THE ROLES OF OBSTRUCTIVE SLEEP APNEA AND INSOMNIA ON MOOD, DIABETES-RELATED DISTRESS, AND GLYCEMIC CONTROL IN ADULTS WITH TYPE 2 DIABETES MELLITUS

by

Bomin Jeon

Bachelor of Science in Nursing, Seoul National University, Republic of Korea, 2010

Master of Science in Nursing, Seoul National University, Republic of Korea, 2016

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This dissertation was presented

by

Bomin Jeon

It was defended on

March 25, 2022

and approved by

Faith S. Luyster, Assistant Professor, School of Nursing

Judith A. Callan, Assistant Professor, School of Nursing

Susan M. Sereika, Professor, School of Nursing

Monica M. DiNardo, Adult Care Nurse Practitioner, VA Pittsburgh Healthcare System

Dissertation Chair: Eileen R. Chasens, Professor, School of Nursing

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Bomin Jeon, PhD

University of Pittsburgh, 2022

Background: Obstructive sleep apnea (OSA) and insomnia are common sleep disorders and frequently coexist. Mood disturbances and diabetes-related distress are common psychological symptoms in type 2 diabetes mellitus (T2DM) and known barriers to glycemic control. Understanding how comorbid OSA and insomnia (OSA+I) contribute to mood and diabetes-related distress could be significant to improve glycemic outcomes in T2DM.

Purpose: The aims of this study were to 1) compare mood states and diabetes-related distress in OSA+I, OSA, and insomnia in adults with T2DM, 2) examine insomnia as a possible moderator of the association between OSA with mood states and diabetes-related distress in adults with T2DM and OSA, and 3) examine mood disturbances and diabetes-related distress as potential mediators of the relationship between OSA and insomnia with glucose outcome in adults with T2DM and OSA.

Methods: This study was a secondary analysis of the pooled baseline data from two independent randomized controlled trials. OSA severity was determined by an Apnea-Hypopnea Index from in-home ApneaLinkPlus® device data. Questionnaires measured insomnia severity, mood states, and diabetes-related distress. Glucose outcome was measured by hemoglobin A1c (HbA1c). Aim 1 used one-way analysis of covariance and one-way multivariate analysis of covariance. Aim 2 used hierarchical multiple linear regression and multivariate linear analysis. Aim 3 used mediation

analysis with bootstrapped samples. Clinical and sociodemographic covariates were controlled in all analyses.

Results: Insomnia group had greater mood disturbances (p = .017) and OSA+I group had greater diabetes-related distress than OSA group (p = .033) in adults with T2DM. As insomnia severity increased, the deleterious effect of OSA on mood disturbances decreased (b = -.048, p = .017) and only insomnia was associated with diabetes-related distress in adults with T2DM and OSA (b =1.133, p < .001). Persons with greater insomnia severity had greater diabetes-related distress, which was associated with heightened HbA1c (indirect effect: b = .0169, se = .0083, 95% CI [.0028, .0348]).

Conclusions: Insomnia, not OSA, was the primary underlying sleep disorder associated with mood disturbances and diabetes-related distress in T2DM. Insomnia could be a modifiable factor to reduce diabetes-related distress and improve glycemic outcomes in T2DM.

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Preface

I could not have successfully finished my Ph.D. journey without the support of so many who have provided me with tremendous support, patience, and encouragement. First and foremost, I would like to express my deepest gratitude to my dissertation committee, each of whom has provided unwavering support and guidance throughout my doctoral training and the dissertation project. Thank you to *Dr. Eileen Chasens* for her endless support, guidance, and communication that provided me with clear insight. Her sincerity, integrity, and compassionate nature continue to inspire me. I do not know what I would have done without her guidance in developing my dissertation work and beyond. Thank you to *Dr. Faith Luyster* for your invaluable advice and guidance from writing my dissertation project to submitting the manuscript. She has always been willing to share her expertise and courage to reach the finish line. Thank you to *Dr. Susan Sereika* for opening my eyes to how to apply rigorous statistical approaches. I greatly appreciate your kindness, responses to my questions and emails, and meticulousness during the data analysis phase. *Dr. Judith Callan*, you have shown incredible faith in me throughout my Ph.D. journey, and thank you for all your encouragement and counsel. Thank you to *Dr. Monica DiNardo* for providing insights into the significance of my dissertation work among persons with type 2 diabetes mellitus.

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1.0 Introduction

The following dissertation proposal, *The Roles of Obstructive Sleep Apnea and Insomnia on Mood, Diabetes-Related Distress, and Glycemic Control in Adults with Type 2 Diabetes Mellitus,* describes a dissertation study that partially fulfills the requirements for the doctor of philosophy degree from the School of Nursing at the University of Pittsburgh. Mood disturbances (e.g., depression, anxiety) and diabetes-related distress are known barriers to diabetes self-care behaviors and subsequent glycemic control. Multiple previous studies have identified that poor glycemic control is associated with an increased risk of diabetes complications, mortality, and health care costs (Einarson et al., 2018; Kosiborod et al., 2018; Rao Kondapally Seshasai et al., 2011; Van Dieren et al., 2010; American Diabetes Association [ADA], 2013; ADA, 2018). Increased understanding of modifiable factors for early detection and prevention of mood disturbances and diabetes-related distress in type 2 diabetes mellitus (T2DM) is essential to improve self-care behaviors and prevent poor glycemic control and subsequent poor health outcomes in persons with T2DM (Piette et al., 2004; Robertson et al., 2012).

Sleep disorders, obstructive sleep apnea (OSA), and insomnia are modifiable factors that affect negative emotional regulation, which has been associated with mood disturbances (Baglioni et al., 2011; Chen et al., 2013; Hein et al., 2017b; Li et al., 2016; Peppard et al., 2006). A better understanding of the role of OSA and insomnia may improve mood disturbances and diabetes-related distress in persons with T2DM. This information is important to optimize treatment options for adults with T2DM who are vulnerable to mood disturbances and diabetes-related distress.

In the **Aim 1 manuscript**, we compared mood states (Aim 1a) and diabetes-related distress (Aim 1b) among adults with T2DM with either 1) comorbid OSA and insomnia (OSA+I), 2) OSA

alone, or 3) insomnia alone using one-way analysis of covariance (ANCOVA) and one-way multivariate analysis of variance (MANCOVA). In the **Aim 2 manuscript**, we used hierarchical multiple linear regression analysis and multivariate linear regression analysis to examine insomnia as a moderator of the association between OSA with mood states (Aim 2a) and diabetes-related distress (Aim 2b) in adults with T2DM and OSA. The Aim 3 manuscript examined mood states (Aim 3a) and diabetes-related distress (Aim 3b) as potential mediators of the association between insomnia and OSA with HbA1c in adults with T2DM and OSA. We believe this study will contribute to increased knowledge on the role of sleep disorders in mood, diabetes-related distress, and glycemic control in adults with T2DM.

1.1 Specific Aims

Mood disturbances (e.g., depression, anxiety) and diabetes-related distress, are significant challenges in persons with T2DM (Esbitt et al., 2013; Fisher et al., 2014). Adults with T2DM are diagnosed with depression twice as frequently as those without T2DM (Anderson et al., 2001). Diabetes-related distress, emotional distress in response to the responsibilities of diabetes self-management (Esbitt et al., 2013; Fisher et al., 2014), is problematic in almost five out of every ten adults with T2DM (Azadbakht et al., 2020; Chew et al., 2016; Jeong & Reifsnider, 2018; Perrin et al., 2017). Previous studies found that mood disturbances and diabetes-related distress in T2DM have known barriers to diabetes self-care behaviors and glucose management (Fisher et al., 2010; Gonzalez et al., 2008; Snoek et al., 2015). As a result, these psychological symptoms consequently increase the rates of diabetes complications, mortality, and health care costs in persons with T2DM (De Groot et al., 2001; Egede et al., 2002; Finkelstein et al., 2003; Himelhoch et al., 2004;

Kasteleyn et al., 2015; Katon et al., 2005). Increased understanding of modifiable factors associated with mood and diabetes-related distress among adults with T2DM is essential to improve diabetes self-care behaviors and prevent poor glycemic control and subsequent adverse health outcomes. However, modifiable factors affecting mood and diabetes-related distress in T2DM are not fully understood.

Obstructive sleep apnea (OSA) and insomnia are two common sleep disorders associated with a higher prevalence of mood disturbances, including depression (Gruber & Cassoff, 2014; Garbarino et al., 2020; Ohayon, 2003; Sharafkhaneh et al., 2005; Vandeputte & De Weerd, 2003; Wahner-Roedler et al., 2007). OSA is a sleep-related breathing disorder characterized by repetitive upper airway obstruction causing apnea (cessation of breathing) or hypopnea (reduction of airflow) during sleep that results in hypoxia and sleep fragmentation (Sateia, 2014). Insomnia is defined as sleep-specific complaints that include difficulty initiating sleep, difficulty maintaining sleep, or early morning awakenings with an inability to return to sleep (American Psychiatric Association [APA], 2013). Previous studies found that insomnia and OSA are independent risk factors for depression and affect the progression of depressive symptoms (Baglioni et al., 2011; Hertenstein et al., 2019; Nutt et al., 2008; Peppard et al., 2006). When insomnia and OSA co-exist, the risk of developing depression increases, and depressive symptoms are worse relative to when each condition exists alone (Lang et al., 2017; Lee et al., 2014; Mysliwiec et al., 2013; Yang et al., 2011). Therefore, OSA and insomnia may contribute to mood disturbances and diabetes-related distress in individuals with T2DM, especially when they coexist; this may eventually lead to poor glycemic control. However, the effect of comorbid OSA and insomnia on mood and diabetes-related distress has not been examined in adults with T2DM.

The overarching purpose of this study was to elucidate the role that OSA and insomnia have, individually and jointly, in mood states, diabetes-related distress, and glycemic control in adults with T2DM.

Our specific aims and hypotheses were:

Aim 1: To compare mood states and diabetes-related distress among three types of sleep disorder groups: comorbid OSA and insomnia (OSA+I), OSA, and insomnia in adults with T2DM

H1a: Adults with OSA+I have greater mood disturbances and diabetes-related distress than those with OSA only.

H1b: Adults with OSA+I have greater mood disturbances and diabetes-related distress than those with insomnia only.

H1c: Adults with insomnia only have greater mood disturbances and diabetes-related distress than those with OSA only.

Aim 2: To examine insomnia severity as a moderator of the association between OSA severity with mood states, and between OSA with diabetes-related distress in adults with T2DM and OSA

H2a: As insomnia severity increases, greater OSA severity is associated with greater mood disturbances.

H2b: As insomnia severity increases, greater OSA severity is associated with greater diabetes-related distress.

Aim 3: To examine mood disturbances and diabetes-related distress as potential mediators of the association between insomnia severity and glucose outcome, and the association between OSA severity and glucose outcome in adults with T2DM and OSA

H3a. Greater insomnia severity and OSA severity lead to increased mood disturbances, which in turn leads to heightened HbA1c

H3b. Greater insomnia severity and OSA severity lead to increased diabetes-related distress, which in turn leads to heightened HbA1c

This study is a secondary analysis of the pooled baseline data from two independent randomized control trials with similar eligibility criteria and instruments: Diabetes Sleep Treatment Trial (DSTT; R01-DK096023) and Diabetes Sleep Treatment Trial: Insomnia (DSTT-I; K24-NR016685). Participants from both studies had self-reported T2DM. OSA severity was determined by an Apnea-Hypopnea Index (AHI) using ApneaLinkPlus® (Collop et al., 2007), and insomnia severity was determined by the Insomnia Severity Index (ISI) (Morin et al., 2011). These were used to determine the grouping of T2DM patients with OSA (AHI ≥ 10 events/hour and ISI < 15), insomnia (AHI < 10 events/hour and ISI ≥ 15), or OSA+I (AHI ≥ 10 events/hour and ISI ≥ 15) status in Aim 1. The eligibility criteria for OSA in Aim 2 and Aim 3 was AHI ≥ 5 events/hour. The total sample size for Aim 1 was 255 (OSA: n = 99; insomnia: n = 85; OSA+I: n = 71). The total sample size for Aim 2 and 3 was 240. Outcome data include the Total Mood Disturbance (TMD) score and the six subscale scores (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment) measured by the Profile of Mood States (POMS) (McNair & Heuchert, 2007), diabetes-related distress measured by the Problem Areas in Diabetes scale (PAID) (Polonsky et al., 1995), and glucose outcome measured by HbA1c. A blood sample (no more than 30cc) was collected to get the value of HbA1c. This study contributed to increased knowledge regarding the role of OSA, insomnia, comorbid OSA, and insomnia, and their association with mood, diabetes-related distress, and glycemic control in persons with T2DM.

1.2 Background

This section will present important background information to the dissertation "*The roles of obstructive sleep apnea and insomnia on mood, diabetes-related distress, and glycemic control in adults with type 2 diabetes mellitus.*" This section includes a brief description of obstructive sleep apnea (OSA), insomnia, comorbid OSA and insomnia, type 2 diabetes mellitus (T2DM), the association between sleep disorders and T2DM, mood disturbances, and diabetes-related distress in T2DM, and the impact of insomnia and OSA on mood disturbances.

1.2.1 Obstructive sleep apnea (OSA)

OSA is characterized by repetitive upper airway obstruction during sleep that results in apneas (cessation of breathing) or hypopneas (decreased airflow by at least 30% from pre-event baseline, accompanied by a 3% reduction in oxygen saturation lasting at least 10 seconds) (Berry et al., 2012). An overnight in-laboratory polysomnography or a home sleep apnea study is the standard diagnostic test for OSA (Malhotra et al., 2018). Apnea-Hypopnea Index (AHI) measures the average hourly number of apneas and hypopneas to determine the presence and severity of OSA (Malhotra et al., 2018; Sateia, 2014). OSA severity is categorized by the American Academy of Sleep Medicine (AASM) as either mild (AHI 5 to 14 per hour), moderate (AHI 15 to 29 per hour), or severe (AHI 30 or more) (Berry et al., 2012). Some sleep researchers use the respiratory disturbance index (RDI) as an alternative method of determining the presence and severity of OSA. RDI includes respiratory effort-related arousals, that is, arousals without oxygen desaturation, in addition to apneas and hypopneas (Berry et al., 2012; Malhotra et al., 2018). Snoring, breath-holding, or a feeling of gasping or choking when awakening from sleep are common nighttime

symptoms of OSA. Several self-reported questionnaires measure these clinical symptoms to assist in the assessment of OSA risk, including the Berlin Questionnaire (Netzer et al., 1999), the Multivariable Apnea Prediction (MAP) index (Maislin et al., 1995), and the STOP-Bang questionnaire (Chung et al., 2016).

The estimated prevalence of OSA in the general population, defined as an AHI of five or more, ranges from 9% to 38%. At the level of AHI of 15 or more, OSA is found between 6% to 17% of the general population (Senaratna et al., 2017). Despite variations in prevalence due to different criteria determining OSA severity, the prevalence of OSA was greater in males, obese or middle-aged, and older adults (Senaratna et al., 2017). These are the most well-recognized risk factors for OSA (Foldvary-Schaefer & Waters, 2017; Jordan et al., 2014). Hispanics and African Americans have a higher OSA prevalence than Whites (Foldvary-Schaefer & Waters, 2017).

Repetitive apneas and hypopneas during sleep are terminated by cortical arousals. The frequent arousals lead to sleep fragmentation, which results in excessive daytime sleepiness, fatigue, changes in cognition, and mood disturbances (Foldvary-Schaefer & Waters, 2017). Impaired concentration, attention, and vigilance are more severe in persons with OSA than in normal sleepers (Jackson et al., 2011; Vaessen et al.,2015); these impairments decrease work productivity (Mulgrew et al., 2007) and create a 2 to 3 times higher risk of having motor-vehicle accidents (Ellen et al., 2006; Garbarino et al., 2016; Sanna, 2013). Several studies found moderate-severe OSA (AHI $\geq$ 15) increased the risk of developing depression (Odds ratio; OR = 2.2, 95% confidence interval; 95% CI 1.5, 3.1; OR = 2.6, 95% CI 1.7, 3.9, respectively) (Chen et al., 2013; Peppard et al., 2006). A high prevalence of depression (30% to 41%) was found among persons with OSA (Garbarino et al., 2020; Harris et al., 2009).

OSA was found to be an independent risk factor for cardiovascular disease (e.g., hypertension, coronary heart disease, heart failure, and stroke) (Dong et al., 2013) and metabolic disorders (e.g., metabolic syndrome, type 2 diabetes) (Gaines et al., 2018). Intermittent hypoxia was the proposed mechanism for the physiological changes that lead to cardiovascular and metabolic function alteration among persons with OSA (May & Mehra, 2014). Intermittent hypoxia activates the sympathetic nervous system and systematically increases inflammation and oxidative stress, which act to induce hypertension, atherosclerotic changes, and metabolic dysregulation (Foldvary-Schaefer & Waters, 2017; May & Mehra, 2014). Several studies found that patients with cardiovascular disease and severe OSA had twice the risk of death compared with patients without OSA (OR = 1.9, CI 1.4, 2.7) (Lavie, 2007; Wang et al., 2013).

1.2.2 Insomnia

Insomnia is defined as subjective complaints of difficulty initiating sleep, difficulty maintaining sleep, and early morning awakenings with an inability to return to sleep, resulting in non-restorative or poor sleep quality and significant daytime impairments (APA, 2013). Based on the prominent nighttime symptoms, insomnia is often characterized as having three subtypes: sleep onset, sleep maintenance (i.e., difficulty maintaining sleep or early morning awakenings), and mixed symptom subtypes (Morin et al., 2015). Among the subtypes of nighttime symptoms, the sleep maintenance subtype is more prevalent than the sleep onset subtype among persons with primary insomnia (Morin et al., 2015; Walsh et al., 2011).

Insomnia symptoms are subjectively assessed by structured or semi-structured interviews, self-reported questionnaires, and sleep diaries (Morin et al., 2015). Insomnia symptoms can also be quantified with objective polysomnographic or actigraphic measures such as taking more than

30 minutes to initiate sleep (sleep latency > 30 min) or spending more than 30 min awake after sleep onset (wake after sleep onset; WASO > 30 min) (Buysse, 2013; Morin et al., 2015).

Hyperarousal, characterized by an increased level of physiological and cognitive arousal, is a critical factor in the underlying physiological mechanism of insomnia. Physiological hyperarousal among persons with insomnia includes: 1) an elevated activity of the autonomic system (e.g., an increased body temperature or heart rate), 2) an elevated activity of the neuroendocrine system (e.g., an increased activity of the hypothalamic-pituitary-adrenal axis, followed by an increased cortisol level) during sleep, 3) a decreased function in immunity, and 4) the noticeable alteration of activities in specific brain regions. These changes result in increasing dysfunctional cognitive hyperarousal, where persons are unable to "turn off" their thoughts which further perpetuates insomnia symptoms (Riemann et al., 2010).

The estimated prevalence of insomnia varies widely based on the criteria used to define insomnia. Under the clinical diagnostic criteria (i.e., the presence of troublesome insomnia symptoms for at least three months not explained by other medical or psychological conditions with the adequate opportunity for sleep, which cause clinically significant distress or daytime impairment; APA, 2013), the estimated prevalence of insomnia disorders in the general population ranges from 6% to 22.1% (Ohayon, 2002; Ohayon & Reynolds III, 2009; Roth et al., 2011). An estimated 35% to 43% of the general population experienced at least one insomnia symptom (Morin et al., 2011; Ohayon, 2002; Ohayon & Reynolds III, 2009; Walsh et al., 2011). Common factors associated with an increased risk of insomnia are being female, older age, lower socioeconomic status (lower level of education, unemployment status), marital status, and race (Buysse, 2013; Morin et al., 2015). Persons who were divorced or separated were more likely to experience insomnia than persons who were married or never married. Race and ethnicity

influence insomnia prevalence: there was a greater risk of insomnia found in African Americans compared with Whites (Buysse, 2013), and Hispanics had a greater risk of insomnia compared to non-Hispanic Whites and non-Hispanic Blacks (Loredo et al., 2010).

Several studies support the finding that insomnia is frequently associated with impaired daytime functions such as excessive daytime sleepiness (Hein et al., 2017a), fatigue, decreased concentration (Fortier-Brochu et al., 2012; Fortier-Brochu & Morin, 2014), and mood disturbances (LeBlanc et al., 2007). Insomnia patients have higher levels of fatigue, experience worse psychological symptoms, and have poorer levels of attention or concentration than normal sleepers (Fortier-Brochu et al., 2012; Fortier-Brochu & Morin, 2014; LeBlanc et al., 2007). Problems with concentration or alertness are also associated with poor work-related performance (e.g., absenteeism, decreased productivity) (Daley et al., 2009; Léger et al., 2006) and increases both non-motor-vehicle and motor-vehicle accidents (Daley et al., 2009; Garbarino et al., 2017).

Persons with coexisting medical or psychological disorders are more likely to report insomnia symptoms (Sarsour et al., 2010). Insomnia is a predictor of several medical conditions, including hypertension, coronary disease, and heart failure (Bathgate & Fernandez-Mendoza, 2018; Javaheri & Redline, 2017; Laugsand et al., 2011) as well as metabolic syndrome (Troxel et al., 2010) and diabetes (Bathgate & Fernandez-Mendoza, 2018; Budhiraja et al., 2011; Laugsand et al., 2011). Studies of depression in patients with insomnia report that insomnia significantly increases the risk of depression (Baglioni et al., 2011; Li et al., 2016). Untreated insomnia significantly increases all types of medical costs for in-patient hospitalization ($63,607), emergency care ($1,492), and medication ($486) compared to persons without sleep disorders (Wickwire et al., 2019).

1.2.3 Comorbid OSA and insomnia

OSA and insomnia are mutually exclusive sleep disorders regarding different diagnostic criteria and stereotypical risk factors in each sleep disorder. However, growing evidence suggests that OSA and insomnia frequently coexist. An estimated 27% to 88% of patients with OSA were found to experience at least one insomnia symptom (Bailes et al., 2016; Björnsdóttir et al., 2012; Björnsdóttir et al., 2013; Choi et al., 2015; Chung, 2005; Krakow et al., 2001; Krell & Kapur, 2005; Lichstein et al., 2013; Mysliwiec et al., 2014; Saaresranta et al., 2016; Smith et al., 2004; Subramanian et al., 2011; Wallace et al., 2013). Among patients with insomnia, the prevalence of comorbid mild OSA ranges from 36% to 42% (AHI ≥ 5) (Bianchi et al., 2016; Guilleminault et al., 2002; Li et al., 2015) and from 14% to 68.7% with moderate and severe OSA (AHI ≥ 15) (Gooneratne et al., 2006; Kinugawa et al., 2012; Lichstein et al., 1999). In a recent systematic review and meta-analysis which examined the prevalence of comorbid OSA and insomnia (Zhang et al., 2019), the overall prevalence of insomnia among persons with OSA was 38%; furthermore, 35% of insomnia patients had OSA with a level of AHI 5 or more, and 29% had a level of AHI 15 or more. Although the prevalence of comorbid OSA and insomnia varies due to different demographic characteristics (e.g., older adults, females) and different definitions and cut-off values for insomnia and OSA assessment, at least one-third of the clinical population has comorbid OSA and insomnia.

OSA and insomnia share substantial clinical symptoms. Frequent awakenings, difficulty falling asleep, and unrefreshing sleep are common nocturnal sleep disturbances in insomnia and OSA. There was also overlap in daytime impairments, including daytime sleepiness, fatigue, impaired cognitions, mood disturbances, accidents, and decreased quality of life in insomnia and OSA (Luyster et al., 2010). However, distinct symptoms in each sleep disorder (insomnia and

OSA) may exacerbate the severity of each condition. In insomnia, hyperarousal is associated with a decreased respiratory arousal threshold. The respiratory arousal threshold is an index of arousal induced by respiratory stimuli. A low respiratory arousal threshold contributes to continuous unnecessary arousals to mild airway obstructions, leading to higher AHI levels (Bonnet & Arand, 2010; Osman et al., 2018).

On the other hand, OSA can be a precipitating factor of insomnia. Frequent arousals induced by apnea and hypopnea create problems with maintaining nocturnal sleep, which may lead to insomnia (Janssen et al., 2019). Previous studies found that negative thoracic pressure because of upper airway obstruction induces a false signal of volume overload, which causes nocturia (Chasens & Umlauf, 2003; Umlauf et al., 2004; Yalkut et al., 1996). Nocturia can lead to numerous awakenings among persons with OSA and increased time awake after sleep onset (Chasens & Umlauf, 2003).

The substantial overlap of clinical symptoms and the bidirectional relationship between these two sleep disorders indicate that they have high clinical relevance. Comorbid OSA and insomnia are associated with more significant impairments to nocturnal sleep and daytime function than insomnia or OSA alone. OSA patients with comorbid insomnia experience longer sleep latency and time awake after sleep onset and have decreased total sleep time and sleep efficiency (Krakow et al., 2001; Saaresranta et al., 2016; Smith et al., 2004). Persons with comorbid OSA and insomnia reported poorer quality of life, excessive daytime sleepiness (Björnsdóttir et al., 2012), and more cognitive and emotional complaints such as racing thoughts or ruminations about sleep, impaired behavioral alertness, depression, anxiety, and fear (Choi et al., 2015; Gooneratne et al., 2006; Krakow et al., 2001; Saaresranta et al., 2016; Smith et al., 2004). Persons with comorbid OSA and insomnia have been found to have an increased risk of having cardiovascular

and metabolic diseases compared to those who experienced each condition alone (Gupta & Knapp, 2014). Recent studies have found that comorbid OSA and insomnia also affect the treatment outcomes for each sleep disorder. Over two-thirds of insomnia patients for whom pharmacological treatments failed (over-the-counter or prescription sleeping aids) are likely to report comorbid OSA (Krakow, Ulibarri, et al., 2014; Krakow, Ulibarri, & Romero, 2010). Pre-existing insomnia symptoms among patients with OSA negatively affected their short-term (1 to 6 months) or long-term (2 years) adherence to continuous positive airway pressure (CPAP) treatment, which is the first-line treatment for OSA (Björnsdóttir et al., 2013; Pieh et al., 2013; Wickwire et al., 2010).

Although comorbid OSA and insomnia is highly prevalent and has an adverse effect on each sleep disorder's clinical symptoms and treatment, assessing insomnia or OSA among persons with each sleep disorder is not a routine recommendation (APA, 2013; Sateia, 2014). Thus, each sleep disorder is highly likely to be missed at the diagnostic stage. The understanding of the effect of comorbid insomnia and OSA on clinical consequences is still underdeveloped.

1.2.4 Type 2 diabetes mellitus (T2DM)

T2DM is the seventh leading cause of death in the United States (Centers for Disease Control [CDC], 2020). T2DM is widespread in the U.S population. The estimated cost of diagnosed diabetes (e.g., direct medical costs, indirect costs related to reduced productivity) increased from $245 billion in 2012 to $327 billion in 2017 (ADA, 2013; ADA, 2018). Considering the increase in prevalence and cost to the individual and the healthcare system, T2DM is a significant chronic disorder that needs urgent prevention and management.

T2DM is characterized by impaired glucose sensitivity, which results in elevated blood sugar levels. Glycated hemoglobin (HbA1c) is an accurate index of an average level of blood sugar

over a 2 to 3-month period. An HbA1c of 6.5% is the threshold for T2DM, and the treatment target HbA1c for T2DM is usually less than 7% (ADA, 2021). Older age, lower socioeconomic level, and African American or Hispanic race are associated with T2DM (Xu et al., 2018). The primary causes of T2DM are associated with lifestyle factors, including obesity (Zheng et al., 2018), physical inactivity (Smith et al., 2016), a sedentary lifestyle (Patterson et al., 2018), smoking (Akter et al., 2017) and alcohol consumption (Knott et al., 2015).

Delayed management of T2DM is associated with microvascular complications (e.g., nephropathy, peripheral neuropathy, and retinopathy) and macrovascular complications (e.g., cardiovascular disease). Overall, one-third of T2DM patients suffered from these complications (Einarson et al., 2018; Kosiborod et al., 2018), and T2DM patients were twice as likely to have cardiovascular disease as patients without diabetes (Hazard Ratio; HR = 2.00, 95% CI 1.83-2.19) (Sarwar et al., 2010). The risk of mortality from vascular disease among adults with T2DM was two times higher than those without T2DM (OR = 1.73, 95% CI 1.62 to 1.85) (Rao Kondapally Seshasai et al., 2011), and 10% of deaths among persons with T2DM resulted from kidney disease (Van Dieren et al., 2010). Painful peripheral neuropathy was also highly associated with poor quality of life (Girach et al., 2019).

The successful management of T2DM requires lifestyle modifications, including increasing self-management skills for T2DM to prevent diabetes complications (ADA, 2018). Self-management in T2DM is an individual's capacity to employ their knowledge, skills, and abilities toward diabetes self-care behaviors, including lifestyle modifications, self-monitoring of blood glucose, and medication administration (Powers et al., 2017). The lifestyle modifications include increased physical activity, dietary modifications, weight loss, or smoking cessation, all of which reduce the incidence of T2DM and cardiovascular complications among persons with prediabetes

conditions (e.g., impaired glucose tolerance) (Horton, 2009; Schellenberg et al., 2013). Recent systematic reviews and meta-analyses reported that diabetes self-management education significantly improved the level of HbA1c among persons with T2DM (Chrvala et al., 2016; Odgers-Jewell et al., 2017). As a result, it is clear that understanding the factors which contribute to increased incidence of T2DM and poor self-management are important for optimal diabetes management.

1.2.5 Sleep disorders in T2DM

OSA and insomnia are common sleep disorders among patients with T2DM. In several cross-sectional and prospective studies, insomnia and OSA have been associated with the prevalence and the incidence of T2DM (Ford et al., 2015; Lin et al., 2018; LeBlanc et al., 2018; Einhorn et al., 2007; Foster et al., 2009; Resnick et al., 2003; Laaban et al., 2009; Heinzer et al., 2015; Nagayoshi et al., 2016). The prevalence of OSA with AHI ≥ 5 in persons with T2DM was estimated in 2007 as approximately 71% (Einhorn et al., 2007). Among obese older adults with T2DM (mean age over 60 years old), an estimated 86% had OSA with AHI ≥ 5 (Foster et al., 2009). In a population-based sample aged 40 years or older from the baseline Sleep Heart Health Study (SHHS), the estimated prevalence of OSA with RDI ≥ 5 was greater in persons with T2DM (58%) than those without T2DM (42%) (Resnick et al., 2003). An estimated 63% of older patients hospitalized for poorly controlled T2DM suffered from OSA, as defined by RDI ≥ 5 (Laaban et al., 2009). OSA is also a risk factor for T2DM. In a population-based sample, persons with moderate or severe OSA with AHI > 20 at baseline are likely to develop diabetes at the 5-year follow-up after adjusting for age, sex, alcohol consumption and smoking, BMI, neck circumference, and waist-to-hip ratio (OR 2.00, 95% CI [1.05, 3.99]) (Heinzer et al., 2015). In

another study of middle-aged and older adults, during 13 years of follow-up, persons with greater severity of OSA were more likely to develop T2DM compared to those without OSA after adjusting for BMI and waist circumference (moderate OSA: OR = 1.28, 95% CI [0.89 – 1.84], severe OSA: OR = 1.71, 95% CI [1.08 - 2.71]) (Nagayoshi et al., 2016).

Among insomnia patients, an estimated prevalence of T2DM was 21% (Hein M et al., 2018). The prevalence of insomnia increased from 25.3% in 2002 to 32.1% in 2012 among the general population with diabetes (Ford et al., 2015). Increasing evidence also suggests that insomnia is a risk factor for T2DM. In retrospective cohort studies, the incidence rates of T2DM were significantly higher among persons with insomnia (35%) than those without insomnia (23 %) during the 10-year follow-up periods (Lin et al., 2018). Among persons with pre-diabetes, the risk of T2DM in those with insomnia was approximately 1.1 times higher (HR = 1.28, 95% CI 1.24-1.33) than in those without insomnia after adjusting for traditional T2DM risk factors (e.g., age, body mass index [BMI], race, history of cardiovascular disease, hypertension, hyperlipidemia, and smoking status) (LeBlanc et al., 2018). A meta-analysis of prospective or retrospective cohort studies found OSA (OR = 1.49, 95% CI [0.89 – 1.84]) and insomnia symptoms (difficulty initiating sleep: OR = 1.72, 95% CI [1.23 – 2.45], difficulty maintaining sleep: OR = 1.55, 95% CI [1.23 – 2.00]) had the greater risk of T2DM compared to physical inactivity (OR = 1.20, 95% CI [1.11 – 1.32]) after adjusting for BMI (Anothaisintawee et al., 2016).

