Opportunities for optimizing the treatment of Insomnia Disorder

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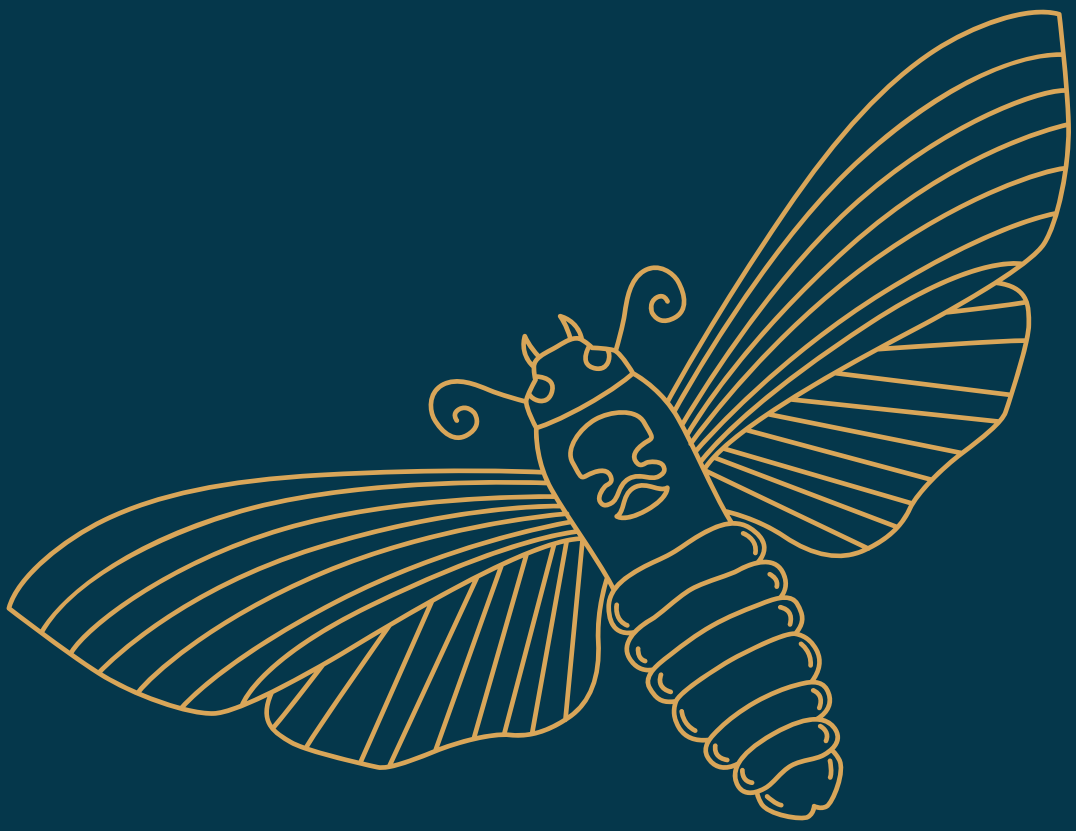

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“In girum imus nocte et consumimur igni”

- Anonymous Roman author

Voor Lisa, Yse, Janne en ♡

Contents

CHAPTER 1: INTRODUCTION

INSOMNIA DISORDER

Many people experience poor sleep once in a while. They may lie in bed for hours unable to 'let go' and stop thinking about an event that occurred that day, or an event in the near future. Or they have random thoughts. Or they wake up in the middle of the night and cannot seem to turn off their thoughts and get back to sleep. Or they wake up in the morning feeling as if it was just seconds ago that they closed their eyes to fall asleep and haven't rested at all, while still, a whole night has passed. Although these experiences may be very frustrating, one night of unsatisfying sleep will most likely hardly influence our daily functioning. Unfortunately, chronic suffering from these symptoms of insomnia can result in fatigue, reduced energy, impaired mood, inability to concentrate and remember things, irritability, proneness for accidents and errors, tension and even headaches.[1-4] In the end insomnia might influence our usual daily activities such as our abilities to work, to care for our children or family, to socialize with friends or to carry out our hobbies.[5]

Luckily, most people will experience only incidental nights or periods of poor sleep and reduced daily functioning, for example during stressful times. Sleep tends to return back to normal within days or weeks. However, some individuals experience recurring nights of bad sleep, of a more persistent nature, e.g. over periods of months or even years. If difficulty initiating or maintaining sleep occurs three nights a week or more, for at least three months, even though the sleep environment is optimal, and the reduced sleep results in impaired daily functioning, Insomnia Disorder can be diagnosed, according to the latest DSM definition.[6] This happens in roughly one out of five to ten people once in their lifetime.[7]

SLEEP REGULATION

Sleep is thought to be regulated by two processes: the sleep homeostat and the circadian rhythm.[8] The homeostat is based on the idea of building up sleep pressure during wake.[9] The longer you are awake, the higher the sleep pressure is. In a healthy sleeper the sleep pressure will have built up so much at the end of a day, after about 16 hours of wake, that it needs to be relieved by going to sleep. During sleep, the sleep pressure will dissipate. The deeper one sleeps, the greater the reduction in sleep pressure, until it completely dissipates, and we wake up feeling rested and refreshed. Taking a short nap during the day will of course also release a bit of sleep pressure, resulting in a lower sleep pressure in the evening. This can be one of the causes of difficulties falling asleep at night.

The homeostatic system interacts with the circadian (24-h) rhythm of the biological clock, the second sleep regulatory process. The biological clock is thought to reside in the hypothalamus of the brain, more precisely in the suprachiasmatic nucleus (SCN),[10] a small nucleus just above the chiasm of the optic nerves. It is responsible for the synchronization and orchestration of the day-night rhythms of all organs in the body, such as the sleep-wake cycle, hormone levels, metabolism, body temperature and immune function. To align the rhythms across the body, it synchronizes the slave oscillators in cells

that reside within the local tissue. Although a healthy SCN is thought to have an endogenous near-24-h rhythm, that can persist without external input, it receives input from so-called 'zeitgebers' or exogenous cues, that help the SCN to align to the 24-h light-dark cycle in the environment. These zeitgebers are external factors, like the light-dark cycle, that give the SCN information on the time of day. The strongest zeitgeber is light. Light has the capacity to shift or enhance the body's circadian clock.[11,12] Wams *et al.* (2017) even suggest that light can modulate homeostatic sleep pressure.[13] Light falls on the retina of the eye. The retina is in direct contact with the SCN through the retinohypothalamic tract, that directly innervates the SCN. It sends input from the light that falls on the retina to the SCN (among others).[14] The spectrum and intensity of the light give the SCN information on the time of day. For example, the spectrum of daylight contains more red light during sunset than during midday and more blue during the midday. When a person is in an environment with a lot of blue light, the SCN receives the information that it is daytime and promotes alertness.[15] Since computer and television screens contain a lot of blue light, using these screens in the late evening can disrupt the body's circadian rhythm. Other examples of zeitgebers are the body temperature[16] and the rest-activity pattern. The biological clock, when aligned properly with the circadian rhythm, promotes alertness to keep us awake during the day and in the early evening, when sleep pressure is relatively high, and promotes sleep to keep us asleep during the night and in the early morning, when sleep pressure is already low.[8] The SCN can promote the release of melatonin in the evening, the hormone that can induce some sleepiness. A healthy interplay between the two sleep- and wake regulatory systems results in consolidated periods of wakefulness and sleep.[8]

MODELS OF INSOMNIA

The exact cause(s) of insomnia are still unclear. However, several aetiological and pathophysiological models are available,[17-21] mostly based on the '3P' model of insomnia by Spielman *et al.* (1987).[22] The model proposes that the development of insomnia involves predisposing, precipitating and perpetuating factors. Being predisposed for insomnia, means that one is more likely than other people to develop insomnia under equal circumstances. A predisposition for developing insomnia may be found in our genes. Genome-wide association studies (GWAS) have identified multiple genes that play a role in the susceptibility of insomnia.[23,24] Another predisposing factor is a person's personality profile. It is known, for example that vulnerability to insomnia is associated with neuroticism.[25] Being predisposed for insomnia, does not necessarily mean a person will develop the disorder. Spielman proposes that external circumstances can facilitate the development of chronic sleep problems. These are precipitating factors, like emotional life events, a small child that keeps you awake, stress or shiftwork. These factors can cause a few nights of getting worse sleep. In other words, precipitating factors trigger acute insomnia.[17] Thereupon, it takes perpetuating factors for the insomnia to become a chronic disease. Perpetuating factors can be inadequate behaviors, coping strategies and beliefs that will facilitate insomnia.[22] For example, napping during the day or sleeping in on the weekends, to

catch up on sleep, both reduce homeostatic sleep pressure in the evening, making it harder to fall asleep at night. Less sleep at night, will result in more sleepiness during the day, making it more likely that a person will take nap, et cetera. Such a behavioral response to an acute period of insomnia, may perpetuate the problem into chronic insomnia. Another example is focusing too much on the amount of sleep and counting the hours during the night. This focus will make a person alert and frustrated, making it harder to fall asleep, which feeds the frustration. Some beliefs and attitudes towards sleep may also result in dysfunctional behavior and disturb the two-process control of sleep.[18] An example of a dysfunctional attitude towards sleep is the notion that one cannot function at all after only one night of bad sleep. These beliefs will place so much pressure on sleep, that it can perpetuate the insomnia, just as described above for the focus on the amount of sleep.[26]

These perpetuating factors, especially dysfunctional behaviors and beliefs, can depend on a person's personality traits. Personality traits may, therefore, be seen as both predisposing and perpetuating. The most commonly used model of personality is the five-factor model of the Big Five personality traits, which is based on a considerable body of evidence.[27] The five personality traits are extraversion, agreeableness, conscientiousness, neuroticism and openness. Of those, especially neuroticism has consistently been related to insomnia.[28] However, how neuroticism and insomnia influence each other remains unclear. It could be that highly neurotic people worry and ruminate more in the evening, making it harder to fall asleep (predisposing). Another theory is that people with highly neurotic personality profiles are more inclined to develop dysfunctional behaviors and coping strategies than others when they experience impaired sleep (perpetuating). While neuroticism is a personality trait that has consistently been associated with insomnia disorder, studies on other personality traits show inconsistent results. Several studies suggested insomnia disorder to be associated with low conscientiousness, for example, but showed that when all personality traits were simultaneously evaluated in a single regression model, this association appeared to be secondary to the inverse association of conscientiousness with neuroticism.[29,30]

In short, many factors are involved in the susceptibility to, initiation and continuation of inadequate sleep and eventually insomnia disorder. The factors that are most important in developing insomnia disorder, differ between individuals. A recent study by Blanken *et al.* (2019), showed that we can distinguish five subtypes of insomnia, each possibly different in development trajectories.[31]

PREVALENCE, CO-MORBIDITIES AND CONSEQUENCES

About a third of the Western population experiences at least some insomnia symptoms.[32] The Dutch Central Bureau for Statistics (CBS) recently reported that 1 in 4 Dutch people experienced symptoms of Insomnia Disorder in 2018, compared to 1 in 5 in 2017.[33] The prevalence of a full blown insomnia disorder in the general population, has shown to be between 6 and 19%,[7] making it the second most prevalent mental disorder, next to anxiety disorders and followed by depression.[32] It is significantly

more prevalent in women than in men and prevalence increases with age. Insomnia Disorder is also associated with many other disorders, both mental and physical. For example, insomnia is associated with cardio-vascular diseases[34,35], and type 2 diabetes.[36] Some neurological disorders are often co-morbid with insomnia,[37] like cortical atrophy[38] and dementia.[39] This relationship is thought to be bi-directional.[40] The relationship between insomnia disorder and (other) mental disorders is well studied and is shown to be significant,[41] especially for major depressive disorder.[1] Insomnia has been seen as a symptom of other mental disorders for years.[42] However, more recent studies show that insomnia disorder can precede major depressive disorder.[1] Many symptoms of insomnia, like hyperarousal, are also symptoms of major depressive disorder or posttraumatic stress disorder. The relationship between insomnia and other mental disorders, may not only be bi-directional, but even two expressions of a common underlying problem.[1] The treatment of insomnia disorder in patients comorbid insomnia disorder and major depressive disorder, has shown to relieve both disorders.[43]

The patient burden of insomnia is high. Insomnia severely impairs daytime functioning. Both the DSM-V and the International Classification of Sleep Disorders, 2nd edition (ICSD-2) describe several daytime symptoms of insomnia disorder. These include increased head aches and stomach aches, sleepiness, tiredness, irritability, worry, error proneness and decreased social functioning, mood, physical well-being.[2,3] These daytime consequences of insomnia, combined with increased risk on comorbidities, lead to reduction in work productivity and to increased sick leave and healthcare consumption. Additionally, insomnia patients are more likely to be involved in work-place and motor vehicle accidents.[5] Not only is Insomnia Disorder very debilitating for the patients, but it also has a large economic burden on society. Gustavsson et al (2011) found that direct and indirect costs of insomnia amount to 790 euro on average per individual per year in Europe.[44] About 75% is due to work absenteeism, the rest to health care consumption.[5,45] Insomnia's large impact on society underscores the importance of optimizing treatment.

TREATMENT AND OPTIMIZATION

According to several insomnia guidelines the current first-line treatment of choice is cognitive behavioral therapy for insomnia (CBTI).[7] There is a large body of evidence that supports its effectiveness.[46] CBTI combines, as its name suggests, both cognitive and behavioral components. Standard components are sleep hygiene, stimulus control, sleep restriction, relaxation exercises and cognitive restructuring. Sleep hygiene and stimulus control are a collection of behaviors and habits that are beneficial for good sleep, like spending an appropriate amount of time in bed for sleep, in a room that is well ventilated and is sufficiently dark, within an appropriate and constant timeframe. Establishing an early and constant rise time prohibits weekend lie-ins, which disrupt the circadian rhythm. Also, avoiding napping during the day, limiting caffeine intake and food intake well before bedtime, are considered good sleep hygiene. By only using the bed for sleep and sex (and not for working, watching television, reading et cetera), and sleeping only in bed (and not on the couch for

example), the association between bed and sleep is also enhanced. Sleep restriction is reducing the time spent in bed to be closer to a person's normal total sleep time. By doing so, for a few days, the time spent in bed lying awake and worrying about not sleeping is reduced. It also prevents going to bed too early, before melatonin release, which will confuse the circadian rhythm, making it more difficult to fall asleep. This again links the bed to sleep and not to wakefulness. When sleep efficiency, the percentage of time actually slept while in bed, is increased, the bedtime can be increased step by step, until not only sleep efficiency is better, but total sleep time is also higher. Relaxation exercises aim to reduce hyperarousal, a common symptom of insomnia. Lastly, cognitive restructuring is the process of identifying and disputing maladaptive and dysfunctional beliefs and thoughts about sleep, or the worry that bad or insufficient sleep will affect functioning the next day. Common dysfunctional beliefs are: "I must get eight hours of sleep" and "If I don't sleep now, I will not be able to function at all tomorrow". By being aware of these negative sleep thoughts, and learning that they are inaccurate and exaggerated, they can be restructured to more accurate and positive thoughts. CBTI and pharmacotherapy show comparable short-term effects. However, CBTI has better long-term effects and less side-effects,[46] making it a much better choice of treatment.

Originally, classic face-to-face CBT was developed for insomnia. However, a lack of trained therapists made wide-spread implementation difficult. More recently, several studies showed the beneficial effects of internet-delivered CBTI (ICBTI).[47] ICBTI uses the same components as face-to-face CBTI, but the information and exercises are not explained by a person, face-to-face, but can be read online. Many of the existing and tested ICBTI programs make use of video clips of therapists explaining parts of the treatment and of patients, telling about their experiences. Patients can read and watch the content of the treatment in their own home, at a self-chosen time. The treatment is cut up in sessions, each with a few days or a week apart. After each session the patient does homework, in the form of sleep restriction or other exercises. ICBTI can be completely self-help or guided by a therapist. In the guided version, a therapist is available through email or chat to answer questions or give extra tips or homework. ICBTI shows comparable effects as face-to-face therapy although there is a lack of studies directly comparing the two modalities.[47]

Another form of treatment that may be beneficial for insomnia patients is chronobiological treatment (CT). These forms of treatment focus on the alignment of the biological clock with the environment's day-night cycle. Examples are bright light therapy, physical activity and the manipulation of body temperature.[48] Notably, these are the zeitgebers of the circadian rhythm. Bright light treatment is the timed administration of bright light. Light, as described above, directly influences the SCN. Bright light treatment has shown to enhance sleep quality.[49,50] Just like the light dark cycle, the body shows a 24-h rhythm in body temperature. In a normal sleeper, with a sleep window between 23:00 and 7:00, the core body temperature peaks in the early evening, between 18:00 and 20:00 and has its minimum between 4:00 and 5:00.[14] By heating the body during the natural peak in the evening, for example by

taking a hot bath, the 24-h amplitude of the body temperature is increased. Moreover, the heating will elicit a steeper subsequent decrease in core body temperature. This decrease signals the brain that it is time to sleep. Several studies showed the effect of temperature manipulations on sleep in people with insomnia.[51,52] An additional 24-h rhythm is seen in the level of activity. Being diurnal animals, humans are active during the day and asleep at night. The amplitude of this rest-activity profile can differ greatly between individuals. By increasing physical activity during daytime, the amplitude can be increased. A few studies evaluated the effects of physical activity on sleep in insomnia patients.[53] Although CTs have shown beneficial effects on sleep in both healthy sleepers and in insomnia patients, the body of evidence is not conclusive. Further studies have been recommended to test their applicability for patients with Insomnia Disorder[7].

