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Biopsychosocial Factors Associated with Insomnia and the Effectiveness of Treatment

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Biopsychosocial Factors Associated with Insomnia and the Effectiveness of Treatment

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Abstract

Biopsychosocial Factors Associated with Insomnia and the Effectiveness of Treatment

Greg Roussett

Thirty percent of adults experience insomnia, causing distress, impaired functioning, and adverse health outcomes. However, little is known about biomarkers that may inform the understanding of insomnia, including its salience within different racial and ethnic groups. Additionally, knowledge is limited to one important group of individuals who experience insomnia (short sleepers) and factors that may influence effectiveness of their treatment.

The aims of this dissertation were to: 1) identify evidence-based biomarkers that have been associated with insomnia in adults through a scoping review, 2) determine if insomnia and discrimination are associated with telomere length (TL) among adults from different racial/ethnic groups, and 3) identify the relationship of psychological distress and sleep-related factors to non-response to CBT-I among short sleepers with insomnia.

Twenty-five studies were included in the scoping review. The importance of electroencephalography emerged as a potentially useful biomarker in identifying arousal and inhibition of brain activity associated with insomnia. Conflicting findings regarding relationships of some biomarkers emerged. This review allows researchers to build on what is known and replicate studies to assess reliability.

Results from a secondary analysis of the National Institute on Aging's Health and Retirement Study linked insomnia with shorter telomeres in White individuals. Respondents' perceived discrimination in everyday life initially strengthened the association between insomnia symptoms and telomere shortening in Black individuals, but the effect was not significant after adjusting for covariates. Further research is needed on insomnia's biological mechanisms and its impact on biomarkers in diverse racial/ethnic groups.

Results of a secondary analysis from a Treatment of Insomnia and Depression (TRIAD) study provide evidence that general severity of depression, perceived stress, sleep latency, and

sleep reactivity were not associated with treatment response to CBT-I. However, an individual symptom of stress prior to treatment (trouble controlling irritability) was associated with less improvement in response to CBT-I among individuals who slept less than 6 hours per night. Difficulty controlling irritability may reflect a state of heightened stress that precludes effective engagement in CBT-I.

Results of this dissertation provide an enhanced understanding of biopsychosocial factors associated with insomnia and its treatment. This new knowledge can inform future research.

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List of Abbreviations

AL = allostatic load

ANOVA = analysis of variance

ATP = adenosine triphosphate

BMD = bone mineral density

BMI = body mass index

CBT-I = cognitive behavioral therapy for insomnia

CES-D = Center for Epidemiological Studies for Depression

CINAHL = Cumulative Index to Nursing & Allied Health Literature

CNV = contingent negative variation

CRP = c-reactive protein

CV = coefficient of variation

DNA = deoxyribonucleic acid

DSID = Duke Structured Interview for Sleep

DSM = Diagnostic and Statistical Manual of Mental Disorders

EEG= electroencephalography

EKG = electrocardiogram

FIRST = Ford Insomnia Response to Stress Test

GABA = gamma-aminobutyric acid

GSH = glutathione

GSH-Px = glutathione peroxidate

HDRS = Hamilton Depression Rating Scale

HgbA1c = glycosylated hemoglobin

HRS = Health and Retirement Study

HRV = heart rate variability

Hz = hertz

ICC = intraclass coefficients

ICSD = International Classification of Sleep Disorders

IL-6 = interleukin-6

IRS = Insomnia Rating Scale

ISI = Insomnia Severity Index

LDL = low-density lipoprotein

MDA = malondialehyde

MDD = major depressive disorder

MNI = mean nucleal interface

MPO = myeloperoxidase

MRI = magnetic resonance imaging

NfH = neurofilaments heavy cha in

NfL = neurofilaments light chain

NESDA = Netherlands Study of Depression and Anxiety

NIH = National Institute of Health

NINR = National Institute of Nursing

NSE = neuron specific enolase

OR = odds ratio

PRISMA-ScR = Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

PSG = polysomnography

PSQI = Pittsburgh Sleep Quality Index

PSS = Perceived Stress Scale

RCT = randomized controlled trial

S100B = calcium binding protein B

SCID = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-4

SE = sleep efficiency

SoL = sleep latency

SOD = superoxide dismutase

STAR*D = Sequenced Treatment Alternatives to Relieve Depression

TCC = Tai Chi Chih

TL = telomere length

TNF-α = tumor necrosis factor

TRIAD = Treatment of Insomnia and Depression

TST = total sleep time

VO2 = volume of oxygen

WASO = wakefulness after sleep onset

Chapter 1: Introduction to the Dissertation

Approximately 30% of US adults experience insomnia at some point in their life (Morin et al., 2020). Insomnia is a clinical diagnosis with diagnostic criteria that include subjective distress regarding quality or quantity of sleep (difficulty initiating, maintaining sleep or early final awakenings) while having significant impairment in social or occupational functioning at least three times per week for a period of three months (American Psychiatric Association, 2013). It has been well established that there is a misperception of objective and subjective total sleep time among those with insomnia (Carskadon et al., 1976; Castelnovo et al., 2019; Coleman et al., 2982; Fernandez-Mendoza et al., 2010). Research has also shown that there is a subset of individuals with insomnia and who objectively slept < 5 hours and have lower sleep efficiency and a significantly higher rate of adverse health outcomes (Bathgate, Edinger, Wyatt, & Krystal, 2016; Bertisch et al., 2018; Fernandez-Mendoza et al., 2012; Vgontzas et al., 2009; Vgontzas et al., 2010). These outcomes include multiple chronic conditions such as cardiovascular disease, stroke, diabetes, and depression (Center for Disease Control and Prevention, 2018). Treating insomnia is essential given its deleterious effects on physical health. However, the treatment of insomnia is costly and causes undue strain on the healthcare system. The national economic burden is comprised of over 90 billion dollars per year spent on non-pharmacologic and pharmacologic treatment (Daley et al., 2009; Wickwire et al., 2020).

Statement of the Problem

Biomarkers of Insomnia

In efforts to better understand mechanisms underlying insomnia and its somatic effects, varied biological markers have been studied. Biomarker research has had a significant impact on clinical guidelines and recommendations for conditions such as cancer and hematologic disorders while also guiding interventions in a variety of settings (Haeusler et al., 2013; Tran et al., 2019). A recent scoping review investigated biomarkers associated with obstructive sleep apnea (De Luca Canto et al., 2014) and another on salivary molecules associated with sleep

alterations (Ibáñez-Del Valle et al., 2021). The assessment and treatment of insomnia would benefit substantially from a better understanding of salient biomarkers. However, to date, there are no reviews of biomarkers associated with insomnia in adults.

Linking Biomarkers and Social Determinants in Understanding Insomnia

Telomere length is one biomarker that may help in understanding insomnia. Telomeres are buffering caps at the end of chromosomes that are protective during cellular mitosis (Blackburn et al., 2015). When telomeres are shortened to a length that compromises genomic stability, chromosome ends can induce apoptosis (i.e., cell death) or cell cycle arrest which prevent further cellular replication (Engin & Engin, 2021). Several studies suggest that short and disturbed sleep is associated with shorter telomere length (e.g., (Cribbet et al., 2014; Knowles et al., 2018; Osum & Serakinci, 2020; Prather et al., 2015). These studies have examined shorter sleep duration and poor sleep quality but not clinical insomnia. In only three studies specific to insomnia, investigators also report that it is associated with shorter telomeres. A relationship between insomnia and shorter telomeres has been found among older adults (Carroll et al., 2016) and HIV positive individuals (Ding et al., 2018). Another study found that those with insomnia who slept less than 6 hours had a shortened telomere length (Tempaku et al., 2018).

Numerous studies have found that black individuals who experience discrimination had a significantly shortened telomere length (Beatty Moody et al., 2019; Chae et al., 2016; Hailu et al., 2020; Lee et al., 2017; Liu & Kawachi, 2017; Pantesco et al., 2018). In addition, a key finding of a systematic review was that racial discrimination is associated with reduced telomere length (Coimbra et al., 2020). Adversities such as discrimination are also associated with symptoms of insomnia (Bethea et al., 2020; Gaston et al., 2020; Pengpid & Peltzer, 2021). Studies suggest that insomnia is more prevalent among individuals of color (Kaufmann et al., 2016; Matthews et al., 2019). However, little is known about the related contributions of insomnia, race/ethnicity, and discrimination to biologic markers of stress on the body, such as telomere erosion. Poor sleep and key social determinants might function as biological stressors

that impair neurophysiological functions and lead to changes throughout the body reflective of allostatic load. In particular, there is the potential for discrimination to augment effects of insomnia on telomeres. However, no studies have examined if discrimination moderates the relationship between insomnia symptoms and telomere length.

Cognitive Behavioral Therapy for Insomnia and Factors Associated with Response

In addition to understanding biomarkers and social determinants that may enhance our understanding of insomnia, there is a substantial need to develop knowledge that can improve treatment outcomes for insomnia. Cognitive Behavioral Therapy for Insomnia (CBT-I) is recommended as the first line treatment for insomnia (Trauer et al., 2015). Approximately 45% of individuals who undergo CBT-I will experience remission of insomnia symptoms with between 55%-65% of individuals having clinically significant improvement (Ashworth et al., 2015; Carney et al., 2017; Edinger et al., 2007; Ellis et al., 2015). However, multiple studies have found objectively short sleepers based on polysomnography (PSG) of less than 6 hours do not respond to treatment as robustly as longer sleepers. An RCT examining the effects of CBT-I found that six months post-CBT-I treatment, participants who slept < 6 hours had significantly lower remission rates based on the insomnia symptom questionnaire when compared to those who slept $\geq$ 6 hours (Bathgate et al., 2017). Another RCT found that postmenopausal women with insomnia who had a lower sleep efficiency at baseline, had lower rates of insomnia remission measured by ISI (Kalmbach et al., 2020). Another study found that those who slept $\leq$6 hours observed on PSG had less likelihood of achieving remission from insomnia from brief CBT-I (Troxel et al., 2013). retrospective study found that longer sleepers compared to short sleepers had greater improvement in insomnia symptoms ($\geq$6 point reduction in ISI score) after CBT-I (Miller et al., 2018). Lastly, another study reported that longer sleepers had an improvement in overall daytime functioning and sleep satisfaction that was not experienced by short sleepers (Rochefort et al., 2019).

Despite these findings, other studies have shown a positive response to CBT-I among short sleepers that did not differ from longer sleepers (Crönlein et al., 2020; Galbiati et al., 2021; Lovato et al., 2021).

Although previous research provides an important basis for further research on short sleepers, it shows mixed findings and has not examined potential predictors of treatment response. Little is known about psychological and sleep-related factors that may be associated with reduced treatment response among short sleepers.

Overall Study Purpose and Aims

The overall purpose of this dissertation was to address gaps in knowledge noted above by examining 3 specific aims:

1. To identify evidence-based biomarkers that have been associated with insomnia in adults.
2. To determine if insomnia and discrimination are associated with telomere length among adults from different racial/ethnic groups as well as whether discrimination moderates the relationship between insomnia and telomere length.
3. To identify the relationship of psychological distress and sleep-related factors to non-response to cognitive behavioral therapy for insomnia (CBT-I) among short sleepers with insomnia.

Theoretical Framework: Allostatic Load

Allostasis and the concept of allostatic load (AL) were first developed in 1993 (McEwen & Stellar, 1993). McEwen and Stellar developed the framework to conceptualize the relationship between stressors and an individual's processing of stress, along with their effects on the body (see Figure 1). Allostasis is a dynamic process by which an individual's physiological, cognitive, and behavioral responses adapt to stressors in order to provide or maintain internal stability or homeostasis. AL is the cumulative effect of stress on the individual, leading to prolonged responses that can have adverse health outcomes. The response to stress is mediated by the

autonomic nervous system, hypothalamic-pituitary-adrenal (HPA) axis, metabolic, and immunologic processes (McEwen, 2007). The allostatic load framework explains adverse cumulative effects of both internal and external stressors on an individual, resulting in “wear and tear on the body” as an individual is exposed to repeated or chronic physical or psychological stress. AL can have adverse effects on cardiovascular and psychiatric illness, cognition, and longevity, among other conditions (Beckie, 2012; Borrell et al., 2010; Honkalampi et al., 2021; Juster et al., 2010; Nelson et al., 2021; Sabbah et al., 2008) (Beckie, 2012; Borrell, Dallo, & Nguyen, 2010; Honkalampi et al., 2021; Juster, McEwen, & Lupien, 2010; Nelson et al., 2021; Sabbah, Watt, Sheiham, & Tsakos, 2008).

Poor sleep might function as a biological stressor that leads to changes in biological processes throughout the body that result in greater allostatic load (Chen et al., 2014; McEwen, 2007). Insomnia may also interact with social factors such as discrimination to induce greater allostatic load. Alternatively, factors such as psychological distress or specific types of sleep disturbance (including short sleep) may reflect allostatic signatures from previous stress exposure that persist (Caradonna et al., 2022) and reduce the ability of individuals with insomnia to benefit from treatment.

Innovation: Significance of the Dissertation

Completion of the first aim provides a cohesive and consolidated review of the various biomarkers that have been studied in association with insomnia. Prior to this review, no one had consolidated studies investigating biomarkers associated with insomnia in the adult population. The review provides an overview of existing research that may allow researchers to build on what is known, replicate studies to assess reliability of their findings, and identify the need for other areas of research that have not been explored.

Completion of the second dissertation aim adds to the body of literature of biomarker research while also evaluating the effects of social determinants. I evaluated if insomnia symptoms are adversely associated with telomere integrity, while focusing on possible

differential relationships among distinct racial/ethnic groups. In conducting this analysis, I identified if insomnia symptoms affected telomere integrity, and if differences were found among White, Black, and Latinx older adults. I also determined if discrimination had a moderating role between insomnia symptoms and telomere length among the three distinct racial/ethnic groups. Findings of this research study may provide a foundation in the literature for researchers as well as shed light on assessment of insomnia and discrimination in a clinical setting for clinicians. Furthermore, the study of how the social determinants affect health outcomes is an important endeavor encouraged by the National Institute of Health (NIH) and the National Institute of Nursing Research (NINR).

Completion of the third aim contributes to a preliminary understanding of whether psychological and sleep related factors may be associated with lack of treatment response among objectively short sleepers with insomnia. Results provide a glimpse into specific symptoms that may be associated with lack of remission from CBT-I among short sleepers. These symptoms could be addressed as part of CBT-I treatment to increase its relevance for this group of insomnia patients.

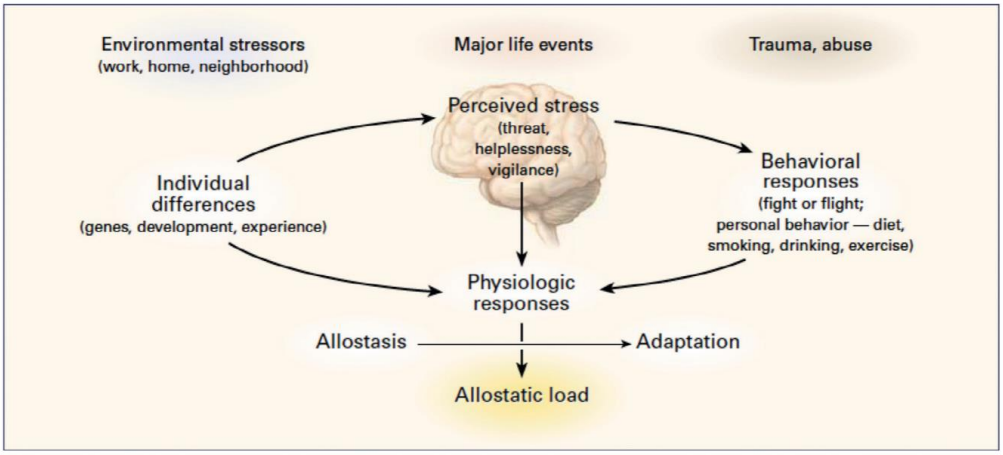

Figure 1: Diagram of Allostatic Load Theoretical Framework

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Chapter 2: Biomarkers Associated with Insomnia Among Adults: A Scoping Review

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Abstract

Approximately 30% of US adults experience insomnia at some point in their life. Insomnia is associated with multiple chronic conditions including cardiovascular disease, stroke, diabetes, and depression. Biomarker research has had a significant impact on clinical guidelines and recommendations for multiple health conditions in a variety of settings, however, to date, there has not been a published scoping review synthesizing biomarker research in association with insomnia in adults. Therefore, the objective was to conduct a scoping review synthesizing biomarkers in adults that are associated with insomnia.

The review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines.

A total of twenty-five studies were included in this review. Of note, a wide variety of biomarkers were examined. Seventeen of the twenty-five studies examined noninvasive blood markers such as electrophysiology and saliva. Eight of the seventeen studies collected were blood-based. A variety of insomnia assessment measures were used. Although results suggest a number of biomarkers are positively associated with insomnia, research to date indicates that electroencephalography may have particular potential for identifying unique characteristics of brain activity associated with insomnia.

This review provides an overview of existing research that may allow researchers to build on what is known, replicate studies to assess reliability of their findings, or identify the need for other areas of research that have not been explored.

Introduction

Rationale

Approximately 30% of US adults experience insomnia at some point in their life (University of Pennsylvania, 2018; Roth, 2007). Insomnia is a clinical diagnosis with criteria being met with perceived subjective distress regarding quality of sleep, difficulty initiating or maintaining sleep while having significant impairment in social or occupational functioning at least three times per week for a period of three months (American Psychiatric Association, 2013). Insomnia is associated with multiple chronic conditions including cardiovascular disease, stroke, diabetes, and depression (Center for Disease Control and Prevention, 2018). Biomarkers are indicators of normal biological processes, pathogenic processes or responses to an exposure or intervention (FDA-NIH Biomarker Working Group, 2016) and are increasingly used for accurate diagnosis and treatment in psychiatry (García-Gutiérrez et al., 2020). Biomarker research has had a significant impact on clinical guidelines and recommendations for conditions such as cancer and hematologic disorders while also guiding interventions in a variety of settings (Haeusler, Carlesse, & Phillips, 2013; Tran, Coleman, McCain, & Cardwell, 2019). However, there are no reviews on biomarkers associated with insomnia in adults. Rather, previous scoping reviews have examined other aspects of sleep disturbance. These included a recent scoping review that investigated biomarkers associated with obstructive sleep apnea (De Luca Canto et al., 2014). Another scoping review examined what salivary molecules were associated with sleep alterations (Ibáñez-Del Valle, Navarro-Martínez, Ballestar-Tarin, & Cauli, 2021). This scoping review addresses this gap in the literature by specifically focusing on biomarkers associated with insomnia in adults.

Objectives

The purpose of this scoping review was to identify biomarkers that have been associated with insomnia in adults.

Methods

Protocol

The protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) Checklist (Tricco et al., 2018).

Eligibility Criteria

Articles selected for review were studies with the primary objective of identifying biomarkers in adult participants experiencing insomnia. Studies were included that measured insomnia by a standardized questionnaire or a structured/semi-structured clinical interview. There was no restriction on study year as there has not been a scoping review conducted on this topic previously. Interventional studies in the treatment of insomnia were also included as long as biomarkers were studied as part of the research. Studies were excluded if participants were under the age of eighteen, were non-human subjects, if a biomarker was not included as part of the study, and if a diagnosis or symptoms of insomnia were not examined. Lastly, studies were excluded if not reprinted in English.