OSA and insomnia are also associated with poor diabetes self-care behaviors and adverse effects on glucose metabolism. In a population-based cross-sectional study, compared with persons with no or minor sleep complaints, persons with frequent self-reported complaints of OSA or insomnia were more likely to be insulin resistant (OR = 2.18, 95% CI 1.33-3.59) with higher levels of 120-min insulin and 120-min glucose concentration on oral glucose tolerance tests (OGTT)

(Pyykkönen et al., 2012). Cross-sectional studies reported that increased OSA severity is associated with poorer glycemic control in patients with T2DM. The level of HbA1c gradually increased with increased OSA severity (mild, moderate, and severe) ($p < .014$) (Pillai et al., 2011). Compared to the adjusted mean HbA1c in patients without OSA, the adjusted mean HbA1c was increased by 1.5% in those with mild OSA ($p = .003$), 1.9% in those with moderate OSA ($p = .003$), and 3.7% in those with severe OSA ($p < .0001$) (Aronsohn et al., 2010). In a community-based sample of middle-aged persons with OSA (n = 2,656) from the SHHS, persons with moderate or severe OSA had an increased risk of having higher levels of fasting glucose (moderate OSA: OR = 1.27, 95% CI 0.92-1.64, severe OSA: OR = 1.46, 95% CI 1.09-1.91, p < .009) and 2-hour glucose (moderate OSA: OR = 1.09, 95% CI 0.88-1.35, severe OSA: OR = 1.44, 95% CI 1.11-1.87, p < .01) compared to those without OSA, after controlling for age, gender, race, BMI, waist circumference, and sleep duration; and the severity of OSA was also positively associated with increased insulin tolerance (Punjabi et al., 2004). Another study also using a community-based sample from the SHHS reported that persons with OSA (n = 2,588) independently increased the risk of impaired fasting glucose and glucose tolerance regardless of obesity status (overweight/obese or normal weight) (OR = 1.4, 95% CI 1.1-1.8) (Seicean et al., 2008). A randomized control trial (n = 50) suggested that CPAP for 6 months significantly improves HbA1c (group difference = -0.4, 95% CI -0.7- -0.04, p =.029) and insulin resistance (group difference = -2.58, 95% CI -4.75- -0.41, p =.023) to a greater degree than the intervention for the control group among patients with OSA and T2DM (Martínez-Cerón et al., 2016). Among patients with OSA, higher levels of AHI had a negative impact on physical activity ($\beta = -64.25$, p <.01) (Chasens et al., 2011), which hinders diabetes self-management.

In a community-based sample of middle-aged adults, insomnia symptoms including difficulty initiating sleep (not falling asleep within 30 min), difficulty maintaining sleep (waking up during sleep over 30 min), and sleep efficiency < 80% were associated with higher levels of fasting glucose and greater insulin resistance in patients with T2DM (Knutson et al., 2011). Among patients with T2DM, those with insomnia were associated with higher fasting glucose and HbA1c levels than those without insomnia (Ding et al., 2019). Insomnia symptoms were also significantly associated with worse attitudes on diabetes self-care behaviors. Patients with T2DM and insomnia symptoms showed worse scores on diabetes self-care behaviors (e.g., the ability of care including weight control, dietary modification, physical activity, medication adherence; the standardized total Diabetes Care Profile [DCP] score = -0.30 ± 0.46) compared to those with T2DM and no insomnia symptoms (the standardized total DCP score = 0.36 ± 0.48, $p < .001$) (Alshehri et al., 2020). Data from a pilot intervention study (n = 28) suggested that cognitive behavioral therapy for insomnia (CBT-I), which is a recommended treatment for insomnia, significantly improved the level of HbA1c ($p = .02$) and diabetes-self care behaviors ($p = .03$), whereas the control intervention did not result in any significant improvement (Alshehri et al., 2020). Because insomnia and OSA have a robust relationship with the incidence of T2DM and are associated with adverse outcomes in general and clinical populations, these two sleep disorders should be considered potential barriers to effective diabetes management in persons with T2DM.

1.2.6 Psychological health in T2DM: Mood disturbances and diabetes-related distress

According to ADA, addressing psychological symptoms should be incorporated into diabetes care because mood disturbances such as depression, anxiety, and diabetes-related distress traditionally have been associated with poor diabetes self-management behaviors and poor glucose

outcomes (Young-Hyman et al., 2016). Depressive symptoms and diabetes-related distress are commonly reported as psychological symptoms in patients with T2DM. According to the findings of a meta-analysis, the estimated global prevalence of depression in patients with T2DM was 28% (95% CI 27-29) (Khaledi et al., 2019), and depression was twice as prevalent in persons with diabetes as in the general population regardless of the type of diabetes (OR = 2.0, 95% CI 1.8-2.2) (Anderson et al., 2001). In multiple large scales of longitudinal studies, persons with depression also had an increased risk of developing T2DM. In an epidemiological study (n = 6,190), persons with a high number of depressive symptoms increased the risk of developing diabetes over 15 years compared with those with a low number of depressive symptoms (Relative risk; RR = 2.19, 95% CI [1.31 – 3.68]) (Carnethon et al., 2003). A similar study that followed subjects over eight years (n = 33,257) reported that a history of depressive episodes was more common in persons with new-onset diabetes when compared with persons without diabetes (OR = 1.29, 95% CI [1.20 – 1.37]) (Brown et al., 2005). In a study of female participants in the Nurse's Health Study over four years (n = 282,317), those who had not been diagnosed with diabetes at baseline were more likely to develop diabetes with depressive symptoms (Arroyo et al., 2004). In a community sample of adults over 55 years old (n = 3,521), diabetes was more likely to develop in persons who had severe depression at baseline after five years (HR = 1.66, 95% CI [1.01 - 2.75]) (Campayo et al., 2010). In a large population-based sample (N = 201,575), anxiety was higher in persons with diabetes than in those without (Li et al., 2008). In the systematic review and meta-analysis study, diabetes was associated with an increased risk of having an anxiety disorder and elevated anxiety symptoms (Smith et al., 2013).

Diabetes-related distress is emotional distress explicitly related to the responsibility of diabetes management (Esbitt et al., 2013; Fisher et al., 2014) and is estimated to affect up to 49%

of persons with T2DM (Azadbakht et al., 2020; Chew et al., 2016; Perrin et al., 2017). Diabetes-related distress conceptually arises from a range of areas related to living with diabetes, such as self-management, treatment adherence, exercise, and glycemic control, and is distinct from the general emotional distress of depression (Esbitt et al., 2013; Fisher et al., 2014). However, diabetes-related distress is positively correlated with the severity of depressive symptoms (Carper et al., 2014; Fisher et al., 2010; Reddy et al., 2013). Among patients with T2DM, the rates of patients with high diabetes-related distress were significantly higher in patients with subclinical (56.3%) and clinical depression (73.6%) than in those with no depression (14.7%, $p < .001$) (Hermanns et al., 2006). In a meta-regression analysis of 55 studies, the prevalence of diabetes-related distress significantly increased with the prevalence of depressive symptoms ($p = .009$) (Perrin et al., 2017). In a longitudinal study among patients with T2DM (n = 640), previously diagnosed major depressive disorder (MDD) was a significant factor in the prediction of diabetes-related distress at 18-months follow-up among those with low diabetes-related distress at baseline (OR = 2.74 95% CI 1.05-7.14) (Fisher et al., 2009). These findings suggest that depression or depressive symptoms amplify diabetes-related distress. Depression and diabetes-related distress may have overlapping constructs, and both depression and diabetes-related distress are associated with poor self-management and glycemic control.

Piett et al. (2004) have developed a model to identify the impact of depression on diabetes care. In this model, depression is negatively associated with diabetes-specific ideation, such as coping with perceived barriers and reduced physical activity and self-care behaviors, which leads to serious physiological outcomes (e.g., poor glycemic control) for individuals with diabetes (Piette et al., 2004). In addition, from the adapted Piett's model by Robertson et al. (2012), negative emotions, including depression or depressive symptoms, and diabetes-related distress are closely

associated with diabetes self-management (e.g., diet, physical activity, blood glucose monitoring) and influence diabetes outcomes (e.g., glycemic control) (Robertson et al., 2012). The considerable evidence supports these models. Results of a meta-analysis of higher levels of depressive symptoms and diabetes-related distress predicted lower adherence to diet, medication, and physical activity (Fisher et al., 2010; Gonzalez et al., 2008). In terms of poor glycemic control, in a meta-analysis of 24 cross-sectional studies, depression was significantly associated with hyperglycemia measured by HbA1c, regardless of the types of diabetes and depression measurement (i.e., depression met diagnostic criteria or self-reported scale that measure the severity of depressive symptoms) (Lustman et al., 2000), and diabetes-related distress was positively associated with the level of HbA1c among patients with T2DM (Fisher et al., 2010; Jeong & Reifsnider, 2018). Eventually, depression and diabetes-related distress heighten the risk of various vascular complications (e.g., diabetic retinopathy, neuropathy, and cardiovascular disease) (De Groot et al., 2001; Kasteleyn et al., 2015). Therefore, to avoid adverse diabetes outcomes, it is crucial to understand mood disturbances and diabetes-related distress in T2DM.

1.2.7 Impact of insomnia and OSA on mood disturbances

A large body of evidence has demonstrated the increased prevalence of mood disturbances, notably, depression in insomnia or OSA patients, when compared to those without insomnia or OSA (Garbarino et al., 2020; Ohayon, 2003; Sharafkhaneh et al., 2005; Vandeputte & De Weerd, 2003; Wahner-Roedler et al., 2007). More recent longitudinal studies have shown that both insomnia and OSA have the potential to increase the risk of depression and the severity of depressive symptoms (Baglioni et al., 2011; Chen et al., 2013; Hein et al., 2017b; Li et al., 2016; Peppard et al., 2006). In two meta-analyses of longitudinal studies of the relationship between

insomnia and the risk of depression, insomnia significantly increased the risk of developing depression; persons with insomnia had a two times higher risk of developing depression compared to those without insomnia (Baglioni et al., 2011; Li et al., 2016). In a longitudinal study of subjects randomly selected from the population, persons who developed OSA during 4-year follow-up periods had an increased risk of developing depression compared with those who remained without OSA (OR 1.8, 95% CI 1.3-2.6). Persons with moderate or severe OSA (OR = 2.6, 95% CI 1.7-3.9) were more likely to develop depression than those without OSA (OR = 1.6, 95% 1.2-2.1) (Peppard et al., 2006), and patients with OSA at baseline had a two times higher risk of depression than those without OSA after a one-year follow-up period (HR 2.18, 95% CI 1.55-3.08) (Chen et al., 2013). The first recommended treatments for insomnia (i.e., CBT-I) and OSA (i.e., CPAP) affect reducing depressive symptoms among persons with each sleep disorder (Blom et al., 2015; Gupta et al., 2016). Thus, sleep disorders are significant factors in regulating depression.

Importantly, our integrative review (Jeon et al., 2021; Appendix D) suggested that comorbid insomnia in persons with OSA contributed to higher severity of depressive symptoms (Cho et al., 2018; Smith et al., 2004) and a higher prevalence of depression compared to those with OSA alone (Bjorvatn et al., 2014; Mysliwiec et al., 2014; Vozoris, 2012). In addition, depressive symptoms were worse in persons with either comorbid OSA and insomnia or insomnia alone than those with OSA alone (Hayley et al., 2015; Lang et al., 2017; Mysliwiec et al., 2013; Yang et al., 2011). However, among persons with insomnia, comorbid OSA did not increase depressive symptoms (Kinugawa et al., 2012; Lichstein et al., 1999; Ong et al., 2009). Overall, in persons with comorbid OSA and insomnia, comorbid insomnia may play a role in significantly increasing the incidence and severity of depressive symptoms compared to OSA.

Recent neuroimaging studies demonstrated strong connections between major depressive disorder and insomnia in neurological activities in the areas of emotional regulation (Khazaie et al., 2017; Wu et al., 2020), whereas OSA had a closer relationship with major depressive disorder in the areas of consciousness and memory than in those of emotional regulation (Huang et al., 2019; Khazaie et al., 2017). Insomnia is more likely to impair emotional processes in major depressive disorder than OSA. Our aforementioned integrative review may identify the role of insomnia as an emotional regulator among persons with comorbid OSA and insomnia, and it underscores the need to evaluate insomnia to prevent and treat depressive symptoms in persons with comorbid OSA and insomnia.

1.2.8 Summary

OSA and OSA are closely associated with diabetes self-care behaviors and glucose management among patients with T2DM. In addition, Psychological symptoms in T2DM inhibit diabetes self-care behaviors and lead to adverse glycemic outcomes. Despite OSA and insomnia being significant modifiable factors in regulating mood, the relationship between sleep disorders and mood disturbances and diabetes-related distress in T2DM is underdeveloped. The additive effect of comorbid OSA and insomnia on psychological symptoms in T2DM has never been examined.

As psychological symptoms in T2DM, mood disturbances, and diabetes-related distress inevitably become a potential threat to the quality of health among patients with T2DM, an understanding of modifiable factors of psychological symptoms in T2DM is pivotal for preventing poor self-management behaviors and adverse glycemic outcomes. A better understanding of the role of OSA and insomnia may optimize treatment options for the management of psychological

symptoms in T2DM and subsequently facilitate improved self-management behaviors and glycemic outcomes.

1.2.9 Hypothesis model

According to the existing research on sleep disorders and T2DM, sleep disorders including OSA and insomnia adversely affect diabetes self-management and glycemic control. In addition, psychological symptoms in T2DM have a relationship with poorer self-management and influence glycemic control.

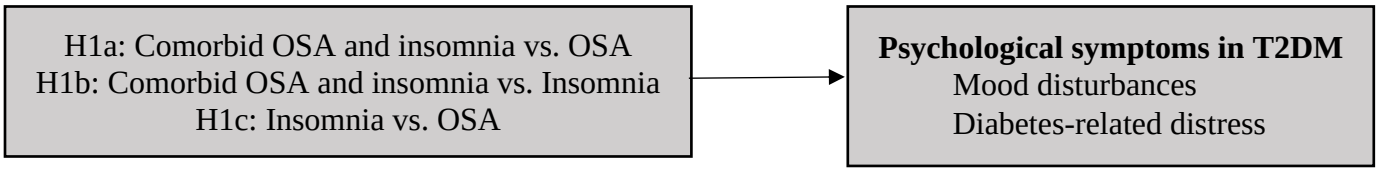
Although sleep disorders, OSA and insomnia, have an important role in regulating mood, including depressive symptoms, the role of comorbid OSA and insomnia has rarely been investigated in the context of diabetes. This study examines the effect of comorbid OSA and insomnia on mood, diabetes-related distress, and glycemic control in adults with T2DM.

To be specific, for Aim 1 (Figure 1), the hypothesis model depicts direct associations between sleep disturbance state (comorbid OSA and insomnia, OSA, insomnia) and psychological symptoms in adults with T2DM. The hypothesis of Aim 1 is that adults with comorbid OSA and insomnia will have greater mood disturbances and diabetes-related distress than those with OSA and with insomnia. Adults with insomnia will have greater mood disturbances and diabetes-related distress than those with OSA.

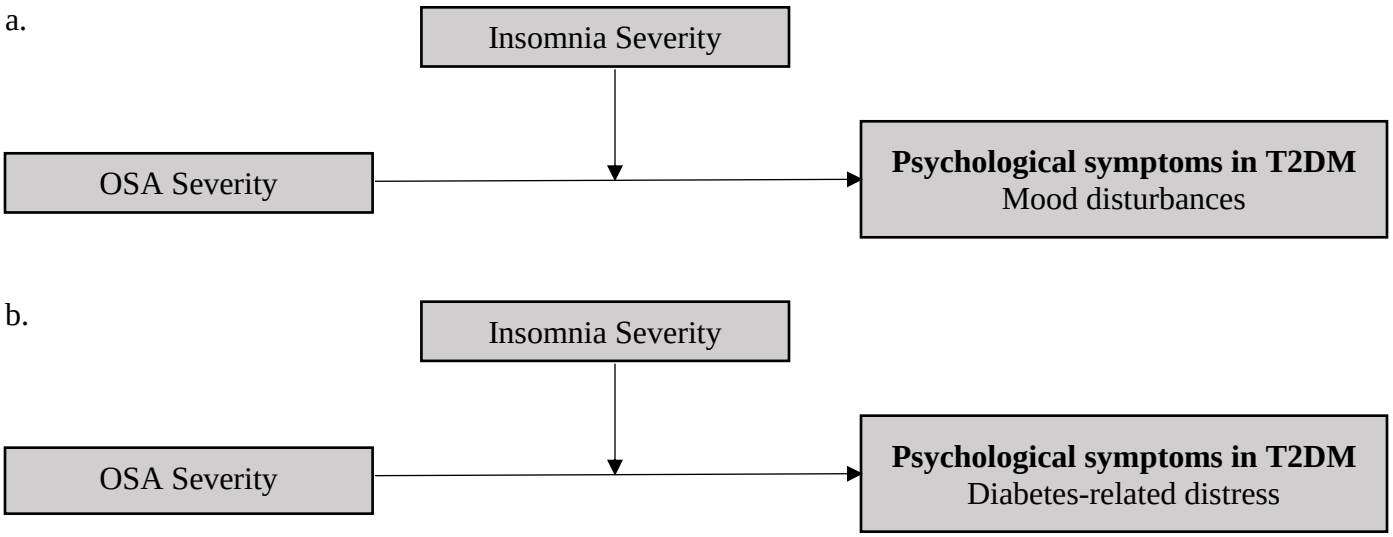
For Aim 2 (Figure 1), the hypothesis model depicts the direct association between OSA severity and psychological symptoms in T2DM and the moderating effect of insomnia severity. The hypothesis of Aim 2 is that insomnia severity moderates the association between OSA severity and psychological symptoms in T2DM.

For Aim 3, the hypothesis model the depicts a direct association between the severity of each sleep disorder (OSA, insomnia) and glucose outcome (HbA1c) and the potential mediation effect of mood disturbances and diabetes-related distress on the relationship between the severity of each sleep disorder (OSA, insomnia) and glucose outcome (HbA1c). The hypothesis for Aim 3 is that the relationship between the severity of each sleep disorder (OSA, insomnia) and glucose outcome (HbA1c) is mediated by psychological symptoms in T2DM, and the severity of each sleep disorder may still be associated with glucose outcome (HbA1c).

Aim 1.

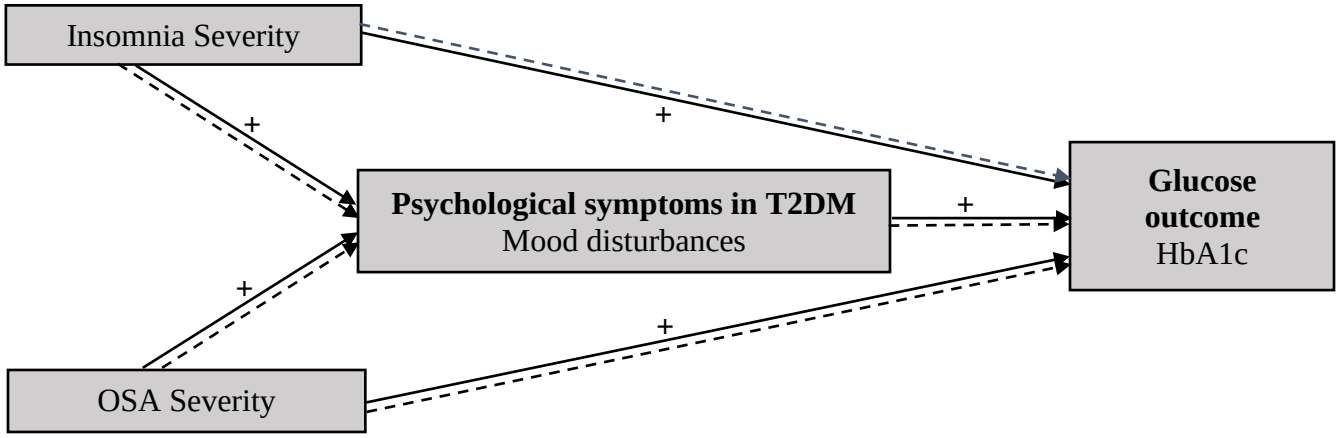


Aim 2.

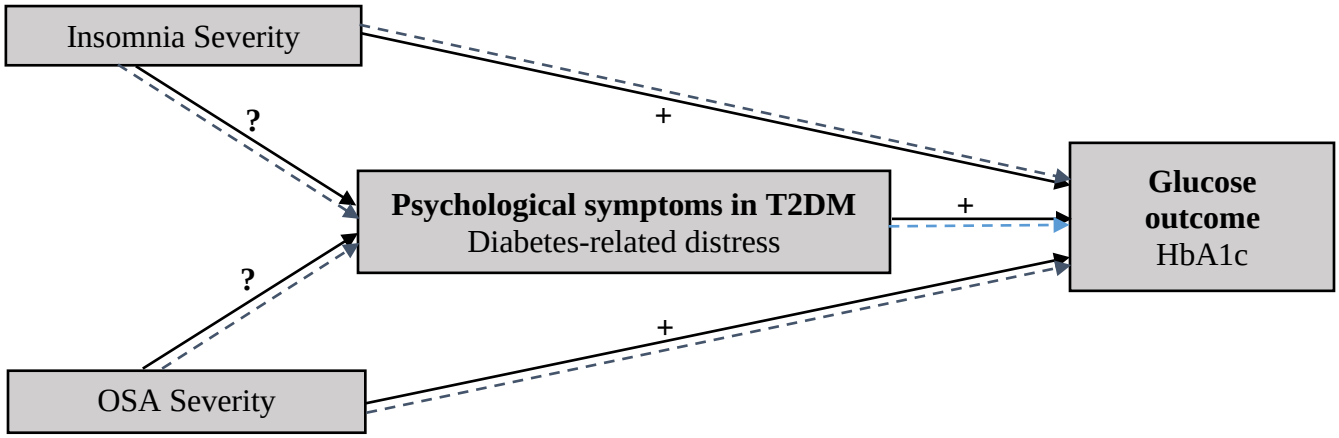


Aim 3.

a.



b.



+: Positive relationship in literature
?: Unknown relationship in literature
Dotted line: mediation pathway which are not fully understood

Figure 1. Hypothesis Model of Each Aim

1.3 Significance

This study is significant because it evaluates the independent roles of insomnia, OSA, and the joint effect of comorbid OSA and insomnia on psychological symptoms, including mood disturbances and diabetes-related distress among persons with T2DM. The effect of comorbid OSA and insomnia on persons with T2DM has never been fully examined.

Understanding modifiable factors for early detection and prevention of mood disturbances and diabetes-related distress may be significant to prevent poor adherence to self-management. This has led to an increasing focus on the impact of sleep disorders on psychological symptoms in persons with T2DM, given that there is already a close association between sleep disorders and mood disturbances.

In response to the NINR's Strategic Plan focus on self-management: improving quality of life for individuals with chronic conditions, a better understanding of the role of comorbid insomnia and OSA of psychological symptoms in T2DM would establish the evidence to develop interventions to improve self-management strategies for individuals with T2DM, which may delay the progression of T2DM.

1.4 Innovation

This study is innovative because it will identify additional strategies to manage psychological symptoms, including mood disturbances and diabetes-related distress, in patients with T2DM. Specifically, as OSA and insomnia are potential key factors to manage mood

disturbances, this study will be the first to identify and understand the role of OSA and insomnia on psychological symptoms in T2DM.

This study employs a novel and innovative methodological approach using the pooled quantitative data from two randomized control trials. Each randomized control trial compared the efficacy of treatment for OSA and insomnia in persons with T2DM. This facilitates the collection of the largest possible sample of patients with T2DM who have comorbid OSA and insomnia. This innovative study may help develop a more comprehensive understanding for providing new directions in management strategies for psychological symptoms in T2DM.

1.5 Research Design and Methods

The dissertation conducted secondary analyses to examine the role that OSA and insomnia have, individually and jointly, on mood, diabetes-related distress, and glycemic control in adults with T2DM. The pooled baseline data from two randomized controlled trials, the DSTT (R01-DK096023) and the DSTT-I (K24-NR016685), were used. The purpose of the two-parent studies was to examine the efficacy of treatment of OSA (DSTT) and insomnia (DSTT-I) on glycemic control and diabetes self-management in persons with T2DM. A full description of the DSTT premise, design, and methodology has been previously published (Chasens et al., 2019)

1.5.1 Design

1.5.1.1 Aim 1 Manuscript

Using secondary data analysis, a quantitative, cross-sectional, descriptive study was conducted to compare mood states and diabetes-related distress among three types of sleep disorder groups: comorbid OSA and insomnia (OSA+I), OSA alone, and insomnia alone in adults with T2DM (Figure 2).

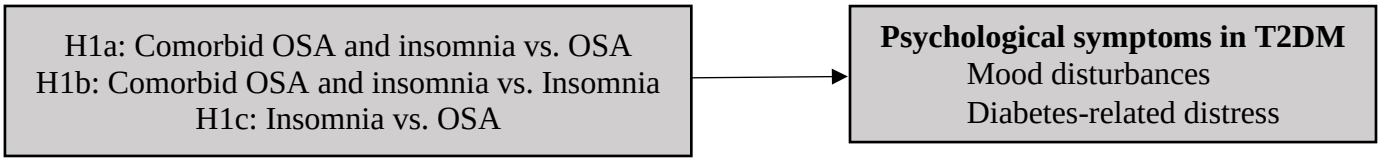


Figure 2. Hypothesis Model Illustrating Comparisons between Three Types of Sleep Disorder and Psychological Symptoms in T2DM (Aim 1)

1.5.1.2 Aim 2 Manuscript

Using secondary data analysis, a quantitative, cross-sectional, descriptive study was conducted to examine insomnia severity as a moderator of the association between OSA severity with mood states, and diabetes-related distress in adults with T2DM and OSA (Figure 3).

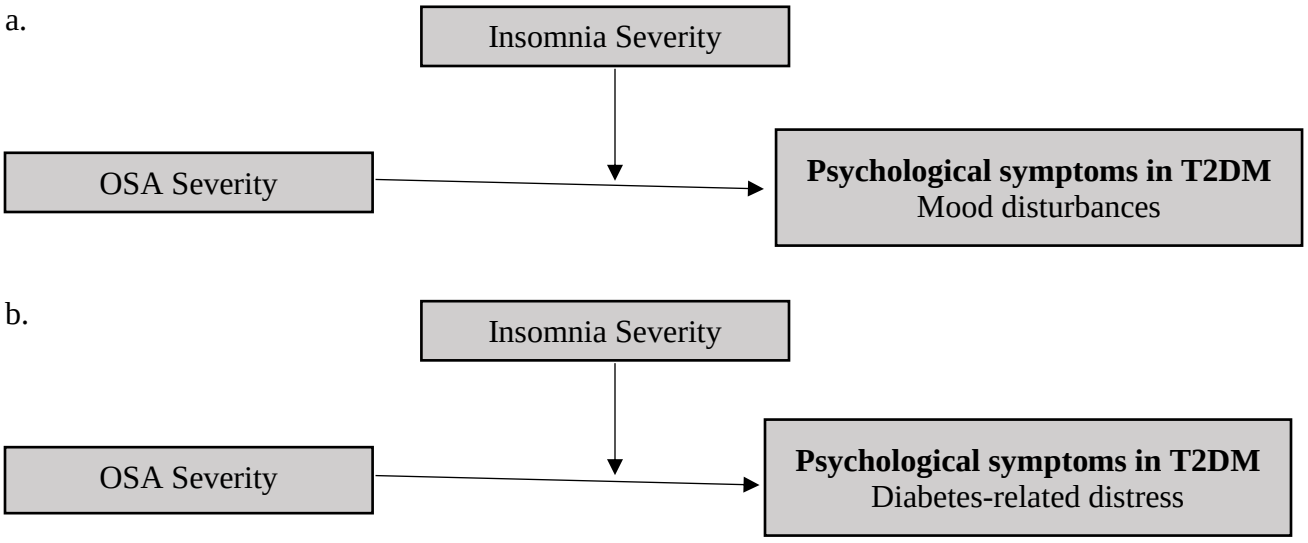
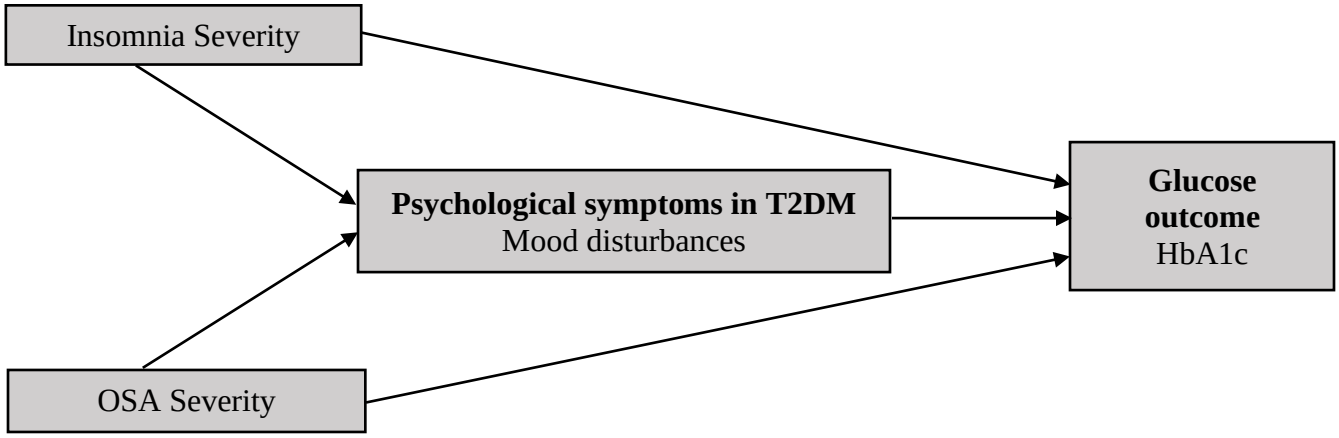


Figure 3. Hypothesis Model Illustrating Relationship between OSA and Psychological Symptoms in T2DM, as Moderated by Insomnia (Aim 2)

1.5.1.3 Aim 3 Manuscript

This secondary analysis used a quantitative, cross-sectional, descriptive study design. Aim 3 was to examine mood disturbances and diabetes-related distress as potential mediators of the association between insomnia severity with HbA1c and between OSA severity with HbA1c in adults with T2DM and OSA (Figure 4)

a.



b.

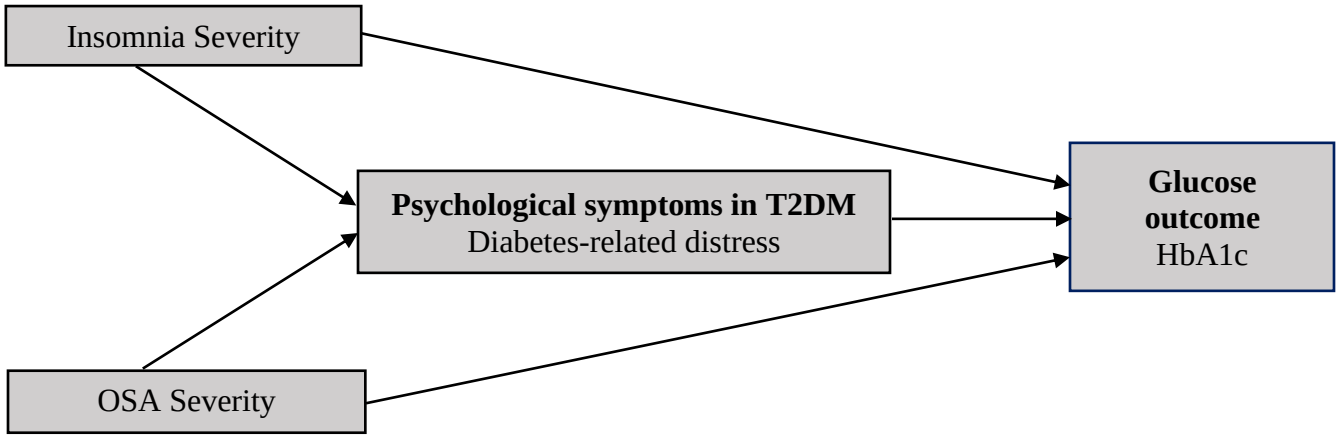


Figure 4. Hypothesis Model Illustrating Relationships between OSA and Insomnia with HbA1c, as Mediated by Psychological Symptoms in T2DM (Aim 3)

1.5.2 Sample

1.5.2.1 Aim 1 Manuscript

The DSTT was a multi-site randomized controlled trial and recruited 351 participants from the Pittsburgh community and multiple endocrinology clinics and sleep outpatient clinics (UPMC, Veterans Administration Pittsburgh Healthcare System, University of West Virginia, and John H. Dingle Veterans Administration Detroit Healthcare System) using various strategies (e.g., using focused mailing, flyers in the community, social media advertisement). The DSTT-I recruited 55 participants at one of the sites from the DSTT (UPMC) using the same strategies. The non-eligible participants from DSTT who did not have a level of AHI 10 or greater were screened for the recruitment in DSTT-I. Eligible criteria for the baseline assessment in the parent studies include self-reported diagnosis of T2DM, age 18 years or older, able to read and write English, being ambulatory, having a level of AHI 10 or greater (DSTT), or moderate-to-severe insomnia symptoms (DSTT-I). Potential participants were excluded from the parent studies if they had an acute illness requiring hospitalization in the last three months, a near-miss or automobile accident due to sleepiness, were employed in a safety-sensitive occupation, or were unwilling to be randomized. For this secondary analysis, the eligible participants should not have missing data in variables for OSA severity, insomnia severity, mood states, and diabetes-related distress, and have either OSA (AHI $\geq$ 10 events/hour) or insomnia (ISI $\geq$ 15). A total of 255 participants were eligible. The parent studies were approved by the Institutional Review Board (IRB) at each site of studies. This study was independently approved by the University of Pittsburgh IRB to combine the data from the DSTT and DSTT-I.