Although CBTI is currently the standard treatment for insomnia, not all patients benefit from it. Studies have shown that about 70% will benefit and 56% will actually remit from insomnia after (I)CBTI[54]. In other words, there is room for improvement. The possibility that the addition of CT to CBTI may increase treatment effects, has only been studied in one study,[55,56] with promising results. One of the disadvantages of ICBTI is that it involves a lot of reading and language skills. People who are not great readers, or cannot concentrate on written text, may benefit from the addition of more practical interventions like CT. Another benefit of adding CT to ICBTI, is that CTs are easy to incorporate in the daily routine and can be continued after the official treatment period, without any additional costs. An additional opportunity for improvement of treatment effect, is focusing on the predisposing factors of insomnia, for example personality traits, to better understand their influence on the disorder. A third opportunity to optimize treatment of insomnia is to redirect the focus to the daytime complaints. Currently the main goal of insomnia treatment is to optimize sleep, whereas the definition of Insomnia Disorder also includes impaired daytime functioning. Equivocal findings have been reported on the effect of ICBTI on daytime functioning in patients suffering from Insomnia Disorder, even including adverse effects.[57]

SCOPE

The present thesis focuses on evaluating the effects of ICBTI, three forms of CT and their combinations on both nocturnal and daytime complaints of insomnia patients. Nocturnal complaints of insomnia are the inability to fall asleep, maintain sleep or waking up unrested. A reliable and well-studied measure of nocturnal sleep complaints is sleep efficiency. Sleep efficiency is the percentage of time spent asleep of the total time spent in bed to sleep. Daytime complaints are defined in the ICSD and DSM and range from headache and stomachache, to sleepiness and tiredness, to the inability to concentrate and memory loss. In addition, this thesis addresses the relationship between personality traits and both nocturnal and daytime insomnia complaints. By improving the understanding on how individual differences may influence how Insomnia Disorder presents, this

thesis aims to identify opportunities to personalize the treatment of Insomnia Disorder and optimize its effectiveness.

OUTLINE

In order to assess the effects of ICBTI, CT and their combinations, a large part of this thesis is dedicated to a randomized clinical trial (RCT). **Chapter 2** describes the study protocol of this RCT. It discusses the rationale and treatment application, the procedure for recruiting and selecting participants and the trial execution, and the statistical methods used to analyze the data.

The main results of this trial are reported in **chapter 3**. In this chapter, we describe the initial and sustained effects of CT, ICBTI and their interaction on sleep efficiency in people suffering from insomnia disorder.

Chapter 4 is a methodological chapter that evaluates if the profile similarity framework can be used as a means improve the within-subject comparability of different assessment formats. The profile similarity framework is a theoretical framework that compares profiles of personality factors, rather than individual components. In order to evaluate the profile similarity framework, we use two versions of the same personality questionnaire, namely the mini-IPIP and the IPIP-NEO-120 that measure the Big Five personality traits. Additionally, this study evaluates the psychometric properties of the Dutch translations of the mini-IPIP and the IPIP-NEO-120.

Chapter 5 investigates how the different complaints of insomnia relate to personality traits. In this chapter, we use network analyses in a large sample, to show direct and indirect associations between the Big Five personality traits and both daytime and nocturnal insomnia complaints.

In **chapter 6** all results will be discussed and put into perspective. Additionally, we explain why not all intended analyses as described in the study protocol of chapter 2 were presented in chapter 3. The additional results are described in the supplement of a paper that was outside the scope of this thesis.[31] Chapter 6 summarizes these results and combines them with all other results, in order to identify limitations of current treatment protocols of Insomnia Disorder and subsequently make recommendations on what future research can do to improve treatment outcome.

CHAPTER 2: EFFECTIVENESS OF INTERNET-SUPPORTED COGNITIVE BEHAVIORAL AND CHRONOBIOLOGICAL INTERVENTIONS AND EFFECT MODERATION BY INSOMNIA SUBTYPE: STUDY PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL

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Trial 2015; 16:292

ABSTRACT

Background: DSM-V criteria of insomnia disorder are met by 6 to 10% of the adult population. Insomnia has severe consequences for health and society. One of the most common treatments provided by primary care givers is pharmacological treatment, which is far from optimal and has not been recommended since a 2005 consensus report of the National Institutes of Health. Treatment of recommendation is Cognitive Behavioral Therapy for Insomnia. Effectiveness, however, is still limited. Only a few studies evaluated effectiveness of chronobiological treatments, including timed application of bright light, physical activity and body warming. Another opportunity for optimization of treatment is based on the idea that the people suffering from insomnia most likely represent a heterogeneous mix of subtypes, with different underlying causes and expected treatment responses. The present study aims to evaluate the possibility to optimize insomnia treatment along the principles of personalized and stratified medicine. It evaluates:

(1) the relative effectiveness of internet-supported cognitive behavioral therapy, bright light, physical activity and body warming;

(2) whether the effectiveness of internet-supported cognitive behavioral therapy for insomnia can be augmented by simultaneous or prior application of bright light, physical activity and body warming;

(3) whether the effectiveness of the interventions and their combination is moderated by insomnia subtype.

Methods/Design: In a repeated measures placebo-controlled randomized clinical trial that included 160 people diagnosed with insomnia disorder, we are evaluating the relative effectiveness of 4 intervention weeks. Primary outcome is subjective sleep efficiency, quantified using a sleep diary. Secondary outcomes include other complaints on sleep and daytime functioning, health-related cost-estimates and actigraphic objective sleep estimates. Compliance will be monitored both subjectively and objectively using activity, light and temperature sensors. Insomnia subtypes will be assessed using questionnaires. Mixed effect models will be used to evaluate intervention effects and moderation by insomnia subtype ratings.

Discussion: The current study addresses multiple opportunities to optimize and personalize treatment of insomnia disorder.

Trial registration: Netherlands National Trial Register NTR4010.

Keywords: insomnia, chronobiological treatment, cognitive behavioral therapy, internet, actigraphy, personalized medicine, stratified medicine

BACKGROUND

Dissatisfaction with sleep is reported by about 25% of the adult Western population.[58] The prevalence is even higher in elderly people and twice as high in women as in men.[59,60] When complaints about difficulties falling asleep, maintaining sleep, early morning awakenings or non-restorative sleep are accompanied by physical or cognitive daytime complaints, and last for at least three months, occurring at least three times a week, without being secondary to environmental factors or co-morbidities that prohibit sleep, a person suffers from insomnia disorder, according to the DSM-V.[6] These criteria are met by 6 to 10% of adults.[59] Daytime complaints of people with insomnia concern cognitive functioning,[3] depressed mood[2] and fatigue.[2] Additionally, people reporting insomnia or low sleep quality have higher risks of depression,[1] metabolic diseases and cardiovascular problems.[4] These daytime consequences and co-morbidities lead to a reduction in work productivity, to increased sick leave and health care consumption and consequently to high economic costs. In summary, insomnia has severe consequences for health and society,[5] underscoring the importance of optimizing interventions to promote better sleep. To do so, the regulation of sleep needs to be considered.

CIRCADIAN RHYTHM AND SLEEP

Virtually all behavioral and physiological processes show a 24-h rhythm even in the absence of environmental time cues. This circadian (circa = about and dies = day) rhythm is for example present in sleep and wakefulness, hormone secretion, alertness, body temperature, metabolism, perception and cognition. Endogenous clock mechanisms that promote the expression of 24-h rhythms are located in all human cells,[10] and are synchronized by the central clock of the brain, the hypothalamic suprachiasmatic nuclei (SCN). The SCN is considered the major clock because only SCN tissue is able to maintain a circadian rhythm in absence of external input.[10] Under normal circumstances, several exogenous cues, or Zeitgebers, entrain the SCN. Light is the strongest Zeitgeber.[14] The retinohypothalamic tract (RHT) is one of the three major input pathways of the SCN, providing it with information from photoreceptor cells in the retina. Secondary Zeitgebers are for example temperature of the environment, body core and skin; metabolism; and the rest-activity cycle. When the circadian rhythms of the body are synchronized with the Zeitgebers, the rhythm is optimally entrained. A type of insomnia that is characterized mostly by complaints about initiating sleep may be due to a misalignment of the circadian rhythm in sleep-promoting physiology and the sleep window the patient tries to adhere to, typically between 23:00 and 7:00.[16,61]

HOMEOSTASIS OF SLEEP

In addition to the circadian regulation of sleep and wake, a homeostatic component affects sleep propensity. Whereas the circadian process is relatively independent of prior sleep or wake, the homeostatic process on the other hand is sensitive to sleep-wake history.[8] The sleep homeostatic process increases sleep propensity during wakefulness until sleep is initiated. Sleep propensity

declines during sleep. The biological mechanisms underlying sleep homeostasis are less well characterized than the mechanisms underlying circadian regulation, but likely involve astrocyte-dependent adenosine accumulation.[9,62]

Some types of insomnia may involve altered homeostatic regulation of sleep propensity.[63]

SLEEP-PERMISSIVE AND WAKE-PROMOTING CONDITIONS

Although the regulation of sleep and wakefulness is well-modeled by interacting circadian and homeostatic processes in lab studies, additional sleep-permissive and wake-promoting conditions have been largely overlooked.[64] Most people sleep best lying in bed, with lights off and the curtains drawn, in a thermally agreeable, safe and relatively quiet environment. These parameters (posture, temperature, environmental light and sound, fear) moderate the expression of sleep and wake. Whether altered sensitivity to sleep-permissive and wake-promoting conditions might be involved in the sleep complaints of some types of insomnia remains virtually unexplored.[51,52,65]

TREATMENT OF INSOMNIA

Even though the underlying causes of insomnia are at present insufficiently understood, one of the most common treatments provided by primary care givers (mainly general practitioners) is sedative or hypnotic drugs mostly benzodiazepines or benzodiazepine receptor antagonists.[58] Unfortunately, pharmacological treatments have a high prevalence of adverse effects. Daytime drowsiness, risk of abuse and addiction, rebound insomnia on withdrawal are a few examples of these side effects.[66] Pharmacological treatment is therefore not recommended.[67]

In the past decades, two other interventions have been developed. The first intervention is cognitive behavioral therapy for insomnia (CBTI). It has similar or even better and more prolonged outcomes than pharmacological treatment, and lacks the negative side effects.[68] A second, less evolved, but promising type of intervention is chronobiological treatment (CT). Chronobiological treatments aim to enhance regular and appropriately timed input to the circadian timing system to support its role in sleep regulation, by use of bright light, body warming or physical activity (for example[50,52,69]; for a review see[48]). These manipulations may become more important with increasing age, to counteract age-related changes in the functional neuroanatomy of the biological clock of the brain.[70]

COGNITIVE BEHAVIORAL THERAPY

Cognitive behavioral therapy for insomnia (CBTI) is a combination of cognitive and behavioral treatments. CBTI usually includes stimulus control (that is, association of bed with sleeping), sleep restriction (that is, restrict an individual's time in bed to average sleep time), relaxation training, cognitive therapy (that is, diminish misconceptions about sleep) and sleep hygiene (for example, general guidelines about behavioral and environmental factors that influence sleep).[71] CBTI has been

shown to be effective in numerous randomized clinical trials.[55,68,71-75] A problem facing implementation on a large scale is the lack of skilled therapists.

CHRONOBIOLOGICAL TREATMENT

Three chronobiological manipulations have been applied successfully and will be discussed below.

Bright Light (BL)

Bright light, including natural daylight, entrains the circadian rhythm [76]. Retinal ganglion cells projecting to the SCN through the retinohypothalamic tract (RHT) inform the circadian timing system about the intensity of light exposure. The SCN uses this information to entrain its intrinsic rhythmic activity to the 24-h light-dark cycle.[10] Studies in humans show that phase shifts can be imposed by manipulation of the light-dark cycle.[76,77] A phase advance can be induced by means of bright light given in the morning, especially closely after the body core temperature minimum; a phase delay can be induced with light applied in the interval from late afternoon to just prior to the body core temperature maximum.[76,78,79] The effect of light on sleep may not be limited to changing the sleep phase, as suggested by studies that found enhanced sleep quality in the absence of clear rhythm shifts.[49,50]

Body and skin warming (BW)

Core body temperature shows a clear 24-h rhythm. In normal sleepers with a sleep period between 23:00 and 7:00, the temperature peaks between 18:00 and 20:00 h and has its minimum between 4:00 and 5:00 h.[14] Apparently, the connection between sleep or vigilance and core body temperature is strong. We sleep when core body temperature is low and are awake when it is high.[64] In contrast, skin temperature is increased during the sleep period, as a result of increased skin blood flow in response to a supine posture.[80] Increased skin blood flow promotes heat loss, resulting in a lower core body temperature. *Romeijn et al*.[64] reviewed the effect of manipulation of skin temperature on vigilance and explain in more detail the underlying processes. Several studies that applied water-perfused thermo suits to increase skin temperature slightly within the thermo neutral zone showed that this manipulation enhances sleep propensity.[64] This effect has not only been demonstrated in healthy adults, but also in people with insomnia.[51,52] A more practical and home-applicable version of this temperature manipulation is to make use of the body's thermoregulatory mechanisms and warm the body prior to sleep by mild physical activity or taking a hot bath.[81] About two hours later, core body temperature has returned to baseline, while skin temperature is still somewhat elevated. This pre-sleep body warming approach has been used with success in insomnia.[82]

Physical Activity (PA)

As diurnal mammals, humans are active during the day and sleep at night. The rest-activity profile of people with a very inactive lifestyle, for example sedentary elderly, shows a small 24-h amplitude. Several studies evaluated the effect of enhancing physical activity or exercising on this amplitude and on sleep.[53,69,83-90] Two possible mechanisms have been proposed to be involved in the effect of

enhanced physical activity on sleep. The thermoregulatory hypothesis proposes that exercise exerts an effect on sleep through initially increasing core body temperature. This subsequently triggers heat loss to decrease the temperature, which is conductive to sleep. The body restoration hypothesis proposes that exercise depletes energy levels and promotes sleep because it increases the need to activate restorative mechanisms. In 2000, Driver & Taylor reviewed the studies done up until that year.[86] Unfortunately, most studies use good sleepers. Their conclusion was that exercise of moderate intensity and focusing on endurance rather than peak intensity, was most beneficial for perceived sleep quality. Tanaka *et al.* [90] showed that exercise is most effective around 17:00 h, supporting the thermoregulatory hypothesis. Benloucif *et al*. [83] however found equal effects of morning and evening exercise on subjective sleep quality. More recently, Passos *et al.*[53] summarized studies using exercise in primary insomnia. This review demonstrated improvement in sleep quality. Additionally, they discuss possible explanations for acute and chronic effects of physical activity on primary insomnia.[53]

OPTIMIZING TREATMENT AND ACCESSIBILITY

Whereas the combination of CT and CBTI may be more effective than their use in isolation, and has successfully been applied in only one study,[55,56] no prior study addressed the relative contribution of the different interventions. More research is therefore needed to compare effectiveness of different combinations of therapies; one of the aims of the present study.

A problem facing implementation of CBTI is the shortage of skilled therapists. Internet-based CBTI may alleviate this problem.[91] Internet-based therapy is highly self-guided, structured and personalized. Knowledge-based technology renders a personalized concept consult, which can be adjusted by a therapist for situations that cannot be pre-programmed. This saves a lot of time for a therapist and subsequently may help to solve the discrepancy between care needed and care available,[74,75] thus allowing for large-scale implementation.

