deficits or significant auditory impairment
	Current night shift work
	Heavy alcohol drinker (≥15 drinks per week for men and ≥ 8 drinks per week for women)
	Dialysis, blindness, or trans-femoral amputation

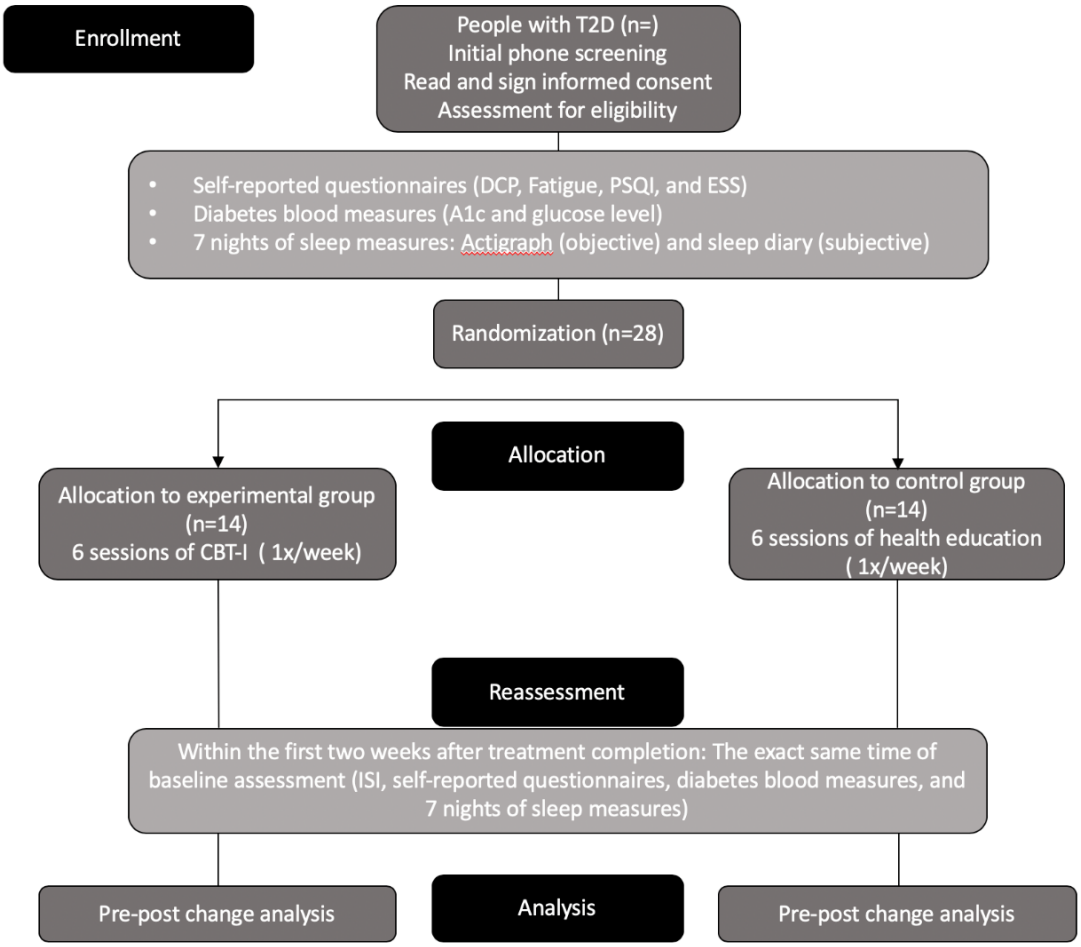
Table 5.2. Description of CBT-I and Health Education components:

CBT-I components

• Sleep restriction therapy
  o Time in bed limited to the total sleep time by identifying the wake time and total sleep time to increase the sleep efficiency. We will not prescribe the total time in bed less than 6 hours.
• Stimulus control therapy
  o Strengthens the association between the bedtime and sleep only. We will ask to use the bed for only sleep and sexual activity to help train the brain. Participants will be asked to leave the bedroom if unable to fall asleep within 20 minutes and return when sleepy.
• Sleep hygiene
  o Minimizes the influence of negative behaviors on sleep quality and quantity. The principles and the effects of diet, exercise, caffeine, alcohol and environment on sleep behavior will be provided.
• Relaxation techniques
  o Diaphragmatic breathing technique:
  ▪ Promotes relaxation by using the diaphragm correctly while breathing.
  o Mindfulness:
  ▪ Reduces cognitive and somatic arousal. The principles of mindfulness (non-judging, patience, trust, acceptance, and letting go) will be discussed.
  o Progressive muscle relaxation:
  ▪ Positively influences physiologically measured muscle tension.
• Cognitive therapy
  o Changes detrimental beliefs and attitudes about sleep. We will work on reducing sleep effort, catastrophic predictions, worry about sleep and fearing of insomnia relapse.
• Insomnia relapse
  o Facilitates the understanding of the risk factors of reoccurrence. We will discuss the approaches to maintain clinical gains.

Health education components

• Brief sleep hygiene:
  o We will discuss 8 items of sleep hygiene including, exercise, comfortable bedroom, temperature of bedroom, food, liquids, caffeine, alcohol consumption, smoking, and naps. Part of sleep hygiene including consistent sleep schedule and association of bed with sleep will not be included in this brief sleep hygiene education.
• Foot care education:
  o We will provide foot education regarding the demographic and comorbidity, foot pathology and assessment, and preventive interventions. In addition, we will provide American Diabetes Association recommendation regarding foot hygiene.
• Causes and diagnosis of diabetes:
  o We will provide information about diagnosis and classification of diabetes mellitus from American Diabetes Association [231]. Following topics will be discussed: Definition and description of Diabetes Mellitus, classification of diabetes mellitus and other categories of glucose regulation, categories of increased risk for diabetes, and diagnostic criteria for diabetes mellitus. A short animation will be provided to explain how diabetes affects the body
• Healthy diet education:
  o A systematic review and meta-analysis of different dietary approaches to manage T2D will be discussed [270]. Following article from American Diabetes Association will be navigated (http://www.diabetes.org/food-and-fitness/food/what-can-i-eat/making-healthy-food-choices/?loc=ff-slabnav).
• Physical activity education:
  o We will use a guide for adults based on the 2008 Physical Activity Guidelines for Americans. We will discuss following points: Wondering about how much activity you need each week, want to be physically active but not sure where to begin, started a program and would like tips on how to keep it up.



Note: T2D: Type 2 diabetes; DCP: Diabetes Care Profile; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; A1c: glycemic control; CBT-I: Cognitive Behavioral Therapy for Insomnia; ISI: Insomnia Severity Index.

Figure 5.1. Timeline of the project

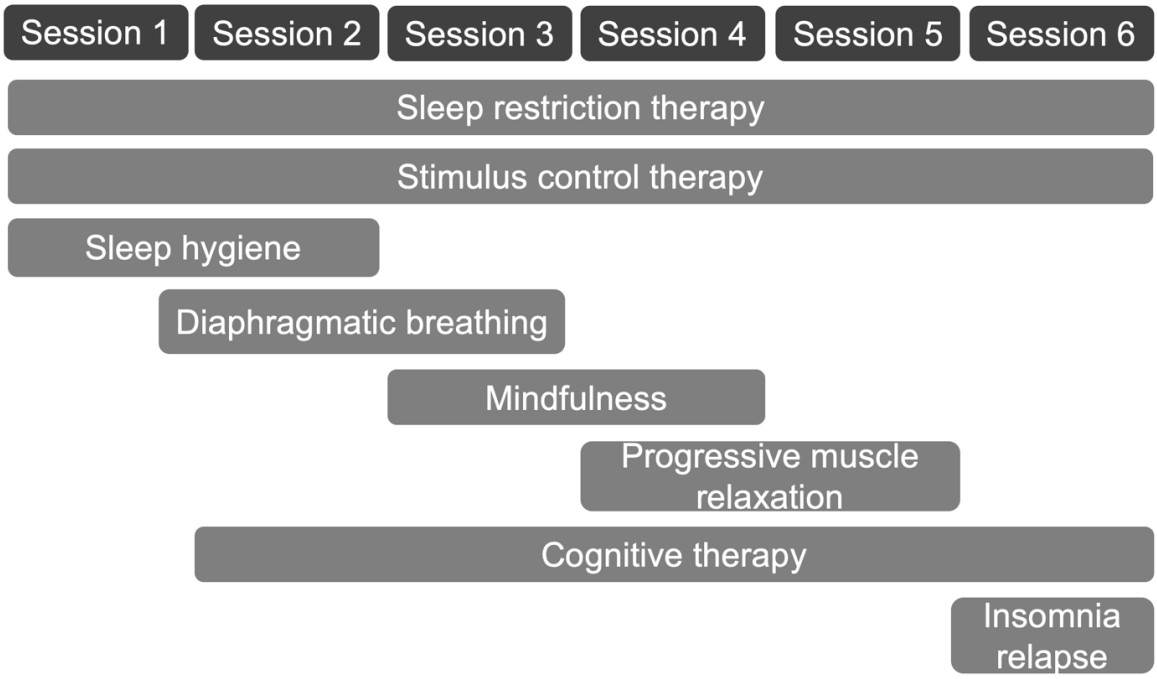


Figure 5.2. The timeline of CBT-I intervention.

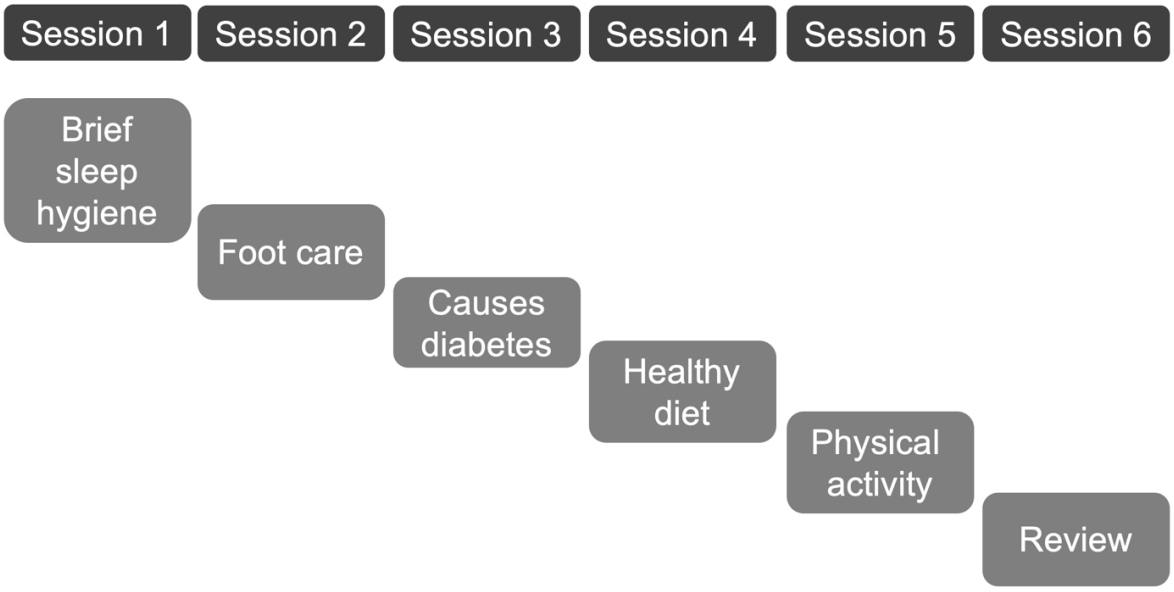


Figure 5.3. The timeline of Health Education intervention.