1.5.2.2 Aim 2 Manuscript

The data for Aim 2 was obtained from the pooled baseline data of DSTT (N = 351) and DSTT-I (N = 55). See the "Sample and Setting" section in Aim 1 for a detailed description and inclusion/exclusion criteria for the parent studies. For this secondary analysis, the eligible participants should not have missing data in variables for OSA severity, insomnia severity, mood states, and diabetes-related distress, and meet the diagnostic criteria of OSA (AHI ≥ 5 events/hour). A total of 240 participants were eligible. This study was approved by the University of Pittsburgh IRB to combine the data from the DSTT and DSTT-I.

1.5.2.3 Aim 3 Manuscript

See the "Sample and Setting" section in Aim 1 for a detailed description and inclusion/exclusion criteria for the parent studies. The eligible participants for Aim 3 are consistent with those for Aim 2. Therefore, the eligible participants should not have missing data in variables for OSA severity, insomnia severity, mood states, and diabetes-related distress, and meet the diagnostic criteria of OSA (AHI ≥ 5 events/hour). A total of 240 participants were eligible. This study was approved by the University of Pittsburgh IRB to combine the data from the DSTT and DSTT-I.

1.5.3 Measures

1.5.3.1 Aim 1 Manuscript

The baseline datasets from two-parent studies were merged to analyze as a single data set based on shared instruments and assessments. These data included: 1) records of ApneaLinkPlus®; 2) Insomnia Severity Index (ISI); 3) Profile of Mood States (POMS); 4) Problem Areas in Diabetes

(PAID); 5) Epworth Sleepiness Scale (ESS); 6) Pittsburgh Sleep Quality Index (PSQI); 7) sociodemographic information (age, gender, marital status, race, education level, financial hardship); 8) health history (insulin use status, the duration of T2DM, other sleep disorders except OSA and insomnia); and 9) clinical evaluation (HbA1c, BMI). The copies of each instrument (ISI, POMS, PAID, ESS, PSQI) are attached in Appendix A.

Key Variables.

Sleep Disturbance Status. Sleep disturbance status was defined as three types of sleep disorder groups: OSA, insomnia, and OSA+I. **OSA** was defined as the level of AHI. Persons with AHI ≥ 10 events/hour (moderate to severe OSA) were classified as having OSA. The ApneaLinkPlus® (ResMed, San Diego, CA), an approved level III device for unattended portable in-home sleep studies, was used to assess respiratory effort, nasal flow, pulse, and oxygen saturation to derive the AHI (Collop et al., 2007). Participants wore the ApneaLinkPlus® for a single night and returned the device in the pre-paid mail packet. All ApneaLinkPlus® data were reviewed by trained polysomnography (PSG) technicians according to the current published standards of the American Academy of Sleep Medicine (AASM) for scoring apnea and hypopneas (Berry et al., 2012). The ApneaLink®, an older version of ApneaLinkPlus®, was found to have 82.1% sensitivity and 83.9% specificity for screening of OSA with AHI ≥ 10 events/hour compared with polysomnography (PSG) (Erman et al., 2007).

Insomnia was defined as the level of ISI. Persons who had ISI ≥ 15 were classified as having insomnia. The ISI is a 7-item self-report questionnaire with a 5-point Likert scale from '0 = no problems' to '4 = very severe problem', measuring the severity and impact of insomnia symptoms. The higher overall score indicates worse insomnia symptoms. The ISI is highly reliable in a clinical sample with insomnia with a Cronbach $\alpha = 0.91$ (Morin et al., 2011). The sensitivity

and specificity of the ISI for screening insomnia with ISI ≥ 15 were 78.1% and 100%, respectively, against the diagnosis derived from a clinical interview in a clinical sample (Morin et al., 2011).

Persons who met both OSA and insomnia criteria were classified as having OSA+I. Therefore, **OSA+I** was defined as AHI ≥ 10/events/hour and ISI ≥ 15.

Mood States. Mood states were measured by the POMS. The POMS (McNair & Heuchert, 2007) is a self-report questionnaire with a set of 65 adjectives (e.g., friendly, tense, shaky, confused, etc.) or phrases (e.g., sorry for things done, unable to concentrate, ready to fight, etc.) related to the six dimensions of mood; Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. Each item was rated on a 5-point Likert scale from '0 = Not at all' to '4 = Extremely'. The five subscales suggest negative dimensions of mood (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Fatigue-Inertia, and Confusion-Bewilderment), and one subscale (Vigor-Activity) represents the positive dimension of mood. Higher scores of each dimension of mood except vigor-activity indicate greater negative moods. The POMS Total Mood Disturbance (TMD) score is calculated by subtracting the score of Vigor-Activity (positive mood) from the sum of the other five dimensions of mood (negative moods). Higher POMS TMD scores indicate greater mood disturbances. The POMS has been validated to be sensitive to change following treatment for OSA and insomnia patients (Haensel et al., 2007; Morin et al., 1990), and the six POMS subscales are internally consistent with the POMS TMD score (Cronbach's α = .84) (McNair & Heuchert, 2007).

Diabetes-related Distress. Diabetes-related distress was measured by the PAID. The PAID (Polonsky et al., 1995) is a 20-item self-reported questionnaire to evaluate emotional distress associated with diabetes management among persons with T2DM. Each item is rated on a 5-point Likers scale from '0 = No a problem' to '4 = Serious problem'. The total score is calculated by

summing all scores and multiplying the total by 1.25. A higher total score indicated greater diabetes-related distress. A total score ≥ 40 indicates emotional burnout. (Miller & Elasy, 2008). The PAID is highly reliable in a clinical sample with T2DM with a Cronbach α = 0.94 (Miller & Elasy, 2008). The PAID has been validated to be sensitive to detecting changes in emotional distress in diabetes patients after receiving educational and psychosocial interventions (Polonsky et al., 1995; Welch et al., 1997).

Secondary Variables.

These variables were used to describe the sample and serve as potential covariates in the analyses.

Sociodemographic and Clinical Information. Sociodemographic information included age (years), gender (male vs. female), marital status (married/partnered vs. single/divorced/widowed), race (non-White vs. White), an education level (< 2-year degree of college or technical training vs. ≥ 2-year degree of college or technical training), and financial hardship (no difficulty to meet their needs vs. having somewhat/extremely difficulty to meet their needs).

Sleep-related clinical information included daytime sleepiness, measured by the ESS, and Sleep quality, measured by the PSQI. The ESS (Johns, 1991) is an 8-item self-reported questionnaire to rate the likelihood of falling asleep in common situations of daily living. Higher ESS scores indicate greater daytime sleepiness; a score greater than 10 indicates excessive daytime sleepiness. The PSQI (Buysse et al., 1989) is a 19-item self-reported questionnaire to evaluate sleep quality. Higher PSQI scores indicate worse sleep quality; a score greater than 5 indicates poor sleep quality. Participants answered the history of restless leg syndrome (yes/no).

Diabetes-related clinical information included insulin use (yes/no), duration of T2DM (years), HbA1c (%), and body mass index (BMI; kg/m^2). A blood sample (no more than 30cc) was

collected by the research staff to get the value of HbA1c. Measured height and weight were used to calculate BMI.

1.5.3.2 Aim 2 Manuscript

Primary measurements included the records of ApneaLinkPlus®, those of the ISI, PAID, and POMS. Secondary measures included sociodemographic and clinical information. (See Appendix A for the copies of each instrument)

Key Variables.

OSA Severity. OSA severity was a primary independent variable. A portable sleep testing device, the ApneaLinkPlus® (ResMed, San Diego, CA), was used to assess OSA severity as measured by the AHI. The ApneaLinkPlus® is an FDA-approved level III device for unattended portable in-home sleep studies (Collop et al., 2007). Participants wore the ApneaLinkPlus® for a single night and returned the device in the pre-paid mail packet. All ApneaLinkPlus® data were reviewed by trained polysomnography (PSG) technicians according to the current published standards of the American Academy of Sleep Medicine (AASM) for scoring apnea and hypopneas (Berry et al., 2012). The higher AHI indicates higher OSA severity. OSA severity was presented as a continuous variable.

Insomnia Severity. Insomnia severity was a moderator variable. The ISI was used to measure insomnia severity. The ISI (Morin, 2011) is a 7-item self-report questionnaire. A 5-point Likert scale is used to rate each item from '0 = no problems' to '4 = very severe problem. A total score ranges from 0 to 28. The higher overall score indicates worse insomnia symptoms. Insomnia severity was presented as a continuous variable.

Mood states. Mood states, measured by the POMS, was the first primary dependent variable. The POMS (McNair & Heuchert, 2007) assessed six dimensions of mood based on a set of 65

adjectives or phrases: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. Each item was rated on a 5-point Likert scale from '0 = Not at all' to '4 = Extremely'. The POMS TMD score was computed by adding the five negative subscale scores (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Fatigue-Inertia, and Confusion-Bewilderment) and subtracting the Vigor-Activity score. Higher POMS TMD scores indicate a greater degree of mood disturbances. Mood states was presented as a continuous variable.

Diabetes-related Distress. Diabetes-related distress was the second primary dependent variable. The PAID (Polonsky et al., 1995), a 20-item self-report questionnaire, was used to evaluate the diabetes-related distress of patients with diabetes. Each item is scored from '0 = Not a problem' to '4 = Serious problem'. The sum of all item scores is multiplied by 1.25 to derive the total score, which can range from 0 to 100. Higher total scores indicate greater emotional distress, and 40 or above indicates severe emotional distress (Miller & Elasy, 2008). Diabetes-related distress was presented as a continuous variable.

Secondary Variables.

These variables were used to describe the sample and potential covariates in the analysis.

Sociodemographic and Clinical Information. Participants answered questions regarding their age (years), gender (male vs. female), marital status (married/partnered vs. single/divorced/widowed), race (non-White vs. White), an education level (< 2-year degree of college or technical training vs. ≥ 2-year degree of college or technical training), and financial hardship (no difficulty to meet their needs vs. having somewhat/extremely difficulty to meet their needs).

For sleep-related clinical information, daytime sleepiness and sleep quality were measured by the ESS and the PSQI, respectively. Higher ESS scores indicate greater daytime sleepiness;

scores > 10 indicate excessive daytime sleepiness (Johns, 1991). Higher PSQI scores indicate worse sleep quality; scores > 5 indicate poor sleep quality (Buysee et al., 1989). Participants answered the history of restless leg syndrome (yes/no).

For diabetes-related clinical information, participants answered questions regarding insulin use (yes/no), duration of T2DM (years). Measured height and weight were used to calculate body mass index (BMI; kg/m^2). A blood sample (no more than 30cc) was collected by the research staff to get the value of HbA1c.

1.5.3.3 Aim 3 Manuscript

Primary measurements included the records of ApneaLinkPlus®, those of the ISI, PAID, POMS, and HbA1c. Secondary measures included sociodemographic and clinical information. See Appendix B for the copies of each instrument.

Key Variables.

OSA severity (i.e., the AHI) and insomnia severity (i.e., the ISI score) were independent variables. Mood states (i.e., the POMS TMD score) and diabetes-related distress (i.e., the PAID score) are mediator variables. See the "Measures" section in Aim 2 for detailed descriptions of OSA severity, insomnia severity, mood states, and diabetes-related distress (i.e., the PAID).

Glucose outcome was a dependent variable. Glucose outcome was measured by HbA1c. HbA1c offered a reliable indication of average glycemic control over the past 2 to 3 months. A blood sample (no more than 30cc) was collected by the research staff to get the value of HbA1c.

Secondary Variables.

These variables were used to describe the sample and as potential covariates in the analysis. See the "Measures" section in Aim 2 for detailed descriptions of sociodemographic, sleep-related

clinical information. Diabetes-related clinical information included insulin use (yes/no), duration of T2DM (years), and body mass index (BMI; kg/m^2).

1.5.4 Procedure

1.5.4.1 Aim 1 Manuscript

In both parent studies, brief in-person or telephone interviews were performed to screen participants who met the initial eligibility criteria for baseline assessment. At the baseline assessment, written informed consent was obtained. Anthropometric measures (i.e., height, weight) and blood samples were obtained. Participants were instructed how to wear and return the ApneaLinkPlus®. The ApneaLinkPlus® device was returned by pre-paid mail packet the next day. The baseline questionnaires were returned by the pre-paid mail packet after seven days. Data from the validated ApneaLinkPlus® and baseline questionnaires were stored in a secure server at the University of Pittsburgh.

1.5.4.2 Aim 2 Manuscript

See the "Procedure" section for Aim 1 for a details data collection procedure for parent studies. This secondary analysis was conducted for adults with T2DM and OSA. As the diagnostic criteria for OSA is a level of AHI 5 or more, those who did not meet the diagnostic criteria were excluded from the analysis.

1.5.4.3 Aim 3 Manuscript

This secondary analysis was conducted for adults with T2DM and OSA, who were consistent with Aim 2. As the diagnostic criteria for OSA is a level of AHI 5 or more, those who did not meet the diagnostic criteria were excluded from the analysis.

1.5.5 Statistical Analysis

1.5.5.1 Aim 1 Manuscript

Before analyses, the amount of and patterns of missing data were screened in the total 406 participants' data (N = 351 from the DSTT; N = 55 from the DSTT-I). Preliminary analyses for eligible participants in Aim 1 (N = 255) were performed. The univariate and bivariate data distributions were checked to determine if the data were distributed normally. To evaluate whether data were missing completely at random (MCAR), Little's test was performed, and the characteristics between eligible and excluded participants were compared (the independent sample t-test for continuous variables; Chi-square (χ^2) test of independence for categorical variables). Covariates were age, gender, marital status, race, education level, and financial hardships based on the literature (Faber-Wildeboer et al., 2013; LeBron et al., 2013; Pintaudi et al., 2015). The Eta Coefficient test measures the statistical associations between categorical and continuous variables. Financial difficulty was found to have significant bivariate associations with mood states and diabetes-related distress by the Eta Coefficient test. The unstandardized coefficient of sleep disorder groups was changed to greater than 10% by adding financial difficulty in the linear regression model of sleep disorder groups with mood states, and diabetes-related distress.

Descriptive statistics included means, standard deviation, median, interquartile range, frequencies, and percentages. The characteristics among OSA+I, OSA, and insomnia groups were

compared using chi-square of independence (for nominal variables) and one-way analysis of variance (ANOVA; for continuous variables). Bonferroni or Games-Howell (if the assumption of homogeneity of variance was violated) post-hoc pairwise comparisons of the three types of sleep disorders were performed for continuous variables, which were found to be significantly different between three types of sleep disorders in ANOVA.

A one-way analysis of covariance (ANCOVA) was performed to examine whether mood states (i.e., the POMS TMD score) and diabetes-related distress (i.e., PAID score) were significantly different between the three types of sleep disorders (i.e., Comorbid OSA and insomnia, OSA, insomnia) after controlling for the covariates. To determine where a significant mean difference existed among the three types of sleep disorders, this was followed by pairwise comparisons with a Bonferroni adjustment to the significance level.

The statistical assumptions were met in the one-way ANCOVA models for POMS TMD score and PAID score, except for the assumption regarding the normality of residuals. Because the distribution of the studentized residual for the POMS TMD score was positively skewed with multiple outliers, a square root transformation was applied. The scores of two outliers identified from the studentized residuals for the PAID score were altered to the next highest non-outlier value. Comparing the results with the transformed variables and those with original variables, the skewness of residuals and outliers did not substantially affect the results in the models for POMS TMD and PAID. The one-way ANCOVA is fairly robust to violation of normality. Therefore, one-way ANCOVA was performed with original variables regardless of the violation of normality assumption and outliers. For all fitted one-way ANCOVA models, potential influential observations were assessed by the scatter plot between studentized deleted residual and centered leverage value; these influential cases did not change the statistical significance of the results.

Differences in the six dimensions of mood state (i.e., the subscale scores of Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment) among the sleep disorder groups were analyzed by one-way multivariate analysis of covariance (MANCOVA) after controlling for the covariates. One-way ANCOVA and pairwise comparisons with Bonferroni adjustment were performed to determine which dimensions of mood states were significantly different between the three types of sleep disorders.

With the exception of the Vigor-Activity and the Fatigue-Inertia subscale scores, the distributions of the standardized residual for the other subscale scores were positively skewed with multiple univariate outliers. Multivariate outliers, assessed by Mahalanobis distance ($p > .001$), were also found in the overall one-way MANCOVA model. The standardized residuals of the four subscale scores had better distribution after applying a square root transformation. However, several outliers were still found, and the one-way MANCOVA is fairly robust to violation of normality. Therefore, the original variables were used in our analysis. All analyses were performed using SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY), and the level of statistical significance for two-sided hypothesis testing was set at .05.

1.5.5.2 Aim 2 Manuscript

Preliminary analyses for eligible participants in Aim 2 (N = 240) were performed. The univariate and bivariate data distributions were checked to determine if the data were distributed normally. To evaluate the randomness of missing data, Little's MCAR test was performed, and the characteristics of eligible and excluded participants were compared (the independent sample t-test for continuous variables; chi-square (χ^2) test of independence for categorical variables). Covariates were age, gender, marital status, race, education level, and financial hardships based on the literature (Faber-Wildeboer et al., 2013; LeBron et al., 2013; Pintaudi et al., 2015). In

addition, financial difficulty and education level were found to have significant bivariate associations with mood states and diabetes-related distress by the Eta Coefficient test. The unstandardized coefficients of the severity of sleep disorders (i.e., OSA and insomnia severity) were changed by greater than 10% by adding financial difficulty in the linear regression model of the severity of sleep disorders with mood states and diabetes-related distress. Descriptive analyses were performed for all analyses. The descriptive statistics included means, standard deviation, median, interquartile range, frequencies, and percentages.

The hierarchical multiple regression analysis was performed to examine the moderator role of insomnia severity (i.e., the ISI score) on the relationship between OSA severity (i.e., the AHI) and mood states (i.e., the POMS TMD score). It was also performed to examine the moderator role of insomnia severity on the relationship between OSA severity and diabetes-related distress (i.e., the PAID score) while controlling for the covariates. Covariates were age, gender, marital status, race, education level, and financial hardships. In each model, the covariates were entered into the analysis during the first step. The independent variable, OSA severity, was entered into the analysis during the second model. The moderator variable, insomnia severity, was entered into the regression equations for the third step. In the fourth step, the interactions of independent and moderator variables, OSA severity x insomnia severity, were entered into the regression model. For step four, a significant change in R^2 for the interaction term indicated a significant moderator effect.

The statistical assumptions (no violation of homoscedasticity and multicollinearity) were met, except for the assumptions regarding the normality of residuals and the linearity between independent and dependent variables in the hierarchical linear regression models. Because the distribution of the studentized residual for the POMS TMD score was positively skewed, a square

root transformation was applied to the POMS TMD score. The score of one outlier in the studentized residual for the PAID score was altered to be close to the next highest non-outlier value. Comparing the results with the transformed variables and those with original variables, the skewness of residual and outliers did not substantially affect the results in the hierarchical linear regression models. As the AHI had a weak association with the POMS TMDS score and PAID score, a logarithmic transformation was applied to the value of AHI. However, the VIF values for the ISI score and the interaction term were greater than 10 with log-transformed AHI in the models. In the regression analysis, the variance inflation factor (VIF) value of 10 or more shows a multicollinearity problem (Hayes, 2018). Using the log-transformed AHI was not appropriate. Before the analyses, mean centering was applied to OSA severity and insomnia severity variables to minimize multicollinearity between these variables and their interaction term. The VIF values with original variables were less than 10. This indicates that there were no problems with multicollinearity. Overall, the hierarchical linear regression was performed with original variables. For all fitted hierarchical linear models, potential influential observations were assessed by the scatter plot between studentized deleted residual and centered leverage value. In the models for POMS TMD scores, two influential cases changed the significance of the interaction term. However, these cases are theoretically significant in the patient population (e.g., those with extremely severe insomnia without OSA). All cases were included for hierarchical linear regression.

To examine the moderator role of insomnia severity on the relationship between OSA severity and the six dimensions of mood states (i.e., the subscale scores of Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment), the multivariate linear regression analysis was performed while controlling for the

covariates. Wilks' lambda (λ) test measured the overall model fit, and multiple linear regression analyses for each subscale score were followed. The distributions of the studentized residual for Depression-Dejection and Anger-Hostility subscale scores were positively skewed with multiple outliers; a square root transformation was applied to these subscale scores. Comparing the results with the transformed variables and those with original variables, the skewness of residual and outliers did not substantially affect the results. Therefore, the original Depression-Dejection, Anger-Hostility scores were used regardless of the violation of normality assumption and outliers. All analyses were performed using SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY), and the level of statistical significance for two-sided hypothesis testing was set at .05.

1.5.5.3 Aim 3 Manuscript

For preliminary analyses, see the "Data Analysis" section in Aim 2. Covariates were age, gender, marital status, race, education level, and financial hardships based on the literature (Faber-Wildeboer et al., 2013; LeBron et al., 2013; Pintaudi et al., 2015). Financial difficulty and education level were found to have significant bivariate associations with mood states and diabetes-related distress by the Eta Coefficient test, and age had significant bivariate associations with mood states, diabetes-related distress, and HbA1c by Pearson's correlation test. All analyses were conducted using SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY) and PROCESS version 3.5 (Hayes, 2018). To check the statistical assumptions (no violation of normality, linearity, homoscedasticity, and multicollinearity), the multiple linear regression was performed after controlling for all covariates. In the first model, OSA severity (i.e., the AHI), insomnia severity (i.e. the ISI), and mood states (i.e., the POMS TMD score) were independent variables. Diabetes-related distress (i.e., the PAID score) was included as an independent variable in the second model along with OSA and insomnia severity. Glucose outcome (i.e., HbA1c) was a

dependent variable. There were weak linear associations between the AHI and HbA1c, and between the POMS TMD score and HbA1c. A log transformation was applied to the value of AHI and HbA1c. However, the linearity with the transformed variables did not significantly improve the linearity. Overall, the medication analyses were performed with original variables.

For mediation analyses, PROCESS (model 4) with bootstrapping (10,000 samples) was used to estimate the direct (OSA severity predicting glucose outcome; insomnia severity predicting glucose outcome) and indirect effects of the independent variable (OSA severity, insomnia severity) on the dependent variable (glucose outcome) via mediators (mood states or diabetes-related distress) while controlling for all covariates. In each mediation model, OSA severity and insomnia severity were simultaneously included as the independent variables. The direct and indirect effects of one independent variable are interpreted when the remaining independent variable is considered as a statistical control. If the indirect effects of OSA or insomnia severity are significant, mood states or diabetes-related distress are shown to mediate the association between OSA or insomnia severity with glucose outcome. The level of statistical significance for two-sided hypothesis testing was set at .05 and a 95% confidence interval (CI) not crossing zero indicates the significant indirect effect.

1.6 Potential Limitations and Alternative Approaches

The primary purpose of this proposed study is to examine the role that OSA and insomnia have, individually and jointly, on mood states, diabetes-related distress, and glycemic control in adults with T2DM. Although this study is the first data-driven examination of the independent roles of OSA, insomnia, and the effect of comorbid OSA and insomnia on mood disturbances,

diabetes-related distress, and glycemic control among persons with T2DM, there are potential methodological limitations associated with study outcomes. First, due to the nature of secondary analysis using the existing data, the two-parent studies were not designed and implemented to address the purpose and aims of this proposed study. This can be problematic because the recruited participants for the two-parent studies may not be reflective of those patients population with OSA or insomnia, and mood disturbances. In both parent studies, the participants with current hypnotic medications were excluded and, in DSTT, those who received CPAP treatment for OSA were excluded for baseline assessment. This may underestimate persons who have severe insomnia and OSA in the proposed study. In addition, eligible participants for baseline assessment did not have an acute illness requiring hospitalization, including serious psychiatric conditions in parent studies. This also may underestimate the persons with severe mood disturbances. However, this limitation may have mitigated the bias regarding the effect of treatment and medication, which can alter sleep and psychological conditions in this proposed study. Second, due to the nature of the cross-sectional study design, we cannot confer possible causal relationships between the variables. Future randomized controlled trials to examine the effect of sleep interventions on mood disturbances, diabetes-related distress, and glucose outcomes are needed to confirm the causality.

Measurement can be another issue because the diagnosis of insomnia can be underestimated. In parent studies, the participants who did not have enough recording time for ApneaLinkPlus® (< 4 hours/night) were excluded from the baseline assessment. Therefore, participants who suffer from insomnia with a short sleep duration (< 4 hours/night) may be misclassified. As alternative approaches in future studies, it would be better to use the different devices for the home sleep studies that can validate sleep status regardless of sleep duration. For example, the Nox-A1 PSG system (Nox Medical, Reykjavik, Iceland) is intended for home

unattended sleep PSG and is feasible to diagnose moderate to severe OSA. (Yoon et al., 2019). The WatchPAT® (Itamar Ltd, Israel) device is another home unattended sleep PSG, which was clinically validated in comparative studies with PSG (Yalamanchali et al., 2013). The parent studies used a self-report approach using the ISI questionnaire to measure insomnia severity. However, insomnia can be defined as multiple aspects of sleep such as sleep duration, sleep latency, sleep efficiency, and sleep quality. Therefore, it is important to understand comprehensive insomnia-related symptoms in persons with T2DM for the targeted treatment.

Another limitation of this study is that the participants may have other factors that affect their sleep such as peripheral diabetic neuropathy, which is associated with restless leg syndrome (Akın et al., 2019). However, this limitation was minimized in the proposed study because restless leg syndrome was statistically controlled in all analyses.

1.7 Publications

Referred Articles * = Data Based

1. ***Jeon, BM.**, & Choi-Kwon, SM. (2017). Factors influencing sleep disturbances among older adults living within a community. *Korean Journal of Adult Nursing*. *29*(3), 235-245.
2. ***Jeon, B.**, Sereika, S. M., Callan, J. A., Luyster, F. S., DiNardo, M. M., & Chasens, E. R. (2020). Age-related differences in mood, diabetes-related distress, and functional outcomes in adults with type 2 diabetes mellitus and comorbid obstructive sleep apnea and insomnia. *The Diabetes Educator*. *46*(6), 540-551. https://doi.org/10.1177/014572172095839

3. **Jeon, B.**, Luyster, F. S., Callan, J.A., & Chasens, E.R. (2021). Depressive symptoms in comorbid obstructive sleep apnea and insomnia: An integrative review. *Western Journal of Nursing Research*. *43*(11), 1061-1072. http://doi.org/10.1177/019394592198965
4. Chasens, E. R., Imes, C. C., Kariuki, J. K., Luyster, F. S., Morris, J.L., DiNardo, M. M., Godzik, C. M., **Jeon, B.**, & Yang, K. (2021). Sleep and metabolic syndrome. *Nursing Clinics of North America*. *56*(2), 203-217. https://doi.org/10.1016/j.cnur.2020.10.012
5. ***Jeon, B.**, Luyster, F. S., Sereika, S. M., DiNardo, M. M., Callan, J. A., & Chasens, E. R. (2022). Comorbid obstructive sleep apnea and insomnia and its association with mood and diabetes-related distress in type 2 diabetes mellitus. *Journal of Clinical Sleep Medicine*. *18*(4), 1103-1111. https://doi.org/10.5664/jcsm.9812
6. *Morris, J. L, Belcher, S. M., **Jeon, B.**, Godzik, C. M., Imes, C. C., Luyster, F. S., Sereika, S. M., Scott, P. W., & Chasens, E. R. (2021). Financial Hardship and its Associations with Perceived Sleep Quality in Participants with Type 2 Diabetes and Obstructive Sleep Apnea. Chronic Illness. Advanced online publication. https://doi.org/10.1177/17423953211065002
7. *Baniak, L. M, Chasens, E. R., Imes, C. C., **Jeon, B.**, Shi, X., Strollo, P. J., & Luyster, F. S. (2021). Sleep Problems and Associations with Cardiovascular Disease and All-Cause Mortality in Asthma-COPD Overlap: Analysis of the National Health and Nutrition Examination Survey (2007-2012). Journal of Clinical Sleep Medicine. Advanced online publication. https://doi.org/10.5664/jcsm.9890

Articles in Progress * = Data Based

1. *Wilckens, K. A., Jeon, B., Morris, J. L., Buysse, D. J., Chasens, E. R. Effects of CPAP treatment on sleep architecture in adults with obstructive sleep apnea and type 2 diabetes.

Selected Presentations

1. **Jeon, B.**, Baniak, L. M., Zheng, Y., Sereika, S. M., Atwood, C. W., Strollo, P.J., Stansbury, R., Chasens, E. R. (2019, June). *Comparison of sleep quality and functional outcomes between younger and older adults with comorbid obstructive sleep apnea and insomnia.* Poster presentation at Sleep 2019 Annual Meeting. San Antonio, TX.
2. Zheng, Y., Korytkowski, M., Sereika, S. M., Burke, L. E., Atwood, C. W., Strollo, P. J., Stansbury, R., **Jeon, B.**, Chasens, E. R. (2019, June). *Association between insomnia and insulin adherence.* Poster presentation at the 79th American Diabetes Association Scientific Sessions. San Francisco, CA.
3. **Jeon, B.**, Luyster, F. S., Chasens, E. R. (2020, August). *Associations between circadian preference and sleep-related thoughts: Data from the 2015 Sleep in America Poll.* Poster presentation at Virtual Sleep 2020 Annual Meeting.
4. Tran, L., **Jeon, B.**, Chasens, E. R. (2020, August). Sleep, chronic pain, and global health in adults ages 65 or older. Poster presentation at Virtual Sleep 2020 Annual Meeting.
5. **Jeon, B.**, Luyster, F. S., Sereika, S. M., DiNardo, M. M., Callan, J. A., Chasens, E. R. (2021, June). Chronotype, mood, and diabetes-related distress in adults with type 2 diabetes. Oral and poster presentation at Virtual Sleep 2021 Annual Meeting.
6. **Jeon, B.**, Luyster, F. S., Sereika, S. M., DiNardo, M. M., Callan, J. A, Chasens, E.R. (2021, November). *Comorbid obstructive sleep apnea and insomnia and its associations with mood and diabetes-related distress in type 2 diabetes mellitus*. Oral presentation at Sigma Eta Chapter Scholars Night. Pittsburgh, PA.
7. **Jeon, B.**, Luyster, F. S., Sereika, S. M., DiNardo, M. M., Callan, J. A, Chasens, E.R., (2021, November). *Comorbid obstructive sleep apnea and insomnia and its associations with mood*

and diabetes-related distress in type 2 diabetes mellitus. Poster presentation at University of Pittsburgh Center for Sleep & Circadian Science Research Day. Pittsburgh, PA.

8. **Jeon, B.**, Luyster, F. S., Sereika S. M., DiNardo, M. M., Callan J. A., Chasens, E. R. (2022, June). *The moderating effect of comorbid insomnia on the association of obstructive sleep apnea with mood, and with diabetes-related distress in adults with type 2 diabetes*. Oral and poster presentation at Sleep 2022 Annual Meeting. Charlotte, NC
9. Chasens, E. R., **Jeon, B.**, Orbell, S., Morris, J. L., Luyster, F. (2022, July). *Functional Outcomes and Daytime Sleepiness in Adults with Type 2 Diabetes and Sleep Disorders.* Oral presentation at Sigma Theta Tau's 33rd International Nursing Research Conference. Edinburgh, Scotland

1.8 Research Participant Risk and Protection

The proposed study was approved by exemption from the University of Pittsburgh Institutional Review Board (IRB) because this study was categorized as secondary research on an existing dataset (Appendix B). IRB approved the study protocols at each of the sites where parent studies were conducted.