Another opportunity for optimization of treatment is based on the idea that the people suffering from insomnia most likely represent a heterogeneous mix of subtypes, with different underlying causes and expected treatment response. These subtypes may not only be distinguished by type of sleep problems. Other factors such as personality traits, medical complaints and medical history, the ability to perceive comfort[51,92-94] may represent variables that differ between the proposed subtypes as well. Our research group commenced a large-scale study using web-based assessment of questionnaires to collect data on these variables (the Netherlands Sleep Registry, NSR, www.sleepregistry.org). The use of latent class analysis on these data will allow for the data-driven detection of multivariate subtypes, calculation of subtype probability for participants according to this data-driven subtype nosology, and evaluation of differential treatment responses, depending on the subtype probability. The present study aims to evaluate the possibility to optimize insomnia treatment along the principles of personalized and stratified medicine, by making the first step towards the development of a

protocol for individualized optimal treatment for specific subtypes of insomnia, which each may show different responsiveness to CBTI and the different CT manipulations.

OBJECTIVES

The objective of this study are as follows:

1. To evaluate the relative effectiveness of internet-based CBTI, three different types of CT (light, temperature and physical activity) and the combined application of CBTI and each of the CT's, as compared to placebo treatment, on [1] subjective sleep efficiency (primary outcome) [2] subjective day-time functioning [3] actigraphic sleep estimates and [4] cost effectiveness.
2. To evaluate whether insomnia subtype moderates the effectiveness of the individual and combined treatments.
3. To evaluate whether the effect of CBTI is enhanced by prior CT.

METHODS/DESIGN

TRIAL DESIGN

The study is a double blind, randomized, placebo-controlled trial. Aiming at 160 completers with a drop-out rate of 10%, 180 participants will be recruited, who will be randomly assigned to one of eight limbs in a repeated measures design with two factors (CBTI and CT), of respectively 2 levels (active CBTI treatment versus waitlist monitoring) and 4 levels (light, physical activity, body warming and placebo) (see Fig. 1). Covariate-adaptive randomization aims at an equal representation of insomnia subtypes within each treatment limb. Assessment will be performed at baseline (week 0), after a 4-week treatment period (week 5), and after a second 4-week treatment/monitoring period (week 10).

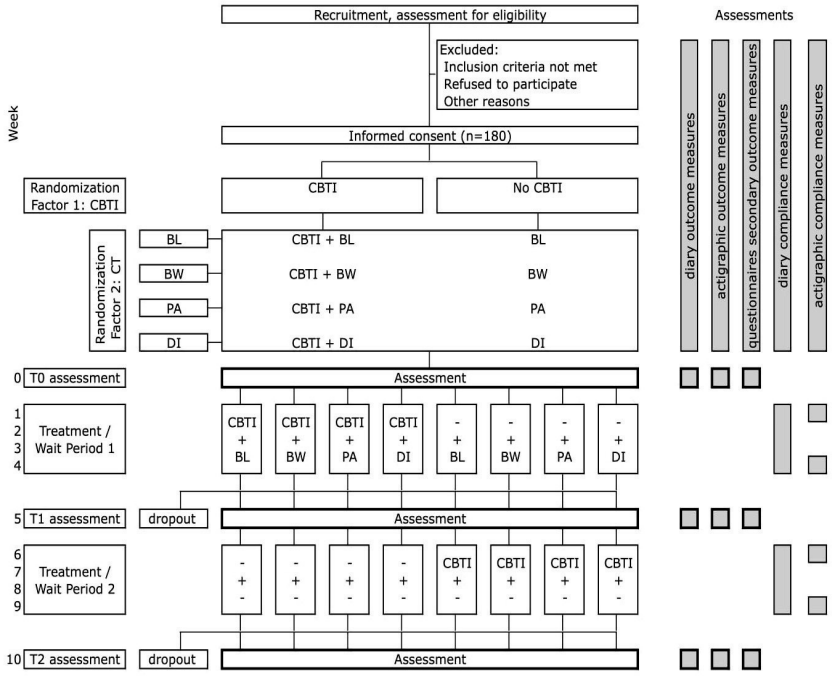

Fig. 1 Flow chart of trial design and outcome assessments. In the recruitment phase, participants fill out a questionnaire to assess their eligibility to participate. This questionnaire includes the Duke Structured Interview for Sleep Disorder Diagnosis (30 min). During week 0, 5 and 10, participants fill out questionnaires and sleep diaries and wear an actigraph for subjective and objective sleep estimates respectively. The diary is continued in all other weeks to support cognitive behavioral therapy. During week 1, 4, 6 and 9, participants will wear actigraphs for objective measures of compliance to chronobiological treatment.

PARTICIPANTS

Inclusion and exclusion criteria

Participants will be included that meet the criteria of an insomnia disorder as defined in the DSM-V. Furthermore, participants have to be between 18 and 70 years old. Because meta-analysis[95] indicate insomnia to be more prevalent in females (odds ratio (OR) = 1.41) we aim for inclusion of 60% females and 40% males.

This study follows the Helsinki Declaration's principles, meaning that all patients sign a written informed consent stating that participation is voluntary and that participation can be withdrawn at any

time, without any negative consequences concerning their current or future treatment. Approval has been obtained on 21 May 2013 from the medical ethical committee of the VU University medical center in The Netherlands (Protocol 12/472). The trial is registered at the Netherlands National Trial Register (NTR4010)[96].

Participants are recruited through the Netherlands Sleep Registry and (social) media. Interested candidates fill out a screening questionnaire regarding health status and insomnia diagnostic criteria (relevant items of Duke Structured Interview for Sleep Disorders, DSISD),[97] level of physical activity,[98] light exposure (by asking about habitual hours spent outside during daylight hours) and bathing habits (frequency and duration of bathing/showering). Participants will be excluded for the following reasons:

1. their estimated baseline level and timing of activity, bright light or body warming are already similar to the CT interventions planned;
2. they report an eye disease incompatible with light treatment (aphakia or retinopathy), or cardiovascular or movement disorder incompatible with the exercise treatment;
3. they report to be currently diagnosed with a psychiatric or neurological disorder;
4. they are shift workers, since the treatment protocol doesn't allow for alternative schedules and their sleeping problems may not be due solely to insomnia;
5. they use sleep medication regularly, unless they are willing and able to restrict their usage to a maximum use of twice a week, at least 1 month prior to enrollment.

RANDOMIZATION

Participants that meet the criteria and sign informed consent will be randomly assigned to CBTI or to the waitlist and to one of the four CT conditions (including one placebo). Simple randomization will be applied to the first batch of 48 participants. During the staggered entry of subsequent participants covariate-adaptive randomization[99] will be applied in order to maintain balanced groups throughout the study. The covariates are age, sex, use of non-sleep related medication and time of year. Since some covariates are continuous rather than categorical, randomization will be done following the method proposed by Frane [100]. This method temporarily assigns each new participant one by one to each treatment group and obtains a *P* value of the test for between-group differences for each of the covariates for that assignment, using analysis of variance (ANOVA) for continuous variables and a X^2 test for categorical variables. This renders a *P* value for each of the four covariates for each of the eight possible assignments. The lowest of four *P* values thus represents the least balanced covariate in that assignment situation. These lowest, or minimum, *P* value per assignment will then be used to make the actual assignment to one of the treatment conditions, where a participants will be assigned to the group for which this minimum *P* value is highest, thus resulting in a group assignment that keeps imbalance over groups as small as possible. If group sizes become unbalanced (that is, differing

by more than five participants), the Frane method will be applied only to the six smallest groups instead of all eight. All randomization will be done using R.[101] Randomization will be scripted, so actual group assignment is automated.

BLINDING AND EXPECTATION ASSESSMENT

A patient information letter explains the four CT manipulations (including placebo CT) and CBTI. All treatments in the study are presented to the participants as possibly effective. It is not possible to blind participants to the different treatment conditions. Since all information is given via email or through postal service, there will not be a blinding of instructors. However, CBTI counselors are instructed not to correspond about expected outcome of CT treatments and participants will be asked not to mention their CT condition in possible correspondence with the CBTI counselor. When participants however, do reveal their condition, the CBTI counselor will be replaced. In order to secure blinded data analysis, information regarding treatment conditions will be coded. Only once data processing is finished and the dataset is finalized, the code will be broken. The analyst (KD) will not have access to the key document. Because all outcome assessments are either self-reported through internet or obtained from recording devices, blinding of assessors is not applicable.

Judgments of the participant on expected effectiveness will be assessed at T0, T1 and T2 using a 7-point Likert-scale for each of the treatments. After randomization, at T0, participants will be asked about the expectation regarding their assigned CT and CBTI. After treatment, at T1 and T2, participants will be asked to what extent their sleep problems have changed compared to baseline and to what extent they attribute this change to the treatment.

STUDY SETTINGS

All measurements and therapies are conducted at participants' homes, using the Internet.[7,102] Treatment devices are sent to their homes. Participants are informed on the types of treatment used in the study and the objective of comparing them.

INTERVENTIONS

Cognitive behavioral therapy for insomnia

All participants will receive internet-based, personalized cognitive behavioral treatment for insomnia provided through the Somnio website for four weeks. The Somnio Internet therapy uses knowledge-based technology to prepare a consult and support the therapist to apply the protocol in a consistent and comprehensive way.[103] The personally assigned CBTI therapist can adjust each consult if needed. CBTI will consist of four consults, one every Monday morning. Every morning and evening, participants fill out the Dutch online version of the Consensus Sleep Diary.[104] The first consult will be

based on the sleep diary data of the previous week, in combination with the person's beliefs and attitude towards sleep, as assessed during week 0 by the Dysfunctional Beliefs and Attitudes towards Sleep (DBAS) questionnaire.[26] Sleep diary data of the consecutive weeks will be used to determine which cognitive and behavioral components are emphasized during the treatment.[103] A more detailed description of CBTI has been given above.

CHRONOBIOLOGICAL TREATMENT (CT)

Physical Activity

At enrollment participants are asked to fill out questionnaires to assess their health status as well as the habitual level and timing of activity.[98] The answers on an extended Baecke questionnaire will provide the necessary information to determine the specific personalized implementation if they are randomized to the physical activity condition. More specifically, in the active treatment limb, the most intense physical activity that participants report to habitually maintain for at least half an hour (for example, walking, running, cycling) will be (re)scheduled to be performed daily for half an hour preferably starting three hours before ideal bedtime, and never ending closer than two hours prior to ideal bedtime. The physical activity (PA) will thus at no point exceed the participants usual duration and intensity but will be daily and set to a specific time of the day.

Body Warming

For body warming (BW), participants randomized to the temperature condition are instructed to take a warm bath daily for half an hour, starting three hours before ideal bedtime, and never ending closer than two hours prior to ideal bedtime. The physical activity and temperature manipulation procedures will result in elevated skin temperature at bedtime, which can enhance sleep onset.[64] If the manipulations would be done closer to bedtime, core body temperature would not have returned to baseline at bedtime and possibly interfere with sleep.[65,64]

Bright Light

Participants randomized to the bright light (BL) condition will receive a Philips goLITE BLU light device (HF3220/01, Philips Consumer Lifestyle, Drachten, The Netherlands). They will be instructed to install the light on a table facing a window to minimize glare by reducing contrast between relatively small bright light source and the background. The light will be set on the side, within the range of vision, but not straight across the participant. This will reduce strain on the eyes. They will be asked to sit facing the light in close proximity for half an hour at a fixed time each morning within an hour after habitual wake-up time, for example during breakfast.

Deactivated Ionizer

Many randomized controlled trials testing the effect of morning bright light on seasonal affective disorders (SAD), compare bright light with negative air ionization.[105-108] These studies show that morning High Density Negative Ionization (HDNI) is as effective as morning bright light treatment. Negative air ionization has been shown to positively affect cognitive performance and depression.[109]

The application has not been evaluated for its possible effect on insomnia. In one study on SAD, a deactivated ionizer (DI) was used as placebo condition.[110] The ionizer was modified to suggest normal functioning, as indicated by airflow, while negative ion production had been deactivated. Treatment outcome expectancy for the (deactivated) negative ionizer was equal to that of BL. In the present study, participants randomized to the placebo treatment will therefore receive a likewise deactivated ionizer (DI) device (Ionic Air Purifier, XJ-2100, Shanghai Neo.Tec Electron Co., Ltd, Shanghai, China). Participants will be instructed to install the device on a table where they can sit in close proximity to it for half an hour each morning at their earliest convenience after ideal wake-up time, for example during breakfast. This placebo has been applied successfully in several studies in the USA,[105,110] but not yet in the Netherlands, making it unlikely to be recognized as a placebo.

Assessments and Outcomes

To assess subjective sleep parameters as well as daytime complaints, participants will be keeping a diary both in the morning and evening for the entire 11-week protocol. Sleep is assessed in the morning using the Dutch version of the Consensus Sleep Diary.[104] Primary outcome, sleep efficiency (the percentage of time slept during the time in bed for sleep), is calculated from the sleep diary variables as follows:

$$SE = \frac{(LightsOn - LightsOff) - SOL - WASO - EMA}{LightsOn - LightsOff}$$

Where *SE* is sleep efficiency; *LightsOn* is the moment people indicated they stop trying to sleep, calculated from their final wake up time and time they stayed in bed to try to fall asleep again; *LightsOff* is the time people turn off the lights and/or disengage from activities to go to sleep; *SOL* is sleep onset latency; *WASO* is time awake after sleep onset; *EMA* is early morning awakening, or time people spend trying to fall back asleep after final awakening.

Daytime functioning is assessed in the evening using a dedicated questionnaire on all complaints listed in the DSM-V and the International Classification of Sleep Disorders, 2nd edition (ICSD-2). During week 0, participants will fill out the complete Duke Structured Interview for Sleep Disorders in order to have a complete overview of sleep complaints and other medical and psychological complaints they currently have or have had in the past.

During week 0, 5 and 10, participants will fill out a comprehensive set of questionnaires:

1. Expectations or subjective outcome of the selected treatments;
2. Health related costs during the last 4 weeks (Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness: TiC-P);[111]
3. Functional health (Quality of Life Questionnaire, Short Form 36, SF-36);[112]

4. Depression and anxiety (Hospital Anxiety and Depression Scale, HADS);[113]
5. Mood (Positive Affect, Negative Affect Scale, PANAS);[114]
6. Experience of pleasure and comfort (Temporal Experience of Pleasure Scale, TEPS);[115]
7. Thoughts during resting state (Amsterdam Resting State Questionnaire, ARSQ);[93]
8. Hyper arousal. Because this is considered a key feature of insomnia, it is queried using four different scales; the Arousal Predisposition Scale (APS);[116] the Hyper Arousal Scale (HAS);[117] the adult ADHD Self-Report Scale (ASRS);[118] and the Pre-Sleep Arousal Scale (PSAS);[119]
9. Insomnia severity (Insomnia Severity Index, ISI);[120]
10. Beliefs and attitudes regarding sleep (DBAS);[26]
11. Sleep effort (Glasgow Sleep Effort Scale, GSES);[121]
12. Sleep self-efficacy (Sleep Self-Efficacy Scale, SSES);[122]
13. Sleep locus of control (SLOC).[123]

As shown in Fig. 1, ambulatory recordings will be performed during the baseline week and first week of treatment (week 0 and 1), the last week of the CT treatment period and the first week following completion (week 4 and 5) and during weeks 9 and 10. During these weeks, participants continuously wear a wrist actigraph to estimate sleep and light exposure (Philips Actiwatch Spectrum, Philips Respironics, Murrysville, PA, USA), and an accelerometer worn on the trunk to estimate energy expenditure (Philips DirectLife, DL8700/01, Philips, Eindhoven, The Netherlands).

Compliance

CBTI

Compliance with some aspects of CBTI, for example sleep restriction and stimulus control, can be monitored using the sleep diary combined with actigraphic sleep estimates.

CT

Compliance with the chronobiological treatments will be monitored by means of questions added to the sleep diaries. Moreover, objective measures of compliance for BL and PA can be derived from ambulatory monitoring of physical activity and light exposure by the Actiwatch Spectrum and DirectLife devices. Participants randomized to BL are instructed to expose the Actiwatch Spectrum to the light when sitting in front of the goLite BLU. Participants assigned to BW receive a digital bath thermometer (type: Lotus, Béaba, Oyonnax Cedex, France) and are asked to register temperature of the bathing water to monitor compliance with the body warming treatment.