Chapter 6: The effects of Cognitive Behavioral Therapy for Insomnia in People with Type 2 Diabetes, Pilot Randomized controlled Trial Part I: Sleep Outcomes and Concomitant Symptoms

ABSTRACT

Objective/Background: Almost half of individuals with type 2 diabetes (T2D) report insomnia symptoms. Therefore, the primary aim of this study was to examine the effect of CBT-I on insomnia severity in people with T2D compared to a health education (HE) control group. The secondary aim was to explore the effect of CBT-I on other sleep outcomes and concomitant symptoms**.**

Methods: Twenty-eight participants with T2D were randomly assigned to CBT-I (n=14) or HE (n=14). Validated assessments were used at baseline and post-intervention to assess insomnia severity, sleep quality, daytime sleepiness, sleep self-efficacy and severity of depression, anxiety, and pain. In addition, Actigraph devices were used to measure sleep outcomes. Independent sample *t* tests and Mann-Whitney tests were utilized to measure between-group differences. Chi-Square tests were utilized to assess the treatment responses based on clinically meaningful differences in sleep outcomes. **Results:** Participants in the CBT-I group showed improvement in the following sleep outcomes: insomnia symptoms (62.22%, $p<.001$), sleep quality (29.48%; $p=.001$), sleep self-efficacy (63.49%; $p=.003$), sleep latency (44.68%; $p=.001$), sleep efficiency (6.24%; $p<.001$), wake after sleep onset (37.06%; $p<.001$), and number of awakenings (23.63%; $p=.003$). In addition, participants in the CBT-I group showed improvement in depression symptoms (39.45%; $p=0.02$) and anxiety symptoms (54.31%; $p=0.02$).

Conclusion: This study identified a clinically meaningful effect of CBT-I on sleep outcomes and concomitant symptoms in people with T2D and insomnia symptoms. Further work is needed to investigate the long-term effects of CBT-I in people with T2D and insomnia symptoms.

Keywords: Insomnia, Diabetes, Cognitive behavioral therapy, Depression, Anxiety

6.1. INTRODUCTION

According to the Centers for Disease Control and Prevention, there are approximately 30 million adults in the United States diagnosed annually with diabetes mellitus, and that number increases by 1.5 million per year [271]. Diabetes is the 7th leading cause of mortality, with more than 79 thousand deaths due to diabetes complications [272]. Type 2 diabetes mellitus (T2D) is the predominant classification of diabetes mellitus, with around 90% of cases diagnosed with T2D due to relative insulin deficiency and peripheral insulin resistance [ADA Standards of Medical 273]. Subsequently, T2D results in elevated amounts of glucose in the bloodstream that can lead to multiple health complications, such as excessive thirst, pain, headaches, fatigue, and nocturia [274], which may then cause sleep disturbances [201].

Insomnia symptoms are some of the most common sleep disturbances in people with T2D, as approximately half report insomnia symptoms [15]. Insomnia symptoms are characterized by a difficulty in staying asleep, maintaining sleep, and/or waking up too early, each of which impact daytime functioning [13]. Based on insomnia characteristics, 21.9–30.5% of people with T2D reported difficulty in falling asleep, 23–40% reported difficulty staying asleep, and 26–43% reported difficulty in both initiating and maintaining sleep [30, 41].

Generally, sleep disturbances are associated with activation of the hypothalamic pituitary-adrenal (HPA) axis [233], which may further impair the management of T2D [31]. When combined with the possibility that physiological symptoms of T2D lead to sleep disturbances, it is possible that a bidirectional relationship exists between sleep disturbances and hyperglycemia. Further, the relationship between insomnia and T2D could also be influenced by shared concomitant symptoms including depression, anxiety and pain [15].

Despite the apparent association between insomnia and T2D, the underlying mechanisms of this relationship are still unknown. As a result, it has been difficult to determine optimal treatments for insomnia symptoms in people with T2D. Thus, more research on treatments for insomnia symptoms in people with T2D is needed.

Currently, medication is often used to manage insomnia, although pharmacological treatments have been shown to potentially lead to serious side effects. The risk of T2D increases for people with insomnia who take benzodiazepines or nonbenzodiazepines due to potential alterations in insulin secretion and sensitivity [109]. With increased prevalence of sleep apnea in people with T2D, hypnotics may also increase the mortality risk by suppressing individuals' ability to breath [275]. Therefore, promoting positive sleep behavior for treating insomnia symptoms in people with T2D may provide safer treatment compared to pharmacological approaches.

The American Academy of Sleep Medicine recommends treating insomnia symptoms using Cognitive Behavioral Therapy for Insomnia (CBT-I) as the first-line intervention [119]. A meta-analysis has shown CBT-I produced clinically meaningful improvements in sleep outcomes including sleep latency (SL), sleep efficiency (SE), total sleep time (TST), wake after sleep onset (WASO) and the number of awakenings (NWAK) [121]. Additionally, CBT-I is superior to medications to treat insomnia in terms of cost and long-term benefits [142]. However, there is currently limited evidence about the effects of CBT-I on people with T2D. Because T2D is associated with a set of psychological and behavioral challenges, the T2D population might respond differently to CBT-I, and thus further investigation is needed to show the effectiveness of CBT-I on insomnia symptoms in people with T2D.

The primary objective of this pilot RCT was to investigate the effectiveness of CBT-I on the severity of insomnia symptoms in people with T2D and insomnia symptoms. The secondary objective was to explore the effect of CBT-I on sleep outcomes and depression, anxiety, and pain symptom severity. We hypothesized that participants in the CBT-I group would have greater improvements in sleep outcomes as well as the severity of depression, anxiety, and pain compared to participants in the health education (HE) group. We anticipated that improvements in insomnia severity will positively impact the depression, anxiety and pain symptoms due to their known relationship.

6.2. METHODS

6.2.1. Participants and study setting:

A detailed protocol for this randomized clinical trial has been published [276]. In brief, a total of 28 participants with self-reported T2D and insomnia symptoms were recruited between November 2018 and May 2019 through different recruitment sources at a University Medical Center. Potential participants were first screened over the phone to determine their eligibility. The eligibility criteria are presented in Table 6.1. For those passing the phone screening, participants were scheduled for the baseline visit.

This study was registered in the Clinical Trials Registry (NCT03713996; https://clinicaltrials.gov/ct2/show/NCT03713996?term=diabetes&cond=Cognitive+behavioral+therapy&rank=5) [277]. This study was approved by the University of Kansas Medical Center Institutional Review Board. All participants signed a written informed consent during the first study visit.

6.2.2. Study design:

A block size randomization was used to randomly allocate participants to either the CBT-I group (n=14) or the HE group (n=14) [258]. Participants were stratified by age into a younger age group (40-62 years old) or an older age group (63-75 years old). A computer program was used to generate the random mixed block size randomization sequences. Participant allocations were placed in sealed envelopes by a research assistant. After finishing the baseline assessment, participants were asked to open the sealed envelope to receive their group allocation.

6.2.3. Blinding:

A blinded assessor (AMA), who had no involvement in providing the interventions, scored the Actigraph data. The lead author (MMA), who provided the CBT-I and HE treatments and administered questionnaires, was not blinded. In addition, participants in the CBT-I group and HE group were not blinded.

6.2.4. Outcomes:

All measurements were performed and gathered at baseline and one-week the interventions (Figure 6.1). Treatment adherence was calculated as the number of sessions attended divided by 6 and multiplied by 100.

6.2.4.1.Demographic and clinical variables:

Age, sex, ethnicity, marital status, highest degree earned, number of people living in the home, presence of health insurances, and diabetes duration were gathered at the first assessment session. Passive Airway Pressure (PAP) utilization was obtained by asking a yes/no question (e.g., "Do you use any type of a passive airway pressure machine?"). Body mass index was calculated using the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute website (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm).

6.2.4.2.Sleep outcomes:

Insomnia severity (Primary Outcome). The insomnia severity index (ISI) is a self-report measure designed to evaluate the type, severity, and impact of insomnia [161]. The ISI is a valid and reliable measure of clinical insomnia. Each of the 7 items on the ISI uses a 5-point Likert scale, ranging from 0 to 4. Thus, total scores range from 0 (indicating low severity) to 28 (indicating high severity) [161]. The ISI has a cut-off score of 10, which provides optimal sensitivity and specificity for the detection of insomnia based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (Area Under the Curve = 0.82, 95% Confidence Interval = 0.78 to 0.86) [262]. A 6-point change on the ISI indicates a clinically meaningful difference [278].

Daytime sleepiness. The Epworth daytime sleepiness scale (ESS) is an 8 item measure, indicating how likely participants are to fall asleep in 8 different types of daily activities using a 4-point Likert scale. The ESS has demonstrated satisfactory psychometric properties, such as

test–retest reliability (r = .82) and internal consistency (α = .88). The ESS has a cutoff score of 10 to distinguish between normal and pathological sleepiness [62].

Sleep quality. The Pittsburgh Sleep Quality Index (PSQI) is a validated 19-item questionnaire that differentiates between poor sleepers and good sleepers. The PSQI is a 7-item measure, where each item uses a 4-point Likert scale. The PSQI yields a global sleep quality score ranging from 0 to 21, with lower scores indicating poorer sleep quality. The PSQI has a cutoff score of 5, which provides satisfactory sensitivity (89.6%) and specificity (86.5%). A 3-point change in PSQI score indicates a clinically meaningful difference [279].

Sleep self-efficacy scale. Self-efficacy for sleep was assessed by the Sleep Self-Efficacy Scale (SESS) in which 9-items measure the participants ability to carry out behaviors for optimum sleep. Higher scores on SESS indicates higher self-efficacy that ranges from 9 to 45 [280].

Average and variability of sleep parameters. The averages of each sleep outcome including SE, SL, TST, WASO, and NWAK were measured objectively using the Actigraph. In addition, the variability of SE ($SEobj_{var}$) and variability of TST ($TSTobj_{var}$) were measured also by Actigraph, and we used the sleep diary to measure the variability of SE ($SEsub_{var}$) and variability of TST ($TSTsub_{var}$).

The Actigraph device is a small and non-invasive device that has been validated for use in people with insomnia [263]. Participants were asked to wear the Actigraph on their non-dominant wrist for 7 nights. In addition to the Actigraph, we used a sleep diary to better estimate the time in and out of bed as well as to remove invalid sleep periods that are measured by the Actigraph [264]. During the baseline and reassessment visits, the assessor initiated the Actigraph

device and provided a mailing package for the participant to return the device and a sleep diary. All sleep outcomes were calculated with data collected over 7 nights to determine the mean and the Coefficient of Variance (CV), which was calculated using the following equation (CV = standard deviation / mean × 100) for each sleep outcome; a higher number indicates higher variability [167].