Information Sources

To identify relevant studies, PubMed, Web of Science, and CINAHL were searched on December 20, 2021. The following search strategies were drafted in collaboration with an experienced librarian at UCSF. The search results were exported into EndNote, and duplicates were removed. The electronic database search was supplemented by searching Google Scholar using the same key words as the PubMed search. An additional search with the search term ‘PSG’ and ‘insomnia’ was also conducted on June 18th, 2021, for completeness to obtain any other PSG articles that may have not been originally perceived as a biomarker. This additional search enabled assessment for completeness by scanning for other articles that would meet search criteria within the first 500 articles. No authors of potentially eligible fully reviewed articles were contacted during this scoping review.

Search Strategy

Implemented search strategies for PubMed (Table 2.1), Web of Science (Table 2.2), and CINAHL (Table 2.3) are visualized below.

Selection of Sources of Evidence

Study selection was conducted by one individual. The first phase consisted of removal of duplicate articles in the citation manager. Initially, the search strategy identified 1,407 publications in PubMed, 384 publications in Web of Science, and 124 publications in CINAHL based on inclusion and exclusion criteria. After duplicates were removed, 1,733 articles remained. Titles and abstracts were screened based on the aims, and inclusion and exclusion criteria, leading to exclusion of 1,642 articles. The 1,642 articles were excluded for the following reasons: no human participants, no biomarker, no questionnaire/standardized measure was used in investigating insomnia, and the publication was an abstract/proposal (not a study). Phase two consisted of reviewing the full text of all remaining 91 articles. If the studies did not meet aims or inclusion/exclusion criteria because it was not apparent based on initial abstract review, they were excluded from the synthesis of results. Of the 91 studies, 37 did not examine an associated biomarker, 29 studies investigated disturbed sleep related to other conditions (i.e.: sleep deprivation or insomnia as a symptom of a mood disorder), 5 studies were not studying insomnia, 2 studies focused on participants younger than 18 years of age, and 1 study consisted of non-human subjects. Seventeen articles remained for complete review and synthesis of the findings (see Figure 2).

Data Charting Process and Data Items

Data was charted in table format independently without the use of any other calibrated forms or tools. Investigators were not contacted to confirm data. Table 4 presents the 17 articles selected, with a breakdown of the data items selected for synthesis of results and review. As articles were reviewed, the data items were documented in chronological order based on year.

The following information was documented: year of publication, author, sample size, diagnostic criteria for insomnia, mean/range of participant ages, biomarker source and type, and the identified biomarker, along with statistical significance of results. Sample size was further classified within each study by number of participants with insomnia against those participants without insomnia if applicable. Biomarker source was classified as either noninvasive or invasive. Noninvasive biomarker sources include polysomnography (PSG), electrocardiogram (EKG), imaging, and saliva. Invasive biomarker sources required venipuncture for serum collection. Biomarkers were further classified based on categories based on how this author conceptualized the biomarker. The categories are not mutually exclusive, and studies may have investigated multiple types of biomarkers. The biomarker types were classified as: electrophysiologic, metabolic, endocrine, oxidative stress, cerebral structure, bone density, and genomic. Studies investigating multiple types of biomarkers were labeled in the table. Diagnostic measures of how the researchers' operationalized insomnia was also included in the table.

No formal software was used. Table 2.4 below includes each study by year in chronological order with sample size, stated measures used to assess insomnia, mean/range age of participants, biomarker classification and type, and findings. Strength of findings (e.g., effect size) and risk of bias was not evaluated. Assessing bias and strength of findings, although required in a systematic review, is optional in a scoping review (Tricco et al., 2018).

Results

Sources of Evidence

Figure 2 visually depicts the study selection and decisions in a flow diagram using the PRISMA guidelines attached below (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

Study Characteristics

The quantitative studies' years of publication ranged from 1993 to 2021. Sample size of participants without insomnia (control) ranged from 10 to 1,439. Sample size of participants with

insomnia (case) ranged from 10 to 7,280. Studies with no controls had a range from 24 to 2,253. Ages of cases ranged from 21 to 48.9 while those in control groups ranged from 31 to 55.4. Ages of studies that had no control group ranged from 18 to 80 years of age.

Eight of the twenty-five studies collected biomarkers that were blood-based (Ban, Kim, Seo, Kang, & Choi, 2011; Gulec et al., 2012; Iloabuchi, Innes, & Sambamoorthi, 2020; Prather, Vogelzangs, & Penninx, 2015; P. Zhang et al., 2018). Ten of the twenty-five studies used sources that were noninvasive. The biomarkers' type included: 12 electrophysiologic markers (Bastien et al., 2008; Colombo et al., 2016; Dang-Vu et al., 2017; Eddie et al., 2020; Krystal et al., 2002; Krystal & Edinger, 2010; Lundsford-Avery, Edinger & Krystal, 2021; Ran et al., 2017; Regestein, Dambrosia, Hallett, Murawski, & Paine, 1993; Rosa & Bonnet, 2000; Varkevisser, Van Dongen, & Kerkhof, 2005; Zhang et al., 2019), 5 metabolic markers (Bonnet, 1996; Chen, Redline, WIlliams, & Williams, 2014; Harper et al., 2013; Rosa & Bonnet, 2000; Varkevisser et al., 2005), 4 inflammatory markers (Carroll et al., 2015; Chen et al., 2014; Irwin et al., 2015; Prather et al., 2015), 3 cerebral structure markers (Leerssen et al., 2019; Winkelman et al., 2008; Zhang et al., 2018), 1 non-invasive neurotransmitter marker (Winkelman et al., 2008), 3 genomic markers (Ban et al., 2011; Iloabuchi et al., 2020; Irwin et al., 2015), 1 endocrine marker (Varkevisser et al., 2005), 1 oxidative stress marker (Gulec et al., 2012), 1 cardiovascular marker (Chen et al., 2014), and 1 bone density marker (Niu et al., 2015).

Overview of the Studies

The following section reviews how studies evaluated insomnia and biomarker findings. Studies are organized in chronological order of when published.

Regestein et al. (1993) tested whether there were electrophysiologic differences based on PSG readings between those with and without insomnia. They recruited 20 participants with insomnia and 20 participants without insomnia. Twenty-seven participants were female. Mean age of participants with insomnia was 31 years with mean age of those not experiencing insomnia being 37 years. They determined insomnia based on a 173 item questionnaire that

included questions to diagnose participants with insomnia. However, how the questionnaire was used to diagnosis insomnia was not described. In addition to this questionnaire, the investigator also utilized a 26-item hyperarousal scale to measure alertness throughout the day with a higher score indicating more arousal. There was a positive correlation between the hyperarousal scores among participants who experienced insomnia and the alpha brain activity depicted on PSG ($r=0.38$, $p=0.03$). They also found PSG readings showed significantly higher levels of both alpha and non-alpha PSG activity during stage 1 sleep with an increase in amplitude between 15%-131% when compared to longer sleepers ($p<0.05$).

Bonnet (1996) also investigated if PSG signatures can be detected in participants with insomnia when compared to those without insomnia. They recruited 10 participants with insomnia and 10 participants without insomnia, 10 of the matched participants were female. They also calculated basal metabolic rate (BMR) based on body temperature (BT) readings and oxygenation readings (VO2). Mean age of all participants ranged from 21 to 48 years of age. They determined insomnia based on a questionnaire that diagnosed insomnia if participants endorsed experiencing a sleep problem, have sleep latency (SL) of $\geq$ 45 minutes, with wakefulness after sleep onset (WASO) of $\geq$ 60 minutes for $\geq$ 4 nights per week for 1 year. The investigators found an increase in V02 in association with insomnia on night 7 of the study (302 vs 274 ml/minute) and a decrease in temperature (98.8F vs 99.2F), however, confidence intervals or p values were not listed.

Rosa and Bonnet (2000) also investigated if there were differences of PSG readings among those with insomnia and those without. They recruited 121 participants with insomnia and 56 participants without insomnia. Approximately 65% of the participants were female. The diagnostic criteria for insomnia were the same criteria as Bonnet (1996), described above. They found no differences between groups.

Krystal et al., (2002) conducted a study examining differences in PSG between 12 long sleepers who have insomnia, 18 short sleepers with insomnia, and 20 participants without

insomnia. Lower delta (F=8.2, p<.003) and greater alpha (F=3.3, p<.08), sigma (F=16.3, p<.0007), and beta NREM EEG activity (F=10.1, p<.007) were prominent in participants who were longer sleepers with insomnia but not among those who are short sleepers with insomnia in comparison to the normal subjects. They also found participants who were shorter sleepers with insomnia had significantly greater NREM relative power than did the healthy participants only for the sigma band (F=6.0, p<.03).

Varkevisser, Dongen, & Kerkhof (2005) also investigated if physiological arousal would be noted more prominently in comparison to those without insomnia. They collected temperature, salivary cortisol, and calculated heart rate variability. Thirteen participants with insomnia and 13 participants without insomnia were recruited. Twelve participants were female. A diagnosis of insomnia was made based on the International Classification of Sleep Disorders (ICS). The criterion was met if an insomnia complaint was for $\geq$ 6 months, $\geq$ 3 nights per week, and SE% confirmed by PSG of less than 85%, SL $\geq$ 30 minutes and/or WASO $\geq$ 45 minutes. PSG readings were conducted each night 3 days prior to the start of the study and cross referenced with actigraphy. They found no differences between those with insomnia and control participants across all three biomarkers.

Bastien et al., (2008) examined on PSG how event-related potentials (ERPs), which are markers of arousal, compared in those with insomnia (n=15) vs those without (n=16). They found during the hours of morning ($t_{14} = -2.52$, $P = 0.02$) and evening ($t_{14} = -2.16$, $P < 0.05$), those with insomnia exhibited larger N1 amplitudes compared to those without. Those with insomnia also exhibited greater P2 amplitudes than those without ($F=1.29 = 6.58$, $P = 0.02$).

Winkelman et al., (2008) sought to investigate if GABA levels differed among those with insomnia compared to healthy controls based on 4T proton magnetic resonance spectroscopy (1H-MRS). They studied an equal split of 16 participants with insomnia compared to 16 without. They found participants with insomnia showed a nearly 30% reduction in brain GABA levels (0.18 +/- 0.06) compared to those without insomnia (0.25 +/- 0.11). Furthermore, there was a

negative association between GABA levels and wake after sleep onset (WASO) based on two separate PSGs, with correlation coefficients of -0.71 ($p = 0.0024$) and -0.70 ($p = 0.0048$).

Krystal and Edinger (2010) conducted a study to evaluate the relationship of non-rapid eye movement (NREM) electroencephalographic (EEG) spectral measures and the response to CBT-I in insomnia in comparison to those in a placebo group who received a sham therapy. Those with insomnia had higher EEG delta power with a rapid decline overnight after receiving CBT-I in comparison to the placebo group ($F = 4.5$, $P < 0.05$). They also found that those with insomnia with a lower pretreatment peak EEG delta power ($R2 = 0.33$, $F = 8.0$, $P < 0.02$) in the first NREM cycle and higher pre-treatment delta power leading to a gradual decline ($R2 = 0.23$, $F = 4.9$, $P < 0.05$) predicted a better response to CBT-I.

Ban et al. (2011) conducted a secondary analysis based on a Korean national genome wide project identifying 1,439 participants with insomnia and 7,280 without. Demographic results including gender were not reported in this published article although referenced to be available at (http://compgen.kaist.ac.kr). However, the link was not available online. Their objective was to identify if single nucleotide polymorphisms (SNPs) could be located that were associated with insomnia. Insomnia was classified based on a four-item questionnaire that asked participants about concerns with initiating sleep, maintaining sleep, problems with final awakenings, and overall difficulty related to sleep. The most significant polymorphisms (SNPs) were located on ROR1 (rs11208305, $p=5.6X10^{-6}$) and PLCB1 (rs718712, $p=8.5x10^{-6}$) that were associated with insomnia.

Gulec et al. (2012) investigated the effects of primary insomnia on oxidative stress by evaluating glutathione peroxidate (GSH-Px), superoxide dismutase (SOD), myeloperoxidase (MPO), glutathione (GSH), and malondialdehyde (MDA). A diagnosis of insomnia was established at baseline utilizing the DSM-5. The study consisted of a total of 60 participants, half with primary insomnia and the other were healthy controls. Approximately 55% of participants were female. MDA levels were significantly higher in the insomnia group (5.41 μmol/L, $p=0.028$)

than in the healthy controls while GSH-Px activity was lower (11.10 U/g Hb) p=0.041). No significant differences between groups were found when comparing both GSH or MPO and SOD levels.

Harper et al. (2013) conducted a cross-sectional study evaluating if cellular metabolic markers are associated with insomnia. They evaluated 16 participants who met criteria for insomnia and matched them against 16 control participants, 47% of participants were female. Insomnia was verified in a semi-structured interview using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-4 (SCID). Polysomnography was also evaluated within 2 weeks of the study. Cell membrane metabolites including adenosine triphosphate (ATP) and phosphocreatine, phosophocoline, and beta-nucleoside triphosphate were evaluated via magnetic resonance spectroscopy. Individuals with insomnia showed lower phosophocreatinine in gray matter (insomnia group: t_{463} =2.35, p=.04 vs control- t_{463} =3.46, p=.0006 and decrease in phosphocholine in white matter (t_{463} =-3.72, p=.0005).

Another study evaluated the effects of insomnia on allostatic load (AL) using metabolic, cardiovascular, and inflammatory indicators (Chen et al., 2014). The researchers conducted a secondary analysis using the US National Health and Nutrition Examination Survey. Total sample size was 3,330 without a control group. Age ranged from 18 to 17 years of age. Approximately 47% of the participants were female. Insomnia was evaluated based on a standardized 4 item questionnaire asking participants about difficulty initiating, maintaining, or waking too early from sleep, and if they felt unrested the next morning. The biomarkers under investigation in the analysis included: systolic/diastolic blood pressure, heart rate, total cholesterol, low-density lipoprotein (LDL), body mass index (BMI), glycosylated hemoglobin (HgbA1c), albumin, and c-reactive protein (CRP). They created a variable with the sum of the values of the biomarkers. A score of 3 or higher was considered allostatic overload. Insomnia was associated with high AL (OR, 1.70; CI [1.16-2.47], p<.006).

Irwin et al. (2015) evaluated if C-reactive protein (CRP), monocyte proinflammatory cytokine production, and proinflammatory gene expression levels would decrease after a trial of cognitive behavioral therapy for insomnia (CBT-I) and/or Tai Chi Chih (TCC), in comparison to a control group. The total sample size of the study was 123, with approximately 72% were female. Insomnia diagnosis was confirmed based on clinical interview using the DSM-IV and International Classification of Sleep Disorders (ICSD). Insomnia was subsequently evaluated based on the PSQI questionnaire. For individuals who responded to CBT-I and had less severe symptoms of insomnia, there was an associated reduction of CRP ($t_{105.4}$ = 2.08; p= .04), a reduction in monocyte production of proinflammatory cytokines at month 2: ($t_{100.1}$ = 3.75 ; p<.001, and a downregulation of proinflammatory gene expression (β: 0.5, p=0.0447).

Carroll et al. (2015), utilizing the primary data from Irwin et al. (2015), investigated the effects of CBT-I (n=47) and TCC (n=39) on 8 serum biomarkers. Approximately 71% of participants were female. The 8 serum markers included: high and low-density lipoprotein, triglycerides, hemoglobinA1c, glucose, insulin, C-reactive protein, and fibrinogen. Using cut-off scores based on normal lab values, a multisystem score was computed. Scores were categorized as low risk or high risk group. Those with insomnia had higher odds of being in the high risk group as those with improved sleep quality had reduced odds of being in the high risk group (OR=.08, p<.01) at 16 months post treatment. They also found that among those in the CBT-I group who, if they had improved sleep quality there was a reduced likelihood as having high risk abnormal lab values (OR=.06, p<.01).

Niu et al. (2015) conducted a secondary cross-sectional study utilizing the Boston Puerto Rican Osteoporosis Study. 750 Puerto Rican adults were evaluated to find if insomnia symptoms were associated with reduced bone mineral density (BMD) measured by dual-energy x-ray. Approximately 72% of the participants were female. Symptoms of insomnia were based on a 5-item questionnaire. Men who slept over 9 hours had lower femoral neck BMD relative to

those with 8 hours of sleep (β -0.085, [-0.17, -0.0014], p<.05) though symptoms of insomnia were not associated with BMD.

Prather, Vogelzangs, & Penninx (2015) conducted an analysis utilizing the Netherlands Study of Depression and Anxiety (NESDA). They investigated if insomnia and sleep duration were associated with inflammatory biomarkers: CRP, interleukin (IL)-6, and TNF-α. They examined 2,553 men and women (67%) who had completed a 5-item measure of insomnia; the tool used to measure insomnia was based on the Women's Health Initiative Insomnia Rating Scale (IRS). Longer sleep duration was associated with elevated CRP (β .041, p-0.026), and elevated IL-6 β .028, p=.067). However, insomnia symptoms were not associated with markers of inflammation.

Colombo et al., (2016) evaluated the spatial and spectral characteristics of high-density wake EEG in two groups: 51 individuals with insomnia and 43 matched controls who did not report any sleep issues during wakefulness. Participants with insomnia exhibited widespread higher beta power during wakefulness with closed eyes (ρ = −0.32, Z = −2.4, P = 0.02) than in healthy control subjects (ρ = −0.25, Z = −1.7, P = 0.09). However, when their eyes were open, their EEG displayed relatively lower power in a narrow band within the upper-alpha range m 11 to 12.7 Hz, (p<.05). The limited correlation between these two features suggests that they may represent separate processes, indicating high arousal and low inhibition, respectively.

Dang-Vu et al. (2017) evaluated in their pilot study if spindle density pre-treatment of CBT-I can predict treatment response as measured on PSG. The study included 24 participants, 19 of which were female participants. Sleep spindles are approximately 11-15 Hz seen on PSG that occur predominantly in stage N2 but are also present in stage N3 of non-REM sleep (Dang-Vu et al., 2017). A clinical diagnosis of insomnia was made by a licensed clinician in a semi-structured in-person interview with evaluation of sleep quality conducted with episodic administration of the PSQI throughout the study. A total of 24 participants were enrolled in the

study. They found reduced spindle density pre-treatment was associated with insomnia as evidenced by a small reduction in PSQI (β -4.66, p<.001).

Ran et al., (2017) examined the amplitude of low-frequency fluctuations (ALFF) and explored the correlation between these altered ALFF regions using resting-state fMRI and PSG data. They enrolled 25 participants with insomnia and 25 individuals with normal sleep (NS) as a control group. They found heightened ALFF in regions associated with hyperarousal, including the midbrain and bilateral extra-nucleus (peak MNI coordinate: 24, -9, -6, t = 5.27, cluster size = 213 voxels), p<.05). Conversely, reduced ALFF was observed in areas related to memory and attention, such as the parietal (peak MNI coordinate: -21, -42, 66; *t* = 4.60; cluster size = 218, and occipital lobules (peak MNI coordinate: -27, -87, 15; *t* = 3.7, cluster size = 206).

Zhang et al., (2018) evaluated if power spectral density on polysomnography (PSG) was different among those with insomnia (n=30) compared to those without (n=30). Results showed A-latency had statistically longer values in the insomnia group (729.5 ± 106.8) compared to the control group (492.9 ± 67.36, p=0.0357). Conversely, the iCNV-latency (contingent negative variation) in the insomnia group exhibited statistically shorter values (337.3 ± 60.21) than the control group (492.6 ± 53.52 p=0.0307). The research findings demonstrated diverse patterns of attentional and information processing in individuals with insomnia, suggesting that the frontal lobe plays a crucial role in sustaining cognitive processing, requiring higher energy consumption. Consequently, this leads to a decrease in fast EEG activity in the frontal cortex, resulting in reduced cortical inhibition, which is represented as abnormal CNV.