Outcome Measures

The primary outcome measure is the change from week 0 to week 5 in subjective sleep efficiency derived from the sleep diary. Secondary subjective sleep estimates include difficulties falling asleep, difficulties maintaining sleep, early morning awakening and non-restorative sleep. A secondary

outcome regarding daytime consequences is the average rating of evening diary ratings on eighteen major daytime functioning complaints. Ancillary analyses on persistence of treatment use the same variables obtained in week 10.

Actigraphically estimated objective sleep parameters (sleep efficiency, sleep onset latency, sleep duration, wake after sleep onset, and the average durations of uninterrupted periods of sleep and wakefulness) are secondary outcome measures meant to complement the subjective evaluations. These are calculated from the ActiWatch Spectrum recordings using the Respironics Actiware software (version 5.71.0, Philips Respironics, Murrysville, PA, USA). Given the variability in subjective [124] and objective [48] sleep estimates, they will be assessed for 7 subsequent days at each assessment. Additional questionnaires, assessed in week 0, 5 and 10, will provide secondary outcome measures (see the list above). Specifically, the direct en indirect medical costs (TiC-P) will be included.

Effect moderation by subtype score

Preliminary results of Latent Class Analysis on comprehensive psychometric data of a large sample of participants of the Netherlands Sleep Registry suggests the existence of four different subtypes of insomnia, each with about equal prevalence. From the extensive number of questionnaires on traits these volunteers filled out, we are presently selecting the minimal subset of questions required to still obtain good estimates of the a posteriori probabilities of a participant to belong to each one of the four classes. These items will be included in a Sleep Subtype Survey that will be assessed in all participants of the present RCT. The resulting four Insomnia Subtype Probabilities (ISP) will be included in analyses aimed at evaluating treatment effect moderation by each of the four insomnia subtype probabilities.

Statistical analysis

Data reduction and reporting

The data of qualitative variables (for example, gender, type of treatment, insomnia subtype) will be presented as incidence rates (number and percent). The data of continuous variables (for example, age, measures derived from sleep diaries, questionnaires and actigraphy) will be presented by measures of central tendency (that is, mean, median) and dispersion (that is, standard deviation, range).

Treatment effects and moderation estimates

Mixed effect models will be applied to estimate all time by treatment effects, time by treatment interaction effects and effect moderation by the individual's insomnia subtype probabilities. For each outcome measure, all effects will be estimated simultaneously in one single linear regression equation. The primary outcome measure of sleep efficiency will be illustrated below. The diary and actigraphy based outcome measures have a two-level hierarchical data-structure: repeated measures of

14 diary inputs *i* across T0 and T1 are nested within subjects *j*. The 14*160=2,240 data points can be used to simultaneously estimate all effects ß using the following mixed effect model:

$$SE_{ij} = ß_{0ij} + ß_1*Time_{ij} + ß_2*CBT\text{-}I_j + ß_3*BL_j + ß_4*PA_j + ß_5*BW_j + ß_6*ISP_j + ß_7*Time_{ij}*ISP_j +$$
$$\mathbf{ß_8*CBT\text{-}I_j*Time_{ij}} + ß_9*CBT\text{-}I*ISP_j + \mathbf{ß_{10}*CBT\text{-}I_j*Time_{ij}*ISP_j} +$$
$$\mathbf{ß_{11}*BL_j*Time_{ij}} + ß_{12}*BL*ISP_j + \mathbf{ß_{13}*BL_j*Time_{ij}*ISP_j} +$$
$$\mathbf{ß_{14}*PA_j*Time_{ij}} + ß_{15}*PA*ISP_j + \mathbf{ß_{16}*PA_j*Time_{ij}*ISP_j} +$$
$$\mathbf{ß_{17}*BW_j*Time_{ij}} + ß_{18}*BW*ISP_j + \mathbf{ß_{19}*BW_j*Time_{ij}*ISP_j} +$$
$$ß_{20}*CBT\text{-}I_j*BL_j + \mathbf{ß_{21}*CBT\text{-}I_j*BL_j*Time_{ij}} + ß_{22}*CBT\text{-}I_j*BL_j*ISP_j + \mathbf{ß_{23}*CBT\text{-}I_j*BL_j*Time_{ij}*ISP_j} +$$
$$ß_{24}*CBT\text{-}I_j*PA_j + \mathbf{ß_{25}*CBT\text{-}I_j*PA_j*Time_{ij}} + ß_{26}*CBT\text{-}I_j*PA_j*ISP_j + \mathbf{ß_{27}*CBT\text{-}I_j*PA_j*Time_{ij}*ISP_j} +$$
$$ß_{28}*CBT\text{-}I_j*BW_j + \mathbf{ß_{29}*CBT\text{-}I_j*BW_j*Time_{ij}} + ß_{30}*CBT\text{-}I_j*BW_j*ISP_j + \mathbf{ß_{31}*CBT\text{-}I_j*BW_j*Time_{ij}*ISP_j}$$

In this regression equation, SE = sleep efficiency; $ß_{0ij}$=intercept; time denotes the post intervention (T1) versus baseline (T0) assessment week; CBT = Cognitive Behavior Therapy assignment; BL = bright light assignment; PA = physical activity assignment; BW = body warming assignment; ISP = insomnia subtype probability; and $ß_1$ to $ß_{31}$ denote effect estimates. The effects and terms of interest are shown in bold font. For example, line 2 shows in bold font the overall treatment by time interaction effect $\mathbf{ß_8}$ of CBTI versus waitlist and the moderation of this effect $\mathbf{ß_{10}}$ by one's Insomnia Subtype Probability. Lines 3 to 5 show the corresponding effect estimates for BL, PA and BW interventions, and lines 6 to 8 the for their interaction with CBTI. For clarity, the regression equation shows only one of the four expected ISPs. Wald tests will be used to evaluate the significance of the effect estimates. Statistical significance is thresholded at p = 0.05. The simultaneous estimation of all effects of interest in a single regression model compensates for multiple comparisons. Mixed effect model analyses will be implemented in MLwiN (version 2.02, Centre for Multilevel Modelling, University of Bristol, Bristo, UK.) and R (R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria.).

POWER AND SAMPLE SIZE

Statistical Power Estimates

The statistical power for mixed effect regression models with seven repeated measures (diaries) both before and after intervention have been calculated according to the equations given by Twisk, page 280[125], similar to those calculations made in a previous repeated measures RCT we published[50]. Statistical power calculations on repeated measures require an estimate of the intraclass correlation coefficient (ICC, that is, within-subject). We estimated the ICC for the primary outcome measure of subjective sleep efficiency from 9-day sleep diaries[104] that we recently assessed through internet in 27 people suffering from insomnia according to an Insomnia Severity Index ≥ 10[126]. In agreement with the robust observation that night-by-night sleep variability is an intrinsic part of the insomnia

symptomatology (reviewed in [124]) we found only a moderate ICC of 0.27, supporting the use of repeated assessment of the primary outcome measure to increase statistical power of the design.

Given this moderate ICC of 0.27, seven pre-assessments at T0, and seven post-assessments at T1, the 160 completing participants provide a power 1-beta of 0.80 to allow for the detection, at a significance of alpha=0.05, of even small to medium main effects of CBTI (minimal detectable difference d=0.27 standard deviations), of each of the three CTs (d=0.31) and of their interaction with CBTI (d=0.41). The minimally detectable difference in the time by treatment interaction between any two types of CT is small to medium as well (d=0.38).

There is unfortunately no readily available methodology to estimate the minimally detectable moderation effects of continuous variables (insomnia subtype probabilities) on a time by treatment interaction effect on a continuous outcome variable (sleep efficiency). In order to obtain a conservative estimate of minimally detectable moderation effects, we can dichotomize the continuous insomnia subtype probability variable by means of a median split, effectively generating two equal groups. The design then becomes one of three factors, each with two levels: time (T1 versus T0), treatment group (Treated versus Untreated on the specific intervention) and insomnia subtype (high versus low probability) and provides the ratio of available data in the subgroup of interest relative to the other available data, to be used once more in the equations given by Twisk, page 280[125]. According to this conservative approach of mapping the continuous insomnia subtype probabilities onto a dichotomous variable, 160 completing participants provide a power 1-beta of 0.80 to allow for the detection, at a significance of alpha = 0.05: of a small to medium moderation effects of insomnia subtype (1) on the time by CBTI treatment interaction (d = 0.31); (2) on the time by each CT treatment interaction (d = 0.41); and (3) on the difference in the time by treatment interaction between any two types of CT (d = 0.44). The smallest detectable moderation effect of insomnia subtype on the time by combined CBTI and CT interaction is medium sized (d = 0.55). We follow the convention on effect size given by Cohen[127], who suggested to consider an effect size d of about 0.2 as "small" and an effect size of about 0.5 as "medium". With an estimated dropout of 10%, we will recruit 180 volunteers. The expected 160 completers thus allow for the detection of small to medium effect sizes.

DISCUSSION

The ultimate goal of this study is to develop a personalized treatment protocol for insomnia disorder. Primary caregivers could use this protocol to decide on the primary choice treatment for each individual patient. Assessment of insomnia subtype probabilities using the Sleep Subtype Survey results in four ISPs, which can be used to determine the expected treatment outcome of each of four treatments, their combinations and their simultaneous versus sequential application for the individual patient.

Since all treatments used in this study are noninvasive, easily applicable at home and require only the use of a computer and Internet (CBTI) and/or a readily available therapy light (BL), the implementation of treatments is straightforward, low-cost and scalable.

The current study addresses multiple opportunities to optimize and personalize treatment of insomnia disorder. First, no prior study has evaluated the relative effectiveness of CBTI, three different forms of CT and their simultaneous or sequential combinations. Second, the moderation of outcome by insomnia subtype probability follows the principles of personalized and stratified medicine. Treatment effects with subtype-specificity may come to light that would have remained hidden in unrecognized heterogeneity of samples.

CHAPTER 3: COMBINED INTERNET-BASED COGNITIVE-BEHAVIORAL AND CHRONOBIOLOGICAL INTERVENTION FOR INSOMNIA: A RANDOMIZED CONTROLLED TRIAL.

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Insomnia Disorder is the second-most common mental health problems[32] and a major risk factor for depression.[1] Cognitive behavioral therapy for insomnia (CBTI) is the treatment of choice, and has successfully been provided through internet (ICBTI).[7,47,58,128] Unfortunately, the intervention is not sufficiently effective for all people that suffer from insomnia.[129] Meta-analysis also shows that it is not that common for ICBTI to improve sleep beyond the cutoff for normal sleep efficiency of 85%,[128] thus leaving ample room for additional improvement. It has moreover been stated that long-term maintenance therapies to reduce recurrence need to be developed.[58]

A less studied type of intervention for insomnia, that might provide additional improvement if effective, is chronobiological treatment (CT). CT aims to enhance the entrainment and amplitude of the biological clock by utilizing its sensitivity to, and interaction with, regularly timed bright light, physical activity or body warming.[130] Although the European Sleep Research Society does recommend light and exercise in the treatment of Insomnia Disorder,[7] support for their effectiveness is much smaller than for CBTI. The combination of CT and CBTI has been applied in one study, with promising results.[131] No prior study compared the effectiveness of CTs, ICBTI and their combination in treating Insomnia Disorder.

The primary aims of the present study were therefore to evaluate the initial and sustained separate, additive and interaction effects of CT and ICBTI on sleep. To this end, we conducted a randomized controlled trial including 175 adults with insomnia who applied for ICBTI (See Supplement for details). After pre-assessment in week 0 (T0) randomization assigned half of them to receive four weeks of ICBTI in week 1-4, the other half in week 6-9. In both groups, participants were then additionally randomized to receive scheduled CT, being either bright light, physical activity, warm baths, or a placebo (a deactivated ionizer) in week 1-4. A post-assessment was made during week 5 (T1) and a final follow-up assessment in week 10 (T2).

The preregistered primary outcome[132] was the change of diary-reported Sleep Efficiency (SE), a composite score that includes the three diagnostically defining complaints about sleep quality: difficulties initiating sleep, difficulties maintaining sleep, and early morning awakening. For each of the assessment weeks T0 to T2, the composite score was calculated for each of the seven days. Several secondary outcomes including expectation and compliance were assessed as well (Supplement).

Participants were diagnosed with Insomnia Disorder according to ICSD3 and DSM-5[7] without another neuropsychiatric diagnosis. They did not use sleep medication daily, nor performed shift work. The mean (SD) age was 51.0 (11.2) years (range 20-70) and 79% was female. Compliance to interventions and assessments was high and completed by 167 (95%) of the participants at T1 and by 156 (89%) at T2. The CONSORT flowchart (Supplement) provides detailed information on attrition, which did not differ between groups.

The overall SE at baseline was 69.4% (15.0%). ICBTI increased SE by 6.69% (95% CI: 0.34 – 13.03%, *P* = .04) in addition to the increase between T0 and T1 seen across all participants irrespective of condition (5.55%, 95% CI: 0.95 – 10.15%, *P* =.02). At T1, SE was not affected by any CT or CT by ICBTI interaction (all *P* > .15, Supplement). A noticeable effect of combining ICBTI with CT between T0 and T1 emerged only at T2. At T2 relative to T0, SE had increased by 12.89% (95% CI: 10.06 – 15.71%) in participants that combined ICBTI between T0 and T1 with any active CT, which was almost twice (*P* =.003, Supplement) the increase seen in participants that had received ICBTI in combination with placebo CT (6.90%, 95% CI: 2.76 – 11.04%). The effectiveness was robust, irrespective of the type of CT (scheduled light, activity, or baths).

Secondary outcomes indicated that adding CT to ICBTI resulted in significant late benefits at T2 as compared to not adding an active CT: Sleep Onset Latency decreased by 23.60 versus 0.49 minutes (*P* = .04); Wake After Sleep Onset decreased by 64.29 versus 12.94 minutes (*P* = .005); and Total Sleep Time increased by 49.87 versus 17.38 minutes (*P* = .01) (for Figures, CI, details and other outcomes, see Supplement).

Summarizing, this first study to evaluate within a single design the effects of CTs, ICBTI and their interaction on sleep efficiency in Insomnia Disorder, showed that stand alone CT is not as effective as ICBTI. However, adding CT to ICBTI did bring on late benefits that appeared in the follow-up assessment in the sixth week after completing the interventions. Those that received ICBTI in combination with any active CT better maintained their initial gain in sleep efficiency by 6%, fell asleep more easily by 23 minutes, had less nocturnal wakefulness by 51 minutes and slept longer by 32 minutes. The value of adding CT seem clinically relevant, notably because of the half hour of extra sleep it entails: meta-analysis indicates that sleep duration shows little improvement with stand-alone CBTI.

In conclusion, four weeks of ICBTI benefits the sleep efficiency of people suffering from Insomnia Disorder more than a similar period of stand-alone CT. A CT intervention for more than four weeks, or a combination of the three CTs, may be required for stronger immediate effects of stand-alone CT. However, the addition of a single CT to four weeks of ICBTI already gives clinically relevant delayed enhancements of the benefits of ICBTI.

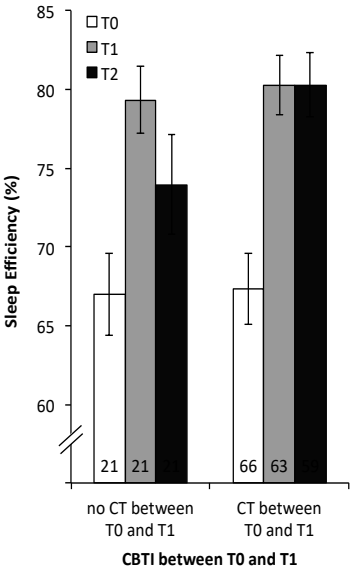


Figure 1. Sleep efficiency at T0, T1 and T2 for participants that received ICBTI between T0 and T1, both without CT (left) and combined with CT (right). Sleep efficiency at baseline (T0, white), week 5 (T1, light grey) and week 10 (T2, dark grey) for the groups that received ICBTI in week 1-4 (between T0 and T1) either without CT (three bars on the left-hand side) or with CT (three bars on the right-hand side). Numbers in bars indicate the sample size of participants included at in each condition at each time point. Comparison of the light and dark grey bars shows little effect of adding CT on sleep efficiency immediately after CBTI. Only at follow-up it shows that adding CT has been of value, by promoting maintenance of the initial sleep efficiency response to ICBTI.