Potential Risks and Benefits of the Proposed Research

A potential risk for participants in this study could be a breach of confidentiality. However, the data from the parent studies do not have individual identifiers. Therefore, identifiable information about human subjects is not knowable in this secondary analysis. While this study has no direct risks to the participants, there is no direct benefit to the research participants. This study may provide increased knowledge on the role of comorbid OSA and insomnia sleep disorders in mood disturbances, diabetes-related distress, and glycemic control in persons with T2DM which may be beneficial for future management of overall health outcomes in T2DM.

Procedures for Protection against Risk.

The data from the parent studies are stored on a secure centralized server. Unique numeric identifiers were used for each participant for all parent data and linkages are separated in locked storage. The data for this proposed study also are stored in a secure server where they can be accessed by the PI and research member with a designated ID and password. Identities of participants are not to be revealed in publications and presentations derived from this study.

2.0 Aim 1 Manuscript: Compare mood states and diabetes-related distress, among adults with comorbid OSA and insomnia (OSA+I), OSA, and insomnia

2.1 Abstract

Purpose: Previous research suggests that obstructive sleep apnea (OSA) and insomnia frequently co-exist and are prevalent in persons with type 2 diabetes mellitus (T2DM). This study compared mood and diabetes-related distress in OSA, insomnia, and comorbid OSA and insomnia (OSA+I) groups in persons with T2DM.

Methods: A secondary analysis was conducted with baseline data from two independent randomized controlled trials evaluating the efficacy of OSA and insomnia treatment. The pooled sample (N = 255) included participants with OSA only (n = 99 [38.8%]), insomnia only (n = 85 [33.3%]), and OSA and insomnia (OSA+I; n = 71 [27.8%]). OSA was defined as an apnea-hypopnea index (AHI) ≥ 10 events per hour: insomnia was defined as an Insomnia Severity Index score ≥ 15. Mood was measured by the Profile of Mood States Total Mood Disturbance (POMS TMD) score and subscale scores; the Problem Areas in Diabetes assessed diabetes-related distress. One-way analysis of covariance (ANCOVA) and multivariate analysis of covariance (MANCOVA) were conducted, controlling for demographic characteristics and restless leg syndrome.

Results: The insomnia group had on average, significantly higher scores for POMS TMD (insomnia vs. OSA = 43.34 vs. 28.39, p = .017), Tension-Anxiety (insomnia vs. OSA = 12.66 vs. 8.92, p = .001), and Fatigue-Inertia (insomnia vs. OSA= 13.55 vs. 10.19, p = .003) subscale scores

than OSA group. The OSA+I group had on average significantly greater diabetes-related distress than the OSA group (OSA+I vs. OSA = 38.44 vs. 30.56, p = .033).

Conclusions: Insomnia may have a greater impact on mood disturbance and diabetes-related distress than OSA in persons with T2DM. Comorbid insomnia may contribute to greater diabetes-related distress in persons with T2DM and OSA.

2.2 Introduction

Diabetes affects 34 million adults in the United States and is the seventh leading cause of death. Type 2 diabetes mellitus (T2DM) affects approximately 90-95% of adults with diabetes (CDC, 2020). In the United States, obstructive sleep apnea (OSA) and insomnia are two of the most common sleep disorders (Ferrie et al., 2011; Ram et al., 2010). Importantly, 60% of persons with T2DM have OSA (Khalil et al., 2020), and about 40% of persons with T2DM have insomnia symptoms (Koopman et al., 2020).

OSA is a condition in which individuals experience repetitive upper airway obstruction or narrowing during sleep, resulting in a cessation of breathing or a reduction in airflow associated with hypoxia, sleep fragmentation, and daytime sleepiness (Berry et al., 2012). Insomnia is a state of hyperarousal characterized by difficulty initiating, maintaining, or early morning awakenings with an inability to return to sleep. As a result, individuals with insomnia experience significant daytime fatigue, tiredness, or sleepiness due to the inability to obtain refreshing sleep (APA, 2013). In those with T2DM, both OSA and insomnia have been independently linked to poor glycemic control and self-management behaviors (Alshehri, Alenazi et al., 2020; Alshehri, Alothman et al., 2020; Koopman et al., 2020; Reutrakul & Mokhlesi, 2017). However, the effect of OSA or insomnia on psychological symptoms in persons with T2DM remains unclear.

Persons with T2DM suffer from widespread psychological symptoms, including depression and diabetes-related distress (Khaledi et al., 2019; Perrin et al., 2017). Depression is twice as common in persons with T2DM as in those without T2DM(Anderson et al., 2001). Diabetes-related distress affects up to 44.5% of persons with T2DM (Perrin et al., 2017; Nicolucci et al., 2013). These psychological symptoms traditionally have been linked to poor diabetes self-management behaviors and poor glucose outcomes (Fisher, Glasgow et al., 2010; Fisher, Mullan

et al., 2010; Gonzalez et al., 2008; Lustman et al., 2000). Psychological care for comorbid conditions, such as diabetes-related distress, depression, and anxiety, has been recommended to improve diabetes health outcomes in persons with T2DM (Young-Hyman et al., 2016).

OSA and insomnia are linked to increased psychological symptoms, the most common of which is depression (Baglioni et al., 2011; Edwards et al., 2020; Li et al., 2016). A recent review highlighted that comorbid insomnia and sleep apnea is common and associated with higher impairment of daytime function and worse quality of life (Sweetman et al., 2019). Our recent integrative review reported that persons with comorbid OSA and insomnia (OSA+I) had higher depressive symptoms than those with OSA alone. Insomnia, not OSA, contributed to increased depressive symptoms in persons with OSA+I (Jeon et al., 2021). Because comorbid OSA and insomnia have a synergistic effect on psychological symptoms, comorbid OSA and insomnia may contribute to greater psychological symptoms in persons with T2DM. However, the impact of comorbid OSA and insomnia on mood and diabetes-related distress has not been examined in persons with T2DM. It is still unknown which sleep disorders strongly influence mood and diabetes-related distress.

This study compared mood states and diabetes-related distress among adults with T2DM and OSA, insomnia, and OSA+I. We hypothesized that 1) adults with OSA+I have greater mood disturbances and diabetes-related distress than those with OSA only; 2) adults with OSA+I have greater mood disturbance and diabetes-related distress than those with insomnia only; 3) adults with insomnia only have greater mood disturbances and diabetes-related distress than those with OSA only among persons with T2DM.

2.3 Methods

2.3.1 Study Design, Sample, and Setting

We did a secondary analysis of pooled cross-sectional baseline data from the two randomized control trials: DSTT (R01-DK096023) and DSTT-I (K24-NR016685). The purpose of the two-parent studies was to examine the efficacy of treatment of OSA (DSTT) and insomnia (DSTT-I) on glucose control and diabetes self-management in persons with T2DM. The DSTT recruited 351 participants from multisite endocrinology and sleep outpatient clinics using various strategies (e.g., focused mailing, flyers in the community, social media advertisement). The DSTT-I recruited 55 participants at one of the sites from the DSTT using the same strategies and the excluded participants from DSTT who did not have a level of AHI 10 or more. Eligible participants for baseline assessment had self-reported T2DM, were 18 years or older, able to read and write English, and had AHI ≥ 10 events/hour (DSTT) or moderate-to-severe insomnia (DSTT-I), and were willing to be randomized to the respective studies. The eligibility criteria for this secondary analysis were 1) do not have missing data on variables for OSA severity, insomnia severity, mood states, and diabetes-related distress; 2) have either OSA or insomnia. The parent studies were approved by Institutional Review Board (IRB) at each site of studies. This study was independently approved by the University of Pittsburgh IRB to combine the data from the DSTT and DSTT-I.

2.3.2 Measures

Sleep Disturbance Status

OSA was defined as the level of AHI. Persons with AHI ≥ 10 events/hour were classified as having OSA. The ApneaLinkPlus® (ResMed, San Diego, CA), an approved level III device for unattended portable in-home sleep studies, was used to assess respiratory effort, nasal flow, pulse, and oxygen saturation to derive the AHI (Collop et al., 2007). Participants wore the ApneaLinkPlus® for a single night and returned the device in the pre-paid mail packet. All ApneaLinkPlus® data were reviewed by trained polysomnography (PSG) technicians according to the current published standards of the American Academy of Sleep Medicine (AASM) for scoring apneas and hypopneas (Berry et al., 2012). The home sleep testing device, the ApneaLink®, an older version of ApneaLinkPlus®, was found to have 82.1% sensitivity and 83.9% specificity for screening of OSA with AHI ≥ 10 events/hour compared with polysomnography (PSG) (Erman et al., 2007).

Insomnia was defined as the level of Insomnia Severity Index (ISI). The ISI (Morin et al., 2011) is a 7-item self-report questionnaire to measure the severity and impact of insomnia symptoms. Each item was rated on a 5-point Likert scale from '0 = no problems' to '4 = very severe problem'. The higher overall score indicates worse insomnia symptoms. Persons who had ISI ≥ 15 were classified as having insomnia. The ISI is highly reliable in a clinical sample with insomnia with a Cronbach $\alpha = 0.91$, and the sensitivity and specificity of the ISI for screening insomnia with ISI ≥ 15 are 78.1% and 100%, respectively, against the diagnosis derived from a clinical interview in a clinical sample (Morin et al., 2011).

Persons who met both OSA and insomnia criteria were classified as having OSA+I. Therefore, **OSA+I** was defined as AHI ≥ 10 events/hour and ISI ≥ 15.

Mood States

Mood states were measured by the Profile of Mood States (POMS). The POMS (McNair & Heuchert, 2007) evaluates mood states with a set of 65 adjectives or phrases related to the six dimensions of mood; tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion bewilderment. Each item was rated on a 5-point Likert scale from '0 = Not at all' to '4 = Extremely'. Higher scores of each dimension of mood except vigor-activity indicate greater negative moods. The POMS Total Mood Disturbance (TMD) score is calculated by subtracting the score of Vigor-Activity (positive mood) from the total of the other five dimensions of mood (negative moods). Higher POMS TMD scores indicate greater mood disturbances. The POMS has been validated to be sensitive to change following treatment for OSA and insomnia patients (Haensel et al., 2007; Morin et al., 1990), and the six POMS subscales are internally consistent with the POMS TMD score (Cronbach's $\alpha = .84$) (McNair & Heuchert, 2007).

Diabetes-related Distress

Diabetes-related distress was measured by the Problem Areas in Diabetes (PAID). The PAID (Polonsky et al., 1995) is a 20-item self-reported questionnaire to evaluate emotional distress associated with diabetes management among persons with T2DM. Each item was rated on a 5-point Likers scale from '0 = No a problem' to '4 = Serious problem'. The total score is calculated by summing all scores and multiplying the total by 1.25. A higher total score indicated greater diabetes-related distress. A total score ≥ 40 indicates emotional burnout. (Miller & Elasy, 2008). The PAID is highly reliable in a clinical sample with T2DM with a Cronbach $\alpha = 0.94$ (Miller & Elasy, 2008). The PAID has been validated to be sensitive to detecting changes in emotional distress in diabetes patients after receiving educational and psychosocial interventions (Polonsky et al., 1995; Welch et al., 1997).

Sociodemographic and Clinical Information

Sociodemographic information comprised age (years), gender (male vs. female), marital status (married/partnered vs. single/divorced/widowed), race (non-White vs. White), an education level (< 2-year degree of college or technical training vs. ≥ 2-year degree of college or technical training), and financial hardship (no difficulty to meet their needs vs. having somewhat/extremely difficulty to meet their needs).

Sleep-related clinical information included daytime sleepiness, sleep quality, and a history of restless leg syndrome (yes/no). The Epworth Sleepiness Scale measured daytime sleepiness (ESS); the ESS (Johns, 1991) is an 8-item self-reported questionnaire to rate the likelihood of falling asleep in common situations of daily living. Higher ESS scores indicate greater daytime sleepiness; a score greater than 10 indicates excessive daytime sleepiness. Sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI). The PSQI (Buysse et al., 1989) is a 19-item self-reported questionnaire to evaluate sleep quality. Higher PSQI scores indicate worse sleep quality; a score greater than 5 indicates poor sleep quality.

Diabetes-related clinical information included insulin use (yes/no), duration of T2DM (years), HbA1c (%), and body mass index (BMI; kg/m^2). A blood sample (no more than 30cc) was collected by the research staff to get the value of HbA1c. BMI was calculated from measured height and weight.

2.3.3 Procedure

From the DSTT and DSTT-I, brief telephone or in-person interview was performed to identify participants who met the eligibility criteria for baseline assessment. At baseline assessment, written informed consents were obtained, and anthropometric measurements (i.e.,

height, weight) and venipuncture were performed for BMI and HbA1c. Participants were instructed to return the ApneaLinkPlus® device and baseline questionnaires by pre-paid mail packet the next day and after seven days. ApneaLinkPlus® data were validated by trained polysomnography (PSG) technicians. Data from baseline questionnaires and the validated ApneaLinkPlus® data were stored on a secure server at the University of Pittsburgh.

For this secondary analysis, the baseline datasets from two pertinent studies were merged to analyze as one dataset based on shared measures and questionnaires. Shared measures and questionnaires were 1) Data from ApneaLinkPlus®; 2) ISI; 3) POMS; 4) PAID; 5) ESS; 6) PSQI; 7) Sociodemographic information; 8) Health history, and 9) clinical information from anthropometric measures and venipuncture. Following the eligibility criteria of this secondary analysis, participants who had missing in the AHI, the ISI, the POMS TMD score, and six subscores, or the PAID were excluded. In addition, those who did not have both OSA (i.e., AHI < 15) and insomnia (i.e., ISI < 15) were excluded from the analysis. A total of 255 participants were eligible.

2.3.4 Data Analysis

A total of 406 participants' data were collected from the DSTT (N = 351) and DSTT-I (N = 55). Initially, the amount of and patterns in missing data were screened. Most variables had missing cases over 5% except variables for mood states and demographic information. The pattern of missing data was not completely random, as assessed by Little's MCAR test ($\chi^2 = 320.19$, $df = 270$, $p = .019$). The primary reasons for missing data were associated with the data collection protocol from the parent studies (Table 1). In the DSTT and DSTT-I, participants who did not have sufficient recording time while asleep and wearing the ApneaLinkPlus® (a minimum of 2 hours of

recording time if AHI > 5 or a minimum of 4 hours of recording time if AHI < 5 with the presence of sleep in night verified by sleep diary) were not eligible to proceed in the study. Participants who had missing cases in multiple questionnaires because they did not complete questionnaires in the second pre-paid mail packet were not eligible. In DSTT-I, participants who did not have insomnia or severe depression and/or suicidal ideation were excluded from further evaluation. The participants who had missing data in DSTT-I were more likely to have mood disturbances than those without missing data in DSTT-I. Despite the non-random missing pattern, the data collection protocol cannot be manipulated. We chose a listwise deletion to deal with missing data.

Table 1. The Common Patterns of Missing in the Data and Reasons for Missing

	Pattern of missing		Reasons for missing
DSTT	Missing in AHI	Missing in multiple questionnaires	Insufficient recording time in ApneaLinkPlus® to determine AHI
	Without missing in AHI	Missing in multiple questionnaires/BMI, HbA1c	Did not complete the second questionnaire packet
			Reject to finish anthropometric measurements
DSTT-I	Missing in AHI	Missing in multiple questionnaires	Insufficient recording time in ApneaLinkPlus® to determine AHI
	Without missing in AHI	Missing in multiple questionnaires/BMI, HbA1c	Did not complete the second questionnaire packet
			Reject to finish anthropometric measurements

Among 406 participants recruited from the parent studies, the number of eligible participants was 255 (Figure 5). Preliminary data analyses were performed among these participants to describe the distribution of each variable, evaluate the amount and pattern of missing data, reveal the association between variables to discern possible covariate/confounders, and check for violations in statistical assumptions for planned analyses.

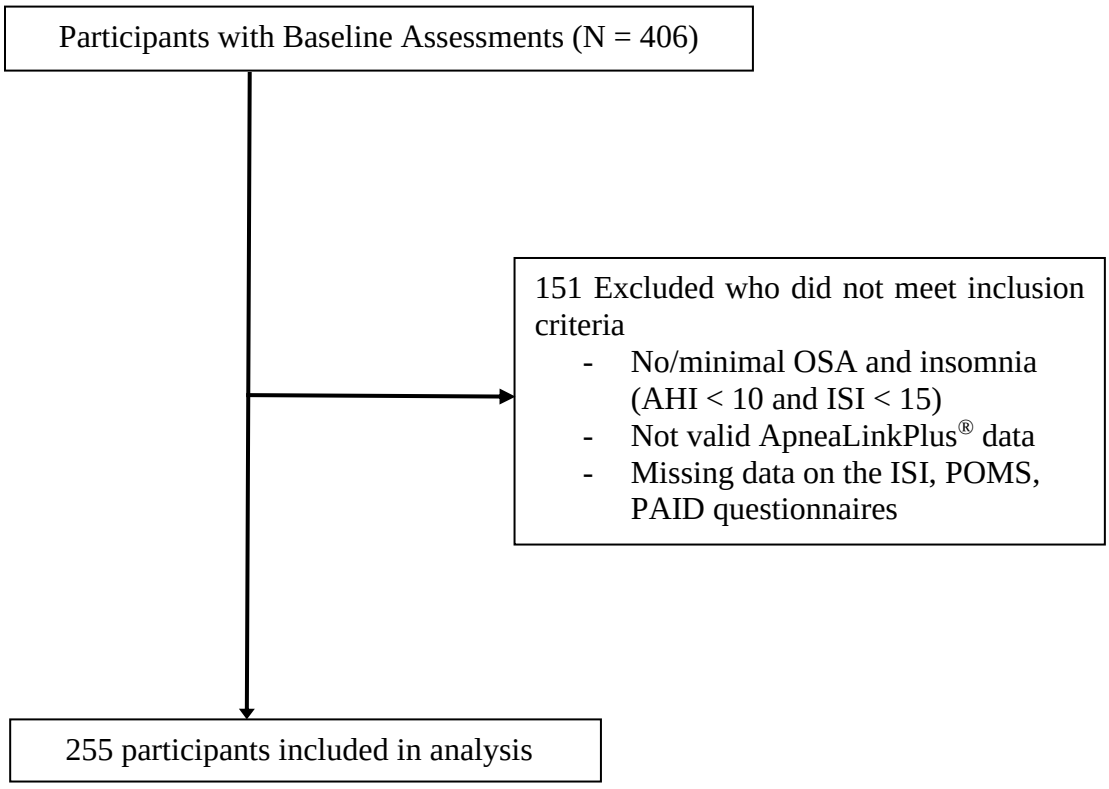


Figure 5. Participant Flow for Inclusion (Aim 1)

The characteristics of the total sample were analyzed with appropriate descriptive statistics based on the level of measurement and the distribution of each variable (i.e., mean, median, standard deviation, interquartile range, frequency, and percentage). The randomness of missing data was investigated, comparing characteristics between eligible and excluded participants for Aim 1. The eligible participants had greater severity of OSA and insomnia and experienced worse sleep-related symptoms (i.e., excessive daytime sleepiness, poor sleep quality). In terms of diabetes-related characteristics, the eligible participants used insulin more than the excluded participants. The eligible participants experienced greater diabetes-related distress than the excluded participants (Table 2). Little's MCAR test demonstrated that that missing data was completely at random among the eligible participants (χ^2 = .00, *df* = 74, *p* = 1.000). Regrading

socioeconomic variables, there were 10% missing in the poverty index because participants did not want to reveal their household income. Most participants answered the questions asking whether they have a subjective financial hardship to meet their basic needs. Therefore, we decided to use financial difficulty variables to measure the socioeconomic status of participants.

Table 2. Comparison of Characteristics between Eligible Participants and Excluded Participants for Aim 1 (N = 406)

Baseline Characteristic	Eligible participants N = 255	Excluded participants N = 151	*p*
Sociodemographic information			
Age, years	56.87 ± 10.62	55.97 ± 10.39	.402
Gender			
Female	126 (49.4)	81 (53.6)	.410
Male	129 (50.6)	70 (46.4)	
Marital status			
Never married/Separated/divorced/widowed	140 (54.9)	88 (59.1)	.416
Married/partnered	115 (45.1)	61 (40.9)	
Race			
Non-white	96 (37.6)	68 (45.0)	.143
White	159 (62.4)	83 (55.0)	
Education level			
< 2-years college degree, or technical training	114 (44.7)	66 (44.6)	.983
≥ 2-years college degree, or technical training	141 (55.3)	82 (55.4)	
Financial hardship			
Somewhat/extremely difficult	101 (39.8)	68 (45.6)	.249
Not at all difficult	153 (60.2)	81 (54.4)	
Sleep-related clinical information			
OSA severity			
AHI	17.67 ± 16.75	8.66 ± 14.82	<.001
Insomnia severity			
ISI	15.48 ± 6.07	11.07 ± 5.64	<.001
Daytime sleepiness			
ESS	10.39 ± 4.74	8.87 ± 4.51	.005
Sleep quality			
PSQI	10.74 ± 4.09	8.90 ± 3.63	<.001
Restless leg syndrome, *n* (%)			
Yes	50 (19.8)	15 (14.6)	.243

Baseline Characteristic	Eligible participants	Excluded participants	
No	202 (80.2)	88 (85.4)	
Diabetes-related clinical information			
Insulin use status, *n* (%)			
Yes	122 (47.8)	44 (31.9)	.002
No	133 (52.2)	94 (68.1)	
Duration of T2DM, years	11.41 ± 9.47	9.79 ± 8.29	.112
A1C (%)	7.90 ± 1.63	7.99 ± 2.09	.674
BMI (kg/m^2)	35.29 ± 7.03	33.75 ± 6.64	.030
Mood States	35.29 ± 7.03	33.75 ± 6.64	
POMS Total Mood Disturbance	31.84 ± 36.69	25.54 ± 31.94	.072
POMS Tension-Anxiety	10.05 ± 7.02	9.22 ± 10.05	.222
POMS Depression-Dejection	9.56 ± 10.41	8.54 ± 9.42	.316
POMS Anger-Hostility	7.91 ± 8.28	6.82 ± 6.69	.148
POMS Vigor-Activity	14.83 ± 6.35	15.22 ± 6.62	.564
POMS Fatigue-Inertia	11.69 ± 6.68	9.66 ± 6.61	.003
POMS Confusion-Bewilderment	7.46 ± 5.11	6.52 ± 4.46	.054
Diabetes-related distress			
PAID	31.28 ± 21.30	25.65 ± 18.57	.014

Note. Chi-square test of independence was conducted for nominal variables. Independent t-test was conducted for continuous variables. AHI = Apnea-Hypopnea Index; ISI = Insomnia Severity Index; ESS = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index; T2DM = Type 2 diabetes mellitus; A1C = HbA1c; BMI = Body mass index; POMS = Profile of Mood States; PAID = Problem Areas in Diabetes

The characteristics among OSA, insomnia, and OSA+I groups were compared using chi-square of independence (for nominal variables) and one-way analysis of variance (ANOVA; for continuous variables). Bonferroni or Games-Howell (if the assumption of homogeneity of variance was violated) post-hoc pairwise comparisons of the three types of sleep disorders were done for continuous variables, which were found to be significantly different between three types of sleep disorders in ANOVA.

Based on the data screening and literature review, covariates were age, gender, marital status, race, education level, financial hardship, and restless leg syndrome.

A one-way analysis of covariances (ANCOVA) was performed to examine whether mood states (i.e., the POMS TMD score) and diabetes-related distress (i.e., PAID score) were significantly different between the three types of sleep disorders (i.e., OSA, insomnia, and comorbid OSA+I) after controlling for the covariates. This was followed by a pairwise comparison with Bonferroni adjustment to determine where the significant mean differences existed among the three types of sleep disorders.

The statistical assumptions were met in the one-way ANCOVA models for POMS TMD score and PAID score, except for the assumption regarding the normality of residuals. Because the distribution of the studentized residual for the POMS TMD score was positively skewed with multiple outliers, a square root transformation was applied. The scores of two outliers in the studentized residual for the PAID score were altered to be close to the next highest non-outlier value. Comparing the results with the transformed variables and those with original variables, the skewness of residual and outliers did not substantially affect the results in the models for POMS TMD and PAID. The one-way ANCOVA is fairly robust to violation of normality. Therefore, one-way ANCOVA was performed with original variables regardless of the violation of normality assumption and outliers. For all fitted one-way ANCOVA models, potential influential observations were assessed, but these influential cases did not change the statistical significance of the results.

Differences in the six dimensions of mood state (e.g., the subscale scores of Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment) among the sleep disorder groups were analyzed by one-way multivariate analysis of covariance (MANCOVA) after controlling for the covariates. One-way ANCOVA and pairwise

comparisons with Bonferroni adjustment were performed to determine which dimensions of mood states were significantly different between the three types of sleep disorders.

With the exception of the Vigor-Activity and the Fatigue-Inertia subscale scores, the distributions of the standardized residual for the other subscale scores were positively skewed with multiple univariate outliers. Multivariate outliers were also found in the overall one-way MANCOVA model. The standardized residuals of the four subscale scores had better distribution after applying squared root transformation. However, several outliers were still found, and the one-way MANCOVA is fairly robust to violation of normality. Therefore, the original variables were used in our analysis. All analyses were performed using SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY), and the level of statistical significance for two-sided hypothesis testing was set at .05.

2.4 Results

2.4.1 Sample Characteristics

A total of 255 adults with T2DM were included in this analysis. The characteristics of the sample are shown in Table 3. Our sample was primarily middle-aged (mean age 56.87 ± 10.62 years) with the representation of non-Whites (37.6%), and with many participants expressing they had “somewhat” or “extreme” financial difficulty (39.8%). The sample was well-distributed by gender (49.4% female), marital status (45.1% married or partnered), and education level (55.3% with more than two years of college or technical training). On average, our sample of persons with T2DM was overweight or obese, with a mean BMI = 35.29 ± 7.03. Participants had suboptimal

glycemic control (mean A1C = 7.90% ± 1.63), the average duration of T2DM diagnosis was over ten years (11.41 ± 9.47), and almost half (47.8%) of the sample was prescribed insulin. The total sample had, on average, moderate-to-severe OSA (Berry et al., 2012), moderate insomnia (Morin et al., 2011), moderate levels of excessive daytime sleepiness (Johns, 1991), and poor sleep quality (Buysse et al., 1989).

Table 3. Sample Characteristics of Aim 1 (N = 255)

Baseline Characteristic	n (%)	*Mean*(*Mdn*)	*SD*	Range
Sociodemographic information				
Age, years		56.87 (58.0)	10.62	31-91
Gender				
Female	126 (49.4)			
Male	129 (50.6)			
Marital status				
Never married/separated/divorced/widowed	140 (54.9)			
Married/partnered	115 (45.1)			
Race				
Non-white	96 (37.6)			
White	159 (62.4)			
Education level				
< 2-year college degree, or technical training	114 (44.7)			
≥ 2-year college degree, or technical training	141 (55.3)			
Financial hardship				
Somewhat/extremely difficult	101 (39.8)			
Not at all difficult	153 (60.2)			
Sleep-related clinical information				
OSA severity				
AHI		17.67 (13.10)	16.75	0-95
Insomnia severity				
ISI		15.48 (16.0)	6.07	0-28
Daytime sleepiness				
ESS		10.39 (9.0)	4.74	1-24
Sleep quality				
PSQI		10.74 (11.0)	4.09	1-21
Restless Leg Syndrome				
Yes	50 (19.8)			
No	202 (80.2)			

Baseline Characteristic	n (%)	*Mean*(*Mdn*)	*SD*	Range
Diabetes-related clinical information				
Insulin use status				
Yes	122 (47.8)			
No	133 (52.2)			
Duration of T2DM (years)		11.41 (10.0)	9.47	0.5-57
A1C (%)		7.90 (7.60)	1.63	5.2-13.9
BMI (kg/m^2)		35.29 (34.8)	7.03	22.7-60

Note. Mdn = median; SD = standard deviation; AHI = Apnea-Hypopnea Index; ISI = Insomnia Severity Index; ESS = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index; T2DM = Type 2 diabetes mellitus; A1C = HbA1c; BMI = Body mass index.

The characteristics of the participants in the three types of sleep disorders are summarized in Table 4. Among 255 participants, there were 99 (39.8%) with OSA only, 85 (33.3%) with insomnia only, and 71 (27.8%) with OSA+I. On average, persons with OSA were older than those with insomnia ($p = 0.014$). Persons with OSA+I had an even gender distribution, whereas those with only OSA were predominantly male and those with only insomnia were primarily female ($p < 0.001$). Persons with OSA were more likely to be White ($p = 0.004$), have at least two years of college or technical training ($p = 0.034$), and without financial difficulty ($p < 0.001$) compared with the other two groups. Persons with insomnia were more likely to be single ($p = 0.001$). Insomnia severity was not significantly different between persons with insomnia only and those with OSA+I. OSA severity was not significantly different between persons with OSA only and those with OSA+I. Daytime sleepiness and sleep quality were higher in persons with either insomnia only or OSA+I than those with OSA ($p < 0.001$). BMI was higher in persons with OSA only and those with comorbid OSA+I than those with insomnia only ($p < .001$). The level of HbA1c was higher in persons with comorbid OSA+I than in those with OSA ($p = 0.022$).

2.4.2 Effect of Type of Sleep Disorder on Mood States in Adults with T2DM

After controlling for identified covariates (age, gender, race, marital status, education level, financial hardship, restless leg syndrome), the POMS TMD score was significantly different, on average, among the three types of sleep disorders, $F(2, 241) = 4.041$, $p = .019$, partial $\eta^2 = .032$ (Table 5). The adjusted group means for the POMS TMD score were 28.39 ± 4.12 for persons with OSA, 43.34 ± 3.90 for those with insomnia, and 37.62 ± 4.22 for those with OSA+I (Table 6). Based on Bonferroni adjusted pairwise comparisons, the POMS TMD score for persons with OSA+I was not significantly higher compared to those with OSA (Adjusted mean difference [M_{diff}] = 9.24, 95% CI [-3.28, 21.76], $p = .229$). Persons with insomnia had a significantly higher POMS TMD score than those with OSA ($M_{diff} = 14.96$, 95% CI [2.03, 27.89], $p = .017$). On average the POMS TMD score between persons with OSA+I and those with insomnia was not significantly different ($M_{diff} = -5.72$, 95% CI [-18.91, 7.47], $p = .890$) (Table 7).

As the POMS TMD score consists of six dimensions of mood states, we examined the association of the type of sleep disorder on the six mood subscale scores (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment). The type of sleep disorder was significantly associated with the six mood states after controlling for covariates, $F(12, 472) = 2.810$, $p = .001$, Wilks' $\lambda = .868$, partial $\eta^2 = .068$ (Table 8). Exploring each of the POMS subscale scores individually using one-way ANCOVA revealed that there were significant mean differences in Tension-Anxiety ($F[2, 241] = 6.877$, $p < .001$, partial $\eta^2 = .054$) and Fatigue-Inertia ($F[2, 241] = 6.946$, $p < .001$, partial $\eta^2 = .054$) subscale scores among the three types of sleep disorders ($p < .0083$ after a Bonferroni correction) (Table 9). The adjusted group means for the six subscales scores are shown in Table 10. There was no significant difference in the mean Tension-Anxiety score of persons with OSA+I and those with

OSA (M_{diff} = 2.04, 95% CI [-0.33, 4.40], p = .191) and those with insomnia (M_{diff} = -1.71, 95% CI [-4.20, 0.79], p = .302). The adjusted mean difference score of Tension-Anxiety for persons with insomnia was significantly higher than those with OSA (M_{diff} = 3.74, 95% CI [1.29, 6.19], p = .001). Persons with OSA+I had a significantly higher adjusted mean score of Fatigue-Inertia than those with OSA (M_{diff} = 2.87, 95% CI [0.54, 5.19], p = .010). The adjusted mean score of Fatigue-Inertia in persons with insomnia was significantly higher compared to those with OSA (M_{diff} = 3.36, 95% CI [0.96, 5.76], p = .003). There was no significant difference in the mean Fatigue-Inertia score of persons with OSA+I and those with insomnia (M_{diff} = -0.50, 95% CI [-2.95, 1.95], p = 1.00) (Table 11).

2.4.3 Effect of Type of Sleep Disorder on Diabetes-related Distress in Adults with T2DM

On average, the PAID score was significantly different among the three types of sleep disorders after controlling for covariates, $F(2, 241) = 3.796$, p = .024, partial η^2 = .031 (Table 12). The adjusted group means for the PAID score were 30.56 ± 2.44 for persons with OSA, 37.21 ± 2.32 for those with insomnia, and 38.44 ± 2.50 for those with OSA+I (Table 13). The mean PAID score for persons with OSA+I was significantly higher compared to those with OSA (M_{diff} = 7.89, 95% CI [0.46, 15.32], p = .033). The mean difference for persons with insomnia was not significant compared to those with OSA (M_{diff} = 6.65, 95% CI [-1.02, 4.33], p = .113). There was no significant difference between the mean PAID score between persons with OSA+I and those with insomnia (M_{diff} = 1.24, 95% CI [-6.59, 9.06], p = 1.00) (Table 14).