6.2.4.3.Concomitant Symptoms:

Pain severity symptoms. The Brief Pain Inventory (BPI) is a valid and reliable measure to assess painful diabetic peripheral neuropathy [164]. The BPI uses 4 items including worst pain in last 24 hours, least pain in last 24 hours, pain on average, and pain right now. Each item on the BPI uses a 10-point Interval scale, with the highest score (10) indicating the most severe symptoms of pain. All 4-items were averaged to give the overall pain severity which ranges from 0 to 10.

Depression symptoms. The Beck Depression Inventory (BDI) has shown strong evidence of reliability and validity [189, 190]. The BDI uses 21 self-reported items on a 3-point Likert scale, with scores ≥ 21 indicating severe depression symptoms [189, 190].

Anxiety symptoms. The Generalized Anxiety Disorder GAD-7 uses 7 self-reported items on a 3-point Likert scale. The total score of the GAD-7 ranges from 0 to 21, with higher scores indicating more severe anxiety symptoms. The GAD-7 has been shown to be highly sensitive and specific for the detection of anxiety symptoms and has shown evidence of validity with its relationship to other anxiety scales [166].

6.2.5. Interventions:

6.2.5.1.Cognitive Behavioral Therapy for Insomnia

Participants in the CBT-I group attended weekly one-hour sessions with the CBT-I provider. CBT-I includes several therapeutic components including sleep restriction therapy, stimulus control therapy, sleep hygiene, relaxation techniques, and cognitive therapy. At each session, the CBT-I provider asked about any new difficulties, explained the outline of the session, calculated the sleep efficiency from the previous 7 nights of sleep, and closed the session by assessing any concerns and providing a new sleep diary. At each session, a prescribed time in and out of bed were determined based on the SE calculation from the weekly sleep diary. The SE of each night was calculated by multiplying the ratio of TST and total bedtime by 100. If the SE was greater than 90%, participants were given the opportunity to go to bed 15 minutes earlier. If the sleep efficiency was between 85% and 89.9%, participants were asked to remain on the same sleep schedule as currently prescribed. If the SE was less than 85%, participants were asked to go to bed 15 minutes later, although the total time in bed was not to be less than 6 hours. The CBT-I provider completed training through the University of Pennsylvania and recorded all CBT-I sessions to be supervised by an experienced CBT-I provider.

6.2.5.2.Health Education

Participants in to the HE group attended weekly one-hour HE sessions. We chose HE to serve as the control treatment because HE is the usual care for people with T2D. The HE sessions consisted of several components including brief sleep hygiene, foot care, diabetes classifications, healthy diet, and physical activity. During all of the HE sessions, participants

were encouraged to engage in discussions through open questions about their experiences of diabetes and lifestyles as well as their comprehension of the provided materials.

6.2.6. Sample Size:

The minimal clinically meaningful difference of 6 points for the ISI were used to estimate the expected effect size [257, 278]. This calculation indicated 10 participants per group were needed to reject the null hypothesis of equal means when the population mean difference equaled 8 with a standard deviation of 7. We anticipated an attrition rate of 40%, which implied 14 participants per group were needed to detect a significant difference at the 0.05 significance level with a power of 0.80 [281].

6.2.7. Statistical Methods:

A Chi-square test was used to assess for between-group differences in categorical variables at baseline. Independent two sample *t* tests were used to assess for between-group differences in continuous demographic characteristics and clinical variables at baseline. The effect of the intervention was investigated by calculating the percentage change scores for insomnia severity, sleep quality, daytime sleepiness, actigraphy sleep outcomes, variability of SE and TST, and the symptoms of depression, anxiety, and pain. Percentage change scores were calculated by (post score – pre score / pre score x 100). Based on normality, independent sample *t* tests or Mann-Whitney tests were utilized to investigate the between-group differences in the change score of all outcomes. Paired *t* tests were utilized to compare within-group changes from pre- to post- intervention for both groups. Clinical meaningful changes were assessed using

responders vs. non-responders' analysis for ISI and PSQI by performing Chi-Square tests. Linear regression analyses were used to graph the relationship between SE and the 6-sessions of the CBT-I session. For all analyses, the alpha level was set at .05.

6.3. RESULTS

6.3.1. Descriptive results:

A total of 28 participants were enrolled, and 26 completed the study (Figure 6.1). One participant dropped out of each group (a 7.14% dropout rate in each group). There were two adverse events documented in the CBT-I group (e.g., a participant fell on slippery sidewalk, a participant contracted pneumonia), and neither were related to the intervention study. Both the CBT-I group and HE group had high treatment adherence (88.46% and 80.76%, p=.37, respectively; Table 6.2). There were no significant between-group differences at baseline, including sleep outcomes, concomitant symptoms, and demographic and clinical variables (p>.05). In Figure 6.2, the radial plots show the change from pre- to post-intervention for the participants in the CBT-I group in terms of the average time in bed compared to the change from pre- to post-intervention for the participants in the HE group.

6.3.2. Primary outcome results:

There were significant within-group differences in the mean ISI change scores for the CBT-I group ($\bar{x}$=-9.84±2.70, p=.001) and HE group ($\bar{x}$=-2.79±4.64, p=0.03; Table 6.3). The CBT-I group showed significantly greater improvement on the ISI (62.22%) compared to the HE

group (21.53%) (p<.001). In Figure 6.3, the CBT-I group showed decreases in ISI (62.22%) compared to the HE group that showed no significant decreases in ISI (21.53%).

6.3.3. Other sleep outcomes results:

There were significant within-group differences in the mean change scores for the CBT-I group on the PSQI ($\bar{x}$=-3.19 ±1.95, p=.002), ESS ($\bar{x}$=-3.06±3.72, p=0.01), and SSES ($\bar{x}$=13.21±5.10, p=.001) compared to no significant within-group differences for the HE group. The CBT-I group showed significantly greater improvements in PSQI (29.48%; p=.001) and SSES (63.49%; p=.003) compared to the HE group. In Figure 6.3, the CBT-I group showed decreases in PSQI (29.48%) and ESS (34.84%), and an increase in SSES (63.49%) compared to the HE group that showed no significant decreases in PSQI (3.69%), and ESS (1.03%), and an increase in SSES (11.10%). Linear regression showed a significant positive relationship between SE and CBT-I sessions (R^2=.07, p<.001; Figure 6.4).

6.3.4. Objective sleep measures results:

Data from the Actigraph in Table 6.3 showed significant within-group differences in the change scores for the CBT-I group in SL ($\bar{x}$=-3.74±3.21, p=.004), SE ($\bar{x}$=5.18±3.51, p=.002), WASO ($\bar{x}$=-26.87±16.79, p=.002), and NWAK ($\bar{x}$=-3.93±4.28, p=.002) and significant within-group differences in the change scores for the HE group in SE ($\bar{x}$=-3.64±3.73, p=0.01) and WASO ($\bar{x}$=14.43±17.90, p=.006). The CBT-I group showed significantly greater improvements in SL (44.68%; p=.001), SE (6.24%; p<.001), WASO (37.06%; p<.001), and NWAK (23.63%; p=.003) compared to the HE group. In Figure 6.3, the CBT-I group showed decreases in SL

(44.68%), TST (5.69%), WASO (37.06%), and NWAK (23.63%), and an increase in SE (6.24%) compared to the HE group which showed increases in SL (54.94%), WASO (33.18%), and NWAK (3.77%), and decreases in SE (4.80%) and TST (6.16%).

6.3.5. Sleep variability results:

Table 6.3 shows significant decrease in $SEsub_{var}$ and $TSTsub_{var}$ in the CBT-I group while not significant changes in all variability of sleep outcomes in HE group. There were significant between-group differences in $TSTsub_{var}$. However, there were no significant between-group differences in $SEobj_{var}$, $TSTobj_{var}$, and $SEsub_{var}$.

6.3.6. Concomitant symptoms results:

In addition, there were significant within-group differences for the change scores of the CBT-I group on the BDI ($\bar{x}$=-4.63±3.62, p=.004) and GAD-7 ($\bar{x}$=-3.17±4.16, p=0.02), but there were no significant with-group differences for the HE group (Table 6.4). The CBT-I group showed significantly greater improvements in BDI (39.45%; p=0.02) and GAD-7 (54.31%; p=0.02) compared to the HE group. There were no significant within- or between-group differences in BPI. In Figure 6.3, the CBT-I group showed decreases on the BDI (39.45%), GAD-7 (54.31%), and BPI (7.30%) compared to the HE group that showed increases on the BDI (18.57%), GAD-7 (25.84%), and BPI (3.31%).

6.3.7. Responders vs non-responders' results:

Chi-square tests showed significant between-group differences in the ISI and PSQI responders ($p<.001$ and $p=.005$, respectively). For the ISI responders (i.e., changes greater than 6 were counted as the meaningful clinically difference), 100% of participants in the CBT-I group were responders to treatment compared to 15.38% of participants in the HE group. For the PSQI responders (i.e., changes greater than 3 were counted as the meaningful clinically difference), 69.23% of participants in the CBT-I group were responders to treatment compared to 15.38% of participants in the HE group (Table 6.5).

6.4. DISCUSSION

This is the first randomized clinical trial that investigated the effectiveness of CBT-I on people with T2D and insomnia symptoms to improve insomnia severity, other sleep outcomes, and concomitant symptoms. This study suggests that CBT-I may be an effective intervention to treat symptoms of insomnia, depression, and anxiety in individuals with T2D. The results of the intervention showed that the CBT-I group had greater improvements in sleep outcomes and psychological symptoms compared to the HE group. The data suggest improving weekly SE during throughout the CBT-I sessions.

Six sessions of CBT-I produced clinically meaningful improvements in several sleep outcomes for people with T2D. Three common benchmarks were chosen to test clinical significance. First, presenting the averages of sleep outcomes following CBT-I helped in understanding normative values of achievement. Although the normative values of SL and WASO are not clear in people with T2D, studies have suggested that values below 30 minutes of

SL and WASO are acceptable cutoffs [282]. Our study shows the average SL was ≤11 minutes. However, average of WASO was above 40 minutes, which might be due to increased sleep disturbances, such as nocturia in the T2D population. Second, our findings show an improvement after intervention for the CBT-I group in average of all sleep outcomes, except sleep duration. The magnitude of changes are consistent with previous findings regarding the clinical improvements of CBT-I in the general population [283]. Third, achieving a treatment response based on the ISI and PSQI will help in estimating insomnia remission. Based on previous studies, a 6-point decrease in ISI represents a clinically meaningful improvement in people with primary insomnia [278]; and a score ≥ 3 points reduction on PSQI suggests a clinically meaningful improvement [279]. Our results indicate that all the participants responded to CBT-I based on the ISI, and the majority (69.23%) responded based on the PSQI. Although we observed some improvements in ISI and PSQI for the control group, these were not clinically meaningful for the majority of participants (i.e., Only 15.56% of met the criteria for both ISI and PSQI). Sleep hygiene was provided as a part of the HE for the control group, which has generally been considered ineffective as a monotherapy when treating insomnia symptoms.