SUPPLEMENT

SUPPLEMENTARY BACKGROUND

Insomnia Disorder is the second most common mental health problem, estimated to affect at least 7% of the population.[32,58] The disorder is diagnosed when problems falling asleep or maintaining sleep, accompanied by subjectively impaired daytime functioning, occur three times or more each week for at least three months, and cannot be attributed to unfavorable sleeping conditions.[7] Insomnia is a major risk factor for other health problems, notably depression,[1] reduces work productivity and increases healthcare consumption, thus imposing a large economic burden on patients and society.[5] The combination of high prevalence and high costs of insomnia makes it important to optimize affordable treatment.

Cognitive behavioral therapy for insomnia (CBTI) is the only non-pharmacological treatment supported by sufficient empirical evidence and is often preferable to pharmacotherapy because of its long-term effects[5,7] and cost-effectiveness.[133] Internet-based CBTI (ICBTI) results in comparable improvements.[47,54,128,134] Unfortunately, neither face-to-face CBTI nor ICBTI have satisfying results for all individuals.[58,129] Meta-analysis shows that it is not that common for ICBTI to improve sleep beyond the cutoff for normal sleep efficiency of 85%,[128] thus leaving ample room for additional improvement.

A less studied type of intervention for insomnia is chronobiological treatment (CT). CT aims to enhance regularly timed input to the circadian system by addressing its interaction with bright light, physical activity or body warming.[130] Although the European Sleep Research Society does recommend light and exercise in the treatment of Insomnia Disorder [7], support for their effectiveness is much smaller than for CBTI.[48] The combination of CT and CBTI has been applied in one study, with promising results [131] No prior study compared the effectiveness of CT, ICBTI and their combination in treating Insomnia Disorder.

The primary aims of the present study were to evaluate the initial and sustained separate, additive and interaction effects of CT and ICBTI on sleep efficiency in Insomnia Disorder.

SUPPLEMENTARY METHODS

The detailed protocol of this study has been registered (trialregister.nl Trial ID: NTR4010) and published [132].

PARTICIPANT RECRUITMENT AND SELECTION

Participants were recruited between November 2013 and August 2016 through the Netherlands Sleep Registry (NSR [135]), social media, newspaper advertisements and the website of Somnio, a company offering ICBTI. Interested people filled out an online screening questionnaire. Possibly eligible participants were contacted by phone to discuss the screening information they provided and to

answer their possible questions. Inclusion criteria were: an age between 18 and 70 years and a diagnosis of Insomnia Disorder according to ICSD3 and DSM-5.[6,7,136] Exclusion criteria were daily use of sleep medication, shift work, a current diagnosis of a psychiatric or neurological disorder, eye disease, cardiovascular disease, and disabilities or restrictions with respect to physical activity. Participants incidentally using prescribed or over-the-counter sleep medication were only included after refraining from use one month prior to and throughout participation. All participants signed a written consent form. Of the 946 individuals who completed the online screening questionnaire, 175 enrolled in the study (see Supplementary Figure 1, CONSORT Diagram of Participant Flow).

Study Design, Sample Size, Statistical Power, Randomization and Blinding

Design In a two by four factorial design (figure 1), participants were randomly assigned to ICBTI or not in week 1-4 (factor 1, two conditions) as well as to one of three chronobiological treatments or placebo in week 1-4 (factor 2, four conditions). Those that were not allocated to ICBTI in week 1-4, received it week 6-9, after the post assessment. All interventions and assessments took place at participants' homes. Assessments were conducted at baseline (T0, week 0), following completion of a 4-week treatment period (T1, week 5) and after completion of the second 4-week period (T2, week 10).

Sample size and estimated statistical power.

The sample size required to have sufficient statistical power (1-β = 0.80 at a critical α = 0.05) to detect small-to-medium effects were calculated for a mixed effect model that simultaneously estimated all treatment effects using repeated sleep efficiency values of 7 nights before and 7 nights after the intervention period.[125] According to conventions we considered d=0.2 a small effect and d=0.5 a medium effect. The range implicates that group means differ by 0.2 to 0.5 times the standard deviation. The a priori sample size calculation requires an estimate of the intraclass correlation coefficient (ICC) of repeated sleep efficiency values. At the time we designed the registered protocol including power calculations[132] we could take advantage of available subjective sleep efficiency from the 9-day sleep diaries that we recently assessed through the internet for 27 people suffering from insomnia and found an ICC of 0.2. Sample size calculations [125] indicated that 160 completers would provide, at a significance of alpha=0.05, sufficient power (1-beta=0.80) for minimal detectable differences of d = 0.27 (main effect ICBTI, n=80 vs. n=80), d=0.31 (main effect of any CT vs. II, n=120 vs. n=40), d=0.31 (main effect of a specific CT, n=40 vs. n=120), d=0.28 (interaction effect of ICBTI with any active CT, n=60 vs. n=100), and d=0.41 (interaction effect of ICBTI with a specific CT, n=20 vs. n=140). Expecting a dropout of about 10%, we initially aimed at staggered entry of 180 participants but stopped recruitment at n=175 due to time limitations.

Randomization and blinding.

The first 20 participants were randomized using the sample function in R[101], which generated a random number between 1 and 8, each referring to one combination in the 2 by 4 design. Subsequent randomization was done using covariate-adaptive randomization[99,100] scripted in R[101]. Covariates were: Insomnia Severity Index (ISI) score, sex, age, use of non-sleep medication and time of year of inclusion. Details on the covariate-adaptive randomization can be found in the registered trial protocol [132]. Author TM ran the script and noted the allocated treatment group in the trial master file. Participants were only aware of their own assigned condition and blind to whether or not it was an active treatment and to the existence of parallel other conditions. KD was blinded to case information including treatment allocation while processing the data.

INTERVENTIONS

Internet-guided Cognitive Behavior Therapy for Insomnia

Using the Somnio platform somnio.eu,[103] CBTI with guidance of a therapist was implemented to be online accessed from a computer (not a smartphone). The behavioral and cognitive components included stimulus control, sleep restriction, sleep hygiene and education, relaxation exercises and cognitive restructuring according to the European Guideline for the Treatment of Insomnia [7]. The four-week intervention consisted of four online lessons with information and assignments that were introduced one by one every subsequent week. Within the online platform, the supervising therapist evaluated the sleep diaries, provided feedback, answered questions and adjusted assignments based on progress. The therapist tailored the assignments, for example bedtimes for sleep restriction, utilizing the information from the sleep diary data from the previous week. The therapist estimated to have invested on average 15 minutes for each individual per module, totaling one hour of guidance per participant.

Chronobiological Treatments

Participants were randomly allocated to one of four interventions, being either Bright Light (BL), Physical Activity (PA), Warm Baths (WB) or the placebo condition of an inactivated ionizer (II).[110] All interventions were scheduled daily at a set time, attuned to participants' desired bed and wake-up times, and were instructed and verified to be applied exclusively during weeks 1-4. Enrolled participants were informed about their treatment allocation through email a week before baseline. That same week, they were mailed a package including elaborate information on the protocol and the assigned treatments, an actigraph, a treatment device if appropriate and log-in information for the NSR [135], the internet platform through which all questionnaires were online assessed. Participants received the required equipment (bright light, bath thermometer, inactivated ionizer) at the start of week 1 and handed it back in at the end of week 4 for use by others. They were instructed to apply the allocated CT exclusively during weeks 1-4. Compliance to these instructions was monitored daily using a diary kept from week 0 to week 11.

Bright Light. Participants allocated to the scheduled bright light CT condition were asked to sit facing a goLITE BLU light device (HF3220/01, Philips Consumer Lifestyle, Drachten, The Netherlands) each morning for half an hour, within an hour after a self-selected fixed desired wake-up time. Bright light entrains circadian rhythms [76] and has also been reported to improve sleep quality.[50] The blue LED light device has a peak wavelength of 470 nm (full width half-maximum 25 nm), and was instructed to be used at an arms-length distance of 50 cm, positioned on a table at 45 degrees sideways. That use provides an irradiance of 1.0 Watt/m2 and a photopic illuminance of 100 lux at eye position, which is equivalent to a melanopic illuminance of 770 m-lux.[137] The device specifically targets melatonin-containing retinal ganglion cells in the eyes that project to the biological clock of the brain, and was shown to have a clinical efficacy in seasonal affective disorder that was not different from the use of bright white light treatment of 10 000 lux.[138]

Physical Activity. Participants allocated to the scheduled Physical Activity CT condition were instructed to walk or bicycle daily for half an hour within the one-hour interval 3 to 2 hours prior to a self-selected fixed desired bedtime. Physical activity ameliorates insomnia complaints.[139,140]

Warm Baths. Participants allocated to the scheduled Warm Baths condition were instructed to take a daily warm bath for half an hour within the same one-hour interval 3 to 2 hours prior to a self-selected fixed desired bedtime. The increase in skin temperature induced by a warm bath at this time of day lasts into the sleep onset period and can promote sleep.[52,82] The timing of the warm baths may require some elaboration. As for the other interventions, warm baths were aimed at boosting the amplitude of physiological circadian rhythms. As we reviewed previously, well-timed whole body warming can effectively boost the amplitude of the diurnal rhythm in core body temperature with favorable effects on sleep.[141] Milder warming protocols utilizing foot baths may not affect the amplitude of the diurnal rhythm in core body temperature,[142] although they have also been implemented to promote relaxation and sound sleep (see Haghayegh *et al.* 2019[143]).

Because we could previously not confirm that people with insomnia benefitted of any of several foot warming methods that were effective in good sleepers [65] while two research groups did report favorable effects of whole body baths for insomnia, we chose to implement whole body warming.

In older females with a specific type of insomnia (only difficulties maintaining sleep) a preliminary report[144] and a full report[82] indicated sleep improvements after a warm bath between 20:00 to 20:30 hr, which was timed 2 to 1.5 hours prior to bedtime and 3 hours prior to lights out at 23:30 hr (see Figure 1, page 895 of Dorsey et al 1999[82]). In older patients with insomnia and vascular dementia, a warm bath timed 2 to 1.5 hours prior to bedtime likewise improved sleep.[145] On the contrary, and as to be expected, an evening hot bath could not halt the sleep-disturbing effect of apneas in patients with obstructive sleep apnea.[146] No study in insomnia patients compared different times for bathing. To

choose the optimal timing we therefore critically reviewed prior studies on the effect of timed hot baths in well-sleeping controls.

Bunnell *et al*.,[147] compared how sleep was affected by hot baths taken at different times of the day. As compared to times more distant from lights out, or closer to it, baths ending 4.5 hrs before lights out least elevated core body temperature at bedtime while most pronouncedly reducing nocturnal wakefulness and especially sleep onset latency (by 50%), two major problems of ID. In a study by Jordan *et al*., [148] hot baths ending 4 hrs before lights out reduced disturbed sleep and enhanced slow wave sleep and REM sleep. Horne and Reid[81] heated participants until 17:30 hr which was more than 5 hrs before lights out, and reported an increase in slow wave sleep but a decrease in REM sleep. Using less intense heating, Horne and Shackel[149] concluded that that as the time of the day of heating recedes from nighttime sleep, a larger "dose" of heating is required to produce the same effect. They moreover concluded that half an hour of heating 7-8 h before sleep has little effect, while if administered 2-3 hr before lights out, it enhances slow wave sleep, and finally, that about 2 hr has to elapse before body heating affects SWS. Indeed, a hot bath ending 0.5 hr prior to lights out did not improve nocturnal wakefulness or slow wave sleep in one study,[142] although it did suppress nocturnal movements in another study.[150] Based on the careful review of these studies, and because we aimed to boost the circadian amplitude of the core body temperature rather than to interfere with its normal decline that reliably takes place 2 h prior to sleep onset,[151] we instructed participants to bathe for half an hour immediately before this decline, i.e. between 3 to 2 hours prior to desired sleep onset.

ASSESSMENTS

Diagnosis. To support the diagnosis of Insomnia Disorder[6,7,136] and to evaluate past and current health, participants completed an online version of the Duke Structured Interview for Sleep Disorders (DSISD[152]).

Diary. Throughout the protocol, participants kept an extended Dutch version of the Consensus Sleep Diary (CSD[104]). The primary outcome measure was the change in sleep efficiency (SE) as reported in the diary. Sleep efficiency is a common standard outcome measure for insomnia and has the advantage of covering all three of the diagnostically defining complaints about sleep quality: difficulties initiating sleep, difficulties maintaining sleep, and early morning awakening. We did not consider total sleep time, because sleep quality is the primary issue in insomnia, and a reduction of total sleep time may even be beneficial. Sleep efficiency is the most commonly reported primary outcome measure in recent meta-analyses on ICBTI,[47,128] followed by the insomnia severity index (ISI), which would have been a viable alternative. In our registered trial protocol[132] we did prefer sleep efficiency, derived from the Consensus Sleep Diary,[104] because it has the advantage that it utilizes assessments that are repeated day-after-day, while the insomnia severity index is a single retrospective evaluation of the past two weeks. A review on the accuracy of sleep assessment methods

concluded that better accuracy of diaries than questionnaires because diaries record night-to-night variability of good and bad nights and are less sensitive to retrospective memory bias.[153] This advantage has also been noted by the consensus Recommendations for a Standard Research Assessment of Insomnia[2] which phrased it as follows: "*sleep diaries may yield a more representative sample of an individual's sleep than 1-time questionnaires*".

SE was calculated as the ratio of the subjective total sleep time (TST) relative to time in bed (TIB), expressed as percentage. TIB was defined as the time between lights-off and the moment after final awakening when no further attempt to sleep was made.[96] Secondary outcome measures obtained from the diary were sleep onset latency (SOL), wake after sleep onset (WASO) which included possible time awake after final awakening still attempting to fall asleep; and TST. The sleep diary was extended with 3 questions to assess the major sleep complaints evaluated by the DSM-5 to diagnose Insomnia Disorder: difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS) and early morning awakening with inability to return to sleep (EMA). Participants were asked to rate their night on these 3 complaints on a 7-point Likert scale ranging from 'very good' to 7 'very bad'.

To assess daytime functioning, we developed a dedicated diary with 18 items that queried all daytime impairments relevant to insomnia according to a British Association for Psychopharmacology consensus paper on ICSD, ICD-10 and DSM nosologies.[154] Participants were asked to rate their day on all 18 daytime impairments on a 7-point Likert scale, ranging from 'very bad' to 'very good'. These 18 domains were averaged per day for analyses.

Prior Expectations and Post-intervention Attribution. Prior to the interventions, a dedicated questionnaire was administered to assess expected effectiveness of the allocated treatments on a 7-point Likert scale ranging from 'very much deteriorate' to 'very much improve'. Using the same Likert scale answer options, we also asked for expected change in sleep if no treatment would be given, which provides insight in the patients' conception of expected recovery if their insomnia was left untreated. Finally, at T2, after the interventions, a 7-point Likert scale ranging from 'very much deteriorated' to 'very much improved' was used to assess the sleep changes subjectively attributed to the interventions.

Compliance. Compliance for each CT was assessed by a question on timing of compliance, added to the sleep diary. The number of compliant days was used for analysis. Compliance for the ICBTI sleep restriction part was monitored using the time in bed data from the sleep diary. Unlike sleep restriction, other CBTI lessons were not as suitable for daily quantitative assessment of compliance. However, the ICBTI was guided and the supervising clinical psychologist kept close track of whether participants had read the planned lessons and filled out the questions it contained. Participants were immediately reminded if they did not. One might state that adherence to reading the planned lessons and filling out the contained questions was thus guided to be complete. Nights were marked as non-

compliant if time in bed was longer than the time set by the ICBTI sleep restriction. Again, the number of compliant nights was used for analysis.

Attrition. Participants were marked as drop-out if they (1) contacted us that they wanted to stop, (2) stopped filling out the diaries or showed no compliance to treatment and did not continue after being prompted to do so.

Actigraphy. During assessment weeks T0, T1 and T2, participants wore a wrist actigraph (Philips Actiwatch Spectrum, Philips Respironics, Murrysville, PA, USA) to estimate sleep. Outcome measures derived from the actigraphy data were SE, SOL, WASO, TST, average sleep bout duration and average wake bout duration.

Questionnaires. A comprehensive set of online questionnaires was assessed at T0, T1 and T2 consisted of: Insomnia Severity Index (ISI),[120] Dysfunctional Beliefs and Attitudes Scale,[26] Glasgow Sleep Effort Scale,[121] Sleep Locus Of Control scale[123] and Sleep Self-Efficacy Scale,[122] Pre-Sleep Arousal Scale,[119] Arousal Predisposition Scale,[116] Hyper Arousal Scale[117] and Adult ADHD Self Rating Scale,[118] Hospital Anxiety and Depression Scale,[113] Positive Affect Negative Affect Scale[114] and Temporal Experience of Pleasure Scale,[115] Short Form 36[112] and Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness: TiC-P.[111] The data of the TiC-P however contained over 90% of zeroes, meaning that many participants reported no costs and had no production losses at all during the assessed weeks. Therefore, we were unable to analyze cost-effectiveness.