Zhang et al. (2018) examined if insomnia is associated with neuronal damage by evaluating levels of neurofilaments heavy chain and light chain (NfH, NfL), neuron specific enolase (NSE), and calcium binding protein B (S100B). Fifty-four participants who met criteria for insomnia and who underwent CBT and/or antidepressant pharmacotherapy. Twenty-four participants followed up at 6 months after intervention were compared to 17 healthy control participants. Approximately 69% of the participants were female. Insomnia was determined

based on clinical interview by a senior clinician utilizing criteria from the DSM-5. The PSQI was subsequently used to track sleep quality and baseline PSG was obtained on two consecutive nights at baseline in the lab. Those who did not have successful completion of CBT-I at 6 month had higher levels of all four proteins (NfH: 445.5 ± 60.5, NfL: 4.8 ± 0.6, S100B: 602.9 ± 73.0, NSE: 42.8 ± 5.9, p<.001) than the control group. Participants who successfully completed CBT-I at 6 month follow-up had reduced lower levels of 3 of the 4 proteins (NfH: 355.4 ± 27.9 p<.001), NfL (4.1 ± 0.3, p<.001), and S100B (591.4 ± 68.6, p<.001) than the control group.

Leerssen et al. (2019) investigated if insomnia was associated with structural/functional differences of the brain by having participants undergo functional magnetic resonance imaging (fMRI). They recruited 65 participants with insomnia and 65 without. Approximately 70% of participants were female. Insomnia was diagnosed based on DSM-5 criteria. The Insomnia Severity Index (ISI) and a consensus sleep diary (CSD) were also evaluated. PSG was also conducted in the study. They found insomnia was associated with an increase in bilateral hippocampal connectivity with the left middle gyrus (r=.371, p=9.3e-5). Connectivity was also negatively correlated with subjective sleep efficiency (r=-.307, p=.009) among those with insomnia. Hippocampal volume did not differ among groups.

Eddie et al. (2020) investigated: 1) whether differences in heart rate variability (HRV) existed among those with insomnia when compared to a) those with major depressive disorder (MDD) without a diagnosis of insomnia, and b) healthy controls, and 2) if HRV was moderated by stage of sleep based on home polysomnography. They recruited 14 participants with insomnia, 39 participants with MDD, and 20 participants in the control group. Fifty-four of the participants were female. A diagnosis of insomnia was established based on a clinical interview utilizing the DSM-IV-TR. They found no differences of HRV across all three groups .

Another study conducted a secondary analysis based on data from the Health and Retirement Study (HRS), examining the effects of symptoms of insomnia on telomere length (TL) among 5,268 older adults (Iloabuchi et al., 2020). Approximately 55% of participants were

female. Symptoms of insomnia were based on a questionnaire asking participants if they had difficulty initiating sleep, maintaining sleep, if they had problems with final awakenings, if they felt rested in the morning, and if sedative hypnotic medications were taken to aid with sleep. A composite score was created based on the questionnaires. Cumulative insomnia symptoms were not significantly associated with telomere length; however, not feeling rested in the morning was significantly associated with reduced telomere length (β=-0.08, $p<0.01$).

Lundsford-Avery, Edinger, & Krystal (2021) sought to determine whether delta decline rate is slower overnight as determined by PSG readings among those with insomnia when compared to healthy controls. Fifty-one insomnia patients and 53 participants without insomnia underwent 6 nights of polysomnography. Investigators found those with insomnia displayed a significantly slower linear decline in delta power overnight compared to controls without insomnia ($F [1, 59] = 8.36$, $P < 0.01$).

Discussion

Summary of Evidence

With regard to diagnosis of insomnia, there was a range in how participants were screened for meeting criteria for having insomnia. Sixteen studies established a clinical diagnosis of insomnia based on clinical interview (Bastien et al., 2008; Carroll et al., 2016; Colombo et al., 2016; Dang-Vu et al., 2017; Eddie et al., 2020; Gulec et al., 2012; Harper et al., 2013; Irwin et al., 2015; Krystal et al., 2002; Krystal & Edinger, 2010; Leerssen et al., 2019; Lundsford-Avery, Edinger, & Krystal, 2021; Ran et al., 2017; Winkelman et al., 20018; Zhang et al., 2018, Zhang et al., 2018). Five studies used standardized questionnaires whose psychometric properties were not cited as having been evaluated (Ban et al., 2011; Chen et al., 2014; Iloabuchi et al., 2020; Niu et al., 2015; Prather et al., 2015). Three studies utilized undefined questionnaires to diagnose insomnia (Bonnet, 1996; Regestein et al., 1993; Rosa & Bonnet, 2000). Future studies would benefit from either analyzing the psychometric properties of the questionnaires for validity and internal consistency or using existing standardized

questionnaires that have been known to have high validity while also establishing a clinical diagnosis of insomnia with a clinician interview. Comparison of studies was a challenge given the variation in how insomnia was measured.

With regard to significant findings: 2 investigated metabolic markers (Chen et al., 2014; Harper et al., 2013), 1 investigated oxidative stress, (Gulec et al., 2012), 1 investigated cardiovascular function (Chen et al., 2014), 3 investigated inflammation (Carroll et al., 2015; Chen et al., 2014; Irwin et al., 2015), 3 investigated genomics (Ban et al., 2011; Iloabuchi et al., 2020; Irwin et al., 2015), 2 investigated cerebral structure (Harper et al., 2013; Leerssen et al., 2019), 1 investigated non-invasive GABA levels based on imaging (Winkelman et al., 2008), and 11 investigated PSG signatures (Bastien et al., 2008; Colombo et al., 2016; Dang-Vu et al., 2017;; Krystal et al., 2002; Krystal & Edinger, 2010; Lundsford-Avery, Edinger & Krystal, 2021; Ran et al., 2017; Regestein, Dambrosia, Hallett, Murawski, & Paine, 1993; Rosa & Bonnet, 2000; Varkevisser, Van Dongen, & Kerkhof, 2005; Zhang et al., 2019). Of these studies, three were interventional studies evaluating the effects of CBT-I on associated biomarkers (Carroll et al., 2015; Irwin et al., 2015, Krystal & Edinger, 2010).

Multiple biomarkers did not have significant findings. Body temperature (Rosa & Bonnet, 1985; Varkevisser et al., 2005), findings on EKG (Eddie et al., 2020; Varkevisser et al., 2005), bone density (Niu et al., 2015), and cortisol (Varkevisser et al., 2005) were not associated with insomnia. Of those that had no findings, none described a theoretical framework that informed their research questions. Two of the studies without significant findings did not use standardized questionnaires, and therefore, symptoms of insomnia may not have been accurately evaluated at baseline and throughout their studies (Niu et al., 2015; Rosa & Bonnet, 2000).

Multiple studies have evaluated if there are unique PSG signatures as outcomes associated with clinically diagnosed insomnia, primarily using EEG or neuroimaging. Krystal et al. (2002) found that reduced delta and increased alpha, sigma, and beta NREM EEG activity and higher NREM relative power in the sigma band in short sleepers may be related to arousal

and be associated with insomnia. Krystal & Edinger (2010) also found insomnia was associated with: 1) higher EEG delta power, which showed a rapid decline overnight after cognitive behavioral therapy for insomnia (CBT-I), and 2) lower pretreatment peak EEG delta power and higher pre-treatment delta power leading to a gradual decline, which predicted a better response to CBT-I. Lundsford-Avery, Edinger, & Krystal (2021) also found a slower decline in delta power among those with insomnia. Additionally, an increase in P1 and P2 activity was found to be associated with insomnia (Bastien et al., 2008). Ran et al., (2017) found heightened ALFF in regions that are associated with hyperarousal among those with insomnia. Colombo et al., (2016) found that higher beta activity during wakefulness was higher among those with insomnia. Lastly, Dang et al. (2017) noted that a reduction in spindle activity was associated with poorer response to CBT-I. These varied findings suggest that non-rapid eye movement (NREM) electroencephalographic (EEG) spectral measures may be useful biomarkers in assessing excess arousal or inhibition associated with insomnia in different brain regions and to predict or assess response to cognitive behavioral therapy for insomnia (CBT-I) among individuals with different types of insomnia.

Rosa et al. (2000) studied PSG readings as an outcome and had no significant findings. However, they also did not clinically diagnose insomnia at the start of the study. Future researchers should also consider clinically diagnosing insomnia in recruitment of participants based on clinical interview. Of note, only 2 studies evaluated brain structure or function: one with fMRI and the other with MRS. There is an opportunity for researchers to further investigate associations of insomnia with brain structure using these types of imaging as well as using fMRI in interventional studies targeted towards insomnia. In terms of genomic testing, one study investigated telomere length and another study evaluated candidate genes. However, both studies used a less than 5 item questionnaire, and did not clinically diagnose clinical insomnia when recruiting participants. There is a need for researchers to further investigate the associations of candidate genes and gene expression with clinically diagnosed insomnia.

Two limitations were noted throughout the studies. The study samples for all the studies' gender distribution were unequal making generalizability a challenge. Most of the studies' age range skewed younger with the exception of two studies that targeted older adults (Iloabuchi et al., 2020; Niu et al., 2015).

This scoping review had no publication date limitations and based on the aims, objectives, exclusion, and inclusion criteria; twenty-five articles were found in the literature. Replication of studies that had not established a diagnosis of insomnia prior to testing may provide different results.

Conclusions

Aims of this scoping review were to identify knowledge that has been developed regarding insomnia-related biomarkers and gaps in the literature. To date, there has not been a review that consolidated studies investigating biomarkers associated with insomnia in the adult population. This review identified multiple noninvasive and invasive biomarkers that have been studied in association with insomnia. Although results suggest a number of biomarkers are positively associated with insomnia, research from this review indicates that EEG and neuroimaging (MRS, fMRI) markers have shown the most promise to date in advancing the understanding of insomnia. Studies using these markers have found areas of greater activation and inhibition in specific brain regions among those with insomnia versus those without insomnia as well as in treatment response. However, no other markers have yet shown potential utility in assessing insomnia or its treatment. In fact, there are conflicting findings regarding the relationships of some biomarkers (e.g., inflammatory markers). This review provides an overview of existing research that may allow researchers to build on what is known, replicate studies to assess reliability of their findings, or identify the need for other areas of research that have not been explored.

Table 2.1 PubMed Literature Search Terms

Concept	Search Terms
#1 Biomarker	Biomarkers [MeSH Terms:noexp] OR "biological markers" OR "biological marker" OR "biochemical marker" OR "biochemical markers" OR Biomarkers OR biomarker OR genome[mesh] OR "Telomere"[MeSH Terms] OR "Telomere"[tiab] OR "telomeres"[tiab] OR "Telomere"[MeSH Terms] OR "Telomere"[Title/Abstract] OR "telomeres"[Title/Abstract] OR "leukocyte telomere length" OR (LTL) OR "Tumor Necrosis Factor-alpha"[MeSH] OR "Tumor Necrosis Factor alpha" OR "TNF alpha" OR "Interleukins"[MeSH] OR interleukins [tiab] OR interleukin [tiab] OR "Cytokines"[MeSH] OR cytokines [tiab] intercellular signaling peptides and proteins[meSH] OR monitoring, physiologic[meSH]heart rate variability[meSH] adrenal cortex hormones[meSH] OR electroencephalography[meSH] OR (polysomnography[MeSH Terms]))
#2 Adult	"Adult"[MeSH] OR adult OR adults
#3 Insomnia	"Insomnia" "Dyssomnias"[MeSH:noexp] OR dyssomnias [tiab] OR dyssomnia [tiab] OR "Sleep Deprivation"[MeSH Terms] OR "Sleep Deprivation"[tiab] OR "sleep deprivations"[tiab] OR "Sleep Disorders, Intrinsic"[MeSH:noexp] OR "intrinsic sleep disorders" OR "intrinsic sleep disorder" OR "sleep state misperceptions"

Table 2.2 Web of Science Search Terms

Concept	Search Terms
#1 Biomarker	ts=(Biomarkers OR biomarker OR biological markers OR biochemical marker OR genome OR physiologic monitoring)
#2 Adult	ts=(adult OR adults)
#3 Insomnia	ts=(insomnia OR dyssomnias OR sleep disorders OR intrinsic sleep disorders OR sleep state misperceptions)

Table 2.3 CINAHL Search Terms

Concept	Search Terms
#1 Biomarker	ts=(Biomarkers OR biomarker OR biological markers OR biochemical marker OR genome OR physiologic monitoring)
#2 Adult	ts=(adult OR adults)
#3 Insomnia	ts=(insomnia OR dyssomnias OR sleep disorders OR intrinsic sleep disorders OR sleep state misperceptions)

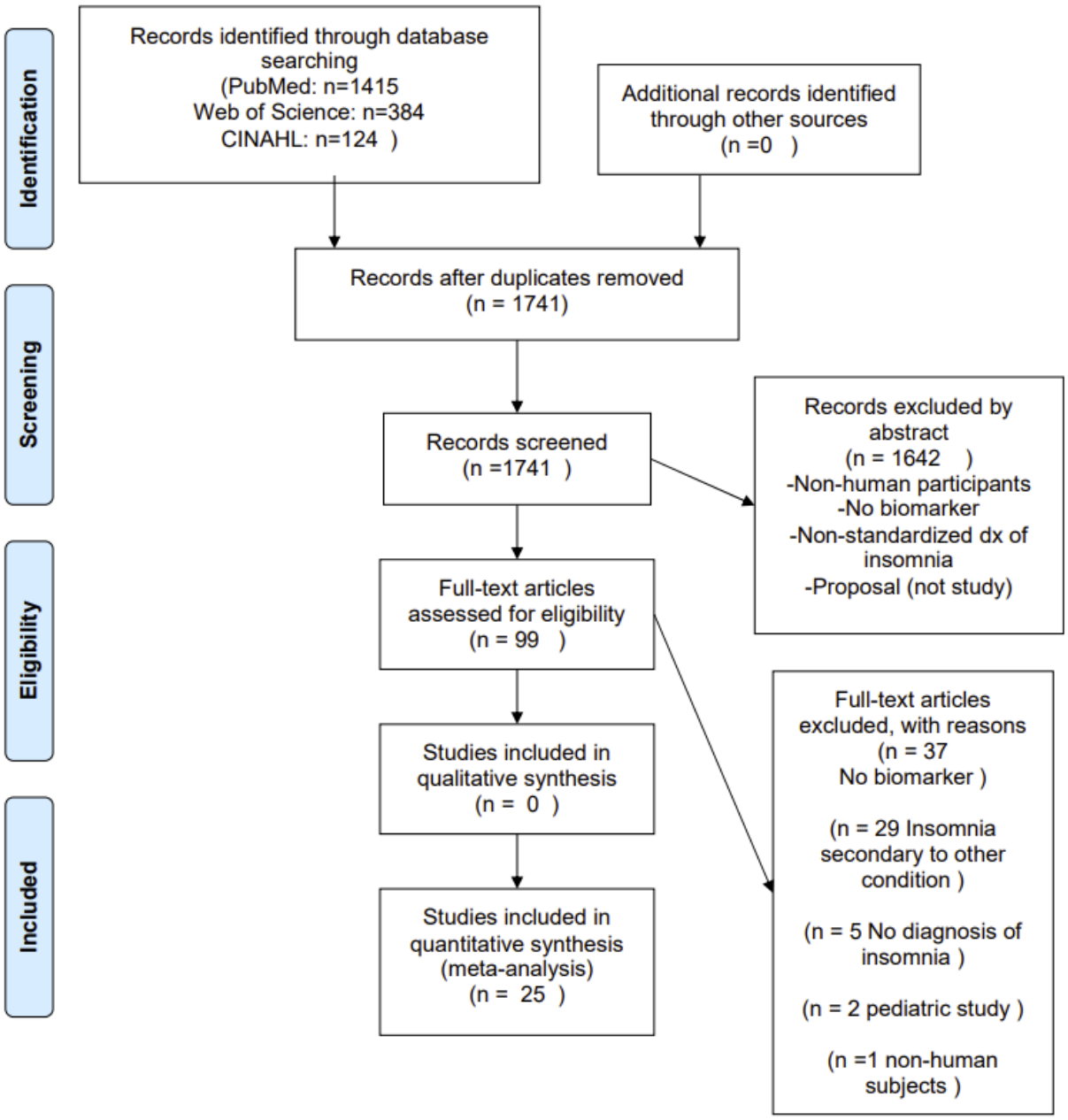

Figure 2 Flow diagram outlining the screening process of literature in search engines

Table 2.4 Summary of study descriptive characteristics and associated reference(s)

Year	Author	Cases n Size	Control n Size	Diagnostic Criteria of Insomnia	Mean age or range if provided	Biomarker Type	Biomarker	Significant Findings
1993	Regestein et al.	20	20	173 item questionnaire	Control-31 Case-37	Electrophysiologic	PSG: ↑P1N1 activity, ↑ Alpha activity	15%-131% higher mean activity (p<0. 05).
1996	Bonnet	10	10	Questionnaire: SL> 45 min. ≥4 nights per week or WASO: ≥ 60 min -For 1 year	21-48	Metabolic	BMR: ↑(V02) BT: ↓ (Celsius)	(302 vs 274ml)-no reported p value (98.8F vs 99.2F)-no reported p value
2000	Rosa and Bonnet	121	56	Questionnaire: SL> 45 min. ≥4 nights per week or WASO: ≥ 60 min -For 1 year	Control-36 Case-35	Electrophysiologic Metabolic	BMR PSG BT	Nonsignificant
2002	Krystal et al.	20	18	DSM-IV	Control-56.1± 11.7 Case subjective- 54.9 ± 10.4 Case objective- 54.3 ± 9.9	Electrophysiologic	PSG: delta waves alpha waves sigma waves NREM activity	Subjective insomnia:↓ delta (F=8.2, p<.003) ↑ alpha (F=3.3, p=.007) ↑sigma (F=16.3, p<.0007) ↑ β NREM activity Objective insomnia: ↑ NREM (F=6, p=.03)
2005	Varkevisser et al.	13	13	ICS PSG	Control-44.9 Case-43.8	Electrophysiologic Metabolic Endocrine	BT EKG Cortisol	Nonsignificant
2008	Bastien et al.	16	15	DSM-IV	Control- 37 ± 10.1 Case- 46 ± 7.5	Electrophysiologic	N1 waves	↑N1 amplitude morning-t 14 = -2.52, p=.02 evening- t 14 = -2.16, p<.05
2008	Winkelman et al.	16	16	DSM-IV-TR	Control- 37.6 +/- 4.5 Case- 37.3 ± 8.1	Cerebral structure and function	GABA	-.71, p= .0024 / -.70, p=.0048