Despite the promise of the clinically meaningful improvements, some sleep outcomes did not improve in the CBT-I group after the intervention. The objective measures of TST showed no changes after CBT-I, which may be a consequence resulting from the sleep restriction therapy. In addition, as mentioned, the sleep duration fell within the normal range in both groups [284], although it is already known that short sleep durations are common in people with T2D and often result in poor sleep quality. Our project focused on T2D by excluding any other health issues that could play role in sleep disturbances, which might explain the odds to previous studies. Further work is needed to investigate the effect of CBT-I on people with T2D and short

sleep durations. Although we did not specify the importance of lowering the variation of other sleep outcomes to participants, subjective variability of TST and SE improved in the CBT-I group following the intervention. A possible explanation for these results is the specificity of CBT-I that provides weekly prescription of time in and out of bed to increase SE. This specification may help in minimizing $SEsub_{var}$ and $TSTsub_{var}$ following CBT-I. In a study of 455 participants with insomnia, participants also reported reduced $TSTsub_{var}$ following CBT-I [80]. In terms of daytime sleepiness, the mean differences were near the minimum clinically important difference on the ESS. People with T2D may present with other pathophysiological symptoms that might impact daytime sleepiness in which long-term improvement in insomnia severity may be needed in this population.

The CBT-I intervention was also associated with improvements in psychological outcomes, including depression and anxiety. The association between insomnia and psychological symptoms has been shown previously [285]. Interestingly, this study's results might suggest that improving one's sleep outcomes may eventually reduce mild to moderate depression and anxiety symptoms, even though T2D may be independently associated with depression and anxiety symptoms. We observed a reduction in the depression symptoms and in the anxiety symptoms for the CBT-I group, which indicates a clinically meaningful difference on depression severity [286] and on anxiety symptoms [287]. There were no significant within- or between-group differences in pain symptoms. This might be due to excluding individuals with severe pain symptoms from the study. Another study has also found CBT-I to be effective in improving pain severity for people with chronic pain [288], which suggests that pain may be more difficult to treat than depression and anxiety symptoms in short-term interventions [288].

Despite the strengths provided in this study such as a targeted population, randomization, including attention group, the utilization of objective and subjective sleep measures, sensitive insomnia symptoms measures, and clinically important implications, some limitations should be noted. First, we were limited in generalizing these study results for all people with T2D due to the low sample size and the heterogeneity in the sleep disturbances related to their T2D symptoms. Investigating CBT-I on people with T2D with different insomnia phenotypes such as short sleep duration or long sleep duration might improve treatment generalizability. Second, people with T2D may present other comorbidities such as cardiovascular issues and hypertension. We did not investigate the treatment response based on the presence of other comorbidities, which might improve the generalizability of CBT-I efficacy on this population. Finally, this study shows clinical improvement in sleep and psychological outcomes, but we were not able to determine the long-term effect of CBT-I in people with T2D and insomnia symptoms.

In conclusion, the initial evidence of the effectiveness of CBT-I on people with T2D is promising. In this study, CBT-I was efficacious in improving insomnia symptoms for people with T2D and insomnia symptoms compared to a control intervention, and CBT-I also led to improvements in depression and anxiety symptoms in this population. Further investigations using larger sample sizes are needed to better understand the generalizability of the effects of CBT-I.

Table 6.1. The inclusion and exclusion criteria.

Inclusion Criteria	**Exclusion Criteria**
Aged 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 of 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

Table 6.2. Baseline comparison of demographics between groups.

	CBT-I (mean±SD), n=14	HE (mean±SD), n=14	*p*-value
Age	61.86±6.48	59.43±9.49	0.43[b]
Gender, Female, n (%)	10 (71.42)	7 (50.00)	0.25[a]
BMI	33.69±4.99	31.42±5.45	0.26[b]
Marital status, n (%)			
Never married	1 (7.14)	1 (7.14)	0.75
Married	11 (78.57)	9 (64.28)	
Separated/Divorced	1 (7.14)	3 (21.42)	
Widowed	1 (7.14)	1 (7.14)	
Education, n (%)			
High school	3 (21.43)	2 (14.28)	0.86[a]
Some college	3 (21.43)	3 (21.43)	
College graduate	4 (28.57)	6 (42.86)	
Graduate degree	4 (28.57)	3 (21.43)	
Ethnicity, n (%)			
White	12 (85.71)	9 (64.28)	0.19[a]
Black	2 (14.28)	1 (7.14)	
Other	0 (0)	4 (28.57)	
Family size, n (%)			
Alone	1 (7.14)	1 (7.14)	0.81[a]
1 person	9 (64.28)	8 (57.14)	
2 people	2 (14.28)	3 (21.43)	
>3 people	2 (14.28)	2 (14.28)	
Health insurance, n (%)			
None	0 (0)	0 (0)	0.66[a]
1-2	11 (78.57)	10 (71.43)	
>2	3 (21.43)	4 (28.57)	
Using PAP, n (%)			
Never	7 (50)	9 (64.28)	0.44[a]
Current	7 (50)	5 (35.71)	
Diabetes Duration (years)	15.71±9.93	15.43±11.21	0.94[b]
Number of medications	9.07±4.65	6.27±3.10	0.10[b]
Adverse event, n (%)			
Yes	2 (14.28)	0 (0)	0.14[a]
No	12 (85.71)	14 (100)	

Note: CBT-I: Cognitive Behavioral Therapy for Insomnia; HE: Health Education; BMI: Body Mass Index; PAP; Passive Airway Pressure

[a] *p-value of Chi-square analysis*

[b] *p-value of Independent sample t test*

Table 6.3. Comparison of sleep outcomes within and between groups.

	CBT-I (mean±SD)		HE (mean±SD)		*p*-value[c]
	Pre, n=14	**Post, n=13**	**Pre, n=14**	**Post, n=13**	
ISI	16.15±3.24	6.31±3.38	15.71±3.19	12.92±6.07	<.001[a]
PSQI	10.57±1.91	7.38±2.02	9.07±2.23	8.92±2.53	.001[a]
ESS	9.21±5.51	6.15±5.08	10.00±5.42	8.23±5.05	0.05[a]
SSES	23.71±7.13	36.92±5.37	25.14±7.76	27.23±8.56	.003[a]
SL	5.27±2.96	1.53±1.05	3.84±3.21	3.74±1.88	.001[b]
SE	85.23±4.26	90.23±3.55	86.95±4.08	83.31±5.22	<.001[a]
TST	423.65±63.35	393.05±66.71	425.45±68.15	395.05±84.27	0.94[a]
WASO	69.63±19.60	42.76±14.45	60.28±20.03	74.71±24.95	<.001[b]
NWAK	16.48±5.12	12.55±4.86	16.36±5.66	15.57±4.47	.003[a]
SEobj$_{Var}$	5.64±3.87	4.17±1.91	6.63±2.91	8.52±5.60	0.12[b]
TSTobj$_{Var}$	14.80±6.75	13.15±8.33	20.37±13.80	17.64±6.95	0.42[b]
SEsub$_{Var}$	9.17±7.02	3.48±4.33	10.49±6.59	6.08±4.01	0.26[a]
TSTsub$_{Var}$	25.33±16.45	12.94±7.03	25.86±22.73	22.90±14.36	0.04[b]

Note: CBT-I: Cognitive Behavioral Therapy for Insomnia; HE: Health Education; ISI: Insomnia Severity Index;; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; SSES: Sleep Self-Efficacy Scale; SL: Sleep Latency; SE: Sleep Efficiency; TST: Total Sleep Time; WASO, Wake After Sleep Onset; NWAK: number of awakenings; SEobj$_{var}$: Objective measure Sleep Efficiency Variability; TSTobj$_{var}$: Objective measure Total Sleep Time Variability; SEsub$_{var}$: Subjective measure Sleep Efficiency Variability; TSTsub$_{var}$: Subjective measure Total Sleep Time Variability

p^a = p-value of Independent sample t *test*

p^b = p-value of Mann-Whitney U test

p^c = p-value of mean change difference between groups

Table 6.4. Comparison of concomitant symptoms within and between groups.

	CBT-I (mean±SD)		HE (mean±SD), n=14		*p*-value[c]
BDI	10.86±6.05	6.23±4.57	10.43±4.99	11.54±5.60	0.02[a]
GAD-7	6.71±4.79	3.54±3.57	8.00±4.38	8.46±5.17	0.02[a]
BPI	3.00±2.02	1.31±0.48	3.26±2.05	1.23±0.44	0.58[b]

Note: CBT-I: Cognitive Behavioral Therapy for Insomnia; HE: Health Education; BDI: Beck Depression Scale; GAD-7: Generalized Anxiety Scale; BPI: Brief Pain Inventory

p^a = p-value of Independent sample t test

p^b = p-value of Mann-Whitney U test

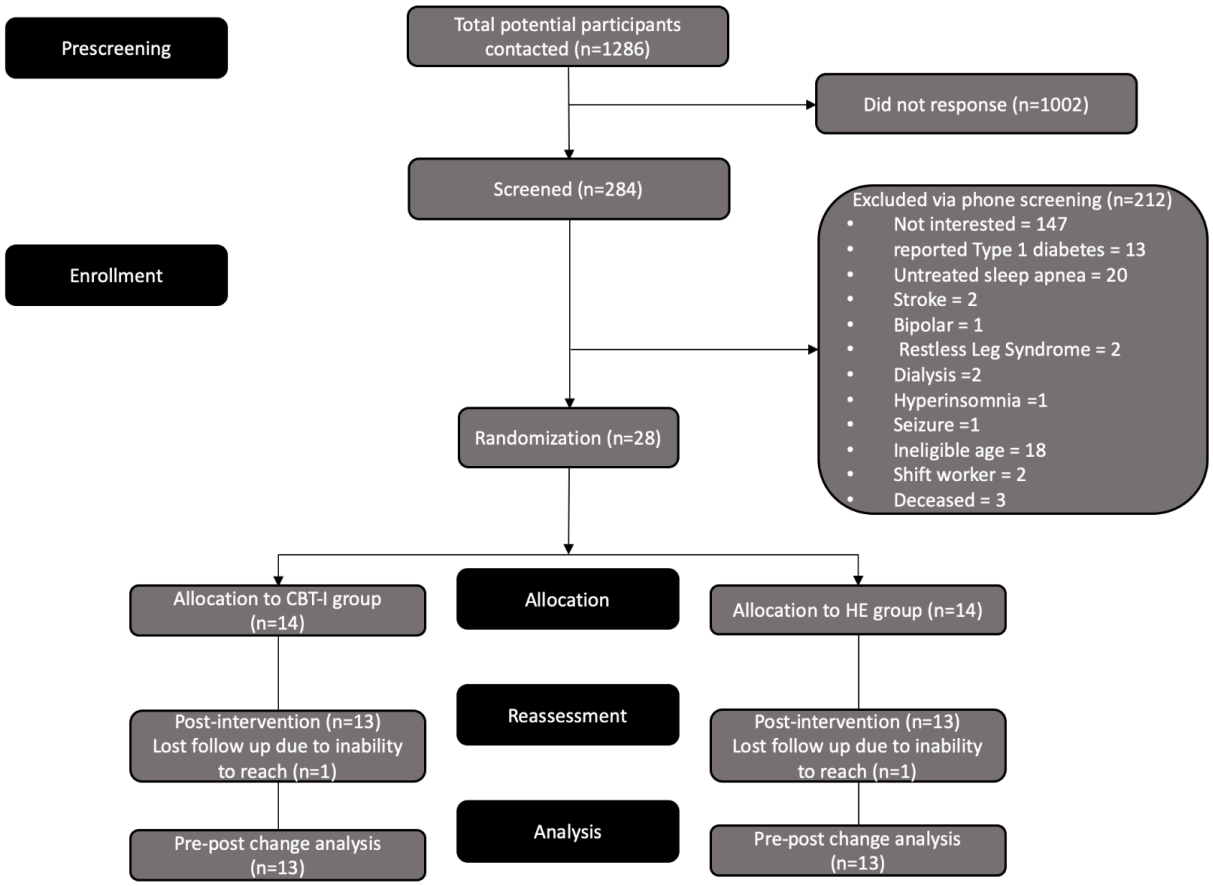
p^c = p-value of mean change difference between groups

Table 6.5. Comparison of treatments response between groups.