STATISTICAL ANALYSES

Immediate post-treatment effects (T1 relative to T0) and follow-up effects (T2 relative to T0) of ICBTI, CTs and their interactions on the primary outcome measure (SE) were estimated using mixed effect models (R software package 'lme4'[155]). This approach provides an intention to treat analysis by allowing inclusion of all observations of all participants, irrespective of missingness. Separate analyses first addressed specific effects of each individual CT and subsequently a possible generic effect of any active CT (irrespective of type BL, PA or WB) versus the placebo condition (II). Diary and actigraphy measures were analyzed with a 3-level mixed effect model with days *i*, nested within week *j*, nested within participant *k*. Questionnaire measures were likewise analyzed, but now using 2-level instead of 3-level mixed effect models since they were not assessed daily. Group differences in expected and attributed treatment effects and in compliance to treatment were analyzed with ANOVAs and t-tests. Group differences in post-intervention attributed effectiveness of treatment were analyzed with a paired-sample t-test. Group differences in attrition were evaluated with a chi-squared test. Treatment conditions were dummy coded with as reference no initial ICBTI (factor 1) and no active CT (i.e. the inactivated ionizer placebo). Analyses on secondary outcomes were considered exploratory and not corrected for multiple comparisons.

SUPPLEMENTARY RESULTS

PARTICIPANTS

The mean (SD) age was 51.0 (11.2) years (range 20-70 years) and 79% was female. Education level was low (secondary education or less) in 36%, average (post-secondary education) in 35% and university level in 29%. The majority of participants was employed (fulltime 45%, part-time 32%) and lived with a partner (66%). About half (54%) presented a current comorbid somatic disorder. The mean (SD) duration of Insomnia Disorder was 9.3 (11.2) years. The severity of insomnia (ISI) at baseline was 16.35 (3.98). The use of the Consensus Sleep Diary allowed us to calculate that the mean (SD) Mid Sleep time[156] at T0 was 3:31 (1:04) hr, indicating that the chronotype of our sample did not deviate from the distribution reported for their age in population-based epidemiological studies.[157,158] Table 1 provides descriptive statistics.

ALLOCATION TO INTERVENTIONS

ICBTI in week 1-4 was randomly assigned to 87 participants and was provided simultaneously with randomly assigned BL (n=21), PA (n=21), WB (n=24), or the inactive II placebo condition (n= 21). The same chronobiological and placebo conditions were randomly assigned in week 1-4, but without initial ICBTI, to 88 participants (BL: n=24, PA: n=24, WB: n=20, II: n=20). These 88 participants were given ICBTI in week 6-9.

T0-T1 CHANGES IN SLEEP EFFICIENCY

Mixed effect models showed a 5.55% (95% CI: 0.95 – 10.15%, P =.02) increase in SE between T0 and T1, irrespective of ICBTI or CT condition (eFigure 1). SE increased by an additional 6.69% (95% CI: 0.34 – 13.03%, P = .04) in participants that completed ICBTI between T0 and T1. Changes in SE were not affected by any CT or CT by ICBTI interaction (all P > .15, Supplementary Table 5). A model that combined the three active CT's into a single 'any CT' condition did not show main or interaction effects either (P > .28, Table 2). The findings indicate that at T1, there was an effect ICBTI but not of any of the three active CTs beyond the CT placebo condition.

T0-T2 CHANGES IN SLEEP EFFICIENCY

At T2 relative to T0, SE had increased by 13.44% (95% CI: 9.48 – 17.40%) in participants that had just received ICBTI from week 6 to 9, which was significantly more (P =.04) than in participants that had received ICBTI already in week 1 to 4, where the increase was 6.93% (95% CI: 2.32 – 11.54%). This difference indicates a gradual loss of the initial gain in SE that the latter group had initially reached immediately after completion of ICBTI.

Of particular relevance to maintenance of initial benefits, a noticeable effect of combining ICBTI with CT in week 1-4 appeared only at T2. At T2 relative to T0, SE had increased by 12.89% (95% CI: 10.06 – 15.71%) in participants that combined ICBTI in week 1 to 4 with any active CT, which was

almost twice (P =.003, Table 3) the increase seen in participants that had received ICBTI in combination with placebo CT (6.90%, 95% CI: 2.76 – 11.04%). Figure 2 shows group means across T0 to T2 within the participants that received ICBTI during week 1-4, either with or without CT. Separate analyses on combining ICBTI with each of the three individual CTs showed highly similar improvements from T0 to T2 (BL: 13.83%, 95%CI: 10.05 – 17.61; PA: 13.28%, 95%CI: 7.22 – 19.36; WB: 11.38%, 95%CI: 6.66 – 16.10). Supplementary Table 6 shows that whole model-estimated effects are also similar. There was no difference in fit between the model with separate CTs and the more parsimonious model that analyzed them as a combined 'any CT' condition (likelihood-ratio test χ^2 = 5.97, df = 8, P =.65).

Prior Expectations and Post-intervention Attribution

Expected effects. Participants expected no significant sleep improvement in case they would not receive intervention (-0.05 ± 0.77, t(173) = -0.89, P = .38) and significantly more with the placebo or any active CT (0.97 ± 0.76, ~slightly improve , t(173) = 13.02, P < .001) and with ICBTI (1.33 ± 1.02, ~slightly improve, t(173) = 15.96, P < .001). Expectancies did not differ among the placebo or active CTs ($F_{3.170}$ = 0.55, P = .64), but were overall lower for CT than for ICBTI (t(173) = 6.19, P < .001). Details can be found in Supplementary Table 4.

Post-intervention attribution of sleep changes to treatment. Assessed at T2, the effects attributed to CT interventions did not differ between groups randomized to the inactive or any of the active CT interventions ($F_{3.162}$ = 1.43, P = .23). Similarly, the effects attributed to ICBTI was not different for participants that received ICBTI in week 1-4 and those that received ICBTI in week 6-9 ($F_{1.154}$ = 0.29, P = .59). However, participants attributed a stronger effect to ICBTI than to CT (t (155) = 7.59, P < .001). Details can be found in Supplementary Table 4.

Compliance. Diaries confirmed adherence to the exclusive use of the allocated CT during the larger part of the days of weeks 1-4. The number of days of compliance differed between CTs ($F_{3,163}$ = 9.77, P < .001). Compliance was better to II and BL than to PA and WB (Tukey, all P < .01). Paired t-tests showed that compliance to ICBTI was worse than compliance to II (t(39) = -5.24, P < .001) and BL (t(40) = -3.01, P = .004) but not different from compliance to PA (t(36) = -0.69, P = .50) and WB (t(41) = 0.90, P = .37). Details can be found in Supplementary Table 4.

Attrition. The CONSORT flowchart (Supplementary Figure 1) provides detailed information on the attrition. Interventions and assessments were completed by 167 (95%) of the participants at T1 and by 156 (89%) at T2 (Figure 1). Attrition was independent of assignment to CT condition (χ^2 = 7.08, df =3, P = .07) and timing of ICBTI (χ^2 = 0.89, df =1, P = .34).

T0-T1 Changes in Secondary Outcome Measures

Supplementary Table 2 shows the estimated effects of time and time by treatment between T0 and T1 for all outcome measures. Supplementary Tables 7 and 8 show group means (SD). A significant time by treatment effect indicated that ICBTI reduced subjectively reported TIB by 31.29 minutes (95% CI: -57.23 – -5.34 min., $P = .02$) and actigraphically estimated TST by 29.89 minutes (95% CI: -54.70 – -5.08 min., $P = .02$). None of the CTs showed any effect on the actigraphy or diary measures. Secondary outcomes assessed by questionnaires suggested that ICBTI induced improvements on the ISI, DBAS, GSES and PSAS-cognitive subscale, indicating reduced insomnia severity, arousal, dysfunctional thoughts and sleep effort (Supplementary Table 2 and 5).

T0-T2 Changes in Secondary Outcome Measures

Supplementary Table 3 shows the estimated effects of time and time by treatment outcome measures between T0 and T2. Supplementary Tables 7 and 8 show group means (SD). Effect estimates indicate that the late benefits on sleep efficiency gained by combining ICBTI with any CT in week 1-4 were also seen in subjective SOL, WASO, TST and complaints about early morning awakening and daytime functioning. To facilitate interpretation of the main and interaction effect coefficients, group mean changes were calculated. In participants that initially combined ICBTI with any active CT, SOL decreased by 23.60 minutes (95%CI: -33.94 – -13.27 min.), which was significantly more ($P = .04$) than in those who combined ICBTI in week 1-4 with the placebo CT (-0.49 min., 95%CI: -16.42 – 15.43 min.). In those who combined ICBTI with active CT, WASO decreased by 64.29 minutes (95%CI: -80.06 – -48.52 min.), which was significantly more ($P = .005$) than in those who combined ICBTI with placebo CT (-12.94 minutes, 95%CI: -44.89 – 19.01 min.). In those who combined ICBTI with active CT, TST increased by 49.87 minutes (95%CI: 37.08 – 62.66 min.), which again was significantly more ($P = .01$) than in those who combined ICBTI with placebo CT (17.38 minutes, 95%CI: -5.28 – 40.04 min.). None of the actigraphy outcome measures showed significant ICBTI by CT by time interaction effects. The secondary outcome measures that were assessed by questionnaires did not show ICBTI by CT by time interaction effects, although some measures showed strongly significant ($P < .001$) improvements between T0 and T2 for all participants, irrespective of treatment or timing (ISI, DBAS, GSES and Sleep Self-Efficacy Scale (SSES), see Table 3).

Supplementary Discussion

The present study is the first to evaluate, within a single design, the effects of CT, ICBTI and their interaction on sleep efficiency in Insomnia Disorder. ICBTI improved SE, whereas none of the active CTs did as compared to their placebo control condition. Adding CT to ICBTI did however have benefits that appeared only at follow-up. For participants that only received ICBTI, a part of the initial sleep efficiency improvement was lost during the month following completion of treatment. Those

that received ICBTI in combination with any active CT better maintained their initial gain in sleep efficiency and moreover fell asleep more easily, slept longer and had less nocturnal wakefulness.

Future studies on combined treatment could extend the follow-up period to evaluate the duration of the benefit.

Since SE indexes the time spent asleep during the time spent in bed, an increase does not necessarily indicate more, or better, sleep. SE increases equally with a mere reduction of TIB without change in time asleep. Immediate effects of ICBTI on SE are indeed at least partly driven by the reduced time in bed demanded by the sleep restriction intervention that is integral part of ICBTI. However, at T2, the participants that had combined ICBTI with CT in week 1-4 experienced more sleep and less wake compared to those who only received ICBTI in week 1-4, while time in bed did not differ. Supported by additional benefits to subjective SOL, WASO, TST and complaints about early morning awakening and daytime functioning, the findings suggest that the addition of either Bright Light, Physical Activity or Warm Baths solidifies the sleep improvement induced by ICBTI.

It was unexpected that four weeks of stand-alone CT, without ICBTI, did not improve sleep efficiency or any of the other outcomes. Meta-analysis suggests the application of bright light to be moderately efficacious in the treatment of Insomnia Disorder[159] Meta-analyses also suggested improvement in sleep[160] and insomnia complaints[140] with physical activity, although it might take a longer intervention to reach clinically relevant effects.[139] Slowly developing and delayed effects of chronobiological interventions have been noted before[50,161] and may involve slow adaptation of the neuronal network of the suprachiasmatic nucleus (SCN[48]), the biological clock of the brain. Such a slow process, however, does not explain why late benefits were only found when CT was combined with ICBTI, not for CT without ICBTI. One possibility is that the presence of disturbed sleep interferes with adaptation of the neuronal network of the SCN.[162,163] A hypothetical mechanism could be that the induction of a more consolidated sleep period by ICBTI might promote effectiveness of CT in slowly adapting the neuronal network of the SCN and promoting sound sleep. It should be noted that the fact that circadian disruption can generate insomnia complaints does not imply that it is the key underlying mechanism for the majority of cases with insomnia disorder. The chronotype of our sample did not deviate from the distribution reported for their age in population-based epidemiological studies.[157,158] CTs may be more effective in themselves for insomnia complaints with an evident involvement of circadian disruption. Likewise, while ample human and animal studies demonstrated that the timed application of bright light, physical activity and warm baths can support a solid circadian rhythm, each of these three interventions can also have effects that do not involve the biological clock.

Actigraphic sleep estimates were not sensitive enough to pick up the subjectively experienced improvement in sleep efficiency. Whereas actigraphy is commonly used to estimate polysomnographic sleep measures, the estimates are not very accurate in people with Insomnia

Disorder.[102] In fact, even the gold standard polysomnographic sleep measures do not reflect the subjective experience of people suffering from insomnia well.[164,165] The conscious experience of wakefulness during sleep concerns complex interactions in brain activity that are insufficiently captured by polysomnography.[166,167] Insomnia disorder is therefore diagnosed on subjective complaints, which are recommended for clinical investigations.

Limitations. A few limitations of our study should be mentioned. First, the intervention period of 4 weeks might not be long enough for effects of stand-alone CT to emerge. As mentioned above, some studies investigating chronobiology-based interventions reported slowly developing effects. Second, the strict exclusion of people diagnosed with psychological disorders, may have led to a sample with low baseline scores on secondary outcome measures related to complaints about mood, affect and quality of life, thus leaving little room for improvement. It remains to be evaluated how our findings generalize to people with other disorders comorbid to Insomnia Disorder. Third, and related, the number of secondary outcome measures was large, and the few significant effects found would not survive adjustment for multiple comparisons. This finding suggests that there is no indication of overall widespread multivariate benefits of the interventions. A fourth limitation of the present study could be that we aimed to evaluate different chronobiological interventions side by side. As detailed in our registered trial protocol[132] the sample sizes were calculated for detecting small to medium effect sizes. The reason for evaluating individual chronobiological interventions next to each other, rather than combining them was based on a previous small uncontrolled open label study [131]. In that study, we did combine the three chronobiological interventions, and learned from participants that it was very taxing. We therefore considered it of both fundamental and clinical value to study the effects of the individual interventions: if effect sizes would differ considerably, future interventions could prioritize the most effective of the three. A direct comparison between the effectiveness of CBTI and the isolated CTs may not be completely fair, because CBTI is a multicomponent treatment. Although the combination of all three CT interventions may be demanding, future studies could investigate whether such a multicomponent CT would have stronger effects. A further limitation of the current study is that we cannot generalize the findings to people with insomnia that use sleep medication. The current study is the first to evaluate whether chronobiological treatment can compare to, and add to, the effects of ICBTI. The most commonly used sleep medications, benzodiazepines and melatonin, both have pronounced effects on the biological clock (for review see[168]), which could mask or interact in unpredictable ways with the nonpharmacological interventions we applied. To maintain a tractable sample size, it therefore seemed appropriate to start with a sample where such unpredictable masking and interaction effects would not increase heterogeneity and dilute effects. Future studies could evaluate added effects of chronobiological treatment in people with insomnia that use sleep medication.

Clinical Relevance. While there is no consensus on what minimal clinically important differences are, we facilitated interpretation by providing whole-sample means and standard deviations at onset and effect sizes *d* of interventions[169,170]. With a (post-hoc assessed) overall between-subject standard deviation of 15.00 at onset, a small (*d*=0.2) effect implies a post-treatment group difference in sleep efficiency of 3%, and a medium (*d*=0.5) effect a post-treatment group difference of 7.5%.

Whereas our study is not directly comparable because it does not include long-term follow-up, some studies found slight decreases at follow-up of initial gains in sleep efficiency immediately after treatment.[68,171] A previous meta-analysis reported a decrease in effect size (ES) of sleep-diary reported sleep efficiency benefits of face-to-face CBTI from immediately after treatment (ES=0.86) to 3-months (ES=0.81) and 12-months (ES=0.54)[172]. Meta-analysis specifically on ICBTI differ in their conclusion. While one found no indication of a decrease in (ES) of sleep efficiency benefits of CBTI from immediately after treatment (ES=0.58) to 1-4-months follow-up (ES=0.57),[47] another meta-analysis reported that the 7.7% sleep efficiency benefit immediately following treatment reduced to a 4.4% benefit at 1-24 months follow-up.[128] Of note however, in these meta-analyses, the improvements in the control groups contribute to the waning group differences over time, which we also found in our study. Still, it has been noted that given the recurrent or persistent nature of insomnia, short-term treatment may not be completely sufficient and maintenance CBT booster sessions might optimize long-term outcomes.[68] In their comprehensive review on insomnia, Morin and Benca concluded that even patients who respond well to short-term therapy can be vulnerable to recurrent episodes of insomnia and that long-term maintenance therapies to prevent or minimize insomnia recurrence need to be developed and assessed.[58] Our motivation to evaluate the possible value of adding chronotherapeutic interventions was based on this need.