Year	Author	Cases n Size	Control n Size	Diagnostic Criteria of Insomnia	Mean age or range if provided	Biomarker Type	Biomarker	Significant Findings
2010	Krystal & Edinger	NA	30	DSM-IV-TR	54.1	Electrophysiologic	PSG: delta waves	↑ delta power decline, after treatment (F=4.5, p<05) ↓delta power pretreatment (r2=.33, F=8, p<.02)
2011	Ban et al.	1,439	7,280	4 item questionnaire (onset, maintenance, final awakening concern)	40 to 69 yrs., not broken down by group	Genomic	Candidate genes: ROR1 PLCB1	rs11208305, $p=5.6X10^{-6}$ rs718712 $p=8.5x10^{-6}$
2012	Gulec et al.	30	30	DSM-IV	Insomnia-38.73 Control-38.60	Oxidative Stress	↑MDA ↓GSH-Px	5.41± 1.07, (p=0.028) 11.10± 1.65 (p =0.041)
2013	Harper et al.	16	16	DSM-IV SCID	37.6	Metabolic	↓phospho-creatine ↓ phospho-choline	t_{463} =2.35, p=.04 t_{463} =-3.72, p=.0005
2014	Chen et al.	3,330	No control	4 item questionnaire	18-77	Cardiovascular Metabolic Inflammatory	AL	OR, 1.70; CI [1.16-2.47], p<.006)
2015	Carroll et al.	CBT-47	Tai Chi-39 Sleep Seminar-23	DSM-IV ICSD PSQI	CBT-64.8 Tai Chi-67.3 Sleep seminar-66	Inflammatory	Multisystem biological composite risk score: CBT group at 16 month- TCC group 16 months	(OR=0.06 p<.01) (OR=.08, p<.01)

Year	Author	Cases n Size	Control n Size	Diagnostic Criteria of Insomnia	Mean age or range if provided	Biomarker Type	Biomarker	Significant Findings
2015	Irwin et al.	CBT-47	Tai Chi-39 Sleep Seminar-23	DSM-IV ICSD PSQI	CBT-64.8 Tai Chi-67.3 Sleep seminar-66	Inflammatory Genomic	↓CRP ↓monocyte production of proinflammatory cytokines ↓ pro-inflammatory gene expression	($t_{105.4}$ = 2.08; p= .04) Month 2 IL-6: ($t_{100.1}$ = 3.75 ; p<.001 (β: 0.5, p=0.0447)
2015	Niu et al.	750	N/A	5 item questionnaire	47-79	Bone density	BMD	No significant findings
2015	Prather	2,253	N/A	IRS	18-65	Inflammatory	CRP, IL-6, TNF-α	Increased sleep duration: ↑CRP (β .041, p-0.026) ↑ IL-6 (β .028, p=.067)
2016	Colombo et al.	43	51	DSM-5	Control- 46.1 ± 14.9 Case- 50.0 ± 13.4	Electrophysiologic	PSG: B power	↑ β power (p= -.32, z=-2.4, p=.—2)-eyes open ↓ power in narrow band- 11-12.7 hz (p<.05)
2017	Dang et al.	24	N/A	Semi-structured interview PSQI	42.84	Electrophysiologic	PSG: spindle activity	β -4.66, p<.001
2017	Ran et al.	25	25	PSQI	Control-38.65 ± 7.4 Case- 40.62 ± 7.52	Electrophysiologic	PSG: ALFF	↑ALFF in midbrain & bilateral nucleus- peak mni coordinate (24, -9, -6, t = 5.27, cluster size=213 voxels, p<.05) ↓ ALFF in parietal lobe- peak mni coordinate (-21, -42, 66; t=4.6; cluster size=218) occipital lobe- peak mni coordinate (-27, -87, 15; t=3.7, cluster size= 206)
2018	Zhang et al.	24	20	DSM-5 PSQI	31.5-51.2	Cerebral structure and function	↑ NfH ↑ NfL ↑NSE ↑S100B	445.5 ± 60.5 4.8 ± 0.6, S100B: 42.8 ± 5.9, 602.9 ± 73.0 (p<.001)

Year	Author	Cases n Size	Control n Size	Diagnostic Criteria of Insomnia	Mean age or range if provided	Biomarker Type	Biomarker	Significant Findings
2019	Zhang et al.	30	30	DSM-IV	Control-44.65 ± 6.3 Case- 47.75 ± 5.7	Electrophysiologic	PSG: a-latency iCNV latency	↑ a-latency- 729 ± 106.8, p=.0357) ↓iCNV latency- 337.3 ± 60.21, p=.0307)
2019	Leerssen et al.	65	65	DSM-D ISI CSD	Insomnia-48.3 Control-44.1	Cerebral structure and function	fMRI: ↑ Bilateral hippocampal connectivity with middle gyrus with ISI Hippocampal volume	ISI: r=.371, p=9.3e-5 Subjective SE: r=-.307, p=.009 No significant findings
2020	Eddie et al.	Insomnia-12	MDD-39 Control-20	DSM-IV-TR ISI	Insomnia-32.14 MDD-28.12 Control-31.50	Electrophysiologic	HRV for each group HRV group x sleep stage:	No significant findings
2020	Iloabachi et al.	5,268	No control	5 item questionnaire	50 to >80 yrs.	Genomic	TL	-β -0.08, p<0.01
2021	Lundsford-Avery, Edinger & Krystal	53	51	DSM-5	Control- 40.70 (15.55) Case- 42.67 (16.51)	Electrophysiologic	PSG: delta power	Slower delta power decline (F[1,59]=8.36, p<.01)

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Chapter 3:

Insomnia Symptoms and Discrimination: Associations with Telomere Length Among Older Adults

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Abstract

The purpose of this study was to determine the relationship of insomnia and discrimination to telomere length (TL) among older white, Black, and Latinx individuals.

We performed a secondary analysis of data from the Health and Retirement Study, sponsored by the National Institute on Aging. Our analysis consisted of 1,315 US older adults who provided salivary samples from which telomere data was assayed. Insomnia was measured using the 'Brief Insomnia Questionnaire' and discrimination with the 'Everyday Discrimination Scale'. We computed linear regressions to examine the relationship of insomnia symptoms and discrimination to TL in each group, including interaction terms to assess moderating effects of discrimination.

Sleep disturbance was associated with shorter TL only among white individuals (β -0.107, p=0.002, [-0.12, -0.03]). In an unadjusted model, discrimination moderated the association between insomnia symptoms and telomere length among Black participants (β -0.282, p=0.045, [-0.33, 0.00]). For Black participants who reported discrimination, insomnia was associated with shorter telomeres while it had no relationship to TL for Black participants reporting no discrimination. However, after adjusting for age, BMI, medical co-morbidities, and depression, the moderating effect of discrimination was no longer significant.

Sleep disturbance appears to be adversely correlated with telomere integrity, but with differential relationships among groups. Research with a larger sample is needed to identify if other biological mechanisms may mediate the effects of insomnia on telomeres and determine if the effect of discrimination is unique to older Black individuals or impacts other groups. In addition, further research is warranted to better understand how covariates such as age, medical comorbidities and depression may interact with discrimination to affect telomere length. Findings suggest the importance of assessing both insomnia and exposure to discrimination in nursing practice so that interventions can be offered to reduce the risk of accelerated damage to telomeres.

Introduction

Approximately 30% of US adults experience insomnia in their lifetime (Morin et al., 2020). In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), insomnia is defined as distress with the quality and quantity of sleep not attributed to any other psychiatric, medical, or substance induced disorder, and causing dysfunction either socially, occupationally, or academically (Association, 2013). Insomnia is a significant public health concern (Vgontzas et al., 2010). However, mechanisms underlying the effect of insomnia on such health conditions remain obscure. Some researchers have proposed that poor sleep might function as a biological stressor that impairs neurophysiological functions and leads to changes throughout the body that result in greater allostatic load. (McEwen, 2007) Allostatic load, a concept first described by McEwen and Stellar,(McEwen & Stellar, 1993) refers to “the wear and tear on the body” which accumulates as an individual is exposed to repeated or chronic physical or psychological stress. This ‘wear and tear’ on the body has been attributed to varied neurobiological mediators (McEwen, 2007). Telomere length may be an associated outcome that is a marker of allostatic load.

Telomeres are buffering caps at the end of chromosomes that are protective during cellular mitosis (Blackburn et al., 2015). When telomeres are shortened to a length that compromises genomic stability, chromosome ends can induce apoptosis (i.e., cell death) or cell cycle arrest which prevent further cellular replication (Engin & Engin, 2021). Telomere length has emerged as a marker of biological aging. There is strong and consistent epidemiologic evidence linking shortened telomere length and increased rates of several age-related conditions, including hypertension, metabolic dysfunction, as well as premature mortality (Zgheib et al., 2018).

Several studies suggest that short and disturbed sleep is associated with shorter telomere length (Osum & Serakinci, 2020). Indeed, a study among middle-aged and older adults found that better sleep quality and longer sleep duration (e.g., sleeping at least 7 hours per night

on average) were associated with longer telomeres (Cribbet et al., 2014). Objective total sleep time also significantly predicts telomere length among veterans (Knowles et al., 2018). However, even more research indicates that sleep disturbance is related to shorter telomeres (Prather et al., 2011; Prather et al., 2015). These studies have examined shorter sleep duration and poor sleep quality but not clinical insomnia. In research specific to insomnia, investigators also report that it is associated with shorter telomeres. A relationship between insomnia and shorter telomeres has been found among older adults (Carroll et al., 2016). Another study found that those with insomnia who slept less than 6 hours, had a shortened telomere length (Tempaku et al., 2018).

Some studies suggest that insomnia is more prevalent among individuals of color (Kaufmann et al., 2016). The rationale for these racial differences is not clear. One possible explanation is the effect of stress experienced by people of color as a result of discrimination. Numerous studies have found that black individuals who experience discrimination had a significantly shortened telomere length (Coimbra et al., 2020). However, to our knowledge, no studies have examined if discrimination moderates the relationship between insomnia symptoms and telomere length.

To address existing gaps in knowledge, we examined two aims: 1) to determine if insomnia or discrimination are associated with shortened telomere length differently among older adults from white, Black, and Latinx heritage, and 2) to evaluate whether discrimination has a moderating effect between insomnia and telomere length in these distinct groups.

Participants and Methods

This study is a secondary analysis utilizing data from the Health and Retirement Study (HRS). The HRS began in 1992 when US Congress directed the National Institute on Aging to prioritize studying health and associations in retirement. The HRS is the first longitudinal study of individuals over 50 years of age that includes economic and health information in the same survey. HRS is supported by an agreement with the National Institute on Aging (U01

AG009740) with funding from the Social Security Administration (Servais, 2010). Enrollment has occurred in 8 waves with participants accepted into the study once they aged into the inclusion criteria (being 50 years of age). Recruitment was yearly between 1992 to 1996, then every other year on even numbered years beginning since 1998 to present. The HRS collects core survey data that includes self-reported physical and psychological factors, diagnoses, disabilities, cognitive tests, and health behaviors in addition to employment history, economic status, and family structure. Physical measures and biomarkers are obtained with enhanced face to face interviews (Servais, 2010).

Data for this analysis came from baseline 2006 data with a follow-up period in 2008 that captured biological markers. The sample included white (n=1,133), Black (n=110), and Latinx (n=83) participants who provided a salivary sample for telomere assay and answered discrimination and insomnia questionnaires.

Measures

Telomere Length. The dependent variable was telomere length (TL) based on DNA collected via salivary specimen. In the initial HRS biomarker cohort, saliva was collected using a mouthwash method but was later changed to the passive drool method, derived with the Oragene DNA Collection Kit (Eileen et al., 2013). Saliva samples were collected by staff during an interview with participants and immediately sent to a central laboratory where DNA was extracted and stored at −80°C.

Telomeres were assayed by Telomere Diagnostics, Inc (www.teloyears.com) using quantitative polymerase chain reaction (Lin et al., 2019; Montpetit et al., 2014). Telomere sequence copy number in each respondent's sample (T) was compared to a single-copy gene number (S). Smaller T/S ratios indicate a shorter telomere length. Samples that had smaller than 12.5% coefficient of variation (CV) were considered ready for analysis while samples with greater than 12.5% CV were re-assayed or eliminated. The overall quality control pass rate was greater than 98% (Eileen et al., 2013). Although whole blood and peripheral blood mononuclear

cells (PBMCs) are common biospecimens used to quantify telomere length, a study investigating salivary telomere length and blood found high correlation (r=0.72) between telomere length from saliva and blood (Mitchell et al., 2014).

Insomnia Symptoms. Insomnia symptoms were measured using the Brief Insomnia Questionnaire (BIQ), representing five questions in the HRS survey pertaining to sleep (Leggett et al., 2018). The BIQ was originally developed and tested as part of a large American epidemiological study on insomnia and is based on sleep-related criteria identified in the Diagnostic and Statistical Manual, the International Classification of Diseases, and the International Classification of Sleep Disorders (Kessler et al., 2010). Since its original development, it has continued to demonstrate reliability and validity in the measurement of insomnia (Chung et al., 2015). The items address: 1) trouble falling asleep, 2) trouble with staying asleep, 3) waking up too early and not being able to fall asleep, 4) not feeling rested upon final awakening, and 5) if a sleep medication/sedative hypnotic was taken for sleep. Participants were asked to select one of the following options for each question: 1) most of the time, 2) sometimes, 3) rarely/never. It was considered a positive endorsement of the symptom if they reported experiencing the problem “most of the time,” or “sometimes.” A composite score was then created with a possible range of 0-5 for the number of items they endorsed.

Discrimination. Discrimination was assessed with the adapted ‘Everyday Discrimination Scale’ (EDS) in the HRS survey (Williams et al., 1997). The EDS is a validated questionnaire with strong predictive validity and an alpha reliability of .88(Stucky et al., 2011). Respondents were asked how often they: 1) were treated with less courtesy or respect than other people, 2) received poorer service than other people at restaurants or stores, 3) experienced people acting as if they think you are not smart, 4) experienced people acting as if they are afraid of you, 5) were threatened or harassed, and 6) received poorer service or treatment than other people from doctors or hospitals. The response options for each question included: 1) almost everyday, 2) at least once a week, 3) a few times a month, 4) a few times a year, 5) less than once a year

and 6) never. Similar to prior analyses using HRS (Liu & Kawachi, 2017), all respondents who reported experiencing discrimination at least a few times a month or more were identified as individuals who experienced ongoing discrimination in contrast to individuals who reported experiencing it infrequently or never per each individual question asked.

Demographic and Clinical Variables. White, Black, and Latinx participants were categorized on race/ethnicity. In addition, demographic, medical and psychiatric history variables were included in the analysis for descriptive purposes and to examine as potential covariates. Demographic variables were age, sex assigned at birth, BMI, smoking status, educational level, employment/retirement status, and private insurance versus Medicare. Medical co-morbidities previously linked to telomere length were also identified, including hypertension, diabetes, cardiovascular disease, cancer, and lung disease (Haycock et al., 2014; Ridout et al., 2015; Xiao et al., 2011). A composite variable was created summing the number of co-morbidities among adults. Because of the compelling evidence for its association with shortened telomere length, depression was not included in the morbidities composite but examined as a separate variable (Ridout et al., 2015). The Center for Epidemiological Studies Depression (CES-D) questionnaire was the measure of depression. The established cutoff score of endorsing at least 5 symptoms was used to indicate a diagnosis of depression. The CES-D has well-established validity and reliability, including among older adults (Vilagut et al., 2016).

Statistical Methods

Descriptive statistics (means or percentages) were used to characterize the sample. Telomere length was log transformed due to positive skew. Multiple linear regression procedures were used to examine the aims. Preliminary analyses of variance (ANOVA) and/or correlations were computed on all covariates (sex assigned at birth, age, educational level, employment/retirement status, insurance coverage, medical co-morbidities, and depression) to determine their relationship to TL. Age and number of medical co-morbidities were associated

with TL. Although in our preliminary analysis depression and BMI were not associated with TL, we also included them as covariates in our regression models because of the substantial evidence linking them to TL (Müezzinler et al., 2014). Aims were tested running both an unadjusted as well as an adjusted model that controlled for depression, age, BMI and number of medical co-morbidities. To test the aims, separate multiple regression models were employed for each of the 3 racial/ethnic groups. To test Aim 1, telomere length was regressed on scores for discrimination and insomnia symptoms. To test Aim 2, an interaction term (insomnia # discrimination) was included in the model. An ANOVA was also run to test for any differences in telomere length, insomnia symptoms and discrimination among white, Black, and Latinx participants. Pearson correlation coefficients were computed to determine the direction and strength of relationships between insomnia symptoms and telomere length when moderated by discrimination.

Results

Demographic and Clinical Characteristics of the Sample

Of the 1,326 participants, 1,133 participants were white, 110 were Black, and 83 were Latinx. Mean age for the entire sample was 78.09. Age range for the entire sample was 50-106. Although the mean age of Latinx participants was somewhat lower (66.99 ±10.1) than white (70.10 ±10.23) and Black (68.33 ±9.72) participants, differences in mean age of the three groups were not significant. Medicare enrollment was the dominant insurance for all three groups. Black participants reported a greater number of medical diagnoses in comparison to white and Latinx participants. The average mean of medical co-morbidities for each racial ethnic group was 1.57 (white), 2.02 (Black), and 1.37 (Latinx). The average BMI for white participants was 28.67, 30.42 for Black participants, and 29.56 for Latinx participants. As shown in Table 3.1, white participants had a significantly lower percentage of individuals who met the threshold for depression on the CES-D (8.57%, p =0.001) than either Black (15.52%) or Latinx (16.07%) participants. Additional sample characteristics are shown in Table 3.1.

Insomnia Symptoms and Telomere Length

Means for telomere length (TL) and insomnia symptoms across the three racial/ethnic groups are shown in Table 3.2. Among white participants, insomnia symptoms were significantly and negatively associated with TL after adjusting for covariates (β= -0.107, p=0.002) (see Table 3.4), as well as when not controlling for covariates (see Table 3.3). In contrast, insomnia symptoms were not associated with shorter TL among Black and Latinx participants in either the adjusted or unadjusted models (Tables 3.5-3.8).

Discrimination and Telomere Length

Means for discrimination scores across racial/ethnic groups are shown in Table 3.2. The mean discrimination score for Black participants was significantly higher than for other racial/ethnic groups ($F_{2,2}$=7.24, p<.001). When considering overall exposure to discrimination, twenty-four percent of Black participants experienced discrimination at least monthly compared to eleven percent of white participants and nearly 15% of Latinx participants. In both the adjusted and unadjusted regression models, discrimination had no direct relationship to TL for any racial/ethnic group (Tables 3.3-3.8). Discrimination did moderate the relationship between insomnia symptoms and TL for Black participants (β = -0.282, p=0.045) in the unadjusted model (Table 3.5). The Pearson coefficient between insomnia and TL for those who did not experience discrimination was r=-0.03 compared to a correlation of r=-0.27 for Black participants who experienced discrimination. However, in adjusted models for all racial/ethnic groups, discrimination did not moderate the relationship between insomnia and TL for any participants (see Tables 3.4, 3.6, and 3.8).

Discussion

This study was a secondary analysis to investigate if insomnia symptoms or discrimination were associated with telomere length in different ways among white, Black, and Latinx participants from older adult populations and to determine if discrimination had a moderating effect between insomnia symptoms and telomere length in the three different racial/ethnic groups. Results indicate that insomnia symptoms are associated with shorter telomere length, but only among white participants. Everyday discrimination was not related to TL nor did it moderate the relationship between insomnia symptoms and telomere length for any racial/ethnic group.

Insomnia and Telomere Length

To some extent, our finding that insomnia among white participants was associated with shortened telomere length is consistent with previous research studies. Samples in previous studies were predominantly white participants. Support for this relationship in middle aged and older adults has been established (Cribbet et al., 2014). These previous findings are not entirely congruent with ours in that 64% of our white participants were women and included individuals in their sixties as well as older age groups.