Table 4. Comparisons of Characteristics Assessed at Baseline among Types of Sleep Disorder (N = 255)

Baseline Characteristic	OSA	Insomnia	OSA+I	
	n = 99	*n* = 85	*n* = 71	*p*
Sociodemographic information				
Age (years); mean ± SD	58.64 ± 10.92	54.21 ± 11.06[a]	57.61 ± 9.04	.014
Gender, *n* (%)				
Female	33 (33.3)	55 (64.7)	38 (53.5)	<.001
Male	66 (66.7)	30 (35.3)	33 (46.5)	
Marital status, *n* (%)				
Never married/Separated/divorced/widowed	44 (44.4)	60 (70.6)	36 (50.7)	.001
Married/partnered	55 (55.6)	25 (29.4)	35 (49.3)	
Race, *n* (%)				
Non-white	25 (25.3)	41 (48.2)	30 (42.3)	.004
White	74 (74.7)	44 (51.8)	41 (57.7)	
Education level, *n* (%)				
< 2-years college degree, or technical training	39 (39.4)	34 (40.0)	41 (57.7)	.034
≥ 2-years college degree, or technical training	60 (60.6)	51(60.0)	30 (42.3)	
Financial hardship, *n* (%)				
Somewhat/extremely difficult	24 (24.2)	48 (57.1)	29 (40.8)	<.001
Not at all difficult	75 (75.8)	36 (42.9)	42 (59.2)	
Sleep-related clinical information				
OSA severity				
AHI, mean ± SD	25.82 ± 17.88	4.03 ± 2.63[b]	22.64 ± 14.72[c]	<.001
Insomnia severity				
ISI, mean ± SD	9.25 ± 3.54	19.69 ± 3.61[a]	19.11 ± 3.30[a]	<.001
Daytime sleepiness				
ESS, mean ± SD	8.77 ± 4.18	10.86 ± 4.73[a]	12.08 ± 4.83[a]	<.001
Sleep quality				
PSQI, mean ± SD	7.48 ± 3.08	13.22 ± 3.22[a]	12.27 ± 3.18[a]	<.001
Diabetes-related clinical information				
Insulin use status, *n* (%)				

Baseline Characteristic	OSA	Insomnia	OSA+I	
Yes	47 (47.5)	38 (44.7)	37 (52.1)	.651
No	52 (52.5)	47 (55.3)	34 (47.9)	
Duration of T2DM (years); mean ± SD	11.90 ± 10.43	10.49 ± 7.13	11.83 ± 10.54	.560
A1C (%), mean ± SD	7.55 ± 1.30	8.11 ± 1.96	8.15 ± 1.56[b]	.022
BMI (kg/m^2), mean ± SD	36.97 ± 7.12	32.56 ± 5.63[b]	36.19 ± 7.53[c]	<.001

Note. Chi-square test of independence was conducted for nominal variables. One-way analysis of variance (ANOVA) was conducted for continuous variables. Bonferroni and Games-Howell post-hoc tests were conducted for pairwise comparison. SD = Standard deviation; OSA = Obstructive sleep apnea; OSA+I = Comorbid obstructive sleep apnea and insomnia; AHI = Apnea-Hypopnea Index; ISI = Insomnia Severity Index; ESS = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index; T2DM = Type 2 diabetes mellitus; A1C = HbA1c; BMI = Body mass index

[a] significant difference with OSA obtained by Bonferroni post-hoc pairwise comparison.

[b] significant difference with OSA obtained by Games-Howell post-hoc pairwise comparison.

[c] significant difference with insomnia obtained by Games-Howell post-hoc pairwise comparison.

Table 5. One-way Analysis of Covariance (ANCOVA) Model for Profile of Mood States Total Mood Disturbance Score

Effect	*F*	*Df*	*P*	partial η^2
Intercept	39.565	1, 241	< .001	.141
Group				
Type of sleep disorder	4.041	2, 241	.019	.032
Covariates				
Age	10.237	1, 241	.002	.041
Gender	0.031	1, 241	.364	.003
Education level	5.012	1, 241	.860	.000
Race	3.241	1, 241	.073	.013
Marital status	2.558	1, 241	.111	.011
Financial difficulty	13.668	1, 241	< .001	.054
Restless leg syndrome	6.905	1, 241	.009	.028

Note. R squared = .241 (Adjusted R Squared = .213). Age, gender, education level, race, marital status, financial hardship, and restless leg syndrome were controlled. Age appearing in the model was evaluated as 56.98.

Table 6. Unadjusted Means, Median, and Adjusted Means from One-way Analysis of Covariance (ANCOVA) for Profile of Mood States Total Mood Disturbance Score

		Unadjusted				Adjusted	
Group	*N*	*M*	*SD*	*Mdn*	*IQR*	*M*	*SE*
OSA	99	18.66	29.70	13.0	(-2, 34)	28.39	4.12
Insomnia	81	45.11	40.36	39.0	(13, 71)	43.34	3.90
OSA+I	71	32.32	33.81	7.0	(7, 46)	37.62	4.22

Note. Age, gender, education level, race, marital status, financial hardship, and restless leg syndrome were controlled. Age appearing in the model was evaluated as 56.98. *M* = Mean; *SD* = Standard deviation; *Mdn* = Median; *IQR* = Interquartile range; *SE* = Standard error; OSA = Obstructive sleep apnea; OSA+I = Comorbid obstructive sleep apnea and insomnia.

Table 7. Pairwise Comparisons of Profile of Mood States Total Mood Disturbance Score for Types of Sleep Disorder

	The difference in adjusted means (95% CI)		
Mood States	OSA+I vs. OSA	Insomnia vs. OSA	OSA+I vs. Insomnia
Total Mood Disturbance	9.24 (-3.28, 21.76)	14.96 (2.03, 27.89)*	-5.72 (-18.91, 7.47)

Note. * = statistically significant difference based on Bonferroni adjustment; 95% confidence interval (CI) is simultaneous confidence interval based on Bonferroni adjustment; OSA+I = Comorbid obstructive sleep apnea and insomnia; OSA = Obstructive sleep apnea.

Table 8. One-way Multivariate Analysis of Covariance (MANCOVA) Model for the Six Subscales of Profile of Mood States

Effect	Wilks's λ	*F*	*Df*	*p*	partial η^2
Intercept	.573	29.345	6, 236	< .001	.427
Group					
Type of sleep disorder	.868	2.891	12, 472	.001	.068
Covariates					
Age	.897	4.497	6, 236	< .001	.103
Gender	.942	2.404	6, 236	.028	.058
Education level	.970	1.216	6, 236	.299	.030
Race	.922	3.306	6, 236	.004	.078
Marital status	.946	2.256	6, 236	.039	.054
Financial difficulty	.897	4.497	6, 236	< .001	.103
Restless leg syndrome	.951	2.026	6, 236	.063	.049

Note. Age, gender, education level, race, marital status, financial hardship, and restless leg syndrome were controlled. Age appearing in the model was evaluated as 56.98.

Table 9. Follow-up Univariate One-way Analysis of Covariance (ANCOVA) of Six Subscales of the Profile of Mood States

Subscales of Mood States	*F*	*Df*	*p*	partial η^2
Tension-Anxiety	6.877	2, 241	.001	.054
Depression-Dejection	2.777	2, 241	.064	.023
Anger-Hostility	0.194	2, 241	.824	.002
Vigor-Activity	3.383	2, 241	.036	.027
Fatigue-Inertia	6.946	2, 241	.001	.054
Confusion-Bewilderment	3.146	2, 241	.045	.025

Note. Age, gender, education level, race, marital status, financial hardship, and restless leg syndrome were controlled. Age appearing in the model was evaluated as 56.98. Statistical significance was accepted when $p < .0083$ based on Bonferroni adjustment. R squared for Tension-Anxiety = .263 (Adjusted R Squared = .235). R squared for Fatigue-Inertia = .222 (Adjusted R Squared = .193).

Table 10. Unadjusted Means, Median, and Adjusted Means from Multivariate Analysis of Covariance (MANCOVA) for Six Subscales of Profile of Mood States

	OSA			Insomnia			OSA+I		
	n = 99			*n* = 81			*n* = 71		
Mood States	*M* (*SD*)	*Mdn* (*IQR*)	M_{adj} (*SE*)	*M* (*SD*)	*Mdn* (*IQR*)	M_{adj} (*SE*)	*M* (*SD*)	*Mdn* (*IQR*)	M_{adj} (*SE*)
Tension-Anxiety	7.26 (5.62)	7.0 (3, 10)	8.92 (0.78)	12.95 (8.11)	12.0 (6, 18)	12.66 (0.74)	9.90 (6.90)	9.0 (6, 14)	10.96 (0.80)
Depression-Dejection	6.21 (8.20)	4.0 (1, 10)	9.21 (1.20)	12.98 (11.39)	11.0 (4, 21.5)	12.87 (1.13)	9.28 (10.19)	6.0 (2, 12)	11.16 (1.23)
Anger-Hostility	6.91 (7.30)	4.0 (1, 10)	9.18 (0.99)	9.33 (9.70)	7.0 (3, 13.5)	9.43 (0.94)	7.76 (8.19)	5.0 (2, 12)	8.63 (1.02)
Vigor-Activity	16.65 (6.25)	17.0 (13, 21)	16.27 (0.75)	13.42 (6.03)	14.0 (9.5, 17)	14.23 (0.71)	14.86 (6.36)	14.0 (9, 18)	14.03 (0.77)
Fatigue-Inertia	9.05 (5.68)	8.0 (5, 13)	10.19 (0.77)	13.96 (6.91)	14.0 (7.5, 20)	13.55 (0.73)	11.61 (6.65)	13.0 (7, 18)	13.05 (0.78)
Confusion-Bewilderment	5.87 (4.22)	5.0 (3, 9)	7.16 (0.59)	9.31 (5.52)	9.0 (5, 12.5)	9.08 (0.56)	7.37 (5.08)	7.0 (3, 9)	7.85 (0.61)

Note. Age, gender, education level, race, marital status, financial hardship, and restless leg syndrome were controlled. Age appearing in the model was evaluated as 57.26. OSA = Obstructive sleep apnea; OSA+I = Comorbid obstructive sleep apnea and insomnia; *M* = Mean; *SD* = Standard deviation; *Mdn* = Median; *IQR* = Interquartile range; M_{adj}= Adjusted mean; *SE* = Standard error.

Table 11. Pairwise Comparisons of Profile of Mood States Tension-Anxiety and Fatigue-Inertia Subscale Scores for Type of Sleep Disorder

	The difference in adjusted means (95% CI)		
Mood States	OSA+I vs. OSA	Insomnia vs. OSA	OSA+I vs. Insomnia
POMS Tension-Anxiety	2.04 (-0.33, 4.40)	3.74 (1.29, 6.19)*	-1.71 (-4.20, 0.79)
POMS Fatigue-Inertia	2.87 (0.54, 5.19)*	3.36 (0.96, 5.76)*	-0.50 (-2.95, 1.95)

Note. * = statistically significant difference based on Bonferroni adjustment; 95% confidence interval (CI) is a simultaneous confidence interval based on Bonferroni adjustment. Comorbid OSA+I = Comorbid obstructive sleep apnea and insomnia; OSA = Obstructive sleep apnea.

Table 12. One-way Analysis of Covariance (ANCOVA) Model for Diabetes-related Distress

Effect	*F*	*df*	*p*	partial η^2
Intercept	42.990	1, 241	< .001	.151
Group				
Type of sleep disorder	3.796	2, 241	.024	.031
Covariates				
Age	2.220	1, 241	.138	.009
Gender	0.826	1, 241	.364	.003
Education level	5.012	1, 241	.026	.020
Race	0.271	1, 241	.603	.001
Marital status	0.000	1, 241	.992	.000
Financial difficulty	15.292	1, 241	< .001	.060
Restless leg syndrome	7.072	1, 241	.008	.029

Note. R squared = .238 (Adjusted R Squared = .199). Age, gender, education level, race, marital status, financial hardship, and restless leg syndrome were controlled. Age appearing in the model was evaluated as 56.98.

Table 13. Unadjusted Means, Median, and Adjusted Means from One-way Analysis of Covariance (ANCOVA) for Diabetes-related Distress

		Unadjusted				Adjusted	
Group	*N*	*M*	*SD*	*Mdn*	*IQR*	*M*	*SE*
OSA	99	23.51	18.16	20.0	(8.75, 35)	30.56	2.44
Insomnia	81	36.69	22.73	32.5	(17.5, 55)	37.21	2.32
OSA+I	71	35.46	20.82	35.0	(18.75, 48.75)	38.44	2.50

Note. Age, gender, education level, race, marital status, financial hardship, and restless leg syndrome were controlled. Age appearing in the model was evaluated as 56.98. *M* = Mean; *SD* = Standard deviation; *Mdn* = Median; *IQR* = Interquartile range; *SE* = Standard error; OSA = Obstructive sleep apnea; OSA+I = Comorbid obstructive sleep apnea and insomnia.

Table 14. Pairwise Comparisons of Diabetes-related Distress for Types of Sleep Disorder

	The difference in adjusted means (95% CI)		
	OSA+I vs. OSA	Insomnia vs. OSA	OSA+I vs. Insomnia
Diabetes-related distress	7.89 (0.46, 15.32)*	6.65 (-1.02, 14.33)	1.24 (-6.59, 9.06)

Note. * = statistically significant difference based on Bonferroni adjustment; 95% confidence interval (CI) is a simultaneous confidence interval based on Bonferroni adjustment. Comorbid OSA+I = Comorbid obstructive sleep apnea and insomnia; OSA = Obstructive sleep apnea.

2.5 Discussion

This study compared mood states and diabetes-related distress between persons with OSA, insomnia, and OSA+I to examine how OSA and insomnia affect mood states and diabetes-related distress, individually and jointly, in persons with T2DM. . Insomnia was associated with greater mood disturbance than OSA, and OSA+I was associated with greater diabetes-related distress than OSA. These findings suggest that in persons with OSA+I, insomnia may lead to additive impairments in mood, and insomnia increases the severity of diabetes-related distress. It is possible that insomnia, not OSA, might be a more potent contributing factor to increased severity of mood disturbances and diabetes-related distress in persons with T2DM.

Our findings support the conclusions of our integrative review that OSA+I has a synergistic effect on depressive symptoms compared to OSA and that comorbid insomnia contributes to increased severity of depressive symptoms in persons with OSA+I (Jeon et al., 2021). The mechanisms underlying the effect of OSA+I on mood and diabetes-related distress in T2DM remain limited. OSA and insomnia are associated with the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (e.g., increased level of cortisol) (Benetó et al., 2009; Morin et al., 2015) and alteration in monoamine neurotransmitters release (e.g., decreased serotonin, dopamine) (Harris et al., 2009; Morin et al., 2015; Reimann et al., 2020). The abnormalities of the HPA axis and the imbalance of monoamine neurotransmitters are also common in persons with depression (Manber & Chambers, 2009; Malhi & Mann, 2018; Murphy & Peterson, 2015). It is possible that when OSA and insomnia coexist, these physiological dysregulations are exacerbated, increasing mood disturbances and diabetes-related distress in persons with OSA+I compared to those with OSA alone. Recent functional neuroimaging studies suggest that persons with OSA, insomnia, and major depressive disorder are commonly associated with increased activity in the emotion-

regulating system and decreased activity in the cognitive-executive system in the brain (Bagherzadeh-Azbari et al., 2019; Gray et al., 2020; Huang et al., 2019; Wu et al., 2020). Specifically, insomnia is associated with an increase in the activity of the emotion-regulating system, while OSA reduces the activity of the cognitive-executive system (Bagherzadeh-Azbari et al., 2019). As a result, it is plausible that insomnia has a stronger association with mood dysregulation than OSA.

This is the first study to indicate that persons with T2DM and OSA+I experienced greater diabetes-related distress than OSA alone, and that comorbid insomnia contributed to increased diabetes-related distress. Diabetes-related distress is defined as a distinct emotional burden associated with the responsibility of maintaining the daily demands of diabetes self-management. Diabetes-related distress is a key influential psychological symptom in persons with T2DM, along with depression and anxiety (McCoy & Theeke et al., 2019). The current literature has focused on the negative impact of diabetes-related distress on health outcomes, such as diabetes self-care behaviors and glucose control (Fisher, Glasgow et al., 2020; Fisher, Mullan et al., 2020; Gonzalez et al., 2008; Lustman et al., 2000). The evidence examining which factors increase the severity of diabetes-related distress is scarce. This study suggests that insomnia, especially comorbid with OSA, is a significant modifiable factor associated with diabetes-related distress. Our findings also show that persons with OSA+I had a 0.57% higher HbA1c value than those with OSA alone. Previous research has identified a 0.5% difference in HbA1c as clinically meaningful (Little et al., 2011). In T2DM, the association between insomnia and diabetes-related distress may have a deleterious impact on glycemic outcomes.

In our findings, persons with insomnia and OSA+I experienced more daytime sleepiness than those with OSA. This implies that comorbid insomnia may exacerbate daytime sleepiness in

persons with OSA. Excessive daytime sleepiness is associated with poor glucose outcomes in persons with T2DM (Huang et al., 2016; Keskin et al., 2015). Insomnia has a detrimental impact on mood and diabetes-related distress and makes excessive daytime sleepiness more severe than in persons with OSA. Exacerbated excessive daytime sleepiness, increased mood impairment, and diabetes-related distress from comorbid insomnia may make it difficult for persons with OSA to regulate their glucose levels effectively.

Although daytime sleepiness is a common symptom of OSA, there is a distinct phenotype of persons with OSA who are not sleepy (Altintas & Riha, 2019). According to data from a large study (N = 16,583) of community-dwelling individuals, excessive daytime sleepiness was significantly ($p < .05$) associated with depression and diabetes but not with the presence of OSA (Bixler et al., 2005). However, this study did not evaluate whether participants had coexisting insomnia. Persons with sleepy OSA may experience greater mood disturbances than those with non-sleepy OSA. Our findings imply that comorbid insomnia may be a factor in sleepy persons with OSA having worse mood disturbances than non-sleepy persons with OSA. In a recent study of persons with sleep apnea in the community, excessive daytime sleepiness was associated with a higher incidence of insomnia symptoms, poorer mental health, and disease-specific functional status (Wanberg et al., 2021).

A recent review article described potential pathways that may be involved in the relationship between insomnia and OSA (Sweetman et al., 2019). Consecutive sleep loss in persons with insomnia may result in a reduction in upper airway muscle tone. Hyperarousal, a key symptom of insomnia, may lower the respiratory arousal threshold, leading to more apnea and hypopnea during sleep. The frequent awakenings after apnea and hypopnea events in persons with OSA may increase insomnia complaints and perpetuate insomnia symptoms (Sweetman et al.,

2019). These bidirectional associations between OSA and insomnia suggest that they may both contribute to the development or exacerbation of the severity of each other.

Despite the bidirectional relationship between insomnia and OSA, insomnia is frequently overlooked in persons with OSA because it has been assumed to be a secondary symptom that will resolve with successful treatment of OSA (Lichstein, 2005). The stereotypical characteristics of insomnia (e.g., common in middle and older age females) are contradictory to those of OSA (e.g., common in middle and older-aged males) (Morin et al., 2015; Senaratna et al., 2017). Several international clinical guidelines for T2DM have focused on better understanding the adverse impact of OSA on diabetes management, although insomnia is rarely included (Smyth et al., 2020). Therefore, comorbid insomnia is likely to be ignored in persons with T2DM and OSA. Due to comorbid insomnia, mood disturbances and diabetes-related distress are likely to remain unresolved in T2DM. Addressing insomnia may be an effective strategy for psychological care in T2DM.

We found that among the six dimensions of mood states, insomnia was associated with higher scores on Tension-Anxiety and Fatigue-Inertia than OSA. According to the ADA's position, treating psychosocial difficulties and reducing diabetes-related distress are important because they are associated with fatigue, diabetes-specific anxiety, including fear of hypoglycemia, failure to meet blood glucose targets, insulin injection, and worse glycemic control (Young-Hyman et al., 2016).

Our study has several limitations. We cannot infer causal relationships because this study was a secondary analysis based on a cross-sectional design of baseline data. Regarding measurement, the use of home-based sleep testing in the parent studies, the ApneaLinkPlus®, may have resulted in an underestimated number of persons with OSA because in-laboratory

polysomnography is a standard measure for OSA diagnosis. The ISI was designed as a screening tool for insomnia rather than a diagnostic tool, and its accuracy is lower than the accuracy of a diagnostic clinical interview. Because there was no information about the exact medication in the parent studies, we could not control the influence of medication that can alter sleep status. Although we found that insomnia contributes to increased mood disturbances and diabetes-related distress in persons with T2DM, this study could not explain how the severity of insomnia interacts with the severity of OSA in impacting mood and diabetes-related distress. This suggests that future studies examining the impact of OSA+I need to explore the interaction between OSA and insomnia severity on mood and diabetes-related distress. Future intervention studies should assess whether reducing the severity of insomnia or OSA is associated with better outcomes in persons with T2DM.

In our study, insomnia played a significant role in increasing mood disturbances and diabetes-related distress in persons with OSA+I. This analysis provided the basis of a manuscript in the *Journal of Clinical Sleep Medicine* (Jeon et al., 2022). The published manuscript differs in that the criteria for OSA was AHI ≥ 15 events/hour. These findings imply that insomnia, rather than OSA, may have a greater impact on mood disturbances and diabetes-related distress in persons with T2DM. Insomnia was associated with a higher HbA1c level, which may have implications for the management of insomnia in persons with T2DM. Future research is needed to see if treatment of insomnia improves impaired mood and diabetes-related distress in persons with T2DM and is associated with improved glycemic control. This association highlights the importance of appropriate clinical screening for insomnia symptoms in persons with T2DM, even after the OSA diagnosis.

3.0 Aim 2 Manuscript: Examination of insomnia as a moderator of the association between OSA severity with mood states and with diabetes-related distress in adults with T2DM

3.1 Abstract

Purpose: Previous findings have shown that insomnia in persons with type 2 diabetes mellitus (T2DM) may have a greater impact on mood disturbances than obstructive sleep apnea (OSA) and that insomnia may contribute to the severity of diabetes-related distress. This study examined insomnia severity as a moderator of the association between OSA severity with mood and diabetes-related distress in adults with OSA and T2DM.

Methods: This secondary analysis used pooled baseline data (N = 240) from two independent randomized controlled trials that evaluated the efficacy of either OSA or insomnia treatment in persons with T2DM. OSA (apnea-hypopnea index [AHI] ≥ 5 events per hour) was determined by in-home ApneaLinkPlus®. Insomnia severity was measured by the Insomnia Severity Index; mood by the Profile of Mood States; and diabetes-related distress by the Problem Areas in Diabetes Scale. The possible moderation effect of insomnia severity was examined using hierarchical multiple linear regression and multivariate linear regression analyses that controlled for demographic characteristics and restless leg syndrome (RLS).

Results: Participants were middle-aged (mean age ± SD [years] = 57.80 ± 10.17), White (65%), educated post high school (56.3%), evenly distributed by gender (49.6% female) and marital status (47.9%), and 34.3% reporting financial difficulty. Participants had poorly controlled diabetes (mean HbA1c ± SD [%] = 7.93 ± 1.62) and 15.5% reported symptoms of RLS. Insomnia severity had a moderating effect on the association between OSA severity and mood states (b = -0.048, *p*

= .017). Insomnia severity had no significant moderating effect on the relationship between OSA severity and diabetes-related distress (b = -0.009, p = .458), but was independently associated with greater diabetes-related distress (b =1.133, p < .001).

Conclusions: Insomnia severity moderated the association between OSA severity and mood states in adults with OSA and T2DM. Counterintuitively, as OSA severity increased, the level of mood disturbances decreased depending on insomnia severity. In addition, insomnia was independently associated with diabetes-related distress. These findings suggest that insomnia may be the primary underlying sleep disorder that is associated with psychological factors in persons with T2DM. Findings need further investigation because psychological factors are known to be associated with worse glycemic control.

3.2 Introduction

Diabetes, a major health concern in the United States, affects more than 9 % of the population (37 million) and was the seventh leading cause of death in 2020. An estimated 90 – 95% of adults with diabetes have type 2 diabetes mellitus (T2DM) (CDC, 2020). Mood disturbances, such as depression and anxiety, and diabetes-related distress are prevalent psychological symptoms in persons with T2DM. For example, the prevalence of depressive disorder was twice as high in persons with T2DM as compared to those without T2DM. One in four persons with T2DM reported elevated depressive symptoms (Anderson et al., 2001). The prevalence of anxiety is higher in persons with diabetes (19.5%) than those without diabetes (10.9%) (Li et al., 2008). Diabetes is associated with an increased risk of having an anxiety disorder and elevated anxiety symptoms (Smith et al., 2013). Diabetes-related distress refers to the unique

emotional burden in persons with diabetes that is associated with concerns about disease diagnosis, meeting the demands of diabetes self-management, and obtaining support in the management of this chronic disease (Polonsky et al., 1995). An estimate of almost half (45.4 %) of community-dwelling adults with T2DM suffer from diabetes-related distress (Fisher et al., 2012).

Therefore, the presence of mood disturbances and diabetes-related distress is a significant problem in persons with T2DM. Depression, anxiety, and diabetes-related distress are associated with poorer self-management behaviors (i.e., physical inactivity, diet, and medication adherence) and worse blood glucose outcomes (Aikens, 2012; Anderson et al., 2002; Fisher, Glasgow et al., 2010; Fisher, Hessler et al., 2012; Gonzalez et al., 2008; Hofmeijer-Sevink et al., 2012; Lustman et al., 2000), which may increase the risk for diabetes-related complications (De Groot et al., 2001; Pintaudi et al., 2015). However, there is limited evidence to understand the modifiable risk factors associated with mood disturbances and diabetes-related distress in persons with T2DM.

Obstructive sleep apnea (OSA) and insomnia are sleep disorders more prevalent in persons with T2DM than in the general population (Schipper et al., 2021). OSA is a sleep-related breathing disorder characterized by repetitive upper airway obstructive (apneas) or decreased airflow (hypopneas) during sleep (Berry et al., 2012). Insomnia is a sleep disorder, characterized by subjective difficulty initiating or maintaining sleep or early morning awakenings with an inability to return to sleep (APA; 2013). OSA and insomnia have been linked to psychological health conditions. In population-based epidemiological studies (Chen et al., 2013; Peppard et al., 2006), OSA was strongly associated with an increased risk of developing depression. Meta-analysis studies of longitudinal epidemiological (Baglioni et al., 2011) or prospective cohort studies in the general population (Li et al., 2016) showed that the risk of having clinical depression in persons with insomnia was two times higher than in those without insomnia. Importantly, persons with

comorbid OSA and insomnia are more likely to have a higher prevalence of clinical depression and to experience greater depressive symptoms than those with OSA (Jeon et al., 2021)

Our findings from Aim 1, which compared mood states and diabetes-related distress in insomnia, OSA only, and comorbid insomnia and OSA among persons with T2DM, show that persons with insomnia and those with comorbid OSA and insomnia had greater mood disturbances and diabetes-related distress when compared to those with OSA (Jeon et al., 2022). These findings suggest that comorbid insomnia may contribute to the severity of mood disturbances and diabetes-related distress in persons with T2DM and OSA.

Therefore, in this study, we examined insomnia as a moderator of the association between OSA with mood states and between OSA with diabetes-related distress. This analysis may help elucidate whether comorbid insomnia adds to the severity of mood disturbances and diabetes-related distress in persons with T2DM and comorbid OSA. We hypothesized that 1) as insomnia severity increases, greater OSA severity is associated with greater mood disturbances, and 2) as insomnia severity increases, greater OSA severity is associated with greater diabetes-related distress.

3.3 Methods

3.3.1 Study Design, Sample, and Setting

This study was a quantitative, cross-sectional secondary analysis of pooled baseline data from two randomized control trials: Diabetes Sleep Treatment Trial (DSTT; R01-DK096028) and Diabetes Sleep Treatment Trial for Insomnia (DSTT-I; K24-NR016685). The purpose of the two-

parent studies was to examine the efficacy of treatment of OSA using continuous positive airway pressure (DSTT), and treatment of insomnia using online cognitive behavioral treatment insomnia (DSTT-I) compared to subtherapeutic treatment on glycemic control and diabetes self-management behaviors in individuals with T2DM.

The DSTT recruited 351 participants from multisite: University of Pittsburgh, Veterans Administration Pittsburgh Healthcare System, University of West Virginia, and John H. Dingle Veterans Administration Detroit Healthcare System. The DSTT-I recruited 55 participants at a single site from the DSTT (University of Pittsburgh). In both parent studies, participants were recruited from endocrinology and sleep outpatient clinics using various strategies (e.g., a research registry, focused mailing, flyers in the community, and social media advertisement). Only for DSTT-I, the excluded participants from DSTT who did not have an Apnea-Hypopnea Index (AHI) $\geq$ 10 events/hour were screened for the DSTT-I. Eligibility criteria for the baseline assessment in parent studies include age 18 years or older, self-reported T2DM, ability to read and write English, no acute illness requiring hospitalization in the last 3 months, no near-miss or automobile accident due to sleepiness, not employed in a safety-sensitive occupation, and willing to be randomized to the respective studies.

For this secondary analysis, the participants did not have missing data on variables for OSA severity, insomnia severity, mood states, and diabetes-related distress, and met the diagnostic criteria of OSA (the AHI $\geq$ 5 events/hour). A total of 240 participants were eligible for this secondary analysis (Figure 6). The parent studies were approved by the Institutional Review Board (IRB) at each site of studies. This study was independently approved by the University of Pittsburgh IRB to combine the data from the DSTT and DSTT-I.

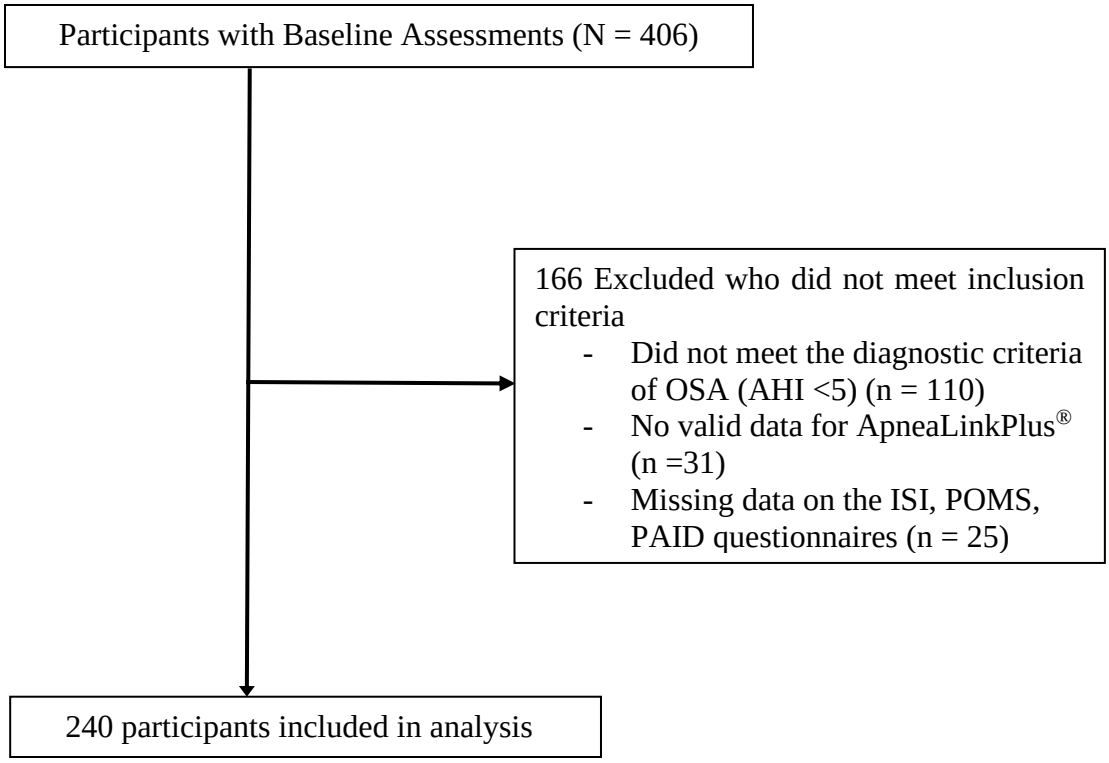


Figure 6. Participant Flow for Inclusion (Aim 2)

3.3.2 Measures

3.3.2.1 Independent variable

OSA severity was an independent variable, defined as the level of AHI. The ApneaLinkPlus® (ResMed, San Diego, CA) is an FDA-approved level III portable sleep testing device for in-home sleep studies. It measures respiratory effort, nasal flow, pulse, and oxygen saturation to derive the AHI (Collop et al., 2007). Participants wore the ApneaLinkPlus® for a single night and returned the device in the pre-paid mail packet; trained polysomnography (PSG) technicians validated all data following the current published standards of the American Academy of Sleep Medicine (AASM) for scoring apneas and hypopneas (Berry et al., 2012). The higher AHI indicates higher OSA severity.