The initial sleep efficiency in our sample was 69.4%, which is at the lower range of the pooled baseline estimate reported in a meta-analysis on ICBTI (mean 72, 95% CI 69-75%).[128] The ICBTI-induced improvements in our study were comparable to the pooled estimate for improvement of this meta-analysis (mean 7.2, 95% CI 5.1-9.3%).[128] The meta-analysis shows that it is not that common for ICBTI to increase sleep efficiency to values well above 85%, which is commonly considered as the cutoff for a normal sleep efficiency.[96] A closer look into the studies reported in the meta-analysis revealed that a post-treatment sleep efficiency >85% was only found in 2 out of the 9 studies that reported sleep efficiency. In these two studies, the pre-treatment sleep efficiency was relatively high. Across studies, the post-treatment sleep efficiency showed a correlation of r=0.56 with the pre-treatment sleep efficiency, and age showed a correlation of r=-0.73 with pre-treatment sleep efficiency[128]. Efficiency is the sleep variable that shows the strongest decline with age, especially from 40 yrs on.[173] Therefore, a post-treatment sleep efficiency >85% may be especially hard to attain for older people and people with more severe insomnia.

Conclusion. The sleep efficiency of people suffering from Insomnia Disorder benefits from four weeks of ICBTI. Whereas this benefit would otherwise weaken over time, the addition of CT helps to maintain the effect on sleep efficiency and moreover improves sleep onset latency, total sleep time, nocturnal wakefulness and complaints about early morning awakening and daytime functioning. No benefit could be demonstrated for CT as stand-alone therapy. CT interventions are low in cost and risk, making them a promising addition to consolidate ICBTI effects on sleep in Insomnia Disorder.

Table 1. Sociodemographic and clinical characteristics of participants

Characteristic	week 1 - 4 / week 6 - 9	Inactive Ionizer ICBTI	Bright Light ICBTI	Physical Activity ICBTI	Warm Baths ICBTI	Inactive Ionizer + ICBTI	Bright Light + ICBTI	Physical Activity + ICBTI	Warm Baths + ICBTI	All	Test Statistic[a]	*P* Value
						no treatment						
N		20	24	24	20	21	21	21	24	175		
Age, mean (SD), y		51.3 (10.2)	47.8 (13.8)	50.8 (11.6)	53.2 (6.4)	52.3 (13.6)	50.4 (9.9)	50.7 (12.8)	51.7 (10.0)	51.0 (11.2)	$F_{7,167} = 0.45$	.87
Female, No. (%)		15 (75)	22 (92)	20 (83)	16 (80)	17 (81)	13 (62)	17 (81)	18 (75)	138 (79)	$\chi^2 = 6.79$	.45
Education Level, No. (%)												
Secondary education or less		7 (35)	9 (38)	8 (33)	4 (20)	9 (43)	9 (43)	11 (52)	6 (25)	63 (36)		
Post-secondary education		7 (35)	12 (50)	8 (33)	5 (25)	8 (38)	6 (29)	6 (29)	10 (42)	62 (35)	$\chi^2 = 16.14$	.30
University		6 (30)	3 (12)	8 (33)	11 (55)	4 (19)	6 (29)	4 (19)	8 (33)	50 (29)		
Occupation, No. (%)												
Employed fulltime		7 (35)	7 (29)	11 (46)	12 (60)	9 (43)	11 (52)	8 (38)	14 (58)	79 (45)		
Employed parttime		7 (35)	10 (42)	8 (33)	6 (30)	4 (19)	7 (33)	8 (38)	5 (21)	55 (32)	$\chi^2 = 12.40$	.57
Other[b]		6 (30)	7 (29)	5 (21)	2 (10)	8 (38)	3 (14)	5 (24)	5 (21)	41 (23)		
Marital Status, No. (%)												
With partner[c]		11 (55)	14 (58)	16 (67)	12 (60)	14 (66)	13 (62)	15 (71)	20 (83)	115 (66)	$\chi^2 = 5.65$	.58
Without partner[d]		9 (45)	10 (42)	8 (33)	8 (40)	7 (34)	8 (38)	6 (29)	4 (17)	60 (34)		
Health, No.(%)[e]												
Current Somatic Disorder[f]		14 (70)	10 (41)	17 (71)	7 (35)	15 (71)	10 (48)	10 (48)	12 (50)	95 (54)	$\chi^2 = 16.23$	.30
Past Somatic Disorder		4 (20)	9 (38)	3 (12)	7 (35)	4 (20)	8 (40)	6 (27)	9 (38)	50 (29)		
Insomnia duration, mean (SD), y[g]		7.2 (9.7)	9.9 (14.4)	12.5 (12.0)	8.6 (12.4)	8.0 (8.6)	9.7 (11.1)	7.1 (6.9)	10.6 (12.5)	9.3 (11.2)	$F_{7,155} = 0.58$	.78
ISI, mean (SD)		16.00 (4.74)	16.92 (3.20)	15.13 (4.61)	16.50 (3.44)	16.76 (4.31)	15.81 (3.30)	16.95 (3.92)	16.79 (4.23)	16.35 (3.98)	$F_{7,167} = 0.61$	.75

Abbreviations: ICBTI, Internet-based Cogntive Behavioral Therapy for Insomnisa; SD, Standard Deviation; ISI, Insomnia Severity Index.

[a] Significance test results are between group effects from ANOVA's for continues variables (F statistic) and chisquared tests for categorical variables (c2 statistic). All 8 combinations of the 2 by 4 factorial design are assessed as separate groups.
[b] including unemployed, homemaker and student
[c] married, legal partnership or legal cohabitation
[d] single, divorced, widowed

[e] If a participant had both a past and a current disorder, they had to indicate 'current'.

[f] Reported somatic disorders reported were high blood pressure, metabolic disorders, hearing loss, trombosis, appendicitis, urinal problem, skin infections, artrosis, bone fractures et cetera. If a somatic disorder was current, it was made sure it was not an exclusion criterium.

[g] Insomnia duration, derived from the Duke's Structured Interview for Sleeping Disorders (DSISD), was not correctly filled out by 12 participants

Table 2. Estimated effects of time and treatment by time interactions on all outcomes measures at T1 relative to T0

	T1 - T0			ICBTI x T1-T0			Any CT x T1-T0			ICBTI x Any CT x T1-T0		
Outcome measure	β (SE)	*d*[a]	*P* Value	β (SE)	*d*[a]	*P* Value	β (SE)	*d*[a]	*P* Value	β (SE)	*d*[a]	*P* Value
Sleep Diary												
Sleep Efficiency (%) (Primary)	5.55 (2.36)	0.34	**.02**	6.69 (3.25)	0.41	**.04**	-2.93 (2.69)	0.18	.28	3.42 (3.73)	0.21	.36
Time in Bed (min)	-8.08 (9.58)	0.13	.40	-31.29 (13.24)	0.52	**.02**	10.31 (10.92)	0.17	.35	1.99 (15.19)	0.03	.90
Sleep Onset Latency (min)	0.41 (8.70)	0.01	.96	-16.71 (12.03)	0.25	.17	-2.60 (9.93)	0.04	.79	-6.25 (13.81)	0.09	.65
Wake After Sleep Onset (min)[b]	-2.54 (16.95)	0.02	.88	-44.34 (23.43)	0.37	.06	-5.94 (19.34)	0.05	.76	-14.64 (26.89)	0.12	.59
Total Sleep Time (min)	16.65 (10.93)	0.19	.13	10.19 (15.08)	0.12	.50	-3.81 (12.47)	0.04	.76	17.03 (17.31)	0.19	.33
Average Daytime Functioning	0.16 (0.16)	0.26	.32	-0.14 (0.22)	0.23	.52	-0.10 (0.19)	0.16	.60	0.22 (0.26)	0.36	.39
Difficulty Initiating Sleep	-0.22 (0.24)	0.16	.36	-0.20 (0.34)	0.14	.55	0.07 (0.28)	0.05	.80	-0.05 (0.38)	0.04	.89
Difficulty Maintainting Sleep	-0.70 (0.19)	0.50	**<.001**	0.01 (0.26)	0.01	.96	0.16 (0.22)	0.11	.47	-0.29 (0.30)	0.21	.33
Early Morning Awakening	-0.54 (0.24)	0.38	**.03**	0.11 (0.33)	0.07	.75	-0.10 (0.27)	0.07	.71	-0.47 (0.38)	0.33	.22
Actigraphy												
Sleep Efficiency (%)	0.01 (1.45)	0.00	.99	1.56 (2.03)	0.19	.44	0.12 (1.69)	0.02	.94	0.76 (2.36)	0.09	.75
Sleep Onset Latency (min)	-0.47 (2.76)	0.03	.87	0.30 (3.87)	0.02	.94	2.66 (3.20)	0.16	.41	-3.52 (4.48)	0.21	.43
Wake After Sleep Onset (min)[b]	3.21 (5.29)	0.09	.54	-14.17 (7.42)	0.40	.06	-6.85 (6.16)	0.20	.27	9.25 (8.61)	0.26	.28
Total Sleep Time (min)	-4.16 (9.02)	0.07	.65	-29.89 (12.66)	0.51	**.02**	7.09 (10.51)	0.12	.50	4.78 (14.69)	0.08	.75
Average Sleep Bout Duration (min)	-0.36 (9.26)	0.01	.97	7.94 (12.97)	0.22	.54	15.21 (10.68)	0.41	.16	-20.40 (14.96)	0.56	.17
Average Wake Bout Duration (min)	-0.01 (0.05)	0.02	.90	0.00 (0.07)	0.01	.96	-0.05 (0.06)	0.14	.38	-0.01 (0.08)	0.03	.90
Sleep related surveys												
Insomnia Severity Index	-1.81 (0.90)	0.65	**.05**	-2.93 (1.25)	1.06	**.02**	1.08 (1.02)	0.39	.29	-1.66 (1.43)	0.60	.25
Dysfunctional Beliefs and Attitudes	-1.92 (1.99)	0.32	.34	-6.65 (2.74)	1.11	**.02**	0.78 (2.25)	0.13	.73	-2.83 (3.13)	0.47	.37
Glasgow Sleep Effort Scale	-0.88 (0.46)	-0.64	.06	-1.28 (0.63)	0.93	**.04**	0.69 (0.52)	0.50	.18	-0.04 (0.72)	0.03	.95
Sleep Locus Of Control	0.71 (0.93)	0.25	.44	-0.26 (1.30)	0.09	.84	-0.51 (1.06)	0.18	.63	2.81 (1.48)	0.98	.06
Sleep Self-Efficacy Scale	1.08 (1.18)	0.29	.36	2.10 (1.65)	0.57	.20	-0.89 (1.35)	0.24	.51	0.49 (1.89)	0.13	.80
Hyperarousal												
Pre-Sleep Arousal Scale - Somatic	1.15 (0.96)	0.46	.23	-0.76 (1.29)	0.30	.56	-0.86 (1.07)	0.34	.42	-0.18 (1.46)	0.07	.90
Pre-Sleep Arousal Scale - Cognitive	0.74 (1.57)	0.18	.64	-4.84 (2.13)	1.18	**.02**	-2.55 (1.76)	0.62	.15	4.83 (2.41)	1.17	**.05**
Arousal Predisposition Scale	-0.99 (1.11)	0.34	.37	1.60 (1.50)	0.55	.29	0.97 (1.24)	0.34	.44	-1.80 (1.70)	0.62	.29
Hyper Arousal Scale	-1.29 (1.13)	0.44	.26	1.83 (1.53)	0.62	.23	1.01 (1.27)	0.34	.43	-1.93 (1.73)	0.65	.27
Adult ADHD Self-Report Scale	-0.55 (0.81)	0.26	.50	0.52 (1.09)	0.25	.63	0.23 (0.90)	0.11	.80	-0.95 (1.24)	0.45	.44
Mood and Affect												
Anxiety (HADS)	-0.19 (0.52)	0.12	.71	-1.21 (0.72)	0.75	.10	0.48 (0.59)	0.30	.42	0.01 (0.83)	0.00	.99
Depression (HADS)	-0.12 (0.59)	0.07	.84	-1.11 (0.82)	0.61	.18	0.02 (0.67)	0.01	.97	0.24 (0.94)	0.13	.80
Positive Affect (PANAS)	1.18 (1.25)	0.30	.35	0.28 (1.75)	0.07	.87	-2.12 (1.43)	0.55	.14	2.25 (2.00)	0.58	.26
Negative Affect (PANAS)	-0.07 (0.97)	0.02	.95	-2.76 (1.36)	0.92	**.04**	0.84 (1.11)	0.28	.45	1.07 (1.55)	0.36	.49
Temporal Experience of Pleasure	3.03 (1.72)	0.57	.08	-3.19 (2.40)	0.60	.19	-3.56 (1.96)	0.67	.07	5.21 (2.75)	0.98	.06
Quality of Life SF36												
Physical Component Summary	-0.18 (1.26)	0.05	.89	0.36 (1.78)	0.09	.84	-0.26 (1.44)	0.07	.86	0.09 (2.03)	0.02	.96
Mental Component Summary	0.72 (1.77)	0.13	.68	2.57 (2.50)	0.47	.31	-1.40 (2.02)	0.26	.49	0.97 (2.85)	0.18	.73

The model intercept and main effects of ICBTI and any CT are not shown. Main effects for ICBTI and any CT were non significant, except for a significantly higher intercept for participants receiving any CT on Depression (HADS) (β (SE) = 2.00 (0.93), P = .03 and SF 36 Physical Component Summary (β (SE) = 3.09 (1.52), *P* = .04)

Abbreviations: SE, standard error of b; ICBTI, Internet-based Cognitive Behavioral Therapy for Insomnia; CT, Chronobiological Treatment; ISI, Insomnia Severity Index HADS, Hospital Anxiety and Depression Scale; PANAS, Positive Affect Negative Affect Scale; SF36, Short Form 36. Effect estimates were obtained from intent-to-treat mixed-effect regression analyses.