Other biologic mechanisms may also underlie an association between insomnia and physiologic stress. Insomnia and sleep disruption have been viewed as neurobiological stressors that have adverse effects on multiple systems (Palagini et al., 2019). There is evidence to suggest that poor sleep quality may induce dysregulation of the inflammatory system (Irwin et al., 2016), neurotransmitter systems, (Longordo et al., 2009) neuroendocrine systems, (Riemann et al., 2015) brain-derived neurotrophic factor,(Schmitt et al., 2016) and circadian rhythmicity (Archer & Oster, 2015). Dysregulation in these various systems has, in turn, been associated with effects on TL (Gavia-García et al., 2021; O'Donovan et al., 2011). There is a substantial need for a systems biology approach while taking into account how social

determinants can affect the potential integrative and coordinated roles of these different mechanisms in the relationship between insomnia and TL.

Although we did not find a relationship between insomnia and telomere length among Black and Latinx participants, it is possible that the smaller size of these samples (in contrast to white participants) reduced the power to detect an effect. This hypothesis is supported by the trend toward a significant relationship between insomnia symptoms and TL among Black participants shown in the adjusted model (Table 3.6). The strength and direction of the beta coefficients were identical for white and Black participants, although the relationship did not reach significance for Black participants ($p = .06$). In addition, the beta coefficient for Latinx participants indicated an even larger effect size for the relationship of these variables than we found for the other 2 racial/ethnic groups (Table 3.8) although the finding was not significant. It is also of interest that, although none of the covariates were associated significantly with TL, controlling for their variance increased the strength of the relationship between insomnia and TL across all racial/ethnic groups.

The differences in strength of the insomnia-TL relationship for different racial/ethnic groups might depend on the specific sleep disturbance being measured. Our measure was a broad-based assessment of varied sleep problems, which could be more relevant to white participants. A recent study found that sleep duration was associated with TL most significantly among Black participants. (Grieshober et al., 2019) This is of particular importance given that US Black Americans are more likely to experience shorter sleep duration in comparison to other racial/ethnic groups (Gaston et al., 2020). Alternatively, our findings may simply indicate that insomnia is a more salient contributor to or marker of reduced cellular integrity for older white adults than for older Black or Latinx adults. Continued research is necessary to differentiate the type and severity of insomnia symptoms that may influence TL among various racial/ethnic groups while also investigating its effects on health and well-being.

Discrimination and Telomere Length

In the adjusted models, discrimination had no direct relationship to TL for any racial/ethnic group. This finding was unexpected in light of previous research that has shown a robust relationship between discrimination and shorter TL.[28-35] However, the nature of the discrimination may be a critical determinant of whether discrimination plays a role in the erosion of telomeres. For example, a recent study found that institutional discrimination, and not everyday discrimination, was associated with reduced TL (Thomas et al., 2021). Our measure of 'everyday discrimination' assessed subjective perceptions of being treated poorly during daily interactions with others. More systemic prejudice or inequities within societal or institutional structures may have a stronger and different effect on TL. This hypothesis is supported by findings that disparities such as living in a disadvantaged neighborhood, financial strain, and educational disparity have been linked to reduced TL among Black Americans (Schrock et al., 2018; Thierry, 2020). Examining social determinants related to institutional discrimination and racism, along with the psychological stress they generate, may be an important area of future research as potential contributors to insomnia and specific sleep disturbances.

Discrimination as a Moderator

In the unadjusted model, everyday discrimination did have a moderating effect on the relationship between insomnia symptoms and TL among Black participants. Based on correlations, insomnia was associated with shorter TL for Black participants who experienced discrimination but not for Black individuals who reported no discrimination. Although this relationship did not remain significant in the adjusted model, this data suggests that the experience of discrimination may increase vulnerability to more adverse effects of insomnia on telomeres. If discrimination is persistent and chronic, resilience to effects of poor sleep quality and sleep disruption could be compromised. This is consistent with the 'weathering hypothesis, (Geronimus et al., 2010) proposing that cumulative, potent stressors cause accelerated 'wear and tear' on the body and greater susceptibility to health decline. Additionally, individuals who

experience discrimination may incur stress-related biological changes, such as hypothalamic-pituitary-adrenal axis dysregulation or elevated systemic inflammation (Bussé et al., 2017), that may increase susceptibility to effects of insomnia on their telomeres. Given the associations of discrimination and reduced resilience from these effects could explain why discrimination played a more significant moderating role for Black individuals than for other participants in the unadjusted model. Black participants reported significantly more discrimination than white or Latinx participants.

Regardless of this finding in the unadjusted model, the moderating effect of discrimination was no longer significant after controlling for the covariates. Although none of the covariates in the model were significant, they did modify the estimates. It is especially notable that the effect sizes of both insomnia and discrimination were increased when including covariates while the moderating effect diminished. Although both variables had small effect sizes, it is possible (as noted earlier) that a significant effect of insomnia or discrimination might be detected with a larger sample size.

Limitations and Strengths

The following limitations should be noted. All data are cross-sectional and correlational, precluding any causal inferences. We could not examine our aims over time to assess reliability of our findings since telomere data was only collected during one year of the HRS study. Although adequate for the purposes of our analysis, the numbers of Latinx and Black participants were substantially less than white participants and may have reduced power to detect a significant effect. Symptoms of insomnia were self-reported; no actual diagnosis of clinical insomnia can be inferred. Given the population focus of HRS, young adults were excluded and generalizability to a younger population cannot be made. However, the study also has strengths. Participants were drawn from a nationally representative sample of older adults from which data were leveraged. Data allowed for distinct examination of insomnia symptoms, everyday discrimination, and telomere length among a large cohort of participants.

Research and Clinical Implications

Future research should address whether a confirmed clinical diagnosis of insomnia is associated with shortened telomere length and include other minority groups such as other racial/ethnic groups and members of the LGBTQIA community. In addition, longitudinal studies are needed to examine potential pathways between insomnia and telomere degradation. The type, extent, and chronicity of discrimination that may intersect adversely with sleep problems and influence TL should also be studied, along with underlying biological mechanisms that may mediate effects of both insomnia and discrimination on telomere integrity. In addition, further research is warranted to better understand how covariates such as age, medical comorbidities and depression may interact with discrimination to affect telomere length. Findings suggest the importance of assessing both insomnia and exposure to discrimination in nursing practice so that interventions can be offered to reduce the risk of accelerated damage to telomeres.

Conclusions

Our study provides evidence that insomnia symptoms may be adversely associated with telomere integrity, but with differential relationships among racial/ethnic groups. Insomnia was only associated with shortened telomere length among white individuals although its effect sizes among both Black and Latinx participants warrant further research with larger samples. Discrimination did not have a direct relationship to TL for any racial/ethnic group nor did it appear to play a moderating role between insomnia symptoms and shortened telomere length when adjusting for covariates. However, assessment of the effects of institutional and other types of structural discrimination beyond everyday interactions is warranted. Findings represent an important foundation for further research as well as in the clinical management of insomnia so that public health interventions can be offered to reduce the risk of accelerated damage to telomeres.

Table 3.1 Frequencies (n) and Percentages for Sample Characteristics by Racial/Ethnic Group

	White	Black	Latinx
Variables			
Sample size	1,133	110	83
Female	64.17 (1,088)	31.32 (162)	35.83 (103)
Education			
High School	21.73 (375)	51.52 (126)	72.58 (116)
Some college	58.42 (1,018)	36.36 (89)	24.19 (38)
College degree	19.85 (352)	12.12 (29)	3.23 (5)
Employment status			
Employed	9.04 (166)	7.17 (16)	8.60 (13)
Retired	8.72 (148)	7.55 (19)	20.43 (29)
Disabled	3.85 (66)	10.94 (27)	8.06 (14)
Retired	78.38 (1,370)	74.34 (183)	62.90 (103)
Medicare enrollment	87.50	78.89	75.68
Smoking status	21.64	29.35	22.62
Depression Screening			
CES-D <5	91.43 (1,423)	84.48 (179)	83.93 (118)
CES-D >5	8.57 (135)	15.52 (34)	16.07 (24)

Table 3.2 Mean of Telomere Length, Discrimination, and Insomnia Symptoms by Racial/Ethnic Group

	White	Black	Latinx
Variables			
Telomere Length, (mean)	1.38	1.38	1.31
Everyday Discrimination (mean)	11.19	23.91	14.84
Insomnia Symptoms (mean)	2.04	1.90	1.97

Table 3.3 Model 1 (Unadjusted): Regression Model for the Relationship of Insomnia Symptoms to Telomere Length among White Participants

Predictor	B	SE	Beta	p	CI
Insomnia Symptoms	-0.038	0.015	-0.052	0.012	-.07, -.01]
Discrimination	-0.023	0.045	-0.025	0.61	[-.11, .07]
Insomnia x Discrimination	0.031	0.044	0.032	0.47	[-.05, .12]

Table 3.4 Model 2 (Adjusted): Regression Model for the Moderating Effect of Discrimination on the Relationship of Insomnia Symptoms and Telomere Length among White Participants

Predictor	B	SE	Beta	p	CI
Insomnia Symptoms	-0.076	0.024	-0.107	0.002	-.12, -.03]
Discrimination	-0.11	0.071	-0.107	0.16	[-.24, .04]
Insomnia x Discrimination	0.058	0.070	0.065	0.41	[-.08, .19]
Age	-.002	0.001	-0.063	0.056	[-0.004, 0.00006]
Medical diagnoses	-.002	.008	-0.009	0.79	[-.02, .01]
Depression	-.006	.006	-.036	0.26	[-.02, 0.005]
BMI	.001	.002	.020	0.56	[-.003, .005]

Table 3.5 Model 1 (Unadjusted): Regression Model for the Relationship of Insomnia Symptoms to Telomere Length among Black Participants

B	SE	Beta	p	CI
-.0168	0.042	-.028	0.68	[-.10, .07]
0.126	0.084	-.043	0.14	[-.04, .29]
-0.169	0.0838	-0.282	0.045	[-.33, 0]

Table 3.6 Model 2 (Adjusted): Regression Model for the Moderating Effect of Discrimination on the Relationship of Insomnia Symptoms and Telomere Length among Black Participants

Insomnia Symptoms	-0.034	0.078	-0.107	.06	-.19, .12]
Discrimination	.093	0.179	-0.107	0.16	[-.26, .45]
Insomnia x Discrimination	-.160	0.167	0.065	0.30	[-.49, .17]
Age	-.0002	.005	-.005	0.97	[-.001, .009]
Medical diagnoses	.012	.03	.06	0.64	[-.04, .07]
Depression	.010	.019	.07	0.60	[-.03, .05]
BMI	.008	.006	.16	0.22	[-.005, .021]

Table 3.7 Model 1 (Unadjusted): Regression Model for the Relationship of Insomnia Symptoms to Telomere Length among Latinx Participants

Predictor	B	SE	Beta	p	CI
Insomnia Symptoms	0.015	0.051	-0.024	0.77	[-.12, .09]
Discrimination	-0.13	0.123	-0.176	0.28	[-.38, .11]
Insomnia x Discrimination	0.076	0.119	.0109	0.52	[-.16, .31]

Table 3.8 Model 2 (Adjusted): Regression Model for the Moderating Effect of Discrimination on the Relationship of Insomnia Symptoms and Telomere Length among Latinx Participants

Insomnia Symptoms	.139	0.094	.203	0.15	-.05, .33]
Discrimination	.110	0.215	.134	0.61	[-.32, .54]
Insomnia x Discrimination	-.215	0.208	-.277	.31	[-.63, .20]
Age	-.002	.005	-.05	0.70	[-.01, .01]
Medical diagnoses	.023	.035	.086	0.51	[-.05, .09]
Depression	-.010	.020	-.071	0.60	[-.05, .03]
BMI	.002	.008	.025	0.85	[-.01, .02]

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Chapter 4:

Perceived Lack of Control of Life Stressors and its Associations with Treatment Response to Cognitive Behavioral therapy for Insomnia among Short Sleepers

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Abstract

The purpose of this study was to identify the relationship of psychological distress and sleep-related factors to non-response to cognitive behavioral therapy for insomnia (CBT-I) among short sleepers with insomnia.

We performed a secondary analysis of data from the Treatment of Insomnia and Depression Study, a multisite randomized clinical trial designed to test the efficacy of combining cognitive behavioral therapy for insomnia with antidepressant pharmacotherapy for co-occurring major depression and insomnia. This analysis included forty-six adults with co-occurring depression and insomnia, twenty-three of which were categorized as short sleepers. Short sleep was categorized with a baseline calculation of objective total sleep time based on polysomnography prior to starting treatment, using a cut off of 6 hours to distinguish between objectively short and longer sleepers. Main outcome measure was the 'Insomnia Severity Index,' (ISI) completed at baseline and again at week 6, at completion of treatment. Independent measures of interest were the Hamilton Rating Scale for Depression (HRDS-17), Perceived Stress Scale (PSS), Ford Insomnia Response to Stress Test (FIRST), and baseline subjective sleep onset latency (SoL) based on self-reported sleep diary. We computed logistic and linear regressions to examine the measures of interest on final score of ISI and a change score between pre and post-treatment respectively and compared results between all forty-six participants as well as short and longer sleepers separately.

Among combined longer and short sleepers, depression, perceived stress, sleep-reactivity, and SoL were not associated with remission or lack of improvement in insomnia after treatment. However, two depressive symptoms, experiencing feelings of guilt ((mean=1.6, (M= .69; t(21) = -2.26, p=.03)) and suicidality ((mean=.60, (M =.08; t(21)= -2.10, p=.047)) were higher at baseline among those who did not remit from CBT-I when compared to those who did respond to treatment. Moreover, perceived lack of ability to control irritability on the PSS was

negatively associated with improvement in insomnia after CBT-I exclusively among short sleepers (β-.45, p=.03).

Results of this exploratory study indicate that some short sleepers may have symptoms prior to initiating treatment that put them at increased risk for a reduced treatment response and that assessment of specific symptoms may be more important than overall global scores when considering potential effects of depressive symptoms and stress on treatment response to CBT-I. This study represents an important foundation for further research as well as preliminary implications for clinical practice on how psychological distress can impact insomnia treatment among short sleepers.

Introduction

Insomnia imposes a national economic burden with over 90 billion dollars per year spent on non-pharmacologic and pharmacologic treatment (Daley et al., 2009; Wickwire et al., 2020). Insomnia and reduced total sleep time are also associated with adverse health outcomes. Research has shown that individuals with insomnia and who objectively slept < 5 hours and have shortened sleep efficiency have a significantly higher rate of adverse health outcomes (Bertisch et al., 2018; Fernandez-Mendoza et al., 2012; Vgontzas et al., 2009; Vgontzas et al., 2010). Treating insomnia is essential given its deleterious effects on physical health.

Cognitive Behavioral Therapy for Insomnia (CBT-I) is recommended as the first line treatment for insomnia (Trauer et al., 2015). Approximately 45% of individuals who undergo CBT-I will experience remission of insomnia symptoms, with between 55%-65% of individuals having clinically significant improvement (Ashworth et al., 2015; Carney et al., 2017; Edinger et al., 2007; Ellis et al., 2015).

However, there are mixed findings regarding the effectiveness of CBT-I for short sleepers. Some studies have shown a positive response to CBT-I among short sleepers. For instance, a recent study found that objectively short sleepers (based on polysomnography (PSG) of less than 6 hours) had a significant response to CBT-I and did not differ from longer sleepers (Galbiati et al., 2021). Two other studies have also reported no difference in improvements in insomnia severity or treatment outcomes between objectively short and longer sleepers who completed a course of CBT-I (Crönlein et al., 2020; Lovato et al., 2021).

In contrast, other research has shown differences between longer and short sleepers in their response to CBT-I. An RCT examining the effects of CBT-I found that six months post-CBT-I treatment, participants who slept < 6 hours had significantly lower remission rates based on the insomnia symptom questionnaire when compared to those who slept $\geq$ 6 hours (Bathgate et al., 2017). Another RCT found that postmenopausal women with insomnia who had a lower sleep efficiency at baseline, had lower rates of insomnia remission measured by ISI (Kalmbach

et al., 2020). Another study that evaluated the effects of brief CBT-I found that those who slept ≤6 hours observed on PSG had less likelihood of achieving remission from insomnia based on the Pittsburgh Sleep Quality Index (PSQI) (Troxel et al., 2013). One retrospective study found that objectively observed longer sleepers compared to short sleepers had greater improvement in insomnia symptoms (≥6 point reduction in ISI score) after CBT-I (Miller et al., 2018). Lastly, other investigators reported that although both objectively observed short sleepers of less than 6 hours and longer sleepers had an improvement in severity of insomnia after CBT-I, longer sleepers had an improvement in overall daytime functioning and sleep satisfaction that was not experienced by short sleepers (Rochefort et al., 2019).

Although previous studies have investigated subtypes of insomnia based on psychosocial factors (e.g., (Blanken et al., 2019) and classified individuals as short and long sleepers (Olaithe et al., 2021), few studies have investigated factors related to CBT-I treatment response specific to short sleepers. In addition, to my knowledge, no other studies have investigated specific symptoms of psychological distress and sleep-related factors that may reflect a potential phenotype of short sleepers associated with lack of remission from CBT-I treatment.

Thus, the aim of this secondary analysis was to identify the relationship of psychological distress and sleep-related factors to remission of insomnia among short sleepers in comparison to longer sleepers after receiving cognitive behavioral therapy for Insomnia (CBT-I). I hypothesized that greater psychological distress (perceived life stress and depression) and sleep-related factors (sleep reactivity and sleep onset latency) will be associated with lack of remission of insomnia symptoms for short sleepers after CBT-I. The rationale for this hypothesis is provided in the section that follows.

Background and Significance

Psychological Distress. In this study, psychological distress refers to negative emotions related to symptoms of stress and depression. Psychological distress has been associated with insomnia (Li et al., 2021) and a reduction in sleep efficiency among those with insomnia (Shaver et al., 2002). Research has also shown that those with a history of psychological distress are more likely to seek treatment for insomnia (Hayward et al., 2010).

Perceived stress is a common type of psychological distress and has been positively correlated with both poor sleep quality and insomnia independent of anxiety and depression (Barutcu Atas et al., 2021). Perceived stress among those who have poor resilience has been strongly associated with insomnia (Zou et al., 2022).

Another form of psychological distress involves symptoms of depression. Nearly 90% of those who seek treatment for depression also complain of sleep disturbance (Thase, 1999; Tsuno et al., 2005)). Additionally, there are nearly double the cases of those with co-occurring major depression and insomnia when compared to those with insomnia alone (Buysse et al., 1994; Coleman et al., 1982; Jacobs et al., 1988). Given both disorders often co-occur, multiple studies have examined the effects of depression when insomnia is treated.

A secondary analysis utilizing data from the Treatment of Insomnia and Depression (TRIAD) study (Manber et al., 2016) found that those with childhood onset major depression had significantly less response to both depressive symptoms (measured on the Hamilton Depression Rating Scale) as well as insomnia symptoms when offered a course of CBT-I compared to those with adult onset depression (Edinger et al., 2017). This TRIAD analysis shed light on potential lack of treatment response among depressed individuals who receive CBT-I, but little is known about specific symptoms of depression that may be associated with lack of CBT-I treatment response (an insomnia severity index score of >7).

Sleep-Related Factors. The first sleep-related factor examined in this study was sleep reactivity. Sleep reactivity measures the susceptibility to insomnia based on stressors that may affect sleep (Drake et al., 2006; Kalmbach et al., 2020). Sleep reactivity is comprised of situational events that are associated with insomnia, including stressful experiences that occur in the day or evening, observing content that may be related to fear, and participating in events that may increase levels of anxiety. Examples of these events are an important meeting, having to speak in public, or interpersonal conflicts such as an argument with others (Jarrin et al., 2016).