	CBT-I (mean±SD), n=13	**HE (mean±SD), n=13**	***p*-value**
ISI responders, n (%)	13 (100)	2 (15.38)	<.001[a]
PSQI, responders, n (%)	9 (69.23)	2 (15.38)	.005[a]

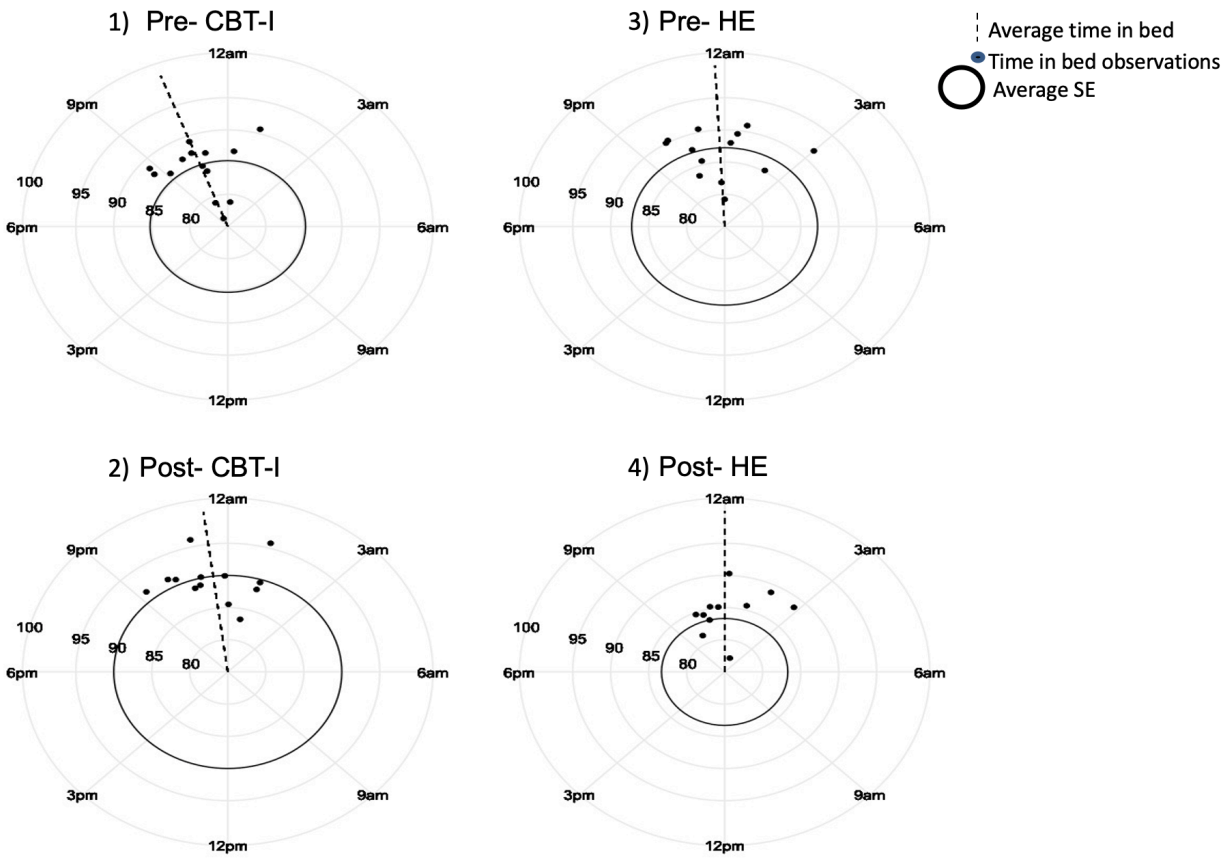
Note: CBT-I: Cognitive Behavioral Therapy for Insomnia; HE: Health Education; ISI: Insomnia Severity Index ((i.e. 6 scores as meaningful clinically difference); and PSQI: Pittsburgh Sleep Quality Index (i.e. 3 scores as meaningful clinically difference)

[a] *p-value of Chi-square analysis*



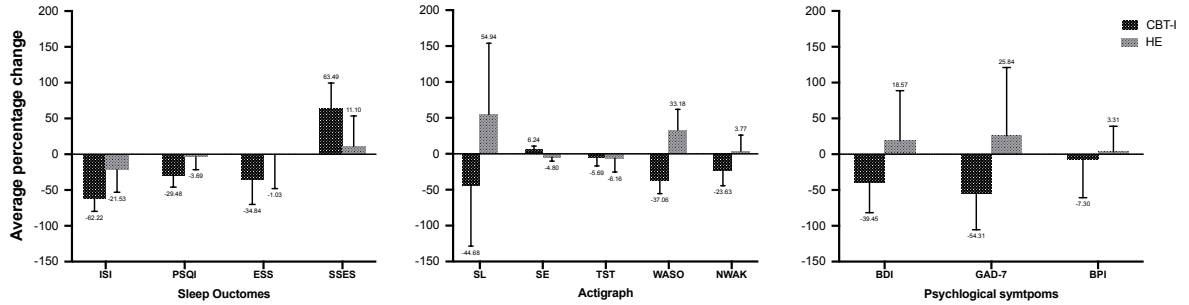
Note: CBT-I: Cognitive Behavioral Therapy for Insomnia; HE: Health Education

Figure 6.1. Consort of the study



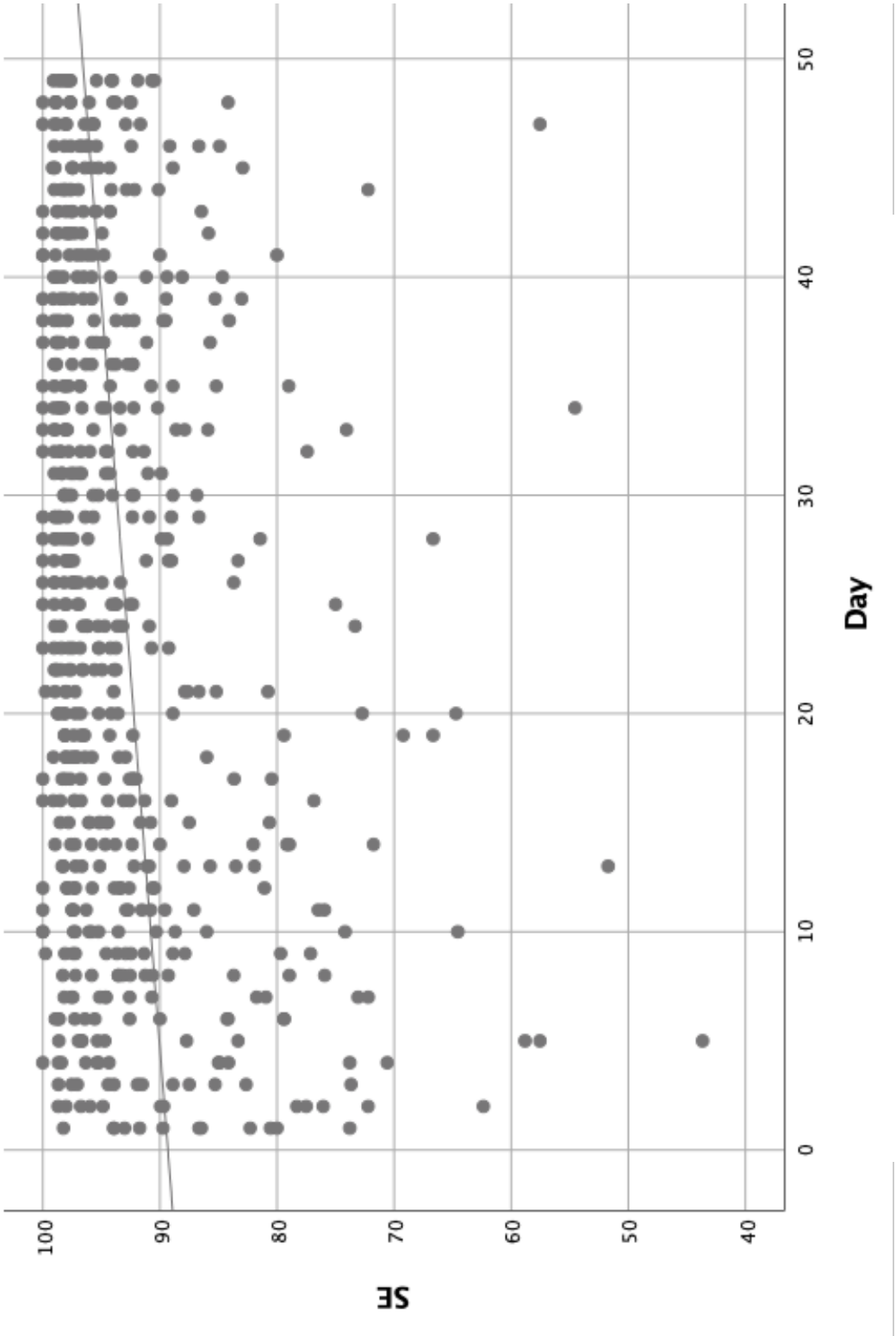
Note: CBT-I: Cognitive Behavioral Therapy for Insomnia; HE: Health Education; SE: Sleep efficiency

Figure 6.2. Radial plots of time in bed distribution with average SE



Note: CBT-I: Cognitive Behavioral Therapy for Insomnia; HE: Health Education; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; SSES: Sleep Self-Efficacy Scale; SL: Sleep Latency; SE: Sleep Efficiency; TST: Total Sleep Time; WASO, Wake After Sleep Onset; NWAK: number of awakenings; BDI: Beck Depression Scale; GAD-7: Generalized Anxiety Scale; BPI: Brief Pain Inventory

Figure 6.3. Percentage change of sleep outcomes and concomitant symptoms of both groups



Note: SE: Sleep efficiency; CBT-I: Cognitive Behavioral Therapy for Insomnia

Figure 6.4. Relationship between SE and 6-session of CBT-I using linear regression analysis

Chapter 7: The effects of Cognitive Behavioral Therapy for Insomnia in People with Type 2 Diabetes, Pilot Randomized controlled Trial Part II: Diabetes Health Outcomes

ABSTRACT

Aims: Previous studies have shown the negative impact of sleep disturbances, specifically insomnia symptoms, on glucose metabolism for people with type 2 diabetes mellitus (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 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. 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.