3.3.2.2 Moderator variable

The moderator variable was insomnia severity. Insomnia severity was measured by the Insomnia Severity Index (ISI). The ISI (Morin et al., 2011) is a 7-item self-report questionnaire. Each item is answered based on a 5-point Likert scale ranging from '0 = no problems' to '4 = very severe problem'. The total score was calculated by adding each item score. A higher overall score indicates higher insomnia severity. The total score is clinically interpreted as follows: absence of insomnia (0 – 7); subthreshold insomnia (8 – 14); moderate insomnia (15 – 21); and severe insomnia (22 – 28) (Morin et al., 2011).

3.3.2.3 Dependent variable

The dependent variables are mood states and diabetes-related distress. Mood states are measured by the Profile of Mood States (POMS). The POMS (McNair & Heuchert, 2007) consists of six dimensions of mood based on a set of sixty-five adjectives or phrases (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment). Each item is answered based on a 5-point Likert scale ranging from '0 = Not at all' to '4 = Extremely'. While separate scores are obtained for every subscale, the POMS total mood disturbance (TMD) score is also calculated. For the POMS TMD score, the Vigor-Activity score (positive mood) was subtracted from the sum of the five negative subscale scores (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment). Higher POMS TMD scores indicate greater mood disturbances.

The Problem Areas in Diabetes (PAID) (Polonsky et al., 1995), a 20-item self-report questionnaire, is used to measure diabetes-related distress. Each item is answered based on a 5-point Likert scale ranging from '0 = Not a problem' to '4 = Serious problem'. The sum of the

twenty items is multiplied by 1.25 to produce a total score that can range from 0 to 100. Higher scores indicate greater diabetes-related distress.

3.3.2.4 Sociodemographic and Clinical Information

Sociodemographic and clinical variables were used to describe the sample and included in models as potential covariates. For sociodemographic information, participants self-reported their age (years), gender (male vs. female), marital status (married/partnered vs. single/divorced/widowed), race (non-White vs. White), an education level (< 2-year degree of college or technical training vs. ≥ 2-year degree from a college or technical training). A question for asking about financial difficulty was 'how difficult is it for you to meet your basic needs?'. The possible responses were dichotomized as 'no difficulty' to meet their needs and having 'somewhat/extremely' difficulty to meet their needs.

Sleep-related information includes daytime sleepiness, sleep quality, and the presence of restless leg syndrome (yes vs. no). The Epworth Sleepiness Scale (ESS) (Johns, 1991) measures subjective daytime sleepiness while engaged in eight common daytime activities (e.g., sitting and reading, watching TV). Higher ESS scores indicate greater daytime sleepiness. A score >10 indicates that a participant has excessive daytime sleepiness. The Pittsburgh Sleep Quality Index (PSQI) (Buysee et al., 1989) identifies good and poor sleepers. Higher PSQI scores indicate worse sleep quality. A global sleep quality score > 5 indicates that a participant has poor sleep quality.

Diabetes-related clinical information included insulin use (yes/no), duration of T2DM (years), BMI (kg/m^2), and HbA1c (%). Measured height and weight were used to calculate BMI. A blood sample (no more than 30cc) was collected to get the value of HbA1c, which is a reliable indicator of glycemic control over the past 2 to 3 months (ADA, 2020).

3.3.3 Procedure

In both parent studies, brief in-person or telephone interviews were conducted to determine the eligibility for the baseline assessment. Before the baseline assessment, informed written consent was obtained. For those who were willing to continue participation, height and weight were measured for BMI, and venipuncture was performed to obtain no more than 30cc blood for HbA1c. Participants were instructed on how to wear the ApnealinkPlus® and how to complete the questionnaires at home, and two pre-paid mail packets were provided to return the ApneaLinkPlus® device the next day and baseline questionnaires after 7 days. The validated ApneaLinkPlus® data and the coded responses for questionnaires were stored on a secure server at the University of Pittsburgh. For this secondary analysis, the DSTT and the DSTT-I baseline data were merged into one data set based on shared instruments and assessments.

3.3.4 Data Analysis

Initially, preliminary data analyses were performed to describe the distribution of each variable, missing data, covariates/confounders, and violation of statistical assumptions. Among a total of 406 participants from whom data were collected during the DSTT (N = 351) and DSTT-I (N = 55) trials, the number of eligible participants was 240 for this investigation (Figure 6). The characteristics of the total sample were analyzed with appropriate descriptive statistics based on the level of measurement and the observed distribution of each variable (i.e., mean, median, standard deviation, interquartile range, frequency, and percentage). Only 2 participants (0.8%) were excluded from the main analyses because they did not complete the questions asking about the financial difficulty and the identification of restless leg syndrome. The characteristics between

eligible participants and excluded participants were compared using the independent sample t-tests (for continuous variables) or chi-square (χ^2) tests of independence (for categorical variables) to examine the randomness of missing data (Table 15). Excluded participants experienced worse insomnia and mood disturbance because the participants with insomnia only are more likely to be included in the excluded participants. Little's MCAR test demonstrated that the missingness of data was completely at random among the eligible participants (χ^2 = 94.853, *df* = 74, *p* = .052). Sociodemographic information (age, gender, marital status, race, education level, financial difficulty) and restless leg syndrome were included as potential covariates following their correlation with the primary variables of interests or evidence from the previous literature.

Hierarchical multiple regression analysis was performed to examine the moderating effect of insomnia severity (i.e., the ISI score) on the relationship between OSA severity (i.e., the AHI) and mood states (i.e., POMS TMD score), and diabetes-related distress (i.e., PAID score) while controlling for the covariates. In the moderation model, OSA severity was the primary independent/predictor variable. Due to positive skewness of the studentized residuals, a square root transformation and logarithmic transformation were considered for the POMS TMD score and the AHI, repectively. Score alteration was considered for the univariate outlier identified for the PAID score. However, we reported results using the original metric since similar results were obtained when using the transformed data. Also, variance inflation factor (VIF) values did not exceed 10 with the untransformed data suggesting that there was no problem with multicollinearity. Mean centering for the ISI score and AHI score was not considered.

Because the distribution of the studentized residual for the POMS TMD score was positively skewed with multiple outliers, a square root transformation was applied. The scores of

two outliers in the standardized residual for the PAID score were altered to be close to the next highest non-outlier value.

In each moderation model, the covariates were entered into the analysis during the first step. The independent variable, OSA severity, was entered into the analysis during the second model. The moderator variable, insomnia severity, was entered into the regression equations for the third step. In the fourth step, the interactions of independent and moderator variables (i.e., OSA severity × insomnia severity) were entered into the regression model. For step four, a significant change in R^2 for the interaction term indicated a significant moderator effect. The graphical representation of the significant interaction between OSA severity and insomnia severity was derived by using the values of the AHI and the ISI that were chosen at the 16^{th}, 50^{th}, and 84^{th} percentiles (Hayes, 2018). For all fitted hierarchical regression models, potential influential observations were assessed by the scatter plot between studentized deleted residual and centered leverage value. Identified influential cases did not change the statistical significance of the results.

The multivariate linear regression analysis was used to examine the moderator role of insomnia severity on the relationship between OSA severity and the six dimensions of mood states (i.e., the subscale scores of Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment) while controlling for covariates. The significance of the multivariate model was assessed by Wilks' lambda (λ) test with multiple linear regression analyses for each POMS subscale score. A square root transformation was considered for Depression-Dejection and Anger-Hostility subscale scores due to positive skewness and multiple univariate outliers, but the original data was used since similar results were obtained when using the transformed data. All analyses were performed using SPSS Statistics Version 25.0 (IBM

Corp., Armonk, NY) and the level of statistical significance for two-sided hypothesis testing was set at .05.

Table 15. Comparison of Characteristics between Eligible and Excluded Participants for Aim 2 (N = 406)

Baseline Characteristic	Eligible participants n = 240	Excluded participants n = 166	*p*
Sociodemographic information			
Age, y	57.80 ± 10.17	54.72 ± 10.80	.004
Gender			
Female	119 (49.6)	88 (53.0)	.497
Male	121 (50.4)	78 (47.0)	
Marital status			
Never married/Separated/divorced/widowed	125 (52.1)	103 (62.8)	.033
Married/partnered	115 (47.9)	61 (37.2)	
Race			
Non-white	84 (35.0)	80 (48.2)	.008
White	156 (65.0)	86 (51.8)	
Education level			
< 2-years college degree, or technical training	105 (43.8)	75 (46.0)	.654
≥ 2-years college degree, or technical training	135 (56.3)	88 (54.0)	
Financial hardship			
Somewhat/extremely difficult	82 (34.3)	87 (53.0)	< .001
Not at all difficult	157 (65.7)	77 (47.0)	
Sleep-related clinical information			
OSA severity			
AHI	19.31 ± 16.20	6.75 ± 14.36	< .001
Insomnia severity			
ISI	13.54 ± 6.01	15.12 ± 6.65	.020
Daytime sleepiness			
ESS	10.13 ± 4.69	9.58 ± 4.77	.300
Sleep quality			
PSQI	9.71 ± 3.90	11.13 ± 4.18	.002
Restless leg syndrome, *n* (%)*			
Yes	37 (15.5)	28 (24.1)	.078
No	202 (84.5)	88 (75.9)	
Diabetes-related clinical information			
Insulin use status, *n* (%)			
Yes	109 (45.4)	57 (37.3)	.110
No	131 (54.6)	96 (62.7)	
Duration of T2DM, y	11.15 ± 9.42	10.49 ± 8.61	.526
A1C (%)*	7.93 ± 1.62	7.95 ± 2.08	.913
BMI (kg/m^2)*	35.78 ± 7.13	33.16 ± 6.31	< .001
Mood States			
POMS Total Mood Disturbance Score	26.00 ± 33.60	34.71 ± 36.72	.014
POMS Tension-Anxiety	8.90 ± 6.37	10.98 ± 7.20	.002

Baseline Characteristic	Eligible participants	Excluded participants	
POMS Depression-Dejection	8.08 ± 9.60	10.80 ± 10.52	.008
POMS Anger-Hostility	7.15 ± 7.47	8.04 ± 8.12	.262
POMS Vigor-Activity	15.35 ± 6.22	14.42 ± 6.75	.154
POMS Fatigue-Inertia	10.56 ± 6.21	11.50 ± 7.39	.168
POMS Confusion-Bewilderment	6.65 ± 4.66	7.80 ± 5.16	.020
Diabetes-related distress			
PAID	29.67 ± 20.46	29.67 ± 21.25	1.00

Note. Chi-square test of independence was conducted for nominal variables. Independent t-test with non-equal variances was conducted for continuous variables. AHI = Apnea-Hypopnea Index; ISI = Insomnia Severity Index; ESS = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index; T2DM = Type 2 Diabetes Mellitus; A1C = HbA1c; BMI = Body Mass Index; POMS = Profile of Mood States; PAID = Problem Areas in Diabetes.

3.4 Results

3.4.1 Sample Characteristics

A total of 240 adults with T2DM and OSA were included in this analysis. The characteristics of the sample are shown in Table 16. Our sample was primarily middle-aged (mean age 57.80 ± 58.0 years). Almost one-third of participants were non-Whites (35.0%) and expressed that they had "moderate" or "severe" financial difficulty (34.3%). The sample was well-distributed by gender (49.6% female), marital status (47.9% married or partnered), an education level (56.3% with more than 2 years of college or technical training). Our sample of persons with T2DM and OSA was overweight or obese, with a mean BMI of 35.78 ± 7.18 kg/m^2. Participants had suboptimal glycemic control (mean A1C = 7.93 ± 1.62%), the average duration of T2DM diagnosis was over ten years (11.15 ± 9.42 years), and almost half (45.4%) of the sample was prescribed insulin. The total sample had, on average, moderate-to-severe OSA (Berry et al., 2012),

subthreshold insomnia (Morin et al., 2011), and moderate levels of excessive daytime sleepiness (Johns, 1991), and poor sleep quality (Buysse et al., 1989).

Table 16. Sample Characteristics of Aim 2 (N = 240)

Baseline Characteristic	n (%)	*Mean* (*Mdn*)	*SD*	Range
Sociodemographic information				
Age (years)		57.80 (58.0)	10.17	31-91
Gender				
Female	119 (49.6)			
Male	121 (50.4)			
Marital status				
Never married/ Separated/divorced/widowed	125 (52.1)			
Married/partnered	115 (47.9)			
Race				
Non-white	84 (35.0)			
White	156 (65.0)			
Education level				
< 2-year college degree, or technical training	105 (43.8)			
≥ 2-year college degree, or technical training	135 (56.3)			
Financial hardship				
Somewhat/extremely difficult	82 (34.3)			
Not at all difficult	157 (65.7)			
Sleep-related clinical information				
OSA severity				
AHI		19.31 (14.15)	16.20	5-95
Insomnia severity				
ISI		13.54 (13.0)	6.01	0-28
Daytime sleepiness				
ESS		10.13 (9.0)	4.69	1-24
Sleep quality				
PSQI		9.71 (10.0)	3.90	1-21
Restless Leg Syndrome				
Yes	37 (15.5)			
No	202 (84.5)			
Diabetes-related clinical information				
Insulin use status				
Yes	109 (45.4)			

Baseline Characteristic	n (%)	*Mean* (*Mdn*)	*SD*	Range
No	131 (54.6)			
Duration of T2DM (years)		11.15 (10.0)	9.42	0.5-57
A1C (%)		7.93 (7.60)	1.62	5.3-14
BMI (kg/m^2)		35.78 (34.80)	7.13	22.7-60
Mood states				
POMS Total Mood Disturbance Score		26.00 (20.0)	33.60	-32-154
POMS Tension-Anxiety		8.90 (8.0)	6.37	0-34
POMS Depression-Dejection		8.08 (5.0)	9.60	0-48
POMS Anger-Hostility		7.15 (5.0)	7.47	0-37
POMS Vigor-Activity		15.35 (16.0)	6.22	0-32
POMS Fatigue-Inertia		10.56 (10.0)	6.21	0-26
POMS Confusion-Bewilderment		6.65 (6.0)	4.66	0-25
Diabetes-related distress				
PAID		29.67 (26.25)	20.46	0-100

Note. Mdn = median, SD = standard deviation, AHI = Apnea-Hypopnea Index; ISI = Insomnia Severity Index; ESS = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index; T2DM = Type 2 Diabetes Mellitus; A1C = HbA1c; BMI = Body Mass Index; POMS = Profile of Mood States; PAID = Problem Areas in Diabetes.

3.4.2 Moderating effect of insomnia severity on the relationship between OSA severity and mood states

Table 17 explains the full details regarding each regression model. The addition of insomnia severity to the prediction of mood states (Model 3) led to a statistically significant increase in R^2 of .093, $F(1, 228) = 28.072$, $p < .001$). The addition of the interaction of OSA severity and insomnia severity to the prediction of mood states (Model 4) also led to the statistically significant increase in R^2 of .019, $F(1, 227) = 5.780$, $p = .017$. The full model (Model 4) was statistically significant, $R^2 = .263$, $F(10, 227) = 8.096$, $p < .001$.

As shown in Model 4, the interaction of the AHI and the ISI was negatively associated with the POMS TMD score ($b = -.048$, $p = .017$). This finding showed that insomnia severity had a moderating effect on the relationship between OSA severity and mood disturbances. As insomnia

severity increases, greater OSA severity is associated with less severe mood disturbances. The graphical representation of the significant interaction between OSA severity and insomnia severity (Figure 7) in adults with T2DM and OSA showed that those without clinical insomnia were associated with a steady increase in mood disturbance as OSA severity increased. On the other hand, those with subthreshold and clinical insomnia were associated with a steady decrease in mood disturbances as OSA severity increased. Insomnia may reduce the deleterious effects of OSA severity on mood disturbances.

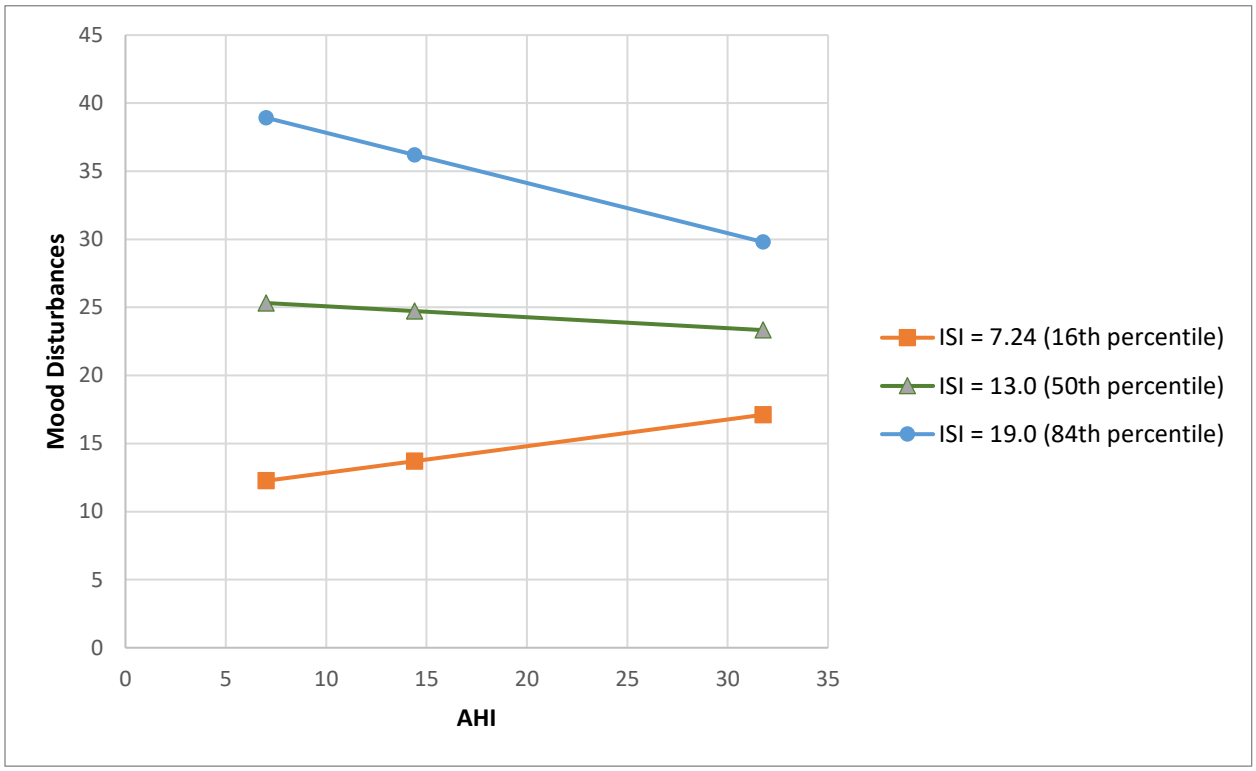
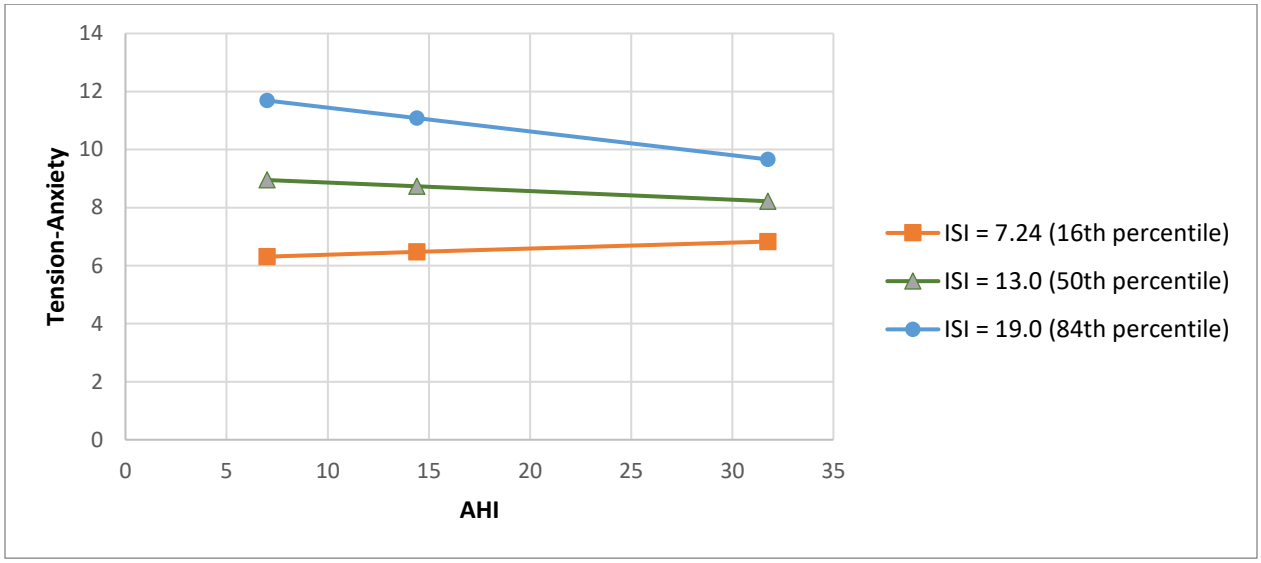
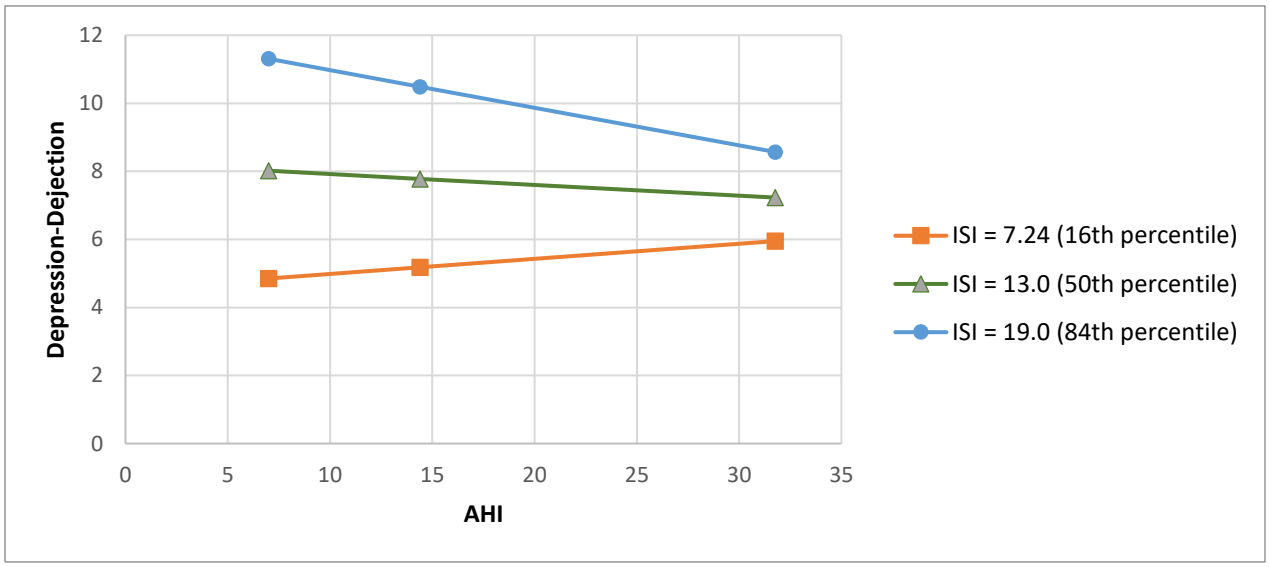


Figure 7. Interaction of OSA Severity and Insomnia Severity on Total Mood Disturbance

The overall model was statistically significant, $F(60, 1168.18) = 2.968$, Wilke's $\lambda = .473$, $p < .001$. All multiple linear regression models for each subscale score are also significant (all $p < .001$). As shown in Table 18, the interaction of the AHI and the ISI was negatively associated with

the Tension-Anxiety (b = -.009, p = .019), Depression-Dejection (b = -.013, p = .025), and Confusion-Bewilderment subscale scores (b = -.009, p = .003). This finding showed that insomnia severity had a moderating effect on the relationship between OSA severity and the Tension-Anxiety, Depression-Dejection, and Confusion-Bewilderment subscale scores (Figure 8). As insomnia severity increases, greater OSA severity is associated with less severe Tension-Anxiety, Depression-Dejection, and Confusion-Bewilderment mood states.





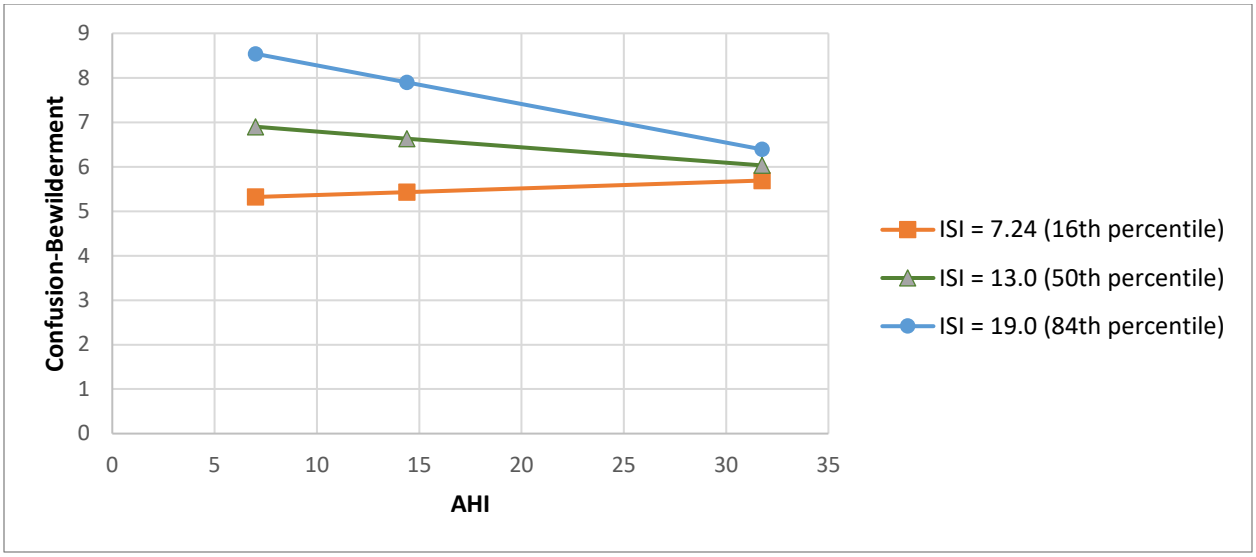


Figure 8. Interaction of OSA Severity and Insomnia Severity on Tension-Anxiety, Depression-Dejection, Confusion-Bewilderment subscale scores

3.4.3 Moderating effect of insomnia severity on the relationship between OSA severity and diabetes-related distress

Table 19 describes the full details of a hierarchical multiple regression model to examine the role of insomnia severity (i.e., the ISI score) as a moderator of the relationships between OSA severity (i.e., AHI) and diabetes-related distress (i.e., the PAID score) in adults with T2DM and OSA while controlling for identified covariates (age, gender, race, marital status, education level, financial hardship, restless leg syndrome). The addition of insomnia severity to the prediction of mood states (Model 3) led to a statistically significant increase in R^2 of .104, $F(1, 228) = 32.849$, $p < .001$). The Model 3 was statistically significant, $R^2 = .280$, $F(9,228) = 9.835$, $p < .001$. The addition of the interaction of OSA severity and insomnia severity to the prediction of mood states (Model 4) did not lead to a statistically significant increase in R^2 of .002, $F(1, 227) = .554$, $p =$

.458. The full model (Model 4) was statistically significant, R^2 = .281, F(10, 227) = 8.889, p < .001.

In Model 4, there was no significant interaction between OSA severity and insomnia severity (b = -.009, p = .458). This indicates that insomnia severity had no moderating effect on the relationship between OSA severity and diabetes-related distress. The relationship between OSA severity and diabetes-related distress did not change depending on the severity of insomnia. According to the Model 3, OSA severity was not associated with diabetes-related distress (b = -.046, p = .527), whereas insomnia severity significantly increased diabetes-related distress (b = 1.133, p < .001). In other words, insomnia severity is independently associated with diabetes-related distress regardless of OSA severity.

Table 17. Results of Hierarchical Linear Regression Analysis for the Moderating Effect of Insomnia on the Relationship between OSA and Profile of Mood States Total Mood Disturbance Score (N = 238)

		Total Mood Disturbance							
		Model 1		Model 2		Model 3		Model 4	
		Unstandardized Regression Coefficients							
Block	Predictor	*b*	*p* value	*b*	*p* value	*b*	*p* value	*b*	*p* value
1	Constant	50.903	<.001	52.393	<.001	32.344	.013	23.794	.074
	Age (years)	-.539	.010	-.540	.010	-.562	.005	-.579	.003
	Female[a]	-3.007	.471	-3.476	.417	-5.722	.160	-5.243	.193
	≥ 2years college degree, or technical training[b]	-4.349	.318	-4.500	.303	-4.039	.329	-5.842	.161
	White[c]	7.771	.102	7.993	.095	8.924	.049	7.299	.107
	Married/living with a partner[d]	-6.645	.125	-6.576	.130	-7.423	.071	-6.788	.096
	Financial difficulty[e]	14.924	.002	15.175	.002	12.099	.008	11.717	.010
	Restless leg syndrome[f]	16.327	.004	16.180	.004	12.677	.018	13.611	.011
2	AHI			-.069	.591	-.057	.636	.544	.051
3	ISI					1.730	<.001	2.604	<.001
4	AHI x ISI							-.048	.017
	R^2	.150		.151		.244		.263	
	R^2 change	.150**		.001		.093**		.019*	

Notes. AHI = Apnea-Hypopnea Index; ISI = Insomnia Severity Index; *$p < .05$; **$p < .001$

[a] Male was treated as the reference category for gender.

[b] < 2-year college degree or technical training (i.e., 8 grades or less, some high school, high school graduate or GED, some college or technical school) was treated as the reference category for education level

[c] Non-white (i.e., American Indian/Alaska Native, Asian, Black or African American, Biracial) was treated as the reference category for race

[d] Never married/separated/divorced/widowed was treated as the reference category for marital status

[e] Do not have financial difficulty was treated as the reference category for financial status

[f] Do not have restless leg syndrome was treated as the reference category for restless leg syndrome

Table 18. Results of Multivariate Linear Regression for the Moderating Effect of Insomnia on the Relationship between OSA and Six Subscales of Profile of Mood States (N = 238)

	Tension-Anxiety		Depression-Dejection		Anger-Hostility		Vigor-Activity		Fatigue-Inertia		Confusion-Bewilderment	
	Unstandardized Regression Coefficients											
Predictor	*b*	*p* value	*b*	*p* value	*b*	*p* value	*b*	*p* value	*b*	*p* value	*b*	*p* value
Age (years)	-.131	<.001	-.067	.240	-.101	.032	.144	<.001	-.086	.020	-.049	.082
Female[a]	-.524	.485	-2.602	.029	-2.400	.014	-.562	.480	-.136	.859	-.141	.810
≥ 2-years college degree, or technical training[b]	-1.557	.046	-1.070	.382	-1.083	.281	.818	.320	-.166	.833	-1.148	.060
White[c]	1.671	.048	.089	.947	.634	.562	-2.131	.018	2.198	.011	.576	.383
Married/living with a partner[d]	-.853	.262	-2.602	.045	-1.725	.080	1.391	.084	.081	.917	-.493	.407
Financial difficulty[e]	2.113	.012	2.785	.036	1.545	.156	-1.257	.158	2.185	.011	1.832	.006
Restless leg syndrome[f]	2.084	.036	4.739	.003	3.082	.017	-.525	.671	2.001	.047	1.181	.128
AHI	.085	.102	.140	.087	.117	.083	-.092	.095	.032	.541	.078	.055
ISI	.519	<.001	.642	<.001	.314	.008	-.385	<.001	.409	<.001	.335	<.001
AHI x ISI	-.009	.019	-.013	.025	-.009	.060	.006	.116	-.002	.599	-.009	.003
Adjusted R^2	.260		.172		.094		.154		.206		.165	
F(10, 227)	9.313**		5.926**		3.457**		5.311**		7.139**		5.683**	

Notes. AHI = Apnea-Hypopnea Index; ISI = Insomnia Severity Index; *$p < .05$; **$p < .001$

[a] Male was treated as the reference category for gender.