Severity of sleep reactivity appears to reduce the effect of CBT-I on insomnia symptoms. After categorizing participants into high and low reactivity groups, a recent study found that 90% of participants in the low sleep reactivity group had a reduction in insomnia symptoms based on ISI score when compared to 55% of the high reactivity group after a course of CBT-I. Those in the high reactivity group also did not have as significant of an improvement in sleep efficiency (100% vs 77%) (Park et al., 2022). To date, only this one study has investigated effects of sleep reactivity on CBT-I outcomes (Park et al., 2022).

Another sleep-related factor is sleep onset latency (SoL), or the time it takes to fall asleep. There has been conflicting evidence on the association of sleep latency with treatment response to CBT-I. One study found those with insomnia who have shorter SoL have reduced likelihood of responding to CBT-I (Troxel et al., 2013). Another study, however, found no change in SoL among groups who had a course of CBT-I (Lovato et al., 2021). Similarly, research distinguishing longer and short sleepers also found no significant change in SoL (Crönlein et al., 2020).

Methods

Study Design

This project was a secondary analysis of data from the Treatment of Insomnia and Depression (TRIAD) study (Manber et al., 2016). The TRIAD study was a 16 week, 3-site randomized controlled trial (RCT) and took place at the University of Pittsburgh, Stanford

University, and Duke University. The investigators sought primarily to evaluate treatment response of CBT-I among individuals with co-occurring insomnia and major depressive disorder (MDD) (Manber et al., 2016). Their main objective was to evaluate if a change in insomnia severity mediated depression severity among participants who completed a course of CBT-I.

Treatment duration was 16 weeks and consisted of pharmacotherapy and CBT-I, in contrast to a control sleep therapy. Medication was managed by a psychiatrist every 2 weeks and seven 45-minute individual psychotherapy sessions occurred between weeks 1-4, week 6 and 8, and week 12 for both treatment groups.

CBT-I consisted of 7 sessions that included sleep education, sleep restriction, stimulus control, educational skills on reducing psychological arousal, cognitive restructuring of distorted beliefs related to sleep, and a relapse prevention plan. The control therapy for insomnia consisted of a protocol where sleep-distressing images were coupled with neutral images. The same sleep education (sleep hygiene) that was provided in CBT-I was also provided to the control group, with no other components of CBT-I provided to controls.

Pharmacotherapy was provided for the treatment of depression to all participants using guidelines based on the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study with a psychiatrist choosing a first line medication and the possibility of switching to another medication due to lack of depression response. Medications prescribed included sertraline, desvenlafaxine succinate, and escitalopram (Trivedi et al., 2006). The primary study has a full description of the pharmacotherapy protocol (Manber et al., 2016).

Data collection occurred between March 2009 and August 2013. Data for this secondary analysis were collected at baseline as well as at week 6 of treatment. Week 6 was chosen as the end point based on previous analyses evaluating dose-response to insomnia (Edinger et al., 2007; Manber et al., 2016).

Participants

Participants were recruited through local advertisements. Individuals qualified for the study if they were adults between the ages of 18-75; spoke and read English fluently; met DSM-IV-TR criteria for insomnia and MDD, had a minimum score of 11 on the ISI and a score of 16 on the Hamilton Rating Scale for Depression (HRSD), with bedtimes between 8p-2a, and waketimes between 4a-11a. Diagnoses of MDD and insomnia were made based on clinical interview using the Structured Interview for Depression (SCID) and Duke Structured Interview for Sleep (DSID). Participants were excluded if they were receiving insomnia or depression treatment, met criteria for other sleep disorders (determined by DSCID), or had a co-occurring psychiatric disorder that was not MDD or insomnia (Manber et al., 2016).

This study used data from a subset of the total sample who underwent CBT-I and were classified as short and longer sleepers. Short sleep was operationalized as <6 hours of total sleep time based on polysomnographic (PSG) interpretation with longer sleepers operationalized as ≥6 hours of sleep based on PSG. PSG was conducted using Compumedics Siesta ambulatory digital PSG. Pre-treatment PSG was conducted to rule out sleep disorders and any other neurological conditions related to sleep disorders including movement disorders. A second baseline PSG was conducted 1 week prior to the start to evaluate treatment effects in the study. The second baseline PSG was used to operationalize short and longer sleepers.

Measures

Demographic Measures

The following demographic variables were used in analysis: age, sex assigned at birth, educational level, and race/ethnicity. A mean age and age range were calculated. A dichotomous variable was created for sex assigned at birth. Educational level was coded as a continuous variable. Race/ethnicity was coded categorically and included those who identified as White, Black, and other.

Dependent Variable

Insomnia Severity Index. Insomnia was the dependent variable examined in the study. It was measured using the Insomnia Severity Index (ISI) at baseline and every 2 weeks. The ISI is a 7-item self-reported questionnaire and measures insomnia severity over a 2 week period based on difficulty with initiation of sleep, maintenance of sleep, and overall satisfaction with sleep (Morin et al., 2011b). The questionnaire also evaluates how much sleep is causing daytime impairment. The seven items are on a five-point Likert scale with a higher score reflecting more severe symptoms of insomnia. The Likert scale responses range from 0 = no problem to 4 = very severe problem. Scores range from 0 to 28. A total score of less than 8 indicates no insomnia; 8-14 indicates sub-threshold insomnia, and greater than 14 indicates clinical insomnia. The first three items evaluate the severity of sleep latency, sleep maintenance, and early morning final awakenings. The remaining four items evaluate the participants' satisfaction or dissatisfaction with the sleep disturbance, and its impact on functioning and impairment. One of the items also assesses the amount of worry the participant has due to the sleep disturbance. The first 6 items are based on symptoms of a clinical diagnosis from the DSM-5 (American Psychiatric Association, 2013). The ISI is a highly reliable and valid measure of insomnia. A recent study found high internal consistency in the use of ISI to measure insomnia symptoms ($\alpha = 0.91$). Evidence also indicates it is 97% sensitive in identifying participants who met criteria for subthreshold insomnia as well as 91.8% specific identifying participants who did not have a diagnosis of insomnia (Morin et al., 2011a).

Non-responders to CBT-I were defined as having an ISI score of >7 after treatment. An ISI cut-off score of >7 was established in previous research, indicating that participants continue to meet criteria for insomnia (Ashworth et al., 2015; Ellis et al., 2015). The total score on the ISI was also used to examine overall change in insomnia symptoms after a course of CBT-I. Week 6 was chosen as the end point for analysis based on previous studies evaluating dose-response to insomnia (Edinger et al., 2007; Manber et al., 2016).

Independent Variables

Sleep Reactivity: The Ford Insomnia Response to Stress Test (FIRST). FIRST is a nine item questionnaire that measures sleep reactivity. Each item is on a four-point scale with the score ranging from 9-36. A higher score indicates higher level of sleep reactivity (Jarrin et al., 2016). A study evaluating its psychometric properties found strong intraclass coefficients (ICC) at baseline and 6 months (ICC=0.81) and at 12 months (ICC=0.77). FIRST has aided in distinguishing which psychological factors are associated with insomnia. Sleep reactivity coupled with anxiety symptoms predicted those meeting criteria for insomnia, with a statistically significant correlation between the FIRST and both the PSQI ($r=.36$, $p<0.001$) and ISI ($r=0.27$, $p=0.04$) (Palagini et al., 2016). The total sum score was used to measure sleep reactivity in this analysis.

Sleep Latency (SoL). Baseline sleep latency was used to measure the time it takes to initiate sleep based on self-report with the sleep diary, a 9-item open-ended questionnaire. Sleep latency was measured on the questionnaire with the following question: "how long did it take you to fall asleep?" The participants answered by estimating the time it took to fall asleep based on their subjective experience in minutes. A continuous variable of minutes was created based on this self-report data. The sleep diary is a well-established and accepted tool that evaluates subjective sleep quantity and quality (Carney et al., 2012). Numerous studies have used the diary to identify self-reported time spent in bed that the participant is sleeping and awake (Carney et al., 2012; Dietch et al., 2019; Maich et al., 2018).

Perceived Stress Scale (PSS). The PSS is a 10 item self-report questionnaire, with each item on a 4 point Likert scale. Questions are endorsed if participants experienced the symptom within the prior month. The total sum score was used to measure perceived stress in this analysis. The PSS has been tested across multiple populations and is considered highly reliable and valid (Cohen, 1988; Lee, 2012).

Hamilton Rating Depression Scale (HRDS). Depression was measured using the (HRSD-17), a 17 item self-reported questionnaire on 4 point Likert-type scales (Hamilton, 1967; Kieslich da Silva et al., 2019). The baseline questionnaire of the parent study was used for this project. Although an HRSD-17 score of < 8 denotes remitted depressive symptoms, the total HRSD-17 sum score was used to measure depression in this analysis.

Statistical Analysis

Descriptive statistics were computed for participants consisting of their age, sex assigned at birth, educational level, and race/ethnicity. Bivariate associations between these covariates and insomnia scores were also computed to determine the need to adjust for them in regression models. Separate regressions were performed using ISI as both a dichotomous and continuous variable. In the dichotomous approach, a cutoff score of >7 denoted non-response from insomnia symptoms in contrast to remission from symptoms. This approach is consistent with a number of previous studies (Amidi et al., 2022; Castronovo et al., 2018; Edinger et al., 2007; Manber et al., 2016; Shaffer et al., 2020). Logistic regression was employed when using the dichotomous score. Multiple studies have also examined the effects of CBT-I on symptoms of insomnia using a continuous sum score of the ISI (Arizmendi et al., 2023; Chakravorty et al., 2019; Galbiati et al., 2021; Kallestad et al., 2021; Kjørstad et al., 2022; Speed et al., 2022; Yang et al., 2023). Linear regression was used when examining the continuous ISI score, with the change score from before to after CBT-I being the dependent variable in the model. Total scores for hypothesized baseline predictors of insomnia remission or improvement (sleep reactivity, sleep latency, stress and depression) were analyzed as continuous variables and regressed on insomnia in the regression models. These logistic and linear regressions were first run with the total sample of both longer and short sleepers, and then followed by regressions with each individual subsample of short sleepers and longer sleepers. This approach allowed for a more careful assessment of any findings that were unique to short sleepers.

In addition to these regressions using total scores of the hypothesized predictors, individual items from three measures of the predictors were also examined for their relationships to insomnia response to CBT-I. First, scores for individual items on the Hamilton Depression Rating Scale, Perceived Stress Scale, and Ford Insomnia Response to Stress Test were correlated with the ISI change score using Pearson correlation coefficients. In addition, t-tests were computed to determine if any item differed significantly between participants who achieved remission from insomnia versus those who did not. Any individual items that were statistically significant were incorporated into an integrated linear regression model to determine their effects when adjusting for the variance of other significant items. Statistical analyses were performed with Stata 17.

Results

Primary Research Findings

Demographic Characteristics of the Sample. Data from 46 individuals classified as longer and short sleepers were used in the study. Mean age was 49. Thirty-two participants were female, 35 participants were white, and 8 participants were black. The average education of participants was approximately 16 years. Twenty-three of the 46 individuals were classified as short sleepers. Their mean age was also approximately 49. Of this group of short sleepers, 19 participants were female, 18 participants were white, and 5 participants were black. Like the total sample, their education mean was approximately 16 years. Twenty-three individuals were classified as longer sleepers. The mean age of longer sleepers was approximately 46. Of the longer sleepers, 13 participants were female, 18 participants were white, and 3 participants were black. Average years of education for the longer sleepers was approximately 15 years. For further breakdown of demographic statistics, please see Tables 4.1, 4.2 and 4.3.

Inclusion of Potential Covariates in Testing of Study Aims. Analyses were performed to evaluate whether demographic variables or medication being prescribed in the TRIAD study might be associated with treatment response to CBT-I.

t-tests were computed to determine associations of age, race, education, or medication type taken during the study. A chi square test was used to evaluate sex differences. Results showed that there were no differences for any covariate between individuals whose insomnia met the criteria for remission in comparison to individuals who did not meet the criteria after receiving CBT-I.

Psychological Distress and Sleep-Related Factors as Predictors of Response to CBT-I Treatment. To enhance understanding of any unique findings for short sleepers, aims were first examined for the total sample and for longer sleepers prior to analyses for short sleepers. In examining the total sample of normal and short sleepers, depression was not associated with remission from insomnia (OR= 1.04, p= .74) nor was it related to degree of improvement in insomnia symptoms (β=-.004, p=.98). Perceived stress was also not associated with remission from insomnia (OR=.94, p=.29) nor with the degree of improvement in insomnia symptoms (β=-.13, p=.46). Sleep reactivity measured with the FIRST questionnaire was also not associated with remission from insomnia (OR=.96, p=.37) nor was it related to degree of improvement in insomnia symptoms (β=-.17, p=.36). Lastly, sleep onset latency was not associated with remission from insomnia (OR=.99, p=.89) nor was it related to degree of improvement in insomnia symptoms (β=-.20, p=.07. These findings are detailed in Tables 4.4 and 4.5.

Findings for longer sleepers paralleled those of the total sample. Depression was not associated with remission from insomnia (OR= .82, p= .35) nor was it related to degree of improvement in insomnia symptoms (β=.63, p=.58). Perceived stress was also not associated with remission from insomnia (OR=1.20, p=.41) nor was it related to degree of improvement in insomnia symptoms (β=.30, p=.35). Sleep reactivity was not associated with remission from insomnia (OR=.90, p=.29) nor was it related to degree of improvement in insomnia symptoms (β=.72, p=.38). Sleep onset latency was also not associated with remission from insomnia

(OR=0.89, p=.21) nor was it related to degree of improvement in insomnia symptoms (β=-.55, p=.06). These results are shown in Tables 4.6, and 4.7.

Results for the primary group of interest, short sleepers, were consistent with those for the group of longer sleepers. As shown in Table 4.8 and 4.9, depression was not associated with remission from insomnia (OR= 1.13, p= .40) nor was it related to degree of improvement in insomnia symptoms (β=.15, p=.63). Likewise, perceived stress was not associated with remission from insomnia (OR=.95, p=.77) nor was it related to degree of improvement in insomnia symptoms (β=-.33, p=.30). Sleep reactivity was not associated with remission from insomnia (OR=1.00, p=.99), nor was it related to degree of improvement in insomnia symptoms (β=-.11, p=.72). Lastly, sleep onset latency was not associated with remission from insomnia (OR=1.01, p=.91) nor was it related to degree of improvement in insomnia symptoms (β= -.38, p=.20). These results are shown in Tables 4.8 and 4.9.

Secondary Research Findings

In addition to testing of the aims using total scores on the measures, individual symptoms or characteristics in the measures were examined for their potential relationship to the effectiveness of CBT-I for short sleepers. The baseline score for each item in the measures of depression, stress and sleep reactivity was assessed for its association with each of the dependent variables: improvement in insomnia symptoms and remission from insomnia. Results of these analyses are presented in Tables 4.10, 4.11, and 4.12, and 4.13, 4.14, and 4.15.

Individual Depressive Symptoms and Effectiveness of CBT-I for Short Sleepers. Correlations in Table 4.10 indicate that no individual baseline symptoms of depression were related to improvement in insomnia after treatment. Although general somatic symptoms (r=.36, p=.09), and psychomotor retardation (r=.35, p=.10) had coefficients on the cusp of a moderate effect size, they did not reach statistical significance. However, as shown in Table 4.13, two depressive symptoms were associated with remission from insomnia. Experiencing feelings of guilt was higher at baseline among those who did not remit from CBT-I (M =1.6) when

compared to those who did respond to treatment (M= .69; t(21) = -2.26, p=.03). Suicidality was also higher at baseline among participants who did not remit from CBT-I (M =.60) when compared to those who did respond to treatment (M =.08; t(21)= -2.10, p=.047).

Individual Stress Symptoms and Effectiveness of CBT-I for Short Sleepers. As shown in Table 4.11, only one baseline stress symptom was associated with improvement in insomnia after CBT-I. Perceived ability of short sleepers to control irritations in life was negatively associated with improvement in insomnia after CBT-I (r=-.49, p=.02). No baseline stress symptoms differed for short sleepers who remitted after treatment and those who did not remit after receiving CBT-I (see Table 4.14).

Individual Vulnerabilities to Sleep Disturbance and Effectiveness of CBT-I for Short Sleepers. There were no significant associations between individual vulnerabilities to sleep disturbance/sleep reactivity (as measured by items on the Ford Insomnia Response to Stress Test) and either improvement in insomnia (Table 4.12) or remission from insomnia after CBT-I (Table 4.15).

Relationships of Irritability, Guilt and Suicidality to the Effectiveness of CBT-I. The 3 individual items showing relationships to a reduced response to CBT-I among short sleepers (difficulty in controlling irritability, feelings of guilt, and suicidality) were examined as predictors of insomnia improvement after treatment in one multiple linear regression model. Results in Table 4.16 indicate that, when all items were adjusted for effects of each other, only one item (difficulty controlling irritability) predicted degree of improvement in insomnia after CBT-I (β-.45, p=.03). Greater difficulty controlling irritability was associated with less improvement. The same regression model was computed for longer sleepers to determine whether the relationship of these 3 items to degree of improvement in insomnia after CBT-I would be similar or different for longer sleepers. As shown in Table 4.17, none of the items (difficulty in controlling irritability, feelings of guilt, or suicidality) were associated with degree of improvement in insomnia for longer sleepers after CBT-I.

Discussion

This study was conducted to explore whether psychological distress (stress and depression) and sleep-related factors (sleep reactivity and sleep onset latency) are associated with lack of treatment response among objectively short sleepers who receive CBT-I. Among short sleepers, results of the regression analyses indicated that none of these factors was significantly related to either remission of insomnia or improvement in insomnia after completion of CBT-I. However, in examining relationships between insomnia outcomes and individual items from the measures of psychological distress and sleep reactivity, three specific items did show significant associations. Individuals with greater feelings of guilt and greater suicidality prior to initiating treatment were less likely to experience remission after treatment when compared to short sleepers who did remit after treatment. In addition, more difficulty in controlling irritations prior to treatment was associated with less improvement in insomnia symptoms after treatment. Demographic factors including age, sex assigned and birth, and race as well as taking an antidepressant were not associated with treatment response to CBT-I.

Consistent with findings for short sleepers, results of the regression analyses also indicated that baseline psychological distress and sleep-related factors were not related to either remission or improvement in insomnia symptoms for longer sleepers after completion of CBT-I. However, in contrast to findings for short sleepers, no individual symptoms of depression, perceived stress, or sleep reactivity were associated with insomnia remission or improvement after treatment for longer sleepers.

Psychological Distress and Response to CBT-I

Severity of Depression. Null findings for the relationship between overall severity of depression and response to CBT-I suggest that higher cumulative depressive symptom burden among short sleepers may not be an important factor in their treatment response to CBT-I. These results are in alignment with other studies in the field which have shown that depression was not a significant predictor of CBT-I treatment response (Currie et al., 2002; Gagné & Morin,

2001; Lancee et al., 2013; Tremblay et al., 2009). However, findings are also in contrast to research reporting that depression severity did predict worse response to CBT-I (Espie et al., 2001; Pruiksma et al., 2020). It is important to note that studies showing an effect of depression did not focus on short sleepers or differentiate between objectively short and longer sleepers. Furthermore, both studies that found a significant effect of depression on treatment response had unique, specialized samples (active military personnel and individuals with co-morbid breast cancer). In conjunction with null results found for depression among longer sleepers in this sample and in the majority of previous research, results of this analysis indicate that overall severity of depressive symptoms is likely not a good predictor of response to CBT-I among short sleepers.