Results: CBT-I participants showed significantly greater improvement in glycemic control, DSCB, and fatigue.

Conclusion: 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.

Keywords: Insomnia, Diabetes, Cognitive behavioral therapy, Self-care, Glycemic control

7.1. 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) [289]. Specifically, a high prevalence of sleep disturbances among people with T2D were associated with poor glycemic control as measured by glycated hemoglobin (HbA1c) and low adherence to optimal diabetes self-care behavior (DSCB) [62, 289]. 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 [160]. Additionally, increases in insomnia severity were associated with suboptimal DSCB among people with T2D [160]. It is possible that sleep disturbances lead to fatigue and physical inactivity, which then contributes to poor diabetes health outcomes [290].

Previous studies have shown insomnia symptoms are common among people with T2D [30, 41], and other studies have shown insomnia symptoms to be a mortality risk, even after controlling for comorbidities [291, 292]. The increased mortality risk in people with insomnia might be due to inflammation, which is also associated with cardiovascular diseases [293]. Therefore, while the mechanisms underlying the relationship between T2D and insomnia symptoms are not well understood [31, 233], 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) [119]. CBT-I has been shown to have a superior treatment effect when compared to sleep medications [142], which is significant since these medications can possibly lead to negative side effects [111] or metabolic alterations [108, 109]. 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 [294].

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 [31, 233], 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 [295]. 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) [247, 296, 297].

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)[186] 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.

7.2. SUBJECTS, MATERIALS AND METHODS

The procedures and interventions for this project were described in a published protocol report [276]. Prior to being enrolled in the study, potential participants were screened according to eligibility criteria, which are presented in Table 1.

7.2.1. Study design

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) [277]. 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.

7.2.2. Outcomes

All participants completed outcome measures at baseline, and all participants completed the same outcome measures one week after completing the intervention.

7.2.2.1.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 [298]. 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 [299]. 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).

7.2.2.2.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 [67, 191]. 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 [67]. A standardized total DCP composite score was established to present all 13 domains that were scored according to the Fitzgerald et al. scoring criteria [67]. 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.

7.2.2.3.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 [300]. 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.

7.2.3. 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. The protocol paper describes session by session of both interventions [276].

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.

7.2.4. Statistical analysis

All data analyses were performed using SPSS 23.0 for Mac (Chicago, IL) and R (https://www.R-project.org/) [194]. 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* [301]. 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.

7.3. RESULTS

The consort of this intervention trial shows a total of 28 participants enrolled in the study, and 26 participants completed the study (Figure 1). There were no baseline differences between groups in demographics including age, sex, ethnicity, and education (p>.05) [186]. In addition, there were no significant between-group differences in the baseline assessments of HbA1c, RBG, DCP composite score, or FSS (Table 2).

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; Figure 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 (Figure 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) (Figure 3).

7.4. 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 Figure 2, there was 0.05% absolute percentage reduction in HbA1c, which suggests a clinically significant change based on the American Diabetes Association (ADA) statistics [302]. 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 [303]. 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 [186]. Previous studies have shown the negative influence of the combination of insomnia and depression on an individual's glucose metabolism [304], which could be adjusted using CBT-I [257].

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 [305].

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 [306]. 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 [306], 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 [209] 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.

In 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.

Table 7.1. 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

Table 7.2. Comparison of clinical variables within and between groups.

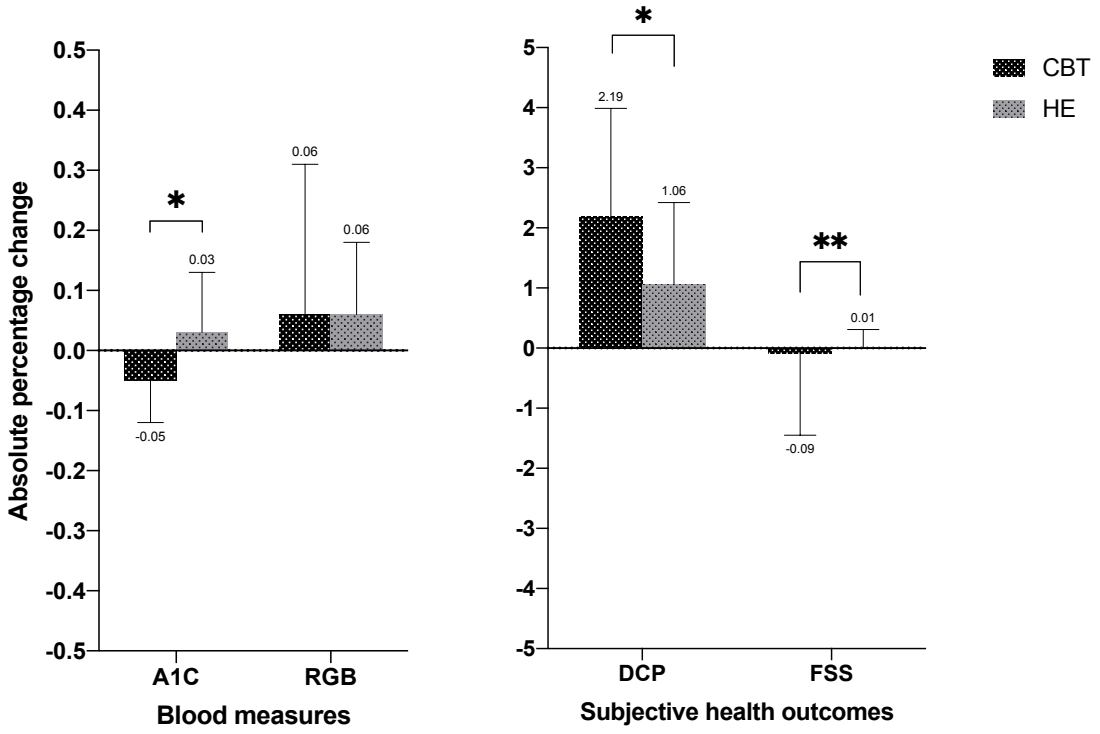
	CBT-I (mean±SD)		p^a	HE (mean±SD)		p^a	p^b	p^c
	Pre, n=14	Post, n=13		Pre, n=14	Post, n=13			
A1C	7.8±2.1	7.3±1.8	.02	6.5±0.6	6.7±0.8	.19	.09	.01
RBG	177.46±110.97	154.70±38.72	.91	137.00±19.16	144.46±30.68	.43	.66	.58
DCP	-0.21±0.53	0.19±0.40	.03	-0.32±0.44	-0.28±0.52	.65	.80	.01
FSS	4.20±1.40	2.79±1.21	.002	4.36±1.44	4.30±1.58	.56	.95	.001

Note: 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*



*Note: CBT-I: Cognitive behavioral therapy for insomnia group; HE: Health education group; A1C: Glycemic control; RGB: Random Blood Glucose Level; DCP: Diabetes Care Profile composite score; FSS: Fatigue Severity Scale; *p=0.01, **p=0.001*

Figure 7.1. Absolute percentage change of all outcomes for both groups

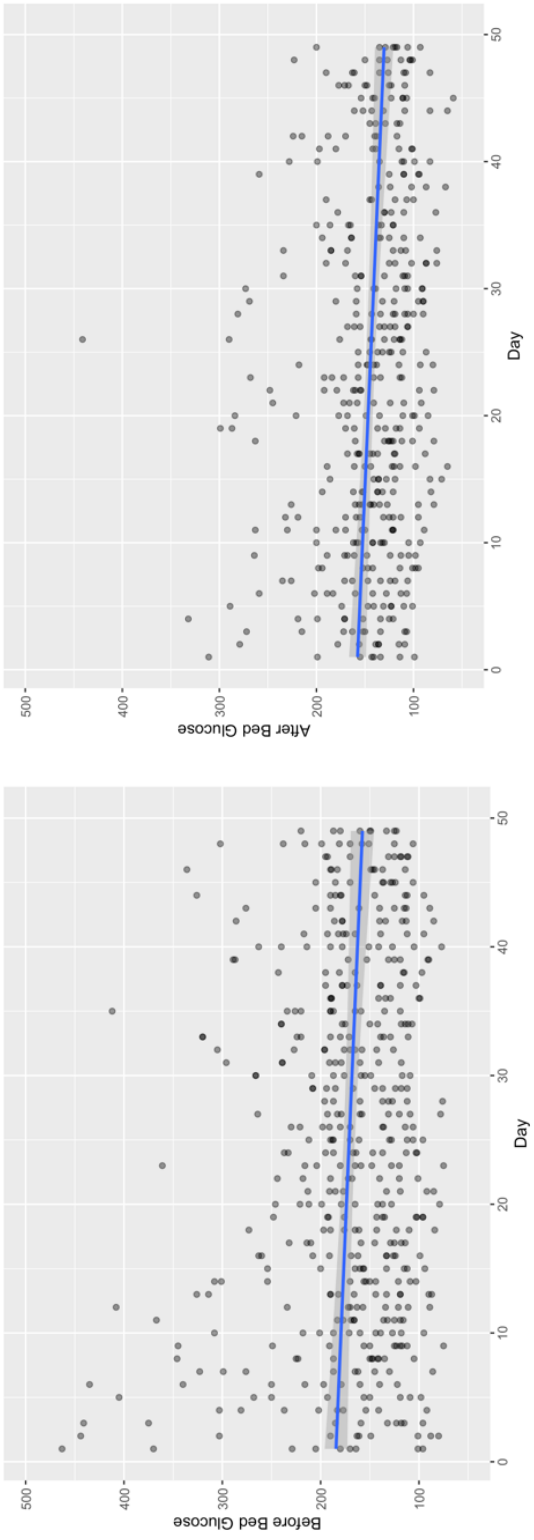


Figure 7.2. Daily glucose blood levels before bedtime and after awakening in the morning during the CBT-I intervention

Chapter 8: Discussion and Conclusion

8.1.SUMMARY OF FINDINGS

This dissertation project compared sleep, diabetes, and health outcomes in people with T2D with and without insomnia symptoms. In this body of work, this was the first study to investigate the benefits of using cognitive behavioral therapy for insomnia (CBT-I) in people with T2D on sleep, diabetes, and health outcomes. We found that worse sleep, diabetes, and health outcomes in people with T2D and insomnia symptoms were improved using CBT-I. This work provides insight into the importance of screening for insomnia symptoms in people with T2D and treating insomnia symptoms for optimal sleep, diabetes, and health outcomes. Chapter 8 summarizes the findings of 5 investigations and describes the mechanisms that potentially underlie poor sleep, diabetes, and health outcomes in people with T2D and insomnia symptoms. This chapter ends with potential clinical implications, limitations, and future directions that can be generalized from this body of work.