[b] < 2-years college degree or technical training (i.e., 8 grades or less, some high school, high school graduate or GED, some college or technical school) was treated as the reference category for education level

[c] Non-white (i.e., American Indian/Alaska Native, Asian, Black or African American, Biracial) was treated as the reference category for race

[d] Never married/separated/divorced/widowed was treated as the reference category for marital status

[e] Do not have financial difficulty was treated as the reference category for financial status

[f] Do not have restless leg syndrome was treated as the reference category for restless leg syndrome

Table 19. Results of Hierarchical Linear Regression Analysis for the Moderating Effect of Insomnia on the Relationship between OSA and Diabetes-related Distress (N = 238)

		Diabetes-related distress							
		Model 1		Model 2		Model 3		Model 4	
		Unstandardized Regression Coefficients							
Block	Predictor	*b*	*p* value	*B*	*p* value	*b*	*p* value	*b*	*p* value
1	(Constant)	35.909	<.001	37.055	<.001	23.922	.002	22.302	.007
	Age (years)	-.165	.193	-.166	.191	-.180	.131	-.183	.124
	Female[a]	2.273	.373	1.906	.465	.434	.860	.525	.831
	≥ 2-years college degree, or technical training[b]	-6.907	.010	-7.025	.009	-6.723	.008	-7.065	.006
	White[c]	2.059	.478	2.233	.444	2.843	.299	2.535	.360
	Married/living with a partner[d]	-.868	.743	-.813	.759	-1.368	.582	-1.248	.616
	Financial difficulty[e]	9.772	.001	9.969	.001	7.954	.004	7.882	.005
	Restless leg syndrome[f]	10.175	.003	10.060	.004	7.765	.017	7.942	.015
2	AHI			-.054	.491	-.046	.527	.068	.691
3	ISI					1.133	<.001	1.299	.000
4	AHI x ISI							-.009	.458
	R^2	.174		.176		.280		.281	
	R^2 change	.174**		.002		.104**		.002	

Notes. AHI = Apnea-Hypopnea Index; ISI = Insomnia Severity Index; **$p < .001$

[a] Male was treated as the reference category for gender.

[b] < 2-years college degree or technical training (i.e., 8 grades or less, some high school, high school graduate or GED, some college or technical school) was treated as the reference category for education level

[c] Non-white (i.e., American Indian/Alaska Native, Asian, Black or African American, Biracial) was treated as the reference category for race

[d] Never married/separated/divorced/widowed was treated as the reference category for marital status

[e] Do not have financial difficulty was treated as the reference category for financial status

[f] Do not have restless leg syndrome was treated as the reference category for restless leg syndrome

3.5 Discussion

This study investigated the moderating role of insomnia between OSA and mood and between OSA and diabetes-related distress in persons with comorbid T2DM and OSA. Our study found that insomnia was a moderator between OSA and mood in an unexpected direction. When insomnia severity increased, the deleterious effect of OSA severity on mood disturbances decreased. Furthermore, insomnia was not a moderator between OSA and diabetes-related distress. However, insomnia was independently associated with an increased level of diabetes-related distress, whereas OSA was not. These findings suggest that insomnia may be the primary underlying sleep disorder associated with negative mood states and diabetes-related distress in persons with T2DM.

Unlike our hypothesis, we found that as insomnia severity increases, there is an inverse relationship between OSA severity and mood disturbances. This unexpected finding requires careful exploration. This may be explained by the possibility that the presence and severity of OSA were not the primary cause of mood disturbances. Several studies have found little or no relationship between the severity of mood disturbances and the severity of sleep apnea (Pillar & Lavie, 1998; Sforza et al., 2002). Results of a study (N= 60) of persons with OSA or snoring (Sforza et al., 2002) found that depression, anxiety, and personality change were not associated with AHI. In a large study (N=2271) of persons with OSA (Pillar & Lavie, 1998), there was a difference between men and women in the association between OSA and insomnia and mood disturbances. In men, OSA severity, measured by the respiratory disturbance index (RDI), was not significantly associated with depressive and anxiety symptoms ($p > .05$); in women, depressive

symptoms were significantly worse in patients with severe OSA compared to patients with mild OSA ($p < .05$), but there was no linear relationship between RDI and depressive symptoms ($p > .05$).

Previous studies that examined the effect of OSA on mood disturbances ignored the effect of comorbid insomnia on mood disturbances. Although OSA severity or the diagnosis of OSA was associated with higher depressive symptoms or higher prevalence of major depressive disorder (Aloia et al., 2005; Ohayon, 2003), insomnia symptoms were not examined covariates in these studies. In population-based longitudinal studies which showed an increased risk of developing depression in persons with OSA, only demographic or clinical information was adjusted for analyses (Peppard et al., 2006). Interestingly, in recent studies that identified OSA phenotypes following clinical symptoms, the 'Disturbed sleep group' for patients with OSA who had the highest probability of experiencing insomnia symptoms had worse mental health status than the 'minimally symptomatic group' (Ye et al., 2014). Among 6,555 patients with OSA, patients with the phenotypes with insomnia symptoms were more likely to have psychiatric diseases than those with excessive daytime sleepiness only and those without any symptoms (Saaresranta et al., 2016). The level of OSA severity, measured by AHI, was not always significantly higher in the phenotypes of OSA with insomnia symptoms than those of OSA without insomnia symptoms (Saaresranta et al., 2016; Ye et al., 2014). The objective measures of OSA do not reflect the clinical presentations of insomnia. Therefore, comorbid insomnia may be a latent factor in increasing mood disturbances in persons with T2DM regardless of OSA severity.

This study is significant, as it is the first to call attention to insomnia as a factor in increasing the severity of diabetes-related distress in persons with T2DM and OSA. Current randomized control trials to improve diabetes-related distress and metabolic outcomes in persons

with T2DM generally focus on patient education to foster self-management behaviors with various strategies (e.g., mobile education, group education, education with peer-support, nurse-coaching) (Quinn et al., 2011; Simmons et al., 2015; Sperl-Hillen et al., 2011; Van Der Wupl et al., 2012; Van Dijk-de Vries et al., 2015) but do not consider the management of modifiable factors of diabetes-related distress. These self-management strategies were not found to be effective in reducing diabetes-related distress in persons with T2DM (Chew et al., 2017). Our findings suggest that insomnia could be a modifiable factor in improving diabetes-related distress. We conclude that it would be beneficial to evaluate and treat insomnia symptoms in persons with T2DM to improve diabetes-related distress, even after being diagnosed with OSA. However, the evaluation of insomnia was not a part of routine screening for OSA (Epstein et al., 2009). Several clinical guidelines for T2DM consider the assessment and management of OSA to reduce its adverse impact on diabetes care (Smyth et al., 2020). Our finding highlights the importance of assessing and managing insomnia in the management of OSA in persons with T2DM.

The ADA asserts that psychological symptoms influence diabetes self-management, glycemic control, and diabetes-related complications, but that is not adequately addressed and treated in diabetes routine care (Young-Hyman et al., 2016). To the best of our knowledge, this is the first attempt to find that improving insomnia in persons with T2DM could improve mood disturbances and diabetes-related distress. This evidence is clinically significant because it may encourage the healthcare provider to consider evaluation and intervention for insomnia in diabetes routine care to reduce mood disturbances and diabetes-related distress, even after OSA diagnosis, the most common sleep disorder in T2DM.

Limitations of this study include that we used data collected cross-sectionally; therefore, we cannot assume a causal relationship between insomnia severity and mood or diabetes-related

distress. In terms of measures, we only used the self-reported questionnaire (i.e., the ISI) to define insomnia severity. Finally, in this analysis, although the participants were eligible for baseline assessment for two clinical trials (DSTT and DSTT-I), they may not be reflective of persons with T2DM who have sleep disorders and mood disturbances. For example, persons with severe depression or suicidal ideation were excluded from DSTT-I, persons with prior or current CPAP treatment for OSA were excluded from DSTT, and persons on current hypnotic medications were excluded from both parent studies.

Insomnia is highly associated with the multiple aspects of sleep (e.g., sleep duration < 6 hours, sleep latency ≥ 30 min, sleep efficiency < 85%, poor sleep quality) (Buysse, 2013). Future studies that examine the association between insomnia and the incidence of psychological disorders in persons with T2DM need to be designed to identify distinct sleep-related symptoms among persons with T2DM to develop more precisely targeted insomnia interventions.

In conclusion, our findings are clinically significant because identifying insomnia as a primary underlying sleep disorder that impacts mood states and diabetes-related distress in persons with T2DM creates the foundation for offering more precise psychological care in persons with T2DM. Follow-up studies are required to examine whether the associations between psychological symptoms of self-management behaviors and glycemic control are affected by insomnia symptoms in persons with T2DM. This will help to understand better the comprehensive role of sleep in improving health outcomes in persons with T2DM.

4.0 Aim 3 Manuscript: Examination of mood states and diabetes-related distress as possible mediators of the association of OSA and insomnia with glucose outcomes in adults with T2DM

4.1 Abstract

Purpose: Obstructive sleep apnea (OSA), the most common sleep disorder in persons with T2DM, frequently coexist with insomnia. Comorbid insomnia is frequently associated with impaired mood and diabetes-related distress in persons with T2DM. In this study, we examined mood disturbances and diabetes-related distress as potential mediators of the association of OSA and insomnia severity with glucose outcomes in persons with T2DM and OSA.

Methods: Baseline data of persons with T2DM and OSA from two independent randomized controlled trials were merged for this secondary analysis. OSA severity was determined by the Apnea-Hypopnea Index (AHI) measured by an in-home ApneaLinkPlus® sleep study. Data were analyzed from participants with OSA (AHI ≥ 5) who completed questionnaires to elicit insomnia severity (Insomnia Severity Index), mood disturbances (Profile of Mood States), and diabetes-related distress (Problem Areas in Diabetes Scale). Glucose outcome was measured by hemoglobin A1c (HbA1c). Mediation analysis with bootstrapped samples was used to examine whether mood disturbances and/or diabetes-related distress mediated the effect of OSA and insomnia severity on HbA1c after controlling for clinical and sociodemographic covariates.

Results: Persons with T2DM and OSA were included (N=240) in this secondary analysis and were middle-aged, well distributed by sex, and well-educated, with suboptimal glucose control (mean 57.8 years of age; 49.6% female; 65% White; 56.3% post high school education, mean HbA1c

7.93%, respectively). Diabetes-related distress significantly mediated the association between insomnia severity and HbA1c (indirect effect: b = 0.0169, se = 0.0083, 95% CI [0.0028, 0.0348]), but not between OSA severity and HbA1c (indirect effect: b = -0.0003, se = 0.0011, 95% CI [-0.0025, 0.0019]). Mood disturbances did not significantly mediate the associations of either OSA or insomnia severity with HbA1c (indirect effect: b = 0.0001, se = 0.0006, 95% CI [-0.0011, 0.0014]; indirect effect: b = -0.0022, se = 0.0068, 95% CI [-0.0167, 0.0105], respectively). That is, persons with greater insomnia severity have greater diabetes-related distress, which in turn leads to heightened HbA1c in adults with T2DM and OSA.

Conclusions: In persons with T2DM and OSA, comorbid insomnia could be a potentially modifiable factor in reducing diabetes-related distress and improving glycemic control. Insomnia should be evaluated and treated in persons with T2DM to improve adequate health outcomes.

4.2 Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent complete (apneas) and partial obstruction (hypopneas) of the upper airway, which results in decreased blood oxygen levels (hypoxemia) during sleep (Berry et al., 2012; Malhotra et al., 2018). Multiple previous studies concur that persons with Type 2 diabetes mellitus (T2DM) have an increased risk of OSA than those without diabetes (Schipper et al., 2021). The prevalence of OSA, defined as an apnea-hypopnea index (AHI) ≥ 5 events/hour, ranges from 55% to 86% in adults with T2DM (Reutrakul & Mokhlesi et al., 2017).

Recent studies find that OSA is not only frequently found in persons with T2DM but commonly coexists with insomnia (Jeon, Luyster, Callan et al., 2021; Jeon, Luyster, Sereika et al.,

2021). Insomnia is characterized by subjective initiating or maintaining sleep or early morning awakenings with an inability to return to sleep (APA, 2013). A recent meta-analysis study (Zhang et al., 2019) found that 38% of persons with OSA had comorbid insomnia.

In the context of T2DM, both OSA and insomnia have been associated with the development of T2DM and negatively impact glycemic control. Persons with OSA or insomnia symptoms (i.e., difficulty initiating and maintaining sleep) had a 1.5 -2 times higher risk of developing T2DM, which was similar to the effect of traditional risk factors of T2DM (e.g., obesity, inactivity) (Anothaisintawee et al., 2016). Several studies which examined the association between OSA severity (assessed by in-lab polysomnography) and glycemic control (measured by HbA1c) in both clinical and population-level samples reported that increasing OSA severity is associated with increasing levels of HbA1c, after controlling for potential confounders (Aronsohn et al., 2010; Grimaldi et al., 2014; Kent et al., 2014; Pillai et al., 2011; Priou et al., 2015). The level of HbA1c is higher in those with severe OSA than in those without OSA (Aronsohn et al., 2010; Kent et al., 2014). A recent meta-analysis showed that in persons with T2DM, those with insomnia are significantly associated with higher HbA1c levels and fasting glucose levels than those without insomnia (Koopman et al., 2020). Comorbid insomnia is often overlooked in persons with OSA (Epstein et al., 2009). There is a notable gap in our understanding of the effects of comorbid OSA and insomnia on glycemic control in persons with T2DM.

Mood disturbances, such as depression and anxiety, and diabetes-related distress are known as key influential psychological symptoms in persons with T2DM. The prevalence of depression in persons with T2DM was twice as high as in those without T2DM; depression was associated with an increased risk of developing T2DM (Brown et al., 2005; Carnethon et al., 2003). Anxiety was higher in persons with type 1 and type 2 diabetes than in those without (Li et al., 2008), and

diabetes is associated with an increased risk of having an anxiety disorder and elevated anxiety symptoms (Smith et al., 2013). Diabetes-related distress, which is a unique emotional burden associated with concerns about disease diagnosis and demanding self-management and support (Polonsky et al., 1995), was found in almost half of adults with T2DM (45.4%) (Fisher et al., 2012). Along with high prevalence, mood disturbances and diabetes-related distress are known barriers to self-management behaviors (i.e., physical activity, healthy diet, and medication adherence) and glycemic control (Aikens, 2012; Anderson et al., 2002; Fisher, Glasgow et al., 2010; Fisher, Hessler et al., 2012; Gonzalez et al., 2008; Hofmeijer-Sevink et al., 2011; Lustman et al., 2000), which lead to diabetes-related vascular complications (Pintaudi et al., 2015). These findings suggest that it is important to understand how to manage these psychological symptoms in persons with T2DM to achieve satisfactory diabetes outcomes.

OSA and insomnia could be modifiable factors for mood disturbances and diabetes-related distress in persons with T2DM. In the general population, having OSA was strongly associated with an increased risk of developing depression (Chen et al., 2013; Peppard et al., 2006); insomnia was associated with two times higher risk of developing depression (Baglioni et al., 2011; Li et al., 2016). Regarding comorbid OSA and insomnia, persons with comorbid OSA and insomnia are associated with a higher prevalence of clinical depression and greater depressive symptoms than those with OSA (Jeon et al., 2021). Persons with T2DM and insomnia were associated with greater mood disturbances than those with OSA; persons with comorbid OSA and insomnia had greater diabetes-related distress than those with OSA (Jeon et al., 2022). Therefore, comorbid insomnia may lead to worse mood disturbances and diabetes-related distress in persons with T2DM and OSA. This association may eventually lead to poor glycemic control in persons with T2DM.

Unfortunately, it is unknown how the effect of comorbid insomnia on mood disturbances and diabetes-related distress is associated with glycemic control in persons with T2DM and OSA.

The purpose of this study was to examine the role that comorbid insomnia has in mood disturbances, diabetes-related distress, and glucose outcome in adults with T2DM and OSA. We examined mood disturbances and diabetes-related distress as potential mediators of the association between OSA and glucose outcomes and the association between insomnia and glucose outcomes in adults with T2DM and OSA. The hypotheses are 1) OSA severity leads to increased mood disturbances and diabetes-related distress, which in turn leads to heightened HbA1c, and 2) insomnia severity leads to increased mood disturbances and diabetes-related distress, which in turn leads to heightened HbA1c in adults with T2DM and OSA.

4.3 Methods

4.3.1 Study Design, Sample, and Setting

This study was a secondary analysis that employed a cross-sectional design using pooled baseline data from two randomized controlled trials: Diabetes Sleep Treatment Trial (DSTT; R01-DK096028) and Diabetes Sleep Treatment Trial for Insomnia (DSTT-I; K24-NR016685). The DSTT was a clinical trial to examine the efficacy of traditional treatment OSA (i.e., continuous positive airway pressure) on glycemic control and diabetes self-management behaviors in individuals with T2DM. The DSTT examined the efficacy of online cognitive behavioral treatment of insomnia on the same outcomes in the DSTT among individuals with T2DM. The DSTT (N = 351) and the DSTT-I (N = 55) recruited participants from endocrinology and sleep outpatient

clinics using various strategies (e.g., research registry, focused mailing, flyers in the community, and social media advertisement). The DSTT-I additionally reviewed the excluded participants from DSTT for randomization because they did not have Apnea-Hypopnea Index (AHI) ≥ 10 events/hour. The DSTT and DSTT-I had common eligibility criteria for the baseline assessment. Participants should 1) have self-reported T2DM, 2) be age 18 years or older, 3) be able to read and write English, 4) not have an acute illness requiring hospitalization in the last three months, 5) not have any near-miss or automobile accident due to sleepiness, and 6) not have a safety-sensitive occupation.

Of the 406 participants who enrolled in the parent studies, data from 240 participants were included for this secondary analysis because 166 (40.8%) participants had missing data on variables for OSA severity, insomnia severity, mood states, and diabetes-related distress or did not meet the diagnostic criteria of OSA (the AHI ≥ 5 events/hour). The study protocol of both the DSTT and DSTT-I studies was approved by the Institutional Review Board (IRB) at each site of the studies. All study participants provide informed consent before the clinical assessment. This study was independently approved by the University of Pittsburgh IRB to pool the baseline data from the DSTT and DSTT-I to conduct secondary analyses.

4.3.2 Measures

4.3.2.1 Independent variable

The independent variables were 1) OSA severity and 2) insomnia severity. The measure for **OSA severity** was the level of AHI. The AHI was measured by the ApneaLinkPlus® (ResMed, San Diego, CA), an FDA-approved level III portable sleep testing device for in-home sleep studies.

ApneaLinkPlus® measures respiratory effort, nasal flow, pulse, and oxygen saturation to derive the AHI (Collop et al., 2007). Higher AHI values indicate greater OSA severity.

The measure for **insomnia severity** was the Insomnia Severity Index (ISI) (Morin et al., 2011). This questionnaire is a 7-item measure assessing both the nighttime and daytime impact of insomnia over the previous month. Each item is rated on a scale of 0 (no problems) to 4 (very severe problem). Total scores can range from 0 to 28, with higher scores indicating worse insomnia severity. The total score is clinically interpreted as follows: absence of insomnia (0 – 7); subthreshold insomnia (8 – 14); moderate insomnia (15 – 21); and severe insomnia (22 – 28) (Morin et al., 2011).

4.3.2.2 Mediator Variables

The mediator variables considered are 1) mood states and 2) diabetes-related distress. **Mood states** were assessed with the Profile of Mood States (POMS). The POMS (McNair & Heuchert, 2007) comprises a set of sixty-five adjectives or phrases related to the five negative mood states (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Fatigue-Inertia, and Confusion-Bewilderment) and one positive mood state (Vigor-Activity), each rated on a 0 (not at all) to 4 (extremely) scale. The POMS Total Mood Disturbance (TMD) score is calculated by adding the five negative mood state scores and subtracting the Vigor-Activity score ranging from -32 to 200. Higher scores for the TMD score indicate greater mood disturbances.

The measure for **diabetes-related distress** was the Problem Areas in Diabetes (PAID) (Polonsky et al., 1995). This questionnaire is a 20-item measure assessing emotional distress in individuals with diabetes. Each item is rated on a 0 (not a problem) to 4 (serious problem) scale. The sum of all item scores is multiplied by 1.25 to produce the total PAID score ranging from 0 to 100. Higher scores for the total PAID score indicate greater overall diabetes-related distress.

4.3.2.3 Dependent variable

The dependent variable is glucose outcome. Glycemic control was determined by glycated hemoglobin (HbA1c). A blood sample (no more than 30cc) was collected to get the value of HbA1c. HbA1c is a reliable indicator of glycemic control over the past 2 to 3 months. Higher levels of HbA1c indicate worse glucose outcomes.

4.3.2.4 Sociodemographic and Clinical Information

These variables were used to describe the sample and serve as potential covariates. Participants reported sociodemographic and health history information, including age (years), gender (male vs. female), marital status (married/partnered vs. single/divorced/widowed), race (non-White vs. White), an education level (< 2-year college degree or technical training vs. ≥ 2-year college degree or technical training), financial difficulty (having somewhat/extremely difficulty to meet their needs vs. no difficulty to meet their needs), and restless leg syndrome (yes/no). Participants reported sleep-related and diabetes-related clinical information. The Epworth Sleepiness Scale (ESS) (John, 1991) assessed the usual changes of dozing off or falling asleep while engaged in eight different daytime activities. A total ESS score > 10 was clinically interpreted as having excessive daytime sleepiness. The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) assessed sleep quality. A PSQI global score > 5 was clinically interpreted as poor sleep quality. Diabetes health questions assessed insulin use (yes/no), duration of T2DM (years), and BMI (kg/m^2).

4.3.3 Procedure

Participants from the parent studies completed an initial in-person or telephone screening to determine the eligibility for baseline assessment and were then invited for the baseline assessment. During the baseline assessment, height and weight were measured for BMI, and a blood sample was obtained. Participants were instructed how to use the ApnealinkPlus® at home and were asked to return the ApnealinkPlus® device (the next day) and self-reported questionnaires (after seven days) by pre-paid mail packets. The trained polysomnographic technicians validated the ApnealinkPlus® data. The DSTT and the DSTT-I share sleep measures and questionnaires. The DSTT and the DSTT-I baseline data were pooled into one dataset based on shared instruments and assessments for this secondary analysis.

4.3.4 Data Analysis

All analyses were conducted using IBM® SPSS® Statistics version 25.0 (IBM Corp., Armonk, NY) and PROCESS version 3.5 (Hayes, 2018). For the total of 406 participants having data collected from the DSTT (N = 351) and DSTT-I (N = 55), the number of eligible participants for this secondary analysis was 240. Descriptive statistics were performed based on the level of measurement and the distribution of each variable to describe the characteristics of the total sample. Means ± standard deviations (SDs), medians, and interquartile ranges were used to describe continuous variables, while frequency counts and percentages were used to summarize categorical variables. Among the total eligible participants (n = 240), participants having any missing data for HbA1c, questions asking about financial difficulty and the identification of restless leg syndrome (n = 3; 1.2%) were also excluded for the analysis because the amount of

missing is acceptable (less than 5%). Sociodemographic information (age, gender, marital status, race, education level, financial difficulty) and restless leg syndrome were included as potential covariates based on their correlations with the primary variables of interest or evidence from the literature.

For all analyses, the normality of each continuous type variable and the linearity between variables entered in a mediation model were assessed. As AHI and HbA1c were positively skewed and HbA1c had weak associations with the AHI and POMS TMD score, a logarithmic transformation was applied to the values of AHI and HbA1c. The linearity between these variables with the transformed variables did not significantly improve. Although the skewness of studentized residuals of AHI and HbA1c were improved after transformation, similar results were obtained when using the transformed data compared with the results using the original metric. Hence, the mediation analyses were performed with variables on their original scale.

As preliminary analyses, bivariate correlations were examined between the independent, mediator, and dependent variables. Mediation analyses were conducted using Model 4 from the SPSS PROCESS macro developed by Hayes (Hayes, 2018). Model 4 is for a simple mediation model, which can include multiple independent variables. The PROCESS macro was applied with bootstrapping (10,000 samples) for each model by entering two independent variables (OSA severity and insomnia severity), one moderator (mood states or diabetes-related distress), and one dependent variable (glucose outcome) while controlling for all covariates (age, gender, marital status, race, education level, financial difficulty, and restless leg syndrome).

The total effect (path c; the effect of an independent variable on a dependent variable), direct effect (path c'; the effect of an independent variable on a dependent variable with the effect of mediator removed), and indirect effect of an independent variable on a dependent variable (a ×

b = ab; path a = the effect of an independent variable on a mediator; path b = the effect of a mediator on a dependent variable) were estimated. If a mediator variable significantly mediates the relationship between an independent variable and a dependent variable, the indirect effect of the independent variable on the dependent variable (ab) must be significant. If the effect of the independent variable on the dependent variable completely disappears, the mediator variable fully mediates the relationship between the independent variable and dependent variable (full mediation). If the effect of the independent variable on the dependent variable still exists, but in a smaller magnitude, the mediator variable partially mediates the relationship between the independent variable and dependent variable (partial mediation). As two independent variables are simultaneously included in the model, the direct and indirect effects of one independent variable are interpreted when the remaining independent variable is considered as a statistical control. The level of statistical significance for two-sided hypothesis testing was set at .05, and a 95% confidence interval (CI) not including the null value (zero) indicates a statistically significant indirect, direct, and total effect.

4.4 Results

4.4.1 Sample Characteristics

A total of 240 adults with T2DM and OSA were included in this analysis (Table 1). Our sample was well distributed by gender (49.6% female), marital status (47.9% married or partnered), and education attainment (56.3% with more than 2-years college degree or technical training) with a mean age of 57.80 (SD = 10.7) years. Almost one-third of participants represented

non-Whites (35.0%) and had “somewhat” or “extremely” financial difficulty to meet their needs (34.3%). Our sample had T2DM on average 11.15 (SD = 9.42) years and was overweight or obese (mean BMI = 35.78 ± 7.18) with suboptimal glycemic control status (a mean HbA1C = 7.93% ± 1.62). Almost half (45.4%) of the sample was prescribed insulin. The total sample was classified as moderate-to-severe OSA (Berry et al., 2012), subthreshold insomnia (Morin et al., 2011) with excessive daytime sleepiness (Johns, 1991), and poor sleep quality (Buysse et al., 1989) based on the mean scores of sleep-related measures.

Table 20. Sample Characterstics of Aim 3 (N = 240)

Baseline Characteristic	n (%)	*Mean*(*Mdn*)	*SD*	Range
Sociodemographic information				
Age (years)		57.80 (58.0)	10.17	31-91
Gender				
Female	119 (49.6)			
Male	121 (50.4)			
Marital status				
Never married/ Separated/divorced/widowed	125 (52.1)			
Married/partnered	115 (47.9)			
Race				
Non-white	84 (35.0)			
White	156 (65.0)			
Education level				
< 2-years college degree, or technical training	105 (43.8)			
≥ 2-years college degree, or technical training	135 (56.3)			
Financial hardship				
Somewhat/extremely difficult	82 (34.3)			
Not at all difficult	157 (65.7)			
Sleep-related clinical information				
OSA severity				
AHI		19.31 (14.15)	16.20	5-95
Insomnia severity				
ISI		13.54 (13.0)	6.01	0-28
Daytime sleepiness				
ESS		10.13 (9.0)	4.69	1-24
Sleep quality				
PSQI		9.71 (10.0)	3.90	1-21
Restless Leg Syndrome				
Yes	37 (15.5)			
No	202 (84.5)			
Diabetes-related clinical information				
Insulin use status				
Yes	109 (45.4)			
No	131 (54.6)			
Duration of T2DM (years)		11.15 (10.0)	9.42	0.5-57
A1C (%)		7.93 (7.60)	1.62	5.3-14
BMI (kg/m^2)		35.78 (34.80)	7.13	22.7-60
Mood states				
POMS Total Mood Disturbance Score		26.00 (20.0)	33.60	-32-154

Baseline Characteristic	n (%)	*Mean*(*Mdn*)	*SD*	Range
POMS Tension-Anxiety		8.90 (8.0)	6.37	0-34
POMS Depression-Dejection		8.08 (5.0)	9.60	0-48
POMS Anger-Hostility		7.15 (5.0)	7.47	0-37
POMS Vigor-Activity		15.35 (16.0)	6.22	0-32
POMS Fatigue-Inertia		10.56 (10.0)	6.21	0-26
POMS Confusion-Bewilderment		6.65 (6.0)	4.66	0-25
Diabetes-related distress				
PAID		29.67 (26.25)	20.46	0-100

Note. M = mean, Mdn = median, SD = standard deviation, AHI = Apnea-Hypopnea Index; ISI = Insomnia Severity Index; ESS = Epworth Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index; T2DM = Type 2 Diabetes Mellitus; A1C = HbA1c; BMI = Body Mass Index; POMS = Profile of Mood States; PAID = Problem Areas in Diabetes.

4.4.2 Bivariate Correlation Analysis

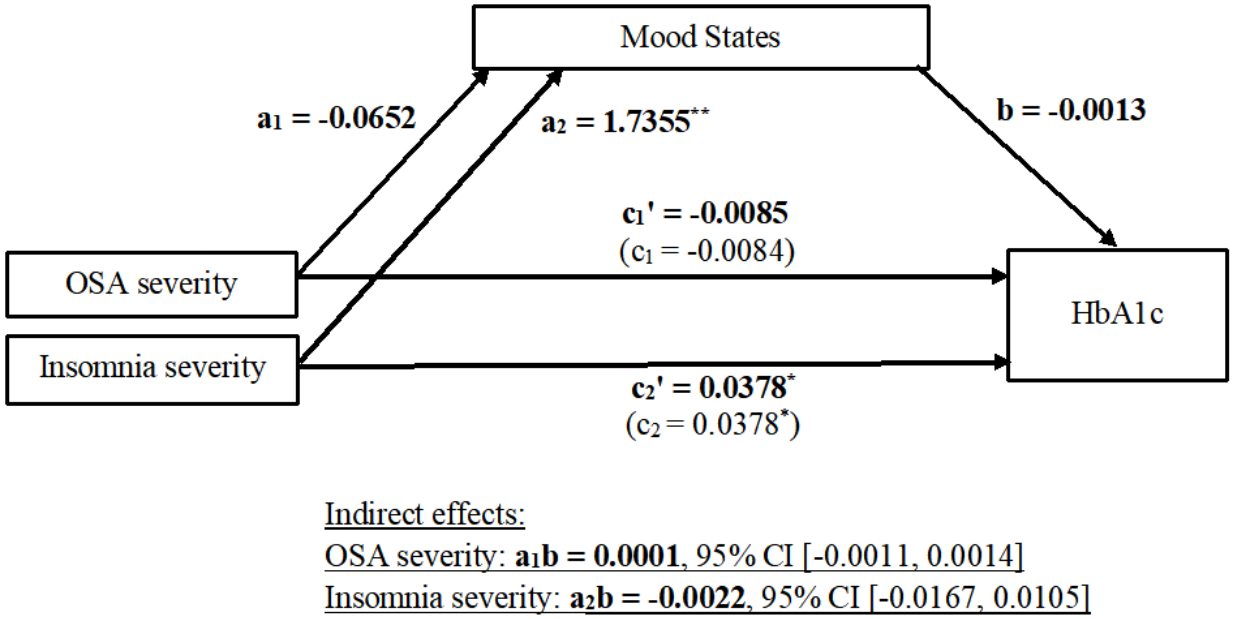
Glucose outcome (HbA1c) was positively associated with insomnia severity (ISI; $r = 0.16$, $p = 0.016$), and diabetes-related distress (PAID; $r = 0.25$, $p < 0.001$). Insomnia severity is also significantly associated with mood states (POMS; $r = 0.37$, $p < 0.001$), and diabetes-related distress (PAID; $r = 0.41$, $p < 0.001$). The proposed mediators (mood states and diabetes-related distress) were positively associated ($r = 0.49$, $p < 0.001$). However, OSA severity was not associated with the insomnia severity (ISI), proposed mediators (mood states and diabetes-related distress) and glucose outcome (HbA1c).

4.4.3 Mediation analysis: the association of OSA and insomnia with HbA1c considering mood states as a mediator

The first mediation model included mood states (i.e., POMS TMD score) as a mediator between the association of the independent variables of OSA and insomnia severity (i.e., AHI, ISI score) with glucose outcome (i.e., HbA1c) among adults with T2DM and OSA while controlling

for all covariates (Figure 9). In the path assessing associations between OSA severity and glucose outcome, mood states were not a significant mediator of the association between OSA severity and glucose outcome because the indirect pathway between AHI and HbA1c via POMS TMD score was not significant (indirect effect: $a_1b = 0.0001$, *se* = 0.0006, 95% CI [-0.0011, 0.0014]).