Degree of Perceived Stress. Findings from this study are the first to show that degree of overall perceived stress among short sleepers was not associated with treatment response to CBT-I. Two previous studies have found that CBT-I improved perceived stress severity (Denis et al., 2020; Moloney et al., 2020) but that was not the specific association examined in this research. Our findings suggest that cumulative or degree of overall perceived stress may not be a useful predictor of who among short sleepers will benefit from CBT-I. A more fruitful line of inquiry may be a focus on specific symptoms of stress and a more nuanced assessment of how CBT-I might affect specific aspects of sleep disturbance. Previous research has shown that varied types of stress have differential associations with sleep disturbance as well as specific relationships to different dysfunctions involving sleep efficiency or REM latency (Hall Brown et al., 2015; Han et al., 2012).

Specific Symptoms of Psychological Distress and Response to CBT-I. Results for analysis of individual symptoms of psychological distress are noteworthy in two ways. First, greater difficulty controlling irritations, feelings of guilt, and suicidality were only associated with worse response to CBT-I for short sleepers but not for longer sleepers. This finding suggests that these particular symptoms could have unique relevance for short sleepers. Second, when

these symptoms were combined in one model, only ‘difficulty controlling irritations in life’ retained significance as a predictor of short sleeper response to CBT-I. This finding indicates that these 3 symptoms may have shared variance that contributes to diminished improvement in insomnia after CBT-I, but the variance is best accounted for by ‘difficulty controlling irritations.’

Difficulty Controlling Irritation. The finding that short sleepers with more difficulty controlling irritations at baseline was associated with worse CBT-I outcomes is in line with previous studies. Psychological irritation is an emotional process associated with negative states of hyperarousal, inclusive of anger, annoyance, and frustration (Barata et al., 2016). Psychological irritation may be interfering with the behavioral strategies of CBT-I such as relaxation and stress reduction. If individuals struggle with managing irritations, this may inherently involve or lead to ongoing states of arousal that limit the individual’s ability to effectively use treatment strategies. Furthermore, CBT-I addresses cognitive distortions around sleep but does not identify ways for individuals to control psychosocial stressors that may be the source of irritation for the individual. The focus on changing stressors themselves is beyond the scope of CBT-I.

Suicidality. Although not retained in the final regression model as a significant predictor of response to CBT-I, the association between suicidality and lack of remission in bivariate analysis warrants comment. This study appears to be the only research that has evaluated if suicidality predicts treatment response to CBT-I. To date, all other studies have examined the effects of CBT-I on suicidality. One study investigating long-term effects of CBT-I on suicidality found that those who received CBT-I had continued reduced suicidal risk at 12 month follow-up (Kalmbach et al., 2022). In contrast, most other studies found a considerable reduction in suicidal ideation following a course of CBT-I (Batterham et al., 2017; Jernelöv et al., 2021; Trockel et al., 2015). In the more general treatment literature, there is evidence that baseline suicidal ideation is associated with lower response and remission rates for a variety of treatments not focused on insomnia, such as antidepressants (Seo et al., 2014) and ECT

(Sienaert et al., 2022). Experiencing insomnia as a short sleeper who also experiences suicidal ideation may have cumulative effects that interfere with treatment response to CBT-I. Although CBT-I does not address suicidal thoughts directly, during cognitive restructuring sessions in CBT-I, clinicians might consider targeting suicidal thoughts that may occur in association or in conjunction with symptoms of insomnia. Personalizing interventions to the client are an opportunity for clinicians to develop more effective treatment plans for individuals with insomnia, considering their specific symptoms and individual needs.

Feelings of Guilt. Like suicidality, a patient's 'feelings of guilt' was not a symptom retained in the final model. However, its relationship to insomnia remission after CBT-I in preliminary analyses suggested its potential importance for future research. Although no other studies have examined the effect of guilt feelings on treatment response, other studies have found that feelings of guilt frequently persist after evidence-based treatments (Taylor et al., 2010; Zhou et al., 2022). After 20 sessions of cognitive therapy for depression, Taylor et al. reported that high endorsement of feelings of guilt persisted at completion. Similarly, (Zhou et al. 2022) found that feelings of guilt continued despite improvement in pharmacologic antidepressant treatment. Thoughts of guilt related to depression are not directly treated during cognitive restructuring of CBT-I. If further research supports the importance of these thoughts for treatment response of short sleepers, tailoring CBT-I to address thoughts of guilt may be a useful approach for clinicians.

Sleep-related Factors and Response to CBT-I

Sleep Latency. The null results in this study for effects of sleep latency are in contrast to a previous study reporting that shorter sleep onset latency is associated with reduced CBT-I treatment response (Troxel et al., 2013). However, that study involved a significantly older patient population who were not short sleepers, used polysomnography (PSG) to assess sleep latency, and employed a brief form of CBT-I intervention. While there are many differences between that study and this one, their divergent results suggest the need to examine if

subjective sleep latency (based on reported sleep diary) or polysomnography may represent a better measure when assessing whether sleep onset latency among short sleepers is associated with treatment response to CBT-I.

Sleep Reactivity. Our null results for sleep reactivity are also in contrast to the one study that has examined the effects of sleep reactivity on CBT-I. Park et al. (2022) found that low reactive participants had an improved response to CBT-I. However, the sample was very small, and the study was based in Korea. Still, both studies did use the same insomnia and sleep reactivity measures. Regardless, many of the questions highlighted in the sleep reactivity measure (the FIRST) are situational and may be state rather than trait specific. In light of this, it may be more appropriate to administer the FIRST at multiple points rather than only once to more accurately assess if sleep reactivity can affect treatment response.

Study Strengths and Limitations

This study had multiple strengths. The full protocol of CBT-I was systematically administered and therefore participants received full dose treatment of CBT-I (Manber et al., 2016). Tools to measure psychological distress and insomnia are widely used and validated. However, it is important to also consider a number of limitations. The total sample as well as the number of short sleepers (n=23) was relatively small, reducing the power to detect significant effects. The sample also consisted primarily of those who identified racially as white, and participants were primarily female. Future studies would benefit from active recruitment of racially and ethnically diverse participants with a more balanced number of individuals identifying as male and female. Only baseline assessments of measures were used; multiple measures over time could provide a better perspective on how symptoms and characteristics may influence treatment response. Also, although total scores on the HRDS and PSS are well-established and validated for use, the validity and reliability of individual items from these measures have not been examined to our knowledge. Another key limitation is that an assessment of beliefs about sleep was not evaluated at baseline or at the end of CBT-I

treatment. The Dysfunctional Beliefs and Attitudes about Sleep (DBAS) is a validated tool that evaluates if the individual completing the questionnaire has faulty beliefs, unrealistic expectations, or a negative bias towards the concept of sleep as well as sleep ability (Morin et al., 2007). There is an opportunity for future research to examine the effects of beliefs around sleep on treatment response to insomnia among those who are short sleepers. Additionally, it is worth noting that we did not control for changes in depression over time or ultimate improvement in depression. These factors might have influenced insomnia outcome severity in relation to the independent variables examined.

Implications for Research and Practice

Further research should include a larger, more gender and ethnically/racially diverse sample with an RCT research design that randomizes short and longer sleepers. Longitudinal studies that examine the effects of difficulty controlling irritations, feelings of guilt, and suicidality both before and after completion of CBT-I could be beneficial in elucidating a temporal relationship among each of these symptoms and response to CBT-I. More comprehensive measures of these variables are also needed. Assessment of sleep reactivity and other variables can also be further evaluated across the course of CBT-I. Dysfunctional beliefs and attitudes about sleep should also be studied to examine the effects of cognitions related to sleep and their effects on treatment response among short sleepers.

These findings can provide useful information for clinicians on approaches to insomnia treatment among short sleepers. Tailoring CBT-I to target co-occurring symptoms that may interfere with CBT-I should be considered. If tailoring interventions to also treat other co-occurring psychiatric symptoms is unrealistic because of time constraints or requiring skills beyond the individual's scope, a collaborative approach to care may be warranted where the CBT-I therapist focuses on insomnia treatment and another psychotherapist may simultaneously support clients in treating co-occurring psychiatric symptoms. Finally, given evidence suggesting that 'difficulty controlling irritations' may be associated with a state of

hyperarousal in some short sleepers with insomnia, the judicious utilization of pharmacology or eye movement desensitization and reprocessing (EMDR) may be warranted. A recent study found that both Lemborexant and Zolpidem tartrate ER showed improvement in both insomnia symptoms and sleep quantity among objectively observed short sleepers and not longer sleepers (Inoue et al., 2023).

Conclusion

This study provides evidence that overall severity of depression and perceived stress as well as the time it takes a person to fall asleep (sleep latency) and the degree of sleep disruption in response to stress (sleep reactivity) were not associated with treatment response to CBT-I for either short sleepers or longer sleepers. However, one symptom of perceived stress was related to significantly less improvement in insomnia after CBT-I for short sleepers: difficulty controlling irritations. This symptom has been associated with a psychological state of hyperarousal, including feelings of anger, annoyance and frustration. Hyperarousal may preclude the short sleeper's ability to effectively engage in CBT-I interventions that involve relaxation techniques or strategies to control negative thoughts and beliefs about sleep. Preliminary bivariate tests also suggested that a short sleepers' depressive symptoms of guilt and suicidality may warrant further study for their potential role in limiting treatment response to CBT-I.

Results of this exploratory study indicate that some short sleepers may have symptoms prior to initiating treatment that put them at increased risk for a reduced treatment response and that assessment of specific symptoms may be more important than overall global scores when considering potential effects of depressive symptoms and stress on treatment response to CBT-I. This study represents an important foundation for further research as well as preliminary implications for clinical practice on how psychological distress can impact insomnia treatment among short sleepers.

Table 4.1: Demographic Characteristics for Total Sample of Short and Longer Sleepers and by their Insomnia Remission Status after CBT-I

Measure	Total (N=46)	ISI > score of 7 (n=19)	ISI ≤ score of 7 (n=27)
Age, mean ± SD, y	49.03 ± 13.44	52.26 ± 17	45.47 ± 11.72
Sex, n (%)			
Male	14 (30.43)	6 7 (31.58)	8 9 (29.63)
Female	32 (69.57)	13 (68.42)	19 23 (70.37)
Race, n (%)			
White	35 (76.01)	12 (63.15)	24 (88.89)
Black	8 (17.40)	6 (31.58)	2 4 (7.41)
Other	3 (6.59)	1 (5.27)	1 (3.70)
Education, mean ± SD	15.93 ± 3.03	15.09 ± 2.02	17.25 ± 3.23

Table 4.2: Demographic Characteristics for Total Sample of Short Sleepers and by their Insomnia Remission Status after CBT-I

				Analysis	
Measure	Total (N=23)	ISI > score of 7 (n=10)	ISI ≤ score of 7 (n=13)	Test Statistic	*p*
Age, mean ± SD, y	48.66 ± 13.55	50.6 ± 17	49.62 ± 11.92	*t*	.87
Sex, n (%)				χ^2	.59
Male	4 (17.39)	2 (20)	2 (15.38)		
Female	19 (82.61)	8 (80)	11 (84.62)		
Race, n (%)				*t*	.14
White	18 (78.26)	6 (60)	12 (85.71)		
Black	5 (21.73)	3 (30)	2 (14.29)		
Other	1 (4)	1 (10)	0 (0)		
Education, mean ± SD	16.26 ± 3.01	15.4 ± 1.96	17.3 ± 3.15	*t*	.11

Table 4.3: Demographic Characteristics for Total Sample of Longer Sleepers and by their Insomnia Remission Status after CBT-I

Measure	Total (N=23)	ISI > score of 7 (n=10)	ISI ≤ score of 7 (n=13)
Age, mean ± SD, y	45.94 ± 13.54	54.1 ± 7.91	40.5 ± 15.60
Sex, n (%)			
Male	10 (43.48)	4 (40)	6 (46.15)
Female	13 (56.52)	6 (60)	8 (53.85)
Race, n (%)			
White	18 (78.26)	6 (60)	12 (92.31)
Black	3 (13.04)	2 2 (20)	1 (7.69)
Other	2 (8.70)	2 1 (20)	0
Education, mean ± SD	15.45 ± 3.35	14.33 ± 2.18	17.29 ± 3.85

Table 4.4: Logistic Regression Model for the Relationship of Psychological Distress and Sleep-Related factors with Remission from Insomnia among both Long and Short Sleepers Receiving CBT-I

Predictor	Odds ratio	SE	p	CI
HRDS Questionnaire	1.04	.10	.74	[.86, 1.25]
Perceived Stress Scale	.94	.09	.29	[.77, 1.13]
FIRST Questionnaire	.96	0.05	.37	[.86, 1.06]
Sleep Onset Latency	.99	.03	.89	[.94, 1.06]

Table 4.5: Linear Regression Model for the Relationship of Psychological Distress and Sleep-Related factors with Degree of Improvement in Insomnia among both Long and Short Sleepers Receiving CBT-I

Predictor	B	SE	Beta	p	CI
HRDS Questionnaire	-.009	.33	-.004	.98	[-.68, .66]
Perceived Stress Scale	-.25	.33	-.13	.46	[-.91, .42]
FIRST Questionnaire	-.17	.18	-.15	.36	[-.54, .20]
Sleep Onset Latency	-.20	.11	-.29	.07	[-.42, .02]

Table 4.6: Logistic Regression Model for the Relationship of Psychological Distress and Sleep-Related factors with Remission from Insomnia among Longer Sleepers Receiving CBT-I

Predictor	Odds ratio	SE	p	CI
HRDS Questionnaire	.82	.18	.35	[.53, 1.25]
Perceived Stress Scale	1.20	.26	.41	[.78, 1.85]
FIRST Questionnaire	.90	0.09	0.29	[.73, 1.19]
Sleep Onset Latency	.89	.09	.21	[.92, 1.09]

Table 4.7 Linear Regression Model for the Relationship of Psychological Distress and Sleep-Related factors with Degree of Improvement in Insomnia among Longer Sleepers Receiving CBT-I

Predictor	B	SE	Beta	p	CI
HRDS Questionnaire	-.37	.66	.63	.58	[-1.81, 1.07]
Perceived Stress Scale	.66	.68	.30	.35	[-.83, 2.16]
FIRST Questionnaire	-.28	.30	.72	.38	[-.95, .39]
Sleep Onset Latency	-.55	.26	.20	.06	[-.1.12, .02]

Table 4.8: Logistic Regression Model for the Relationship of Psychological Distress and Sleep-Related factors with Remission from Insomnia among Short Sleepers Receiving CBT-I

Predictor	Odds ratio	SE	p	CI
HRDS Questionnaire	1.13	.16	0.40	[.85, 1.49]
Perceived Stress Scale	.95	.17	.77	[.67, 1.35]
FIRST Questionnaire	1.00	0.09	0.99	[.84, 1.19]
Sleep Onset Latency	1.01	.04	.91	[.92, 1.09]

Table 4.9: Linear Regression Model for the Relationship of Psychological Distress and Sleep-Related factors with Degree of Improvement in Insomnia among Short Sleepers Receiving CBT-I

Predictor	B	SE	Beta	p	CI
HRDS Questionnaire	.22	.45	.15	.63	[-.75, 1.2]
Perceived Stress Scale	-.64	.58	-.33	.30	[-1.9, .63]
FIRST Questionnaire	-.11	.29	-.11	.72	[-.74, .52]
Sleep Onset Latency	-.19	.14	-.38	.20	[-.49, .12]

Table 4.10: Correlations of Individual Items from the Hamilton Depression Rating with Degree of Improvement in Insomnia among Short Sleepers Receiving CBT-I

Questionnaire Items	r	p
Depressed mood	-.21	.34
Feelings of guilt	-.32	.14
Suicidality	-.28	.20
Psychomotor retardation	-.35	.10
Psychomotor agitation	-.07	.76
Anxiety (psychic)	-.02	.94
Anxiety (somatic)	.13	.57
Somatic symptoms (gastro-intestinal)	-.18	.41
Somatic (general)	-.36	.09

Table 4.11: Correlations of Individual Items from the Perceived Stress Scale with Degree of Improvement in Insomnia among Short Sleepers Receiving CBT-I

Questionnaire Items	r	p
Upset because something happened unexpectedly	-.23	.29
Unable to control important things in life	-.05	.81
Felt nervous and stressed	-.11	.60
Confident about ability to handle problems	.-.09	.69
Things are going your way	-.08	.73
Could not cope with things you had to do	-.13	.56
Difficulty Controlling irritations in your life	**-.49**	**.02**
Felt on top of things	.23	.28
Angered because of things that happened outside of control	-.34	.11
Felt difficulties piling up so high could not overcome them	-.27	.20

Table 4.12: Correlations of Individual Items from the Ford Insomnia Response to Stress Test with Degree of Improvement in Insomnia among Short Sleepers Receiving CBT-I

Questionnaire Items	r	p
Before an important meeting the next day	.19	.42
After a stressful experience during the day	.11	.64
After a stressful experience in the evening	.25	.27
After getting bad news during the day	.24	.29
After watching a frightening movie or TV show	-.28	.29
After having a bad day at work	.09	.70
After an argument	.15	.53
Before having to speak in public	-.11	.61
Before going on vacation the next day	.03	.90

Table 4.13: Differences in Individual Item Scores from the Hamilton Depression Rating Scale for Participants achieving Remission from Insomnia Versus Not among Short Sleepers Receiving CBT-I

Questionnaire Items	Responder – Mean Score [CI]	Non-responders – Mean Score [CI]	t-test (df)	P value
Depressed mood	1.15 [.51-80]	2 [1.17, 2.83]	-1.82 (21)	.08
Feelings of guilt	.69 [.12-1.26]	1.6 [.91, 2.29]	-2.26 (21)	**.034**
Suicidality	.08 [-.09-.24]	.6 [-.003, 1.20]	-2.10 (21)	**.047**
Psychomotor retardation	.23 [-.03-.50]	.7 [.11, .29]	-1.76 (21)	.09
Psychomotor agitation	.08 [-.09, .24]	.1 [-.13, .33]	-.19 (21)	.85
Anxiety (psychic)	1 [.57, 1.4]	1.4 [.43, 2.37]	-.92 (21)	.37
Anxiety (somatic)	1.31 [.48, 2.14]	1 [-.17, 2.17]	-.49 (21)	.63
Somatic symptoms (gastro-intestinal)	.23 [-.13, .59]	.7 [.11, 1.29]	-1.58 (21)	.13
Somatic symptoms (general)	1.08 [.56, 1.60]	1.5 [.99, 2.01]	-1.26 (21)	.22

Table 4.14: Differences in Individual Item Scores from the from the Perceived Stress Scale with Remission from Insomnia among Short Sleepers Receiving CBT-I

Questionnaire Items	Responder – Mean Score [CI]	Non-responders – Mean Score [CI]	t-test (df)	P value
Upset because something happened unexpectedly	3.8 [3.30-4.39]	3.7 [3.11-4.29]	.40(21)	.69
Unable to control important things in life	3.92 [3.54-4.31]	3.8 [3.23-4.36]	.41(21)	.68
Felt nervous and stressed	4.08 [3.62-4.54]	4.5 [4.12-4.88]	-1.50(21)	.15
Confident about ability to handle problems	2.69 [2.24-3.15]	2.4 [1.90-2.90]	.95(21)	.35
Things are going your way	2.46 [2.15-2.78]	2.6 [1.91-3.29]	-.44(21)	.66
Could not cope with things you had to do	3.85 [3.25-4.44]	3.9 [3.27-4.53]	-.14(21)	.89
Control irritations in your life	2.46 [2.06-2.86]	2.8 [2.50-3.10]	-1.41(21)	.17
Felt on top of things	2.53 [2.14-2.94]	2.2 [1.75-2.65]	1.24(21)	.23
Angered because of things that happened outside of control	3.5 [2.90-4.17]	3.3 [2.62-3.98]	.58(21)	.58
Felt difficulties piling up so high could not overcome them	3.92 [3.40-4.44]	3.7 [2.94-4.46]	.56(21)	.58