Summary of chapter 2: Sleep Efficiency and Total Sleep Time in People with Type 2 Diabetes with and without Insomnia Symptoms.

There is increasing awareness regarding the importance of using measures of central tendency and variability of sleep parameters. Therefore, this study aimed to compare the averages and variability of sleep parameters in people with T2D with and without insomnia symptoms. As a secondary aim, we assessed the relationship between the average and variability of sleep parameters in people with T2D with and without insomnia symptoms. This study assessed between-group differences in the averages and variability of sleep efficiency and total sleep time for 59 participants with T2D with and without insomnia symptoms, the insomnia

group (n=32) and non-insomnia control group (n=28). Actigraph and sleep diary measurements were used to assess the averages and variability (i.e., coefficient of variation across 7 nights) of sleep parameters. We also assessed depression, anxiety, and pain using validated instruments. The data suggest people with T2D and insomnia symptoms have poorer average sleep efficiency and higher sleep efficiency variability compared to people with T2D without insomnia symptoms, with statistical analyses suggesting that psychological symptoms may explain the observed difference. There were differences between the objective and subjective measurements of total sleep time, which may reflect the nature of measuring total sleep time with Actigraphs and sleep diaries. Alternatively, it is possible people with T2D have misperceptions pertaining to sleep duration. For our secondary analysis, we observed a negative relationship between average sleep efficiency and sleep efficiency variability within both groups. Because of the high prevalence of insomnia symptoms in people with T2D and the potential distress associated with highly variable sleep parameters, clinicians may consider screening for insomnia symptoms in people with T2D to optimize sleep quality. In addition, clinicians may also rely on both subjective and objective sleep measures to address possible sleep misperceptions and/or poor underlying sleep behaviors.

Summary of chapter 3: Comparison of glycemic control and diabetes self-care behavior in people with type 2 diabetes with and without insomnia symptoms.

Insomnia symptoms may limit the ability of people with T2D to engage in diabetes self-care behavior. Insomnia and the common sequalae accompanying insomnia, such as pain, depression and anxiety, may limit people with T2D from engaging in diabetes self-care behavior.

Therefore, we aimed to compare the glycemic control and diabetes self-care behavior of people with T2D with insomnia symptoms to those with T2D without insomnia symptoms. As a secondary analysis, we measured the association between diabetes self-care behavior and insomnia severity for the entire sample. Sixty participants with T2D were allocated into 2 groups based on the presence of insomnia symptoms (i.e., people with scores on the Insomnia Severity Index > 10), the insomnia group (n=32) and non-insomnia control group (n=28). We established a standardized composite score to account for all the Diabetic Care Profile domains comprising the diabetes self-care behavior. The total DCP composite score was significantly lower for people with T2D and insomnia symptoms compared to people with T2D without insomnia symptoms. Stepwise linear regression showed a one-unit increase in Insomnia Severity Index score significantly predicted a 0.03 point decrease in standardized DCP composite score, after controlling for age, pain, depression, and anxiety. However, there were no group difference in glycemic control, which might be due to the low sample size. These results suggest people with T2D and insomnia symptoms were more likely to engage in less diabetes self-care behavior compared to people with T2D without insomnia symptoms. Improving the awareness of the risk of insomnia symptoms on diabetes self-care behavior may encourage people with T2D to seek sleep promotion programs. Finally, identifying factors affecting diabetes self-care behavior may lead T2D clinicians to increase insomnia symptom screening for people with suboptimum diabetes self-care behavior and to refer them to sleep specialists if necessary.

Summary of chapter 4: Comparison of daytime functioning in people with type 2 diabetes with and without insomnia symptoms.

Daytime dysfunction includes fatigue, daytime sleepiness, vitality or low physical function have been associated with poor sleep quality in people with T2D. Therefore, we compared fatigue, daytime sleepiness, and quality of life related to vitality and physical function in people with T2D with and without insomnia symptoms. We used the Insomnia Severity Index to allocate participants into 2 groups, which were the insomnia group (n=32) and non-insomnia control group (n=28). Daytime functioning, which included fatigue and quality of life related to vitality, and physical function were worse in people with T2D and insomnia symptoms compared to people with T2D without insomnia symptoms. Depression symptoms were possibly related to daytime functioning outcomes in people with T2D and insomnia symptoms. This finding might help clinicians' decision making if patients appear to have poor daytime functioning, and clinicians could consider specific interventional approaches for diabetes management. These findings suggest clinicians may consider screening for insomnia when people with T2D complain of fatigue in order to rule out any secondary consequences of sleep disorders.

Summary of chapter 5: Establishing a protocol to use cognitive behavioral therapy for insomnia in people with type 2 diabetes.

In this chapter, we illustrated a protocol that was used to design the interventions and outcomes for chapter 6 and chapter 7. Several methodological plans were discussed in this chapter including the design, recruitment plan, intervention descriptions, statistical analyses, extraneous variables, exploratory analyses, and utilized graphs. Due to the nature of the protocol project, no results were shown in this chapter in which the next chapters will provide more details for this part.

Summary of chapter 6: The effect of cognitive behavioral therapy for insomnia on sleep outcomes and concomitant Symptoms in people with type 2 diabetes and insomnia symptoms.

This chapter illustrated the benefits of a sleep intervention targeted insomnia symptoms to improve the sleep outcomes. In this chapter, we aimed to examine the effect of cognitive behavioral therapy for insomnia (CBT-I) on insomnia severity in people with T2D and insomnia symptoms. The secondary aim was to explore the effect of CBT-I on other sleep outcomes and concomitant symptoms. Twenty-eight participants with T2D were randomly assigned to either the CBT-I group (n=14) or the health education group (n=14). Participants in the CBT-I group showed improvements in the following sleep outcomes: insomnia symptoms, sleep quality, sleep self-efficacy, sleep latency, sleep efficiency, wake after sleep onset, and number of awakenings. In addition, participants in the CBT-I group showed improvements in depression and anxiety symptoms. Although the health education group received the same amount of face-to-face attention, there were no significant changes in the sleep outcomes or concomitant symptoms for the health education group. This chapter identified the benefits of CBT-I for people with T2D and insomnia symptoms, as several sleep outcomes and symptoms of depression and anxiety improved after receiving the CBT-I. This suggests clinicians may consider offering CBT-I for patients with T2D who complain of insomnia symptoms. In addition, it might be important to screen for insomnia symptoms more frequently during diabetes clinic visits and to potentially refer patients with insomnia symptoms to CBT-I providers.

Chapter 7: The effect of cognitive behavioral therapy for insomnia on diabetes and health outcomes in people with type 2 diabetes and insomnia symptoms.

This chapter illustrated the benefits of CBT-I on diabetes and health outcomes. As noted in a previous chapter, we found suboptimal diabetes self-care behavior in people with T2D and insomnia symptoms compared to people with T2D without insomnia symptoms. However, there is a lack of evidence about the benefits of improving insomnia symptoms to optimize diabetes and health outcomes. Therefore, the aim of this chapter was to explore the effects of 6 CBT-I sessions on glycemic control, diabetes self-care behavior, and fatigue. Similar to chapter 6, we randomized 28 participants with T2D and insomnia symptoms in CBT-I group (n=14) or health education group (n=14). CBT-I participants showed significantly greater improvements in glycemic control, diabetes self-care behavior, and fatigue. We also found that participants in the CBT-I group demonstrated a clinically meaningful effect on glycemic control. In addition, CBT-I positively impacted daytime functioning, including diabetes self-care behavior and fatigue. Improving insomnia symptoms may positively affect diabetes health outcomes. Including insomnia screening in the T2D health sequalae may help to improve glycemic control and strengthen overall T2D management. Clinicians may need to reinforce the importance of maintaining optimal sleep behaviors and use important aspects in CBT-I to avoid associated complications with poor sleep quality. This study may help clinicians in recommending CBT-I for the T2D population because 6 sessions were helpful in improving diabetes and health outcomes in this study.

8.2. POTENTIAL MECHANISMS

This dissertation project carried out two main designs, a cross-sectional study and a pilot randomized clinical trial. First, we aimed to compare sleep, diabetes, and health outcomes between people with T2D with and without insomnia symptoms. After that, we investigated if

insomnia symptoms could be improved using CBT-I for people with T2D and insomnia symptoms. This dissertation project was not designed to investigate mechanisms underlying any improvements resulting from CBT-I. However, possible mechanisms might be important to mention for future studies.

Sleep disturbances have been shown to increase activation of the hypothalamic pituitary-adrenal (HPA) axis,[233] which may further exacerbate poor sleep. During a night of poor sleep, cortisol levels increase because of hyperactivation of the HPA axis, which then leads to an increased levels of glycation in the blood stream [234]. Because individuals with T2D are susceptible to hyperglycemia, increased glycation levels may be particularly problematic [235]. To illustrate that, increasing nighttime glycation levels in people with T2D may increase the number of bathroom visits and awakenings [236]. High blood glucose levels facilitates the body to release extra glucose through the urine. Increasing the number of awakenings during a night of sleep is a part of poor sleep quality [237], which may further contribute in activation of the stress system [235]. These mechanisms may explain the increased sleep efficiency variability and decreased average sleep efficiency that we found in people with T2D and insomnia symptoms using both objective and subjective measures. However, we observed increased total sleep time variability and decreased average total sleep time in people with T2D and insomnia symptoms only using subjective measures. It is possible people with T2D may have misperceptions about their sleep, which may increase the variation in subjectively quantified sleep duration.

T2D and insomnia have a bidirectional relationship [307], which might be due to shared risk factors [31]. People with T2D and insomnia commonly report depression, anxiety, pain, and obesity [31, 98]. These health issues may exacerbate the severity of insomnia symptoms, and may influence the glycemic control [104, 308]. Although the underlying mechanisms of the

relationship between T2D and insomnia are still under investigation, we found psychological symptoms played a role in the increased variability of sleep efficiency and total sleep time, suboptimal diabetes self-care behavior, and increased fatigue severity.

The CBT-I intervention might have been associated with improvements in psychological outcomes, including depression and anxiety. The association between insomnia and psychological symptoms has been shown previously [285]. Interestingly, the results of this dissertation project might suggest that improving one's sleep may eventually reduce mild to moderate depression and anxiety symptoms, even though T2D may be independently associated with depression and anxiety symptoms. However, there were no significant within- or between-group differences in pain symptoms following the interventions. This might be due to excluding individuals with severe pain symptoms from the study. Another study has also found CBT-I to be effective in improving pain severity for people with chronic pain [288], which suggests that pain may be more difficult to treat than depression and anxiety symptoms in short-term interventions [288].