In the path assessing associations between insomnia severity and glucose outcome, the association between insomnia severity and glucose outcome was not mediated by mood states, although the relationship between insomnia severity and mood states was significant ($a_2 = 1.7355$, *se* = 0.3282, $p < .001$, 95% CI [1.0887, 2.3822]). The indirect pathway between ISI score and HbA1c via POMS TMD score was not significant (indirect effect: $a_2b = -0.0022$, *se* = 0.0068, 95% CI [-0.0167, 0.0105]). The relationship between insomnia severity and glucose outcome before the mediator was added was significant (total effect: $c_2 = 0.0378$, *se* = 0.0189, $p = 0.047$, 95% CI [0.0005, 0.0751]). Therefore, insomnia severity was directly associated with greater mood disturbances and higher levels of HbA1c among adults with T2DM and OSA.



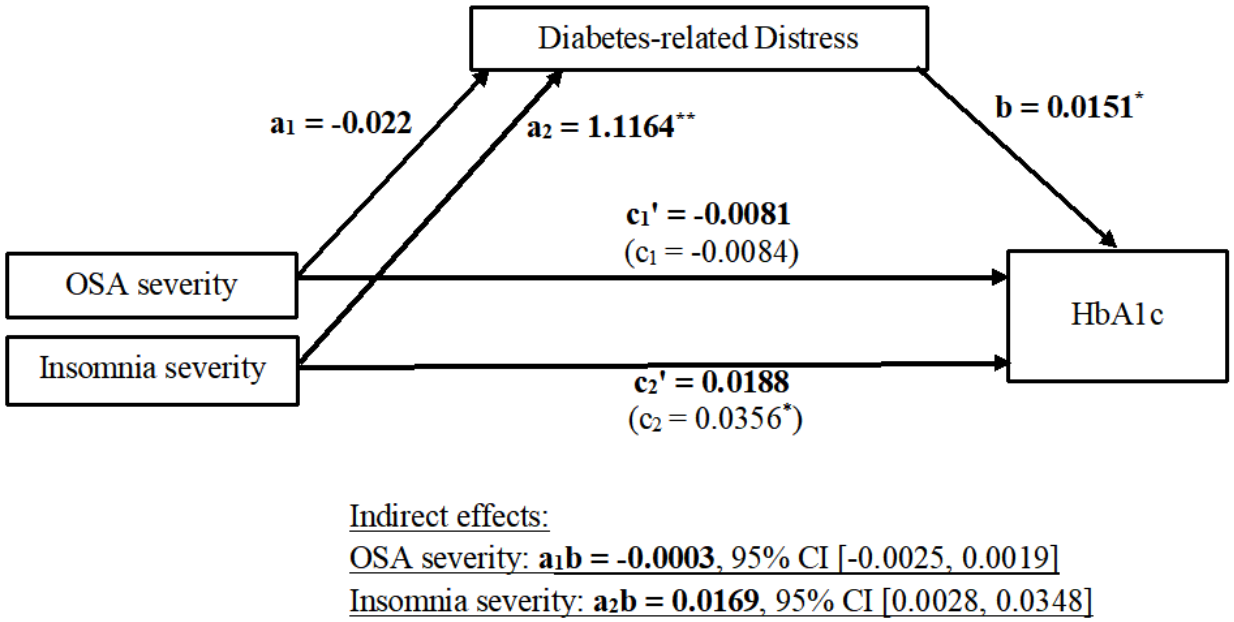
Note. $^{*}p < 0.05$, $^{**}p < 0.001$; c = total effect; c' = direct effect

Figure 9. Mediation Analysis: Unstandardized Regression Coefficient for Each Path of the Association of OSA and Insomnia with HbA1c considering Mood States as Mediator (All Covariates were Controlled)

4.4.4 Mediation analysis: the association of OSA and insomnia with HbA1c considering diabetes-related distress as a mediator

The second mediation model included diabetes-related distress (i.e., PAID score) as a mediator between the association of OSA and insomnia severity (i.e., AHI, ISI score) with glucose outcome (i.e., HbA1c) among adults with T2DM and OSA while controlling for all covariates (Figure 10). In the path assessing associations between OSA severity and glucose outcome, diabetes-related distress was not a significant mediator of the association between OSA severity and glucose outcome since the indirect pathway between AHI and HbA1c via PAID score was not significant (indirect effect: a_1b = -0.0003, *se* = 0.0011, 95% CI [-0.0025, 0.0019]).

In the path assessing associations between insomnia severity and glucose outcome, the indirect pathway between ISI score and HbA1c via diabetes-related distress was significant (indirect effect: $a_2b = 0.0169$, *se* = 0.0083, 95% CI [0.0028, 0.0348]). Therefore, insomnia severity influences glucose outcome indirectly through its effect on diabetes-related distress. Among adults with T2DM and OSA, those with greater insomnia severity reported greater diabetes-related distress ($a_2 = 1.1164$, *se* = 0.1983, $p < .001$, 95% CI [0.7257, 1.5070]), with greater diabetes-related distress associated with a higher level of HbA1c (b = 0.0151, *se* = 0.0059, *p* = 0.011, 95% CI [0.0035, 0.0267]). The relationship between OSA severity and diabetes-related distress was not significant ($a_1 = -0.022$, *se* = 0.0766, *p* = .774, 95% CI [-0.1729, 0.1288]) and OSA severity was not directly influences glucose outcome independent of diabetes-related distress (total effect: $c_1 = -0.0084$, *se* = 0.0069, *p* = 0.225, 95% CI [-0.0220, 0.0052])



Note. $^{*}p < 0.05$, $^{**}p < 0.001$; c = total effect; c' = direct effect

Figure 10. Mediation Analysis: Unstandardized Regression Coefficient for Each Path of the Association of OSA and Insomnia with HbA1c considering Diabetes-related Distress as Mediator (All Covariates were Controlled)

4.5 Discussion

To our knowledge, this study is the first to examine whether mood disturbances and diabetes-related distress mediate the association between OSA severity and glucose outcome, and the association between insomnia severity and glucose outcome in adults with T2DM and OSA, after controlling for clinical and sociodemographic covariates. Our findings suggest that diabetes-related distress mediates the association between insomnia severity and glucose outcome. Mood disturbances do not mediate the association between insomnia severity and glucose outcome, although insomnia severity is associated with greater mood disturbances. Mood disturbances and

diabetes-related distress do not mediate the association between OSA and glucose outcome. That is, persons with greater insomnia severity have greater diabetes-related distress, which in turn leads to heightened HbA1c in adults with T2DM and OSA. This mediation effect supports the idea that diabetes-related distress may be a causal pathway regarding how comorbid insomnia may contribute to glucose outcomes in persons with T2DM and OSA.

Although there is an abundance of evidence demonstrating an association between OSA and glycemic control (Aronsohn et al., 2010; Grimaldi et al., 2014; Kent et al., 2014; Pillai et al., 2011; Priou et al., 2015), our findings showed that only insomnia severity is associated with poor glycemic control via elevated diabetes-related distress in persons with T2DM after being diagnosed with OSA. This may suggest that clinical presentation of OSA, rather than objectively measured severity of OSA, is an important aspect of determining diabetes-related distress and glycemic outcome in persons with T2DM. In a study that examined the association between polysomnographic measures of OSA severity (e.g., AHI, RDI, and oxygen desaturation index [ODI]/hour) and other clinical symptoms of OSA (Lee et al., 2020), the polysomnographic measure of OSA severity were not associated with depressive symptoms and anxiety. Nocturnal symptoms in persons with OSA that were consistent with insomnia symptoms (i.e., frequent awakening during sleep, difficulty maintaining sleep, or waking too early) were associated with depressive symptoms and anxiety. The phenotypes of OSA, characterized by having insomnia symptoms, are more likely to have a worse mental status than the phenotypes without insomnia symptoms; the level of OSA severity, which was measured by AHI, did not differ between the phenotypes (Saaresranta et al., 2016; Ye et al., 2014). This suggests that objectively measured severity of OSA may not reflect the clinical manifestation of mood disturbances or diabetes-related distress in persons with T2DM. Therefore, comorbid insomnia among persons with T2DM and

OSA is highly likely to increase diabetes-related distress, and this association may result in poor glycemic control. Identifying clinical presentation of insomnia symptoms in persons with T2DM is more important to capturing poor clinical outcomes than relying solely on OSA severity using the AHI.

When measured by HbA1c, it was unexpectedly found that diabetes-related distress mediates the association between insomnia severity and glucose outcome; however, mood disturbances are only associated with insomnia severity, not with HbA1c. Considering the association with diabetes self-management behaviors, both mood disturbances and diabetes-related distress have been associated with glycemic control (Aikens, 2012; Anderson et al., 2002; Fisher, Glasgow et al., 2010; Fisher, Hessler et al., 2012; Gonzalez et al., 2008; Hofmeijer-Sevink et al., 2011; Lustman et al., 2000). Among 463 persons with T2DM, diabetes-related distress and depressive symptoms were highly correlated, but diabetes-related distress was associated with higher HbA1c, and the elevated depressive symptoms were independently associated with diet and medication adherence (Fisher, Glasgow et al., 2010). In another study, diabetes-related distress was associated with higher HbA1c in the 6-month follow-up, but the elevated depressive symptoms were associated with diet, physical activity, and glucose testing behaviors (Aikens, 2012). These findings suggest that mood disturbances may play a more important role in self-management behaviors than diabetes-related distress, and poor self-management behaviors could explain the clinical changes in glycemic outcomes. There is no evidence regarding the effect of insomnia on mood disturbances and self-management behaviors in persons with T2DM. The association between insomnia and mood disturbances and their impact on self-management behaviors should be further evaluated.

The mediation effect that diabetes-related distress has between insomnia severity and glucose outcome, after controlling for clinical and sociodemographic covariates, underscores the importance of comorbid insomnia in managing diabetes-related distress. This effect contributes to glycemic outcomes in persons with T2DM, even after an OSA diagnosis. This suggests the potential benefits of sleep intervention to manage insomnia in reducing diabetes-related distress and improving glucose outcomes in persons with T2DM and OSA. The evaluation of comorbid insomnia has not been recommended as part of routine screening for OSA (Epstein et al., 2009). The clinical guidelines for sleep management in persons with T2DM also mainly focus on the evaluation of OSA (Smyth et al., 2020). There is limited evidence of whether the treatment for insomnia symptoms improves health outcomes, diabetes-related distress, and glycemic outcomes in persons with T2DM and OSA. Only one pilot study for persons with T2DM (n = 14) showed that cognitive behavioral therapy for insomnia significantly improves glycemic control when measured by HbA1c (Alshehri et al., 2020). Future studies are needed to determine the extent to which interventions for insomnia improve diabetes-related distress and how these improvements lead to improved glucose outcomes in persons with T2DM.

Although the findings of this study suggest the mediation role of diabetes-related distress between insomnia severity and glucose outcome, the cross-sectional design of the study cannot assume a causal relationship. Future randomized controlled trials to treat insomnia are needed to confirm whether insomnia is causally associated with diabetes-related distress and glucose outcome. The other limitation of our study is that insomnia severity is only measured by the self-reported questionnaire (i.e., the ISI). As insomnia can be defined as multiple aspects of sleep, such as sleep duration, sleep latency, sleep efficiency, and sleep quality (Buysse, 2013), understanding distinct insomnia-related symptoms in persons with T2DM is necessary to develop more targeted

insomnia interventions for this population. Finally, the baseline data did not have specific information regarding medications that can alter sleep status in the parent studies. Eligible participants for baseline assessment did not have an acute illness requiring hospitalization, including serious psychiatric conditions. This may have reduced the bias regarding the medication.

The findings of this study suggest that diabetes-related distress may explain the relationships between insomnia severity and glucose outcomes among persons with T2DM and OSA. Comorbid insomnia could be a potentially modifiable factor in improving diabetes-related distress and glucose outcomes in persons with T2DM and OSA. Future studies are needed to enhance understanding of the multiple aspects of insomnia-related symptoms in persons with T2DM and to examine the effects of interventions for insomnia on diabetes-related distress and glucose outcome to confirm the suggested relationship in this study.

5.0 Conclusion of Dissertation Findings

This dissertation project consists of three complementary studies that address gaps in the knowledge of the role that insomnia and OSA have, individually and jointly, in mood states, diabetes-related distress, and glucose outcomes in adults with T2DM. The first study (Aim 1) examined the effect of comorbid obstructive sleep apnea and insomnia and its associations with mood and diabetes-related distress in type 2 diabetes mellitus. The second study (Aim 2) examined the moderating effect of comorbid insomnia on the association between obstructive sleep apnea with mood and diabetes-related distress in adults with type 2 diabetes mellitus. The third study (Aim 3) examined the mediating effect of mood disturbances and diabetes-related distress on the association between comorbid insomnia and glycemic control in adults with T2DM.

Although each manuscript described a study with a unique purpose, the findings together advance understanding of the impact of comorbid insomnia on mood states, diabetes-related distress, and glycemic outcomes among adults with T2DM and OSA. Below is a summary of the key messages for each manuscript.

First, comparing the influence of two sleep disorders, insomnia may play a greater significant role in increasing mood disturbances and diabetes-related distress than OSA in persons with T2DM. When comparing mood states and diabetes-related distress in three types of sleep disorders: OSA, insomnia, and comorbid OSA and insomnia in adults with T2DM, insomnia was associated with greater mood disturbance than OSA, and OSA+I was associated with greater diabetes-related distress than OSA (Aim 1 manuscript). These findings suggest that insomnia, not OSA, might be a more potent contributing factor to increased severity of mood disturbances and diabetes-related distress in persons with T2DM. These findings confirm our previous integrative

review that persons with comorbid OSA and insomnia had higher depressive symptoms than those with OSA and that insomnia, not OSA, contributed to increased depressive symptoms in persons with comorbid OSA and insomnia (Jeon et al., 2021). In adults with T2DM and OSA, when insomnia severity increased, the deleterious effect of OSA severity on mood disturbances decreased, and insomnia was independently associated with diabetes-related distress, whereas OSA was not (Aim 2 manuscript). Taken together, we found that insomnia, not OSA, maybe the primary underlying sleep disorder, which is associated with mood states and diabetes-related distress in persons with T2DM.

Another core message from this dissertation project is that comorbid insomnia, a potentially modifiable factor, is associated with increased diabetes-related distress. Since diabetes-related distress is a known factor for worse glucose outcomes, reducing diabetes-related distress may contribute to the improvement of glycemic control in persons with T2DM. Specifically based on cross-sectional data, diabetes-related distress mediates the association between insomnia severity and glucose outcome, but not between OSA severity and glucose outcome, in adults with T2MD and OSA. That is, persons with greater insomnia severity have greater diabetes-related distress, which in turn leads to a poor glycemic outcome in adults with T2DM and OSA (Aim 3 manuscript). Diabetes-related distress may be a causal pathway in how comorbid insomnia contributes to glycemic control in persons with T2DM and OSA. Therefore, the evaluation and treatment of insomnia in persons with T2DM would be beneficial to improving diabetes-related distress and glycemic outcomes, even after being diagnosed with OSA.

In summary, this dissertation advances the current state of scientific knowledge about the role that insomnia and OSA have, individually and jointly, on mood states, diabetes-related

distress, and glycemic controls in adults with T2DM. Knowledge obtained from this dissertation project suggests the direction of future research including:

1) Longitudinal investigations exploring the causal relationship between insomnia, diabetes-related distress, and glycemic outcomes in persons with T2DM;
2) Identifying the multiple aspects of insomnia-related symptoms (i.e., sleep regularity, satisfaction, alertness, timing, efficiency, and duration) in persons with T2DM;
3) Examining the effect of interventions for insomnia on diabetes-related distress and glucose outcome in persons with T2DM; and
4) Examining other aspects of impaired sleep that may negatively affect the health and well-being of persons with T2DM.

Information from this study that can be used to improve clinical care of persons with T2DM includes the importance of evaluating and treating, if needed, sleep among persons with T2DM and proactively working to improve sleep in persons at high risk for developing T2DM.

Appendix A : Study Instruments and Assessments

- Insomnia Severity Index (ISI)
- Profile of Mood States (POMS) Standard Form
- Problem Areas in Diabetes (PAID) Questionnaire
- The Epworth Sleepiness Scale (ESS)
- Pittsburgh Sleep Quality Index (PSQI)

Instrument Number: 2701

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Study ID: 267

Insomnia Severity Index

ID Number: _____ Administration Date: ___ / ___ / _____ (month) (day) (year)

Visit Number: 1 Baseline ○ 2 ○ 3 ○ 4 ○ 5 ○

(FOR STAFF USE ONLY)

For each question, please fill in the circle of the number that corresponds to your answer.

1. Please rate the CURRENT (i.e., PAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem(s):	None 0	Mild 1	Moderate 2	Severe 3	Very Severe 4
a. Difficulty falling asleep	○	○	○	○	○
b. Difficulty staying asleep	○	○	○	○	○
c. Problem waking up too early	○	○	○	○	○

2. How SATISFIED /DISSATISFIED are you with your CURRENT sleep pattern?

- ○ 0 Very satisfied
- ○ 1 Satisfied
- ○ 2 Moderately satisfied
- ○ 3 Dissatisfied
- ○ 4 Very dissatisfied

3. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

- ○ 0 Not at all noticeable
- ○ 1 A Little
- ○ 2 Somewhat
- ○ 3 Much
- ○ 4 Very much noticeable

4. How WORRIED /DISTRESSED are you about your current sleep problem?

- ○ 0 Not at all worried
- ○ 1 A little
- ○ 2 Somewhat
- ○ 3 Much
- ○ 4 Very much worried

5. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g., daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

- ○ 0 Not at all interfering
- ○ 1 A Little
- ○ 2 Somewhat
- ○ 3 Much
- ○ 4 Very much interfering

Instrument Number: 3 1 5

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Study ID: 2 6 7

Profile of Mood States (POMS™) Standard Form

By Douglas M. McNair, Ph.D., Maurice Lorr, Ph.D., JW P. Heuchert, Ph.D., & Leo F. Droppleman, Ph.D.

ID Number:

Administration Date: ___ / ___ / ___ (month) (day) (year)

Visit Number: 1 ○ Baseline 2 ○ 3 ○ 4 ○ 5 ○

(FOR STAFF USE ONLY)

Below is a list of words that describe feelings people have. Please read each one carefully. Then fill in ONE circle that corresponds to the answer which best describes **HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY**. Use the following scale as a basis for your answers:

[0] = Not at all
[1] = A little
[2] = Moderately
[3] = Quite a bit
[4] = Extremely

	Not at all 0	A little 1	Moderately 2	Quite a bit 3	Extremely 4
1. Friendly	○	○	○	○	○
2. Tense	○	○	○	○	○
3. Angry	○	○	○	○	○
4. Worn out	○	○	○	○	○
5. Unhappy	○	○	○	○	○
6. Clear-headed	○	○	○	○	○
7. Lively	○	○	○	○	○
8. Confused	○	○	○	○	○

ID Number: _ _ _ _ _ _ _ _ _ _ _ _ (for internal use only)

Date: _ _ / _ _ / _ _ (for internal use only)

Study ID: 2 6 7

	Not at all 0	A little 1	Moderately 2	Quite a bit 3	Extremely 4
9. Sorry for things done	O	O	O	O	O
10. Shaky	O	O	O	O	O
11. Listless	O	O	O	O	O
12. Peeved	O	O	O	O	O
13. Considerate	O	O	O	O	O
14. Sad	O	O	O	O	O
15. Active	O	O	O	O	O
16. On edge	O	O	O	O	O
17. Grouchy	O	O	O	O	O
18. Blue	O	O	O	O	O
19. Energetic	O	O	O	O	O
20. Panicky	O	O	O	O	O
21. Hopeless	O	O	O	O	O
22. Relaxed	O	O	O	O	O
23. Unworthy	O	O	O	O	O
24. Spiteful	O	O	O	O	O
25. Sympathetic	O	O	O	O	O
26. Uneasy	O	O	O	O	O
27. Restless	O	O	O	O	O
28. Unable to concentrate	O	O	O	O	O
29. Fatigued	O	O	O	O	O
30. Helpful	O	O	O	O	O
31. Annoyed	O	O	O	O	O
32. Discouraged	O	O	O	O	O
33. Resentful	O	O	O	O	O
34. Nervous	O	O	O	O	O
35. Lonely	O	O	O	O	O
36. Miserable	O	O	O	O	O
37. Muddled	O	O	O	O	O
38. Cheerful	O	O	O	O	O

ID Number: _ _ _ _ _ _ _ _ _ _ _ _
(for internal use only)

Date: _ _ / _ _ / _ _
(for internal use only)

Study ID: 2 6 7

	Not at all 0	A little 1	Moderately 2	Quite a bit 3	Extremely 4
39. Bitter	○	○	○	○	○
40. Exhausted	○	○	○	○	○
41. Anxious	○	○	○	○	○
42. Ready to fight	○	○	○	○	○
43. Good natured	○	○	○	○	○
44. Gloomy	○	○	○	○	○
45. Desperate	○	○	○	○	○
46. Sluggish	○	○	○	○	○
47. Rebellious	○	○	○	○	○
48. Helpless	○	○	○	○	○
49. Weary	○	○	○	○	○
50. Bewildered	○	○	○	○	○
51. Alert	○	○	○	○	○
52. Deceived	○	○	○	○	○
53. Furious	○	○	○	○	○
54. Efficient	○	○	○	○	○
55. Trusting	○	○	○	○	○
56. Full of pep	○	○	○	○	○
57. Bad-tempered	○	○	○	○	○
58. Worthless	○	○	○	○	○
59. Forgetful	○	○	○	○	○
60. Carefree	○	○	○	○	○
61. Terrified	○	○	○	○	○
62. Guilty	○	○	○	○	○
63. Vigorous	○	○	○	○	○
64. Uncertain about things	○	○	○	○	○
65. Bushed	○	○	○	○	○

Instrument Number: 187

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Study ID: 267

Problem Areas in Diabetes (PAID) Questionnaire

ID Number: _____ Administration Date: ___ / ___ / _____
(month) (day) (year)

Visit Number: 1 Baseline ○ 2 ○ 3 ○ 4 ○ 5 ○

(FOR STAFF USE ONLY)

Please use BLACK Pen Only!

INSTRUCTIONS: Which of the following diabetes issues are currently a problem for you? For each question, fill in the circle next to the response that gives the best answer for you. Please provide an answer for each question.

	Not a problem 0	Minor problem 1	Moderate problem 2	Somewhat serious problem 3	Serious problem 4
1. Not having clear and concrete goals for your diabetes care?	○	○	○	○	○
2. Feeling discouraged with your diabetes treatment plan?	○	○	○	○	○
3. Feeling scared when you think about living with diabetes?	○	○	○	○	○
4. Uncomfortable social situations related to your diabetes care (e.g., people telling you what to eat)?	○	○	○	○	○
5. Feelings of deprivation regarding food and meals?	○	○	○	○	○

64553

ID Number: _ _ _ _ _ _ _ _ _ _ _ _
(for internal use only)

Date: _ _ / _ _ / _ _
(for internal use only)

Study ID: 267

	Not a problem 0	Minor problem 1	Moderate problem 2	Somewhat serious problem 3	Serious problem 4
6. Feeling depressed when you think about living with diabetes?	○	○	○	○	○
7. Not knowing if your mood or feelings are related to your diabetes?	○	○	○	○	○
8. Feeling overwhelmed by your diabetes?	○	○	○	○	○
9. Worrying about low blood sugar reactions?	○	○	○	○	○
10. Feeling angry when you think about living with diabetes?	○	○	○	○	○
11. Feeling constantly concerned about food and eating?	○	○	○	○	○
12. Worrying about the future and the possibility of serious complications?	○	○	○	○	○
13. Feelings of guilt or anxiety when you get off track with your diabetes management?	○	○	○	○	○
14. Not "accepting" your diabetes?	○	○	○	○	○
15. Feeling unsatisfied with your diabetes physician?	○	○	○	○	○
16. Feeling that diabetes is taking up too much of your mental and physical energy every day?	○	○	○	○	○
17. Feeling alone with your diabetes?	○	○	○	○	○
18. Feeling that your friends and family are not supportive of your diabetes management efforts?	○	○	○	○	○
19. Coping with complications of diabetes?	○	○	○	○	○
20. Feeling "burned out" by the constant effort needed to manage diabetes?	○	○	○	○	○

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Instrument Number: 868

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Study ID: 267

The Epworth Sleepiness Scale

ID Number: _____ Administration Date: ___ / ___ / ____ (month) (day) (year)

Visit Number:

1 Baseline ○ 2 ○ 3 ○ 4 ○ 5 ○

(FOR STAFF USE ONLY)

How likely are you to doze off or briefly fall asleep in the following situations? This questionnaire refers to your usual way of life *in the past several weeks*.

Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = Would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Please note: It is important that you choose ONE response for each of the following situations . . . .

	Would never doze 0	Slight chance of dozing 1	Moderate chance of dozing 2	High chance of dozing 3
1. Sitting and reading	○	○	○	○
2. Watching television	○	○	○	○
3. Sitting inactive in a public place, for example: a theater or meeting	○	○	○	○
4. As a passenger in a car for an hour without a break	○	○	○	○
5. Lying down to rest in the afternoon	○	○	○	○
6. Sitting and talking to someone	○	○	○	○
7. Sitting quietly after lunch (when you've had no alcohol)	○	○	○	○
8. In a car, while stopped in traffic	○	○	○	○

36057

CRE-868EPW, V1.9
September 24, 2013

Johns, MW: A new method of measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 14:540-545, 1991.

Page 1 of 1

Instrument Number: 365

Buysse, D.J., Reynolds, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J.: The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research. Psychiatry Research, 28: 193-213, 1989

Study ID: 267

Pittsburgh Sleep Quality Index

ID Number:

Administration Date: ___ / ___ / ___ (month) (day) (year)

Visit Number: 1 (Baseline) 2 3 4 5

(FOR STAFF USE ONLY)

Shade circles like this: ●
Not like this: ⊗ ✓

Please use BLACK Pen Only!

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. ***During the past month*, what time have you usually gone to bed at night?**

USUAL BED TIME: ___ (hours) ___ (minutes) a.m. ○ (1) p.m. ○ (2)

2. ***During the past month*, how long (in minutes) has it usually taken you to fall asleep each night?**

NUMBER OF MINUTES: ___ (minutes)

3. ***During the past month*, what time have you usually gotten up in the morning?**

USUAL GETTING UP TIME: ___ (hours) ___ (minutes) a.m. ○ (1) p.m. ○ (2)

4. ***During the past month*, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)**

HOURS OF SLEEP PER NIGHT: ___ (hours) ___ (minutes)

56993

For each of the remaining questions, fill in the circle that corresponds to the one best response. Please answer ALL questions.

5. *During the past month*, how often have you had trouble sleeping because you . . . .

	Not during the past month 0	Less than once a week 1	Once or twice a week 2	Three or more times a week 3
a.) cannot get to sleep within 30 minutes?	O	O	O	O
b.) wake up in the middle of the night or early morning?	O	O	O	O
c.) have to get up to use the bathroom?	O	O	O	O
d.) cannot breathe comfortably?	O	O	O	O
e.) cough or snore loudly?	O	O	O	O
f.) feel too cold?	O	O	O	O
g.) feel too hot?	O	O	O	O
h.) had bad dreams?	O	O	O	O
i.) have pain?	O	O	O	O
j.) other reason(s)?	O	O	O	O

k.) Please describe: _____

_____

6. *During the past month*, how would you rate your sleep quality overall?

O 0 Very good
O 1 Fairly good
O 2 Fairly bad
O 3 Very bad

	Not during the past month 0	Less than once a week 1	Once or twice a week 2	Three or more times a week 3
7. ***During the past month***, how often have you taken medicine to help you sleep (prescribed or "over-the-counter")?	O	O	O	O
8. ***During the past month***, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	O	O	O	O

9. ***During the past month***, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

O 0 No problem at all
O 1 Only a very slight problem
O 2 Somewhat of a problem
O 3 A very big problem

Appendix B : Human Subjects Training Modules Certificates

COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 1 OF 2 COURSEWORK REQUIREMENTS*

NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

Name:Bomin Jeon (ID: 7483706)

Institution Affiliation:University of Pittsburgh (ID: 2074)

Institution Email:boj8@pitt.edu

Institution Unit:University of Pittsburgh School of Nursing

Curriculum Group:Responsible Conduct of Research

Course Learner Group: Same as Curriculum Group

Stage:Stage 1 - Basic Course

Record ID:28823546

Completion Date:19-Nov-2018

Expiration Date:18-Nov-2022

Minimum Passing:80

Reported Score*:94

REQUIRED AND ELECTIVE MODULES ONLY	DATE COMPLETED	SCORE
Authorship (RCR-Basic) (ID: 16597)	19-Nov-2018	5/5 (100%)
Collaborative Research (RCR-Basic) (ID: 16598)	19-Nov-2018	5/5 (100%)
Data Management (RCR-Basic) (ID: 16600)	19-Nov-2018	5/5 (100%)
Mentoring (RCR-Basic) (ID: 16602)	19-Nov-2018	5/5 (100%)
Peer Review (RCR-Basic) (ID: 16603)	19-Nov-2018	5/5 (100%)

Research Misconduct (RCR-Basic) (ID: 16604)	19-Nov-2018	5/5 (100%)
Plagiarism (RCR-Basic) (ID: 15156)	19-Nov-2018	3/5 (60%)

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

Verify at: www.citiprogram.org/verify/?k41c74870-d17c-4c9e-a8dc-2f04ba70c165-28823546

Collaborative Institutional Training Initiative (CITI Program)

Email: support@citiprogram.org Phone: 888-529-5929

Web: https://www.citiprogram.org

COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)

COMPLETION REPORT - PART 2 OF 2 COURSEWORK TRANSCRIPT**

** NOTE: Scores on this Transcript Report reflect the most current quiz completions, including quizzes on optional (supplemental) elements of the course. See list below for details. See separate Requirements Report for the reported scores at the time all requirements for the course were met.

Name:Bomin Jeon (ID: 7483706)

Institution Affiliation: University of Pittsburgh (ID: 2074)

Institution Email:boj8@pitt.edu

Institution Unit:University of Pittsburgh School of Nursing

Curriculum Group:Responsible Conduct of Research

Course Learner Group: Same as Curriculum Group

Stage:Stage 1 - Basic Course

Record ID:28823546

Report Date:19-Nov-2018

Current Score**:100

REQUIRED, ELECTIVE, AND SUPPLEMENTAL MODULES	MOST RECENT	SCORE
Plagiarism (RCR-Basic) (ID: 15156)	19-Nov-2018	5/5 (100%)
Authorship (RCR-Basic) (ID: 16597)	19-Nov-2018	5/5 (100%)
Collaborative Research (RCR-Basic) (ID: 16598)	19-Nov-2018	5/5 (100%)
Data Management (RCR-Basic) (ID: 16600)	19-Nov-2018	5/5 (100%)
Mentoring (RCR-Basic) (ID: 16602)	19-Nov-2018	5/5 (100%)
Peer Review (RCR-Basic) (ID: 16603)	19-Nov-2018	5/5 (100%)
Research Misconduct (RCR-Basic) (ID: 16604)	19-Nov-2018	5/5 (100%)

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid Independent Learner.

Verify at: www.citiprogram.org/verify/?k41c74870-d17c-4c9e-a8dc-2f04ba70c165-28823546

Collaborative Institutional Training Initiative (CITI Program)

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Web: https://www.citiprogram.org

Appendix C : IRB Approval

University of Pittsburgh
Institutional Review Board

Human Research Protection Office
3500 Fifth Avenue, Suite 106
Pittsburgh, PA 15213
Tel (412) 383-1480
www.hrpo.pitt.edu

APPROVAL OF SUBMISSION (Exempt)

Date:	December 6, 2019
IRB:	STUDY19100353
PI:	Eileen Chasens
Title:	Expanding knowledge of Co-Morbid OSA and Insomnia
Funding:	None

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

Review type:	Initial Study
Approval Date:	12/6/2019
Exempt Category:	(4) Secondary research on data or specimens (no consent required)
Approved Documents:	• CHASENS_Informed_Consent_DSTT-I_4.23.2019_Version_0.02.docx, Category: Other; • DSTT_Consent.docx, Category: Other; • HRP-723 - WORKSHEET - Exemption_Secondary Data.Specimens_Chasens.docx, Category: IRB Protocol;

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Larry Ivanco.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

Pitt_510_Exempt

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