Table 4.15: Differences in Individual Item Scores from the Ford Insomnia Response to Stress Test with Remission from Insomnia among Short Sleepers Receiving CBT-I

Questionnaire Items	Responder – Mean Score [CI]	Non-responders – Mean Score [CI]	t-test (df)	P value
Before an important meeting the next day	2.54 [1.99, 3.10]	2.7 [2.11, 3.29]	-.43(19)	.67
After a stressful experience during the day	3 [2.33, 3.67]	2.9 [2.27, 3.53]	.24 (19)	.81
After a stressful experience in the evening	3.36 [2.67, 4.05]	3.1 [2.57, 3.62]	.67 (19)	.51
After getting bad news during the day	3 [2.33, 3.67]	3.1 [2.57, 3.63]	-.25 (19)	.80
After watching a frightening movie or TV show	1.91 [1.09, 2.73	1.6 [.10, 2.20]	.67 (19)	.51
After having a bad day at work	2.46 [1.76, 3.15]	2.7 [2.11, 3.29]	-.60 (19)	.55
After an argument	3.09 [2.27, 3.91]	3 [2.42, 3.58]	.20 (19)	.84
Before having to speak in public	2.36 [1.45, 3.28]	2.7 [1.94, 3.46]	-.63 (19)	.54
Before going on vacation the next day	2.45 [1.76, 3.15]	2.5 [1.80, 3.20]	-.10 (19)	.92

Table 4.16: Linear Regression for the Relationship of Ability to Control Irritations, Suicidality, and Feelings of Guilt to Improvement in Insomnia among Short Sleepers Receiving CBT-I

Predictor	B	SE	β	p	CI
Difficulty Controlling Irritation	-5.04	2.21	-.45	**.03**	-9.66, -.42]
Suicidality	.51	2.46	.05	.84	[-4.63, 5.66]
Feelings of Guilt	1.46	1.48	.23	.34	[-1.63, 4.56]

Table 4.17: Linear Regression for the Relationship of Ability to Control Irritations, Suicidality, and Feelings of Guilt to Improvement in Insomnia among Longer Sleepers Receiving CBT-I

Predictor	B	SE	β	p	CI
Difficulty Controlling Irritation	.88	2.37	.09	.71	[-4.08, 5.85]
Suicidality	1.72	2.60	.16	.52	[-3.72, 7.16]
Feelings of Guilt	-.55	1.64	-.08	.74	[-3.99, 2.89]

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Chapter 5: Discussion

Summary of Dissertation Findings

This dissertation addressed three aims:

1. To identify evidence-based biomarkers that have been associated with insomnia in adults.
2. To determine if insomnia and discrimination are associated with telomere length among adults from different racial/ethnic groups as well as whether discrimination moderates the relationship between insomnia and telomere length.
3. To identify the relationship of psychological distress and sleep-related factors to non-response to cognitive behavioral therapy for insomnia (CBT-I) among short sleepers with insomnia.

Important findings related to these aims emerged from the research.

Evidence-Based Biomarkers of Insomnia

The scoping review revealed key insights into biomarker research associated with insomnia. First, variations were found in the methods used to diagnose insomnia across the included studies. Clinical interviews were used in sixteen studies, while five studies relied on standardized questionnaires without assessing their psychometric properties. Three studies employed undefined questionnaires for insomnia diagnosis. To enhance future research, it is recommended that psychometrics of questionnaires be examined or established standardized questionnaires be used alongside clinical interviews. The heterogeneity and varied psychometric quality of insomnia measures pose challenges for study comparisons and synthesis of results. Second, significant findings were identified. Studies examining metabolic markers reported decreased temperature, increased V02 max, and reduced levels of phosphocreatine and phosphocholine to be associated with insomnia. Findings on oxidative stress revealed higher malondialdehyde (MDA) levels and lower glutathione peroxidase (GSH-Px) levels in individuals with insomnia, indicating elevated oxidative stress. Cardiovascular

function studies indicated increased blood pressure, heart rate, cholesterol, BMI, and hemoglobin A1c. Inflammation studies found associations between insomnia and monocyte production of proinflammatory cytokines, C-reactive protein (CRP), and interleukin-6 (IL-6). Cerebral structure studies showed associations between untreated insomnia and markers such as NfH, NfL, S100B, and increased bilateral hippocampal connectivity. Genomic investigations revealed reduced telomere length and specific SNPs on ROR1 and PLCB1 associated with insomnia. EEG studies found increased alpha, sigma and beta activity associated with insomnia (indicating hyperarousal and reduced cortical inhibition), reduced spindle activity associated with higher insomnia symptom severity, and a slower decline in delta power during sleep with insomnia. These findings contribute to understanding the diverse biomarker profiles and PSG signatures associated with insomnia.

Insomnia, Discrimination and Telomere Length

In the secondary analysis of the Health and Retirement Study, sleep disturbance was associated with shorter TL only among older white individuals. In an unadjusted model, discrimination moderated the association between insomnia symptoms and telomere length among Black participants. For Black participants who reported discrimination, insomnia was associated with shorter telomeres while it had no relationship to TL for Black participants reporting no discrimination. However, after adjusting for age, BMI, medical co-morbidities, and depression, the moderating effect of discrimination was no longer significant.

Reduced Response to CBT-I among Short Sleepers with Insomnia

In the secondary analysis of the TRIAD study, none of the total scores for psychological distress or sleep reactivity was significantly related to either remission of insomnia or improvement in insomnia after completion of CBT-I by short sleepers. However, in examining relationships between insomnia outcomes and individual items from the measures of psychological distress and sleep reactivity, three specific symptoms did show significant associations. Individuals with greater depressive feelings of guilt and greater suicidality prior to

initiating treatment were less likely to experience remission after treatment when compared to short sleepers who did remit after treatment. In addition, one symptom of stress (perceived difficulty in controlling irritations) was associated with less improvement in insomnia symptoms after treatment. When these 3 symptoms were examined together in a final model, only 'difficulty controlling irritations' retained a significant relationship to reduced improvement in insomnia after CBT-I. This finding was unique to short sleepers: no factors (including individual symptoms) were associated with lack of insomnia remission or decreased improvement after treatment for longer sleepers.

Dissertation Results in the Context of Allostatic Load

The conceptual framework of allostatic load (AL) can help guide how one conceptualizes these findings. AL refers to the cumulative physiological dysregulation resulting from prolonged exposure to stressors and the body's attempts to adapt and maintain stability. In the context of insomnia, chronic sleep disturbances may contribute to an increased allostatic load.

Of note, studies found in the scoping review did not systematically describe a theoretical framework that guided the research. Biomarkers identified in the scoping review (Aim 1) may well reflect indicators of allostatic load. W Elevated oxidative stress markers (e.g., higher MDA levels, lower GSH-Px levels) may indicate disrupted antioxidant defense mechanisms as a result of sustained sleep disruptions and metabolic imbalances. Markers of inflammation (e.g., proinflammatory cytokines, CRP, IL-6) also suggest an amplified immune response and chronic low-grade inflammation associated with persistent sleep disturbances. Increased cardiovascular demand in insomnia may stem from chronic activation of stress response systems leading to sustained physiological arousal, dysregulated autonomic function, and cardiovascular strain.

Differences in cerebral structure and connectivity (e.g., NfH, NfL, S100B, hippocampal connectivity) were also implicated in the scoping review as arising from prolonged sleep disturbances. These disruptions in normal neurobiological processes and related brain activity may be additional indicators of allostatic load from chronic insomnia. Various markers noted in

the review highlight the cumulative physiological dysregulation resulting from sleep disturbances and the body's likely efforts to adapt and maintain physiological stability in the face of chronic insomnia-related stress. However, there may be a range of other factors yet to be identified and there is further need for study of underlying mechanisms.

Results related to the 2nd dissertation aim may provide further evidence of allostatic load. In my analysis of data from the Health and Retirement Study, sleep disturbance among older white individuals (85% of the sample) was associated with shorter telomere length. This finding suggests that disrupted sleep patterns may contribute to increased physiological burden and subsequent telomere degradation in this specific population. In addition, although discrimination was associated with shorter telomere length among Black individuals in preliminary testing, the effects of discrimination were not sustained after controlling for age, BMI, medical co-morbidities, and depression. This finding indicates roles for other health-related factors that potentially covary with discrimination in reducing the integrity of telomeres. As described in Chapter 3 of this dissertation, although telomere erosion may be a putative indicator of allostatic load, there are conflicting findings regarding the meaning of telomere shortening, with some studies showing telomere lengthening under conditions of allostatic load.

Lastly, the allostatic load framework informs our understanding of results related to the 3rd dissertation aim. Findings from analysis of the TRIAD Study data provided evidence that an individual's perceived inability to control irritations may influence response to CBT-I, particularly among individuals with short sleep duration. It is possible that the combined effects of short sleep duration and difficulty controlling irritations were contributing to a higher psycho-physiologic burden that was not measured in this study but was fostering a state of allostatic load. This increased load may impede short sleepers' ability to respond effectively to CBT-I interventions and achieve favorable treatment outcomes.

Although their effects were not sustained when included in a model that adjusted for inability to control irritations, suicidality and feelings of guilt among individuals with short sleep

duration were also related to reduced treatment response in bivariate associations. Short sleepers who reported higher levels of suicidality and guilt at baseline (compared to both short sleepers who did respond to CBT-I and individuals with normal sleep duration) did not achieve remission of insomnia from CBT-I. Like the effect of inability to control irritations discussed earlier, ongoing thoughts of suicide and guilt-related rumination may exacerbate effects of short sleep duration to foster impairments in allostasis that impede the ability to benefit from treatment. Over time, increased allostatic load experienced by non-responsive short sleepers may have a cumulative effect on their psychological well-being and potentially exacerbate the treatment-resistant nature of their insomnia.

Considering study findings within the allostatic load framework enhances a deeper understanding of the interconnectedness of various factors influencing treatment response in CBT-I. The framework highlights the potential for a complex interplay between sleep disturbance and specific symptoms of depression and stress experienced by short sleepers.

Future Research Implications

Implications of the scoping review are many. First, the examination of sleep architecture and its associations with EEG activity shows promise in allowing researchers to further evaluate nuanced differences of PSG readings among those with insomnia compared to others without. Similarly, genetic studies used questionnaires with fewer than five items and did not clinically diagnose insomnia. More research is needed to investigate the associations between candidate genes, gene expression, and clinically diagnosed insomnia. Additionally, only two studies utilized brain structure and function evaluation (with MRS and fMRI). Further investigation of the association between insomnia and brain function using fMRI, as well as incorporating fMRI in interventional studies targeting insomnia, is warranted. In sum, future studies should strive for standardized and clinically validated methods of diagnosing insomnia, explore PSG signatures as outcomes, further investigate brain structure using fMRI, and delve into the associations between candidate genes, gene expression, and clinically diagnosed insomnia.

Implications are also apparent from results of the Health and Retirement Study analysis. Like the recommendation from the scoping review, future research should address whether a confirmed clinical diagnosis of insomnia is associated with shortened telomere length, not only self-reported insomnia. In addition, studies examining the link between insomnia and telomere length should include other minority groups such as other racial/ethnic groups and members of the LGBTQIA community. In addition, longitudinal studies are needed to examine potential pathways between insomnia and telomere degradation. The type, extent, and chronicity of discrimination that may intersect adversely with sleep problems and influence TL should also be studied, along with underlying biological mechanisms other than TL, that may mediate effects of both insomnia and discrimination on telomere integrity. Further research is also warranted to better understand how covariates such as age, medical comorbidities and depression may interact with discrimination to affect telomere length. Additional research is also warranted on other markers of stress independent of TL and whether there is individual variability in telomere length among specific groups of individuals with insomnia.

Examining the interplay between other social determinants and insomnia can also provide valuable insights into the pathways through which social factors influence health outcomes. Future research can explore the effects of chronic stress and other determinants such as socioeconomic status on insomnia. These factors may disrupt sleep patterns, perpetuate sleep disturbances, and exacerbate the risk of developing insomnia. Additionally, the experience of discrimination and socioeconomic disadvantage may contribute to increased psychological distress, which further compromises sleep quality and perpetuates a cycle of sleep disruption and poor health outcomes.

Moreover, investigating other potential mediators and moderators of the relationships among social determinants, insomnia, and health outcomes could provide additional insights. For example, psychological factors, such as resilience and coping strategies, may influence the impact of social determinants on insomnia and subsequent health outcomes. Exploring these

factors can help identify potential intervention targets to mitigate the negative health effects of social determinants and insomnia. By expanding our knowledge in these areas, we can inform the development of targeted interventions to address social determinants, promote healthy sleep, and ultimately improve overall health and well-being.

Results of the TRIAD analysis have important research implications as well. Further research must occur with a larger sample size that enables better detection of potential effects associated with psychological distress and sleep-related factors. It is also essential to highlight that these findings are preliminary as depression outcomes were not accounted for, potentially impacting insomnia severity in relation to the examined independent variables. Further investigation is warranted to validate and expand on these observations. In addition, the samples need to include a broader diversity in terms of gender and ethnicity/race. Utilizing a randomized controlled trial (RCT) design that randomizes individuals with short and normal sleep durations would provide valuable insights into the effects of sleep duration on treatment outcomes. Longitudinal studies examining the relationship between difficulty controlling irritations, feelings of guilt, suicidality, and response to cognitive-behavioral therapy for insomnia (CBT-I) before and after treatment completion would help establish the direction of any relationships that are found. Further research can also include more comprehensive measures of these symptoms and assess sleep reactivity throughout the course of CBT-I. Additionally, investigating dysfunctional beliefs and attitudes about sleep and their impact on treatment response among short sleepers would provide a deeper understanding of cognitive factors in insomnia treatment. Lastly, studying psychopharmacologic and psychotherapeutic modalities other than CBT-I for short sleepers experiencing insomnia is warranted.

Clinical Implications

Dissertation findings have significant implications for clinicians in guiding their approach to managing insomnia. By understanding the associations between biomarkers and insomnia, clinicians can enhance their diagnostic accuracy, develop personalized treatment plans, and

provide comprehensive care to individuals with insomnia. The scoping review suggests that healthcare providers should integrate multiple assessment methods, including clinical interviews, standardized questionnaires with established validity, and when possible, objective measures like polysomnography. This holistic approach could lead to more accurate and comprehensive diagnoses and ensure a better understanding of the individual's sleep patterns, symptoms, and associated biomarkers.

In addition, the identified biomarkers associated with insomnia offer potential targets for personalized treatment plans. Healthcare providers can incorporate interventions that address oxidative stress, inflammation, cardiovascular function, and cerebral functioning. Modifiable lifestyle factors such as incorporating healthy diet, exercise, and stress-reduction techniques can help to reduce oxidative stress and inflammation while also helping with sleep. Furthermore, clinicians can utilize these findings to guide therapeutic approaches. Behavioral interventions, such as cognitive-behavioral therapy for insomnia (CBT-I), have proven effective in improving sleep quality. An integrated approach holds the potential to enhance treatment outcomes and ultimately improve the quality of life for those affected by insomnia.

The research findings regarding the association between sleep disturbance and telomere length also have important clinical implications. It was observed that among older white individuals, sleep disturbance was associated with shorter telomere length. This suggests that addressing insomnia in this population may have potential benefits for maintaining telomere integrity. Although a moderating effect of discrimination between insomnia symptoms and telomere length among Black participants only existed in the unadjusted model, these findings highlight the significance of considering the influence of social determinants on the health outcomes of individuals with insomnia, particularly among Black individuals. Healthcare providers and clinicians should be attentive to the potential impact of discrimination on the health of individuals with insomnia, particularly among minority groups. Additionally, modifiable covariates such as BMI and medical co-morbidities including depression should be considered

by healthcare providers. These covariates may play a role in the complex relationship between discrimination, insomnia, and telomere length. Therefore, when assessing and managing insomnia in diverse populations, it is crucial for healthcare providers to take a holistic approach to care and consider how to also support clients in improving modifiable factors.

Clinical implications are also evident from the analysis of CBT-I response among short sleepers. Tailoring CBT-I to target co-occurring symptoms that may interfere with CBT-I should be considered. If tailoring interventions to also treat other co-occurring psychiatric symptoms is unrealistic because of time constraints or requiring skills beyond the individual's scope, a collaborative approach to care may be warranted where the CBT-I therapist focuses on insomnia treatment and another psychotherapist may simultaneously support clients in treating co-occurring psychiatric symptoms. Finally, given evidence suggesting that 'difficulty controlling irritations' may be associated with a state of hyperarousal in some short sleepers with insomnia, the judicious utilization of pharmacology or eye movement desensitization and reprocessing (EMDR) may be warranted.

Lastly, the heterogeneity of insomnia calls for the development of tailored interventions that address the unique needs of individuals. A one-size-fits-all approach may not be effective in improving sleep outcomes, as factors contributing to insomnia can vary widely among individuals. Tailored interventions aim to identify and target the specific factors that contribute to insomnia in each individual, and biological, psychological, and social factors should be considered. To tailor interventions effectively, comprehensive assessments should be conducted to identify the underlying causes and perpetuating factors of insomnia. Interventions should be multifaceted, incorporating a combination of psychotherapeutic and pharmacologic strategies that are tailored to an individual's presentations.

Chapter 6: Conclusion

Insomnia is common and affects millions of people worldwide. This dissertation allowed me to conduct a comprehensive review of the literature identifying associations between insomnia and biomarkers, research the effect of insomnia on a specific biomarker (telomere length), and examine factors that might influence response to CBT-I among a group of individuals considered treatment resistant (short sleepers).

The scoping review revealed several important biomarkers of insomnia, including markers of inflammation, oxidative stress, and metabolic dysfunction, as well as signatures noted on imaging and polysomnography. While the precise nature of the relationship between these biomarkers and insomnia needs further investigation, they may ultimately serve in assessment of insomnia risk, as targets for potential interventions, or be a diagnostic marker in efforts to investigate if interventions can be effective.

My study of the association between insomnia and telomere length supported the role of insomnia in telomere erosion. Results also suggested the importance of better understanding how discrimination may moderate the effects of insomnia on telomeres among racial groups at greatest risk of discrimination. Further research on the role of social determinants of health and insomnia is necessary to develop effective interventions that can help individuals manage and treat the condition while also driving health policy for equity. While the evidence linking insomnia and biomarkers is still emerging, it is clear that further research is needed to better understand the mechanisms underlying insomnia. In particular, more studies are needed to identify specific biomarkers that are associated with insomnia, as well as the effects of intervention on biomarkers identified.

Results of my final study indicated the importance of specific baseline symptoms rather than more general measures of psychological distress in predicting short sleepers' response to CBT-I. In particular, the short sleeper's perceived inability to control irritations was associated with worse response to treatment. This finding reinforces the need to design interventions for

insomnia that are tailored to particular phenotypes of insomnia, such as short sleepers. Addressing symptoms such as ‘lack of control over irritations’ as part of CBT-I interventions, or in conjunction with standard CBT-I psychoeducation and exercises, may improve insomnia outcomes for short sleepers and, ultimately, advance precision medicine. Short sleepers, who typically sleep less than six hours per night, may require different treatment approaches than nonsleepers, who have difficulty falling or staying asleep despite adequate opportunity. Factors such as other co-occurring conditions need to be carefully considered when designing personalized treatment plans for individuals with insomnia.

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