There are a few physiologic mechanisms that might explain improvements in glycemic control. First, sleep disturbances negatively affect glucose metabolism, which might cause decreased brain glucose utilization and could subsequently lead to hyperglycemia [306]. Reducing sleep disturbances via CBT-I might also help regulate glucose utilization, which could improve glycemic control. Second, previous studies have suggested a U-shaped relationship between sleep duration with glycemic control levels, where excessively short or long sleep durations have been noted to be associated with higher glycemic control levels. Sleep restriction therapy might lead to improved glycemic control levels by maintaining sleep durations within an optimal range of 7-8 hours. Third, sleep disturbances are associated with appetite hormone

dysregulations [306], and these dysregulations could be adjusted through sleep hygiene and stimulus control therapy. Items from sleep hygiene, and scheduled time in bed and out of bed 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 because 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 [209] 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.

8.3. LIMITATIONS

Several limitations of this dissertation project need to be considered when interpreting the results and developing future research proposals. These limitations include study designs, sample sizes, gold standard measurements, and other extraneous variables.

8.3.1. Study designs

In this dissertation project, we utilized two research designs: cross-sectional design and randomized controlled design. These designs were appropriate to answer our research question. However, there are potential limitations that affect the ability to generalize our findings to all people with T2D due to the lack of rigorous research design.

For the cross-sectional aims (Chapters 2, 3, and 4), we were not able to evaluate the temporal precedence or causal relationship between insomnia symptoms and the outcomes of interest because we simultaneously assessed them. Specifically, it is impossible to infer whether worse sleep outcomes or poor diabetes health outcomes came before or after the onset of insomnia symptoms. In addition, replicating our study on larger sample size will improve generalizability because of people with T2D represent with different comorbidities, medications, and glucose metabolism.

For the randomized controlled design aims (Chapters 6 and 7), we utilized the most rigorous research design, which allows for assessing whether a cause and effect relationship exists between CBT-I and insomnia severity in people with T2D, but there are some limitations given the nature of this pilot randomized controlled trial. First, we only utilized blocked random allocations for age as the small size of this pilot randomized controlled trial prevented the use of additional blocking variables that might influence the severity of insomnia symptoms. However, since we focused exclusively on people with T2D, some other factors might influence the causal relationship between CBT-I and insomnia severity, such as baseline insomnia severity, baseline glycemic control, and motivation to change sleep behaviors. Second, although this study focused on people with T2D, including healthy participants as a third group would help in distinguishing the sleep patterns in T2D population. Finally, we were not able to assess the long-term effect of CBT-I in people with T2D and insomnia symptoms. Because our design used only assessed outcomes at two time points, it was not possible to understand the sustainability of the improvements in sleep and diabetes outcomes.

8.3.2. Sample size

Although the sample size for this dissertation project was chosen to provide 80% power based on the primary outcomes for the cross-sectional (sleep efficiency) and pilot randomized controlled trial (insomnia severity) aims, the sample sizes inadequately power the secondary outcomes. Also, we controlled for several potentially confounding variables such as age, gender, and symptoms of depression, anxiety and pain that were not included in the sample size analysis. We observed that depression and anxiety symptoms were influential for the cross-sectional aims. However, we used an appropriate analysis in the cross-sectional aims, generalized linear models, to control for these covariates due to the positive correlation between the insomnia symptoms and the depression and anxiety symptoms. Nevertheless, we provided important estimates for sample size analyses in future studies when controlling for possible covariates and other demographics.

8.3.3. Utilized measurements

This dissertation project was designed based on available funding and lab resources, which limited the choice of outcomes and outcome measures. We measured the sleep parameters for 7 nights using Actigraph, which has been validated for measuring sleep efficiency and total sleep time in people with insomnia. However, there is currently no recommendation on the optimal number of nights that should be assessed to measure sleep parameters in people with T2D and insomnia symptoms. In this study, we measured the variability across 7 nights of sleep, but different findings might be expected if more nights were included as a result of wide range of sleep patterns. Despite the high sensitivity and specificity of the Insomnia Severity Index, using golden standards, insomnia diagnostic criteria or polysomnography may help in confirming the

results. Participants' misperceptions about their sleep quality might worsen the quality and/or accuracy of their responses to subjective sleep questionnaires.

In terms of diabetes outcomes, we measured glycemic control using HbA1c kits, which are less sensitive than hospital laboratory blood work. In future research, it is important to consider using more sensitive measures of glycemic control as well as including other diabetes laboratory outcomes to conceptualize the between-group differences.

Finally, we measured diabetes self-care behavior subjectively, since there is no standardized objective measure that assesses self-care in the T2D population. It could be beneficial to include more objective measures to assess activities related to diabetes self-care behavior, such as physical activity, diet, sleep quality, medication adherence, and glucose monitoring.

8.3.4. Other possible extraneous variables

Our project did not examine the pharmacological issues or medication interactions, as this should be addressed in future research that focuses on the combination between behavioral and pharmacological sleep interventions in people with T2D. Additionally, the prescribed medications for patients with T2D to control diabetes complications, such as poor glycemic control, fatigue, sleep issues or pain, were not controlled in the analysis. However, we used a medication log to confirm T2D diagnosis and categorize our participants based on the number of medications they were taking. Initially, a secondary analysis was utilized to investigate the between-group differences in the number of prescribed medications for all aims. However, we did not find any significant between-group differences in number of medications for all aims. In

future studies, researchers might consider the types of medications prescribed to participants due to the potential risk factors of poor health outcomes associated with the different types of medications.

Menopause is another possible confounding factor that is associated with increasing insomnia symptom severity [309]. There is still a need for further investigation for the influence of menopause on insomnia symptoms, since previous studies were not able to predict specific sleep-disorder symptoms using menopausal status [310]. Another previous study showed that CBT-I is an effective treatment for menopausal symptoms such as hot flashes [311]. However, this study showed that women with menopause might present with minimal treatment response (i.e., <6 point change on ISI). We expect women with T2D and menopause might response differently to CBT-I, in which future studies are needed to examine the treatment response in this population.

Finally, the number of comorbidities was not controlled in this dissertation project because of the known widespread prevalence of diabetic complications, which made it difficult to control for all complications. Our extensive exclusion criteria may have helped in minimizing several comorbidities such as neurological diseases in addition to severe symptoms of depression, anxiety and pain. We also excluded common diabetes complications such as amputations, dialysis, blindness, and risk of severe sleep apnea. However, we used a self-reported questionnaire to exclude these comorbidities. There is a need to use more sensitive measurements to rule out the previously mentioned health issues as well as to assess other comorbidities such cardiovascular diseases, diabetes neuropathy and osteoarthritis. Investigating sleep apnea using gold standard measurements such as polysomnography may help in ruling out confounding variables, which might increase the variation of the sleep parameters.

8.4. FUTURE DIRECTIONS

This dissertation project addressed several research questions regarding the additive effect of insomnia symptoms on sleep, diabetes, and health outcomes in people with T2D. In addition, the effectiveness of CBT-I on sleep, diabetes, and health outcomes in people with T2D and insomnia symptoms was evaluated. However, other interesting research questions still remain unclear. Future work is needed to understand the complex relationship between insomnia symptoms and psychological symptoms in people with T2D. In addition, there is still a need to investigate the physiological mechanisms involved in improving insomnia symptoms and diabetes health outcomes following CBT-I in people with T2D.

Our findings indicate that psychological symptoms including depression and anxiety could contribute in the worse sleep, diabetes, and health outcomes in people with T2D and insomnia symptoms. We were limited to understand if insomnia and psychological symptoms independent or overlapping risk factors for poor health outcomes in people with T2D. However, we showed improving both insomnia and psychological symptoms following CBT-I which is designed to improve insomnia symptoms rather than psychological issues. Although we have excluded people with severe psychological symptoms including depression and anxiety, it seems the minimal to moderate scores of depression and anxiety symptoms impact the relationship between insomnia symptoms and T2D health outcomes. Therefore, future research is needed to examine the causality relationship between insomnia and psychological symptoms in people with T2D. Longitudinal designs might be appropriate to understand the direct and indirect relationship of psychological symptoms and insomnia on health outcomes in people with T2D.

Our data showed a bidirectional relationship between insomnia symptoms and sleep efficiency in people with T2D. The causal relationship between insomnia symptoms and sleep

efficiency in people with T2D remains unclear. In this study, we were limited in identifying whether poor sleep efficiency or high sleep efficiency variability causes insomnia symptoms or vice versa in people with T2D. A longitudinal design is needed to consider the impact of psychological symptoms on the relationship between incidence of insomnia and high variation of sleep parameters or poor sleep outcomes in people with T2D. In addition, establishing a cut-off point for sleep variability of interested sleep parameters that differentiate poor glycemic control from good glycemic control might help in developing preventative strategies for diabetes management.

Mechanisms of poor daytime functioning including diabetes self-care behavior, fatigue, and daytime sleepiness were outside the scope of this dissertation. Although we identified poor daytime functioning in people with T2D and insomnia symptoms, other objective outcomes in diabetes management might assist in understanding how suboptimal diabetes self-care behavior leads to high fatigue and daytime sleepiness. Future research is needed to account for physical activity level, sedentary behavior, and diet and medication adherence to investigate the association of insomnia symptoms and daytime functioning in people with T2D. Equally important, longitudinal designs are needed to understand the causality relationship between insomnia symptoms and daytime functioning in people with T2D after controlling for psychological symptoms.

The majority of our sample were within the recommend range of glycemic control, which might be the reason there were no significant differences in glycemic control between people with insomnia symptoms and without insomnia symptoms. Nevertheless, following CBT-I the intervention, we found a clinically meaningful difference in glycemic control but no significant difference after health education. We are not sure if the range of glycemic control influenced this

significant difference. People in the health education group were also within the recommend range of glycemic control, which might have caused the lack of significant between-group differences. However, glycemic control was not accounted in our sample size analysis, but glycemic control should be considered in sample size analyses for future research projects so that larger sample sizes are used, which may allow a better understanding the impact of insomnia symptoms and CBT-I on glycemic control. Also, using highly sensitive metabolic blood measurements on a larger sample size, such as cortisol tests, homeostatic model assessment and oral glucose tolerance test, may generalize the other effects of CBT-I on diabetes parameters and understand the physiological mechanisms of sleep improvements.

Finally, although this dissertation demonstrated improvements in insomnia severity, other sleep outcomes, glycemic control, diabetes self-care behavior and fatigue after participants underwent 6 sessions of CBT-I, future research is needed to measure the sustainability of these improvements for at least three months using a larger sample size. Because of the common long-term complications related to diabetes, it is imperative to understand the long-term effect of CBT-I on health outcomes for people with T2D. In addition, we did not account for other diabetes complications such as cardiovascular disease and diabetic neuropathy due to low sample size, so more research is needed to address these complications. Finally, understanding the effect of CBT-I using polysomnography for people with T2D and insomnia symptoms might help in assessing important sleep parameters.

8.5. CONCLUSION

This dissertation project provides evidence of the poor sleep and diabetes health outcomes in people with T2D and insomnia symptoms, which were adjusted following CBT-I. In addition, depression and anxiety symptoms were worse in people with T2D and insomnia symptoms compared with people with T2D without insomnia symptoms, which might contribute to poor sleep and diabetes health outcomes. Future work is needed to better understand the complex relationship between insomnia symptoms, psychological symptoms and poor sleep and diabetes health outcomes in people with T2D.

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