[a] Effect size is calculated by dividing the effect estimate (b) by the residual standard deviation of the model

[b] Wake After Sleep Onset includes the time awake after final awakening, but before Lights On

Table 3. Estimated effects of time and time by treatment interactions on all outcome measures at T2 relative to T0

	T2 - T0[a]			ICBTI first x T2-T0			Any CT x T2 -T0			ICBTI first x Any CT x T2-T0		
Outcome measure	**β (SE)**	***d*[a]**	***P* Value**	**β (SE)**	***d*[a]**	***P* Value**	**β (SE)**	***d*[a]**	***P* Value**	**β (SE)**	***d*[a]**	***P* Value**
Sleep Diary												
Sleep Efficiency (%) (Primary)	13.39 (2.26)	0.85	**<.001**	-6.48 (3.12)	0.41	**.04**	-5.08 (2.61)	0.32	.05	11.07 (3.61)	0.70	**.003**
Time in Bed (min)	-29.88 (8.92)	0.51	**.001**	7.56 (12.35)	0.13	.54	5.06 (10.29)	0.09	.62	1.76 (14.29)	0.03	.90
Sleep Onset Latency (min)	-18.40 (8.34)	0.30	**.03**	17.89 (11.53)	0.29	.12	4.04 (9.63)	0.07	.68	-27.21 (13.36)	0.44	**.04**
Wake After Sleep Onset (min)[b]	-58.53 (14.56)	0.54	**<.001**	45.70 (20.13)	0.42	**.02**	14.53 (16.82)	0.13	.39	-66.14 (23.33)	0.61	**.01**
Total Sleep Time (min)	35.34 (11.26)	0.41	**.002**	-17.95 (15.56)	0.21	.25	-14.43 (13.01)	0.17	.27	46.92 (18.04)	0.55	**.01**
Average Daytime Functioning	0.46 (0.17)	0.77	**.01**	-0.49 (0.23)	0.82	**.04**	-0.26 (0.19)	0.44	.18	0.54 (0.27)	0.90	**.05**
Difficulty Initiating Sleep	-0.35 (0.22)	0.25	.12	0.02 (0.31)	0.01	.96	0.03 (0.26)	0.02	.92	-0.12 (0.36)	0.09	.74
Difficulty Maintaining Sleep	-1.00 (0.24)	0.72	**<.001**	0.28 (0.33)	0.20	.40	0.27 (0.27)	0.19	.32	-0.47 (0.38)	0.34	.21
Early Morning Awakening	-1.05 (0.23)	0.75	**<.001**	0.37 (0.32)	0.27	.24	0.23 (0.27)	0.16	.40	-0.74 (0.37)	0.53	**.05**
Actigraphy												
Sleep Efficiency (%)	2.62 (1.47)	0.34	.08	-0.29 (2.10)	0.04	.89	-1.73 (1.74)	0.22	.32	0.88 (2.45)	0.11	.72
Sleep Onset Latency (min)	-2.73 (2.55)	0.16	.29	0.95 (3.66)	0.05	.80	4.13 (3.04)	0.24	.18	0.37 (4.28)	0.02	.93
Wake After Sleep Onset (min)[b]	-5.99 (5.45)	0.18	.27	-8.82 (7.80)	0.27	.26	0.91 (6.48)	0.03	.89	7.67 (9.13)	0.23	.40
Total Sleep Time (min)	-18.87 (9.06)	0.33	**.04**	5.02 (12.98)	0.09	.70	1.75 (10.78)	0.03	.87	-1.91 (15.19)	0.03	.90
Average Sleep Bout Duration (min)	0.98 (9.89)	0.03	.92	14.97 (13.97)	0.50	.28	-0.27 (11.56)	0.01	.98	-5.32 (16.22)	0.18	.74
Average Wake Bout Duration (min)	-0.04 (0.06)	0.10	.53	-0.11 (0.08)	0.30	.18	-0.01 (0.07)	0.02	.92	0.08 (0.10)	0.23	.38
Sleep related surveys												
Insomnia Severity Index	-5.06 (1.04)	1.64	**<.001**	-0.20 (1.42)	0.07	.89	-0.52 (1.19)	0.17	.66	0.58 (1.63)	0.19	.72
Dysfunctional Beliefs and Attitudes	-13.87 (2.57)	1.83	**<.001**	3.63 (3.51)	0.48	.30	2.45 (2.94)	0.32	.41	-4.11 (4.03)	0.54	.31
Glasgow Sleep Effort Scale	-1.92 (0.51)	1.27	**<.001**	-0.67 (0.70)	0.44	.34	0.23 (0.58)	0.15	.69	0.95 (0.80)	0.63	.24
Sleep Locus Of Control	3.12 (1.12)	0.94	**.01**	-3.04 (1.53)	0.92	**.05**	-1.28 (1.28)	0.39	.32	3.45 (1.76)	1.04	.05
Sleep Self-Efficacy Scale	5.23 (1.31)	1.35	**<.001**	-0.17 (1.79)	0.04	.93	-0.82 (1.49)	0.21	.59	-0.87 (2.06)	0.22	.67
Hyperarousal												
Pre-Sleep Arousal Scale - Somatic	-0.31 (1.14)	0.10	.79	1.19 (1.54)	0.40	.44	-0.21 (1.29)	0.07	.87	-1.53 (1.76)	0.52	.38
Pre-Sleep Arousal Scale - Cognitive	-0.90 (1.38)	0.25	.52	-0.48 (1.86)	0.13	.80	-1.69 (1.56)	0.47	.28	0.34 (2.13)	0.10	.87
Arousal Predisposition Scale	-2.98 (1.12)	1.03	**.01**	1.85 (1.52)	0.64	.22	2.73 (1.27)	0.94	**.03**	-2.25 (1.73)	0.77	.20
Hyper Arousal Scale	-0.20 (1.01)	0.08	.85	-0.36 (1.36)	0.14	.79	-0.82 (1.14)	0.32	.47	-0.07 (1.56)	0.03	.97
Adult ADHD Self-Report Scale	-0.32 (0.86)	0.14	.71	-0.71 (1.16)	0.32	.54	-0.37 (0.98)	0.16	.71	1.19 (1.33)	0.53	.37
Mood and Affect												
Anxiety (HADS)	-1.29 (0.60)	0.71	**.03**	-0.08 (0.84)	0.04	.92	0.63 (0.69)	0.35	.37	-0.20 (0.97)	0.11	.84
Depression (HADS)	-1.20 (0.69)	0.57	.09	0.14 (0.97)	0.07	.89	-0.02 (0.80)	0.01	.98	0.08 (1.12)	0.04	.94
Positive Affect (PANAS)	3.77 (1.45)	0.86	**.01**	-3.89 (2.02)	0.89	.06	-2.62 (1.66)	0.60	.12	5.51 (2.33)	1.26	**.02**
Negative Affect (PANAS)	-1.97 (1.08)	0.60	.07	-1.48 (1.51)	0.45	.33	1.68 (1.24)	0.51	.18	0.22 (1.74)	0.07	.90
Temporal Experience of Pleasure	5.26 (1.77)	0.98	**.003**	-4.94 (2.47)	0.92	**.05**	-3.84 (2.04)	0.72	.06	4.78 (2.85)	0.89	.10
Quality of Life SF36												
Physical component summary	0.25 (1.24)	0.07	.84	-1.61 (1.71)	0.43	.35	-0.14 (1.42)	0.04	.92	1.56 (1.97)	0.41	.43
Mental component summary	3.10 (1.65)	0.62	.06	0.67 (2.28)	0.13	.77	-1.28 (1.90)	0.26	.50	1.46 (2.64)	0.29	.58

The model intercept and main effects of ICBTI and any CT are not shown. Main effects for ICBTI and any CT were non significant, except for a significantly higher intercept for participants receiving any CT on Depression (HADS) (β (SE) = 1.92 (0.89), *P* = .03 and SF 36 Physical Component Summary (β (SE) = 3.09 (1.47), *P* = .04)

Abbreviations: SE, standard error of β; ICBTI, Internet-based Cognitive Behavioral Therapy for Insomnia; CT, Chronobiological Treatment; ISI, Insomnia Severity Index HADS, Hospital Anxiety and Depression Scale; PANAS, Positive Affect Negative Affect Scale; SF36, Short Form 36. Effect estimates were obtained from intent-to-treat mixed-effect regression analyses.

[a] Effect size is calculated by dividing the absolute effect estimate (β) by the residual standard deviation of the model

[b] Wake After Sleep Onset includes the time awake after final awakening, but before Lights On

Table 4. Prior Expectations, Post-intervention Attribution and Compliance

Characteristic	Inactive Ionizer	Bright Light	Physical Activity	Warm Baths	ICBTI week 1-4	ICBTI week 6-9
Expected treatment effect						
n	41	44	45	44	87	87
no treatment[a]	0.15 (0.73)	-0.14 (0.67)	-0.18 (0.89)	-0.02 (0.76)	-0.07 (0.90)	-0.03 (0.62)
CT[a]	0.50 (0.75)	0.49 (0.88)	0.68 (1.06)	0.29 (0.77)	0.57 (0.95)	0.40 (0.80)
ICBTI[a]	1.39 (0.80)	1.14 (0.80)	1.47 (0.79)	1.32 (0.93)	1.38 (0.81)	1.28 (0.86)
Post-intervention Attribution						
n	40	43	41	42	84	82
CT[a]	0.50 (0.75)	0.49 (0.88)	0.68 (1.06)	0.29 (0.77)	0.57 (0.95)	0.40 (0.80)
n	39	40	37	40	83	73
ICBTI[a]	1.49 (0.82)	1.15 (1.12)	1.00 (1.20)	1.20 (0.88)	1.25 (0.96)	1.16 (1.09)
Compliance						
n	40	43	42	42	84	83
CT	26.33 (2.40)	25.93 (5.10)	22.17 (5.82)	21.36 (6.63)	23.98 (5.91)	23.88 (5.43)
n	40	41	37	42	84	76
ICBTI[b]	21.68 (6.15)	22.46 (6.42)	21.97 (5.38)	22.45 (5.76)	22.92 (5.46)	21.30 (6.29)

Data are Mean (SD). Test statistics are between treatment effects. ICBTI = Internet-based Cognitive Behavioural Therapy for Insomnia.

Given sample sizes are of available data

[a] -3 = very much deteriorated, -2 = deteriorated, -1 = slightly deteriorated, 0 = no change, 1 = slightly improved, 2 = improved, 3 = very much

[b] Compliance for ICBTI is for sleep restriction

Table 5. Estimated effects of time and treatment by time interactions on all outcome measures at T1 relative to T0

	T1 - T0			ICBTI x T1-T0			Bright Light x T1-T0			Physical Activity x T1-T0			Warm Baths x T1-T0			ICBTI x Bright Light x T1-T0			ICBTI x Physical Activity x T1-T0			ICBTI x Warm Baths x T1-T0		
Outcome measure	**β (SE)**	***d*[a]**	***P* Value**	**β (SE)**	***d*[a]**	***P* Value**	**β (SE)**	***d*[a]**	***P* Value**	**β (SE)**	***d*[a]**	***P* Value**	**β (SE)**	***d*[a]**	***P* Value**	**β (SE)**	***d*[a]**	***P* Value**	**β (SE)**	***d*[a]**	***P* Value**	**β (SE)**	***d*[a]**	***P* Value**
Sleep Diary																								
Sleep Efficiency (%) (Primary)	5.55 (2.35)	0.34	**.02**	6.68 (3.24)	0.41	**.04**	-1.13 (3.20)	0.07	.72	-4.65 (3.23)	0.28	.15	-3.18 (3.28)	0.19	.34	0.41 (4.51)	0.02	.93	5.66 (4.55)	0.35	.22	4.28 (4.53)	0.26	.35
Time in Bed (min)	-8.03 (9.53)	0.13	.40	-31.35 (13.18)	0.52	**.02**	11.27 (12.98)	0.19	.39	16.35 (13.11)	0.27	.21	2.83 (13.36)	0.05	.83	0.04 (18.33)	0.00	1.00	-8.62 (18.48)	0.14	.64	14.74 (18.41)	0.24	.42
Sleep Onset Latency (min)	0.41 (8.67)	0.01	.96	-16.71 (11.99)	0.25	.17	-2.97 (11.83)	0.04	.80	-3.20 (11.94)	0.05	.79	-1.50 (12.17)	0.02	.90	1.77 (16.69)	0.03	.92	-10.59 (16.81)	0.16	.53	-9.87 (16.76)	0.15	.56
Wake After Sleep Onset (min)[b]	-2.54 (16.86)	0.02	.88	-44.35 (23.31)	0.37	.06	-17.07 (23.00)	0.14	.46	-7.92 (23.21)	0.07	.73	9.10 (23.66)	0.08	.70	7.79 (32.43)	0.06	.81	-14.94 (32.68)	0.12	.65	-37.63 (32.59)	0.31	.25
Total Sleep Time (min)	16.66 (10.92)	0.19	.13	10.19 (15.06)	0.12	.50	8.64 (14.90)	0.10	.56	-8.67 (15.07)	0.10	.57	-12.67 (15.29)	0.14	.41	-5.97 (20.99)	0.07	.78	22.17 (21.18)	0.25	.30	35.34 (21.06)	0.40	.09
Average Daytime Functioning	0.16 (0.16)	0.26	.31	-0.14 (0.22)	0.23	.52	0.11 (0.22)	0.18	.60	-0.15 (0.22)	0.25	.48	-0.27 (0.23)	0.44	.23	-0.09 (0.31)	0.15	.77	0.29 (0.31)	0.47	.35	0.48 (0.31)	0.77	.13
Difficulty Initiating Sleep	-0.22 (0.24)	0.16	.36	-0.20 (0.33)	0.14	.55	-0.01 (0.33)	0.01	.97	0.23 (0.33)	0.16	.49	0.00 (0.34)	0.00	1.00	0.09 (0.46)	0.06	.85	-0.30 (0.47)	0.21	.53	0.04 (0.47)	0.03	.93
Difficulty Maintaining Sleep	-0.70 (0.19)	0.50	**<.001**	0.01 (0.26)	0.01	.96	0.05 (0.26)	0.04	.84	0.33 (0.26)	0.23	.22	0.10 (0.27)	0.07	.71	-0.21 (0.37)	0.15	.56	-0.52 (0.37)	0.37	.16	-0.16 (0.37)	0.11	.67
Early Morning Awakening	-0.54 (0.24)	0.38	**.02**	0.11 (0.33)	0.08	.75	-0.37 (0.32)	0.26	.26	-0.04 (0.33)	0.03	.91	0.13 (0.33)	0.09	.70	-0.18 (0.45)	0.13	.69	-0.56 (0.46)	0.40	.22	-0.69 (0.46)	0.49	.14
Actigraphy																								
Sleep Efficiency (%)	0.01 (1.43)	0.00	.99	1.56 (2.00)	0.19	.44	-1.15 (2.02)	0.14	.57	0.12 (2.08)	0.02	.95	1.36 (2.05)	0.17	.51	0.47 (2.85)	0.06	.87	0.82 (2.89)	0.10	.78	0.94 (2.84)	0.12	.74
Sleep Onset Latency (min)	-0.47 (2.70)	0.03	.86	0.30 (3.79)	0.02	.94	0.93 (3.80)	0.05	.81	7.87 (3.91)	0.47	**.05**	-0.39 (3.87)	0.02	.92	0.06 (5.37)	0.00	.99	-11.89 (5.43)	0.70	**.03**	0.84 (5.37)	0.05	.88
Wake After Sleep Onset (min)[b]	3.20 (5.20)	0.09	.54	-14.15 (7.30)	0.40	.05	-3.10 (7.38)	0.09	.67	-5.32 (7.63)	0.15	.49	-11.88 (7.48)	0.34	.11	8.90 (10.40)	0.25	.39	12.15 (10.55)	0.35	.25	6.91 (10.38)	0.20	.51
Total Sleep Time (min)	-4.13 (8.96)	0.07	.65	-29.91 (12.57)	0.51	**.02**	6.86 (12.70)	0.12	.59	9.94 (13.13)	0.17	.45	5.39 (12.87)	0.09	.68	-2.82 (17.89)	0.05	.87	2.67 (18.16)	0.05	.88	13.42 (17.87)	0.23	.45
Average Sleep Bout Duration (min)	-0.36 (9.11)	0.01	.97	7.94 (12.75)	0.22	.53	-0.43 (12.69)	0.01	.97	25.15 (12.92)	0.68	.05	21.04 (13.00)	0.57	.11	0.43 (17.94)	0.01	.98	-28.96 (18.11)	0.79	.11	-32.35 (18.01)	0.88	.07
Average Wake Bout Duration (min)	-0.01 (0.05)	0.02	.90	0.00 (0.07)	0.01	.96	-0.09 (0.07)	0.24	.23	0.02 (0.07)	0.05	.82	-0.07 (0.07)	0.21	.30	-0.02 (0.10)	0.05	.85	-0.05 (0.10)	0.15	.60	0.03 (0.10)	0.08	.76
Sleep related surveys																								
Insomnia Severity Index	-1.81 (0.88)	0.66	**.04**	-2.93 (1.23)	1.07	**.02**	1.24 (1.21)	0.45	.31	1.73 (1.20)	0.63	.15	0.21 (1.24)	0.08	.86	-1.26 (1.71)	0.46	.46	-3.77 (1.72)	1.38	**.03**	0.00 (1.72)	0.00	1.00
Dysfunctional Beliefs and Attitudes	-1.91 (1.98)	0.32	.34	-6.65 (2.73)	1.12	**.02**	0.97 (2.69)	0.16	.72	1.29 (2.67)	0.22	.63	0.06 (2.73)	0.01	.98	-1.78 (3.76)	0.30	.64	-5.06 (3.79)	0.85	.18	-1.70 (3.79)	0.29	.65
Glasgow Sleep Effort Scale	-0.88 (0.45)	-0.65	.05	-1.28 (0.62)	0.94	**.04**	0.73 (0.62)	0.53	.24	0.28 (0.61)	0.21	.64	1.13 (0.63)	0.83	.07	0.25 (0.86)	0.18	.77	-0.06 (0.87)	0.04	.95	-0.40 (0.87)	0.29	.64
Sleep Locus Of Control	0.71 (0.93)	0.25	.44	-0.27 (1.29)	0.09	.84	-0.43 (1.28)	0.15	.74	-0.69 (1.26)	0.24	.58	-0.46 (1.30)	0.16	.72	2.36 (1.80)	0.83	.19	3.05 (1.81)	1.07	.09	3.03 (1.81)	1.06	.10
Sleep Self-Efficacy Scale	1.08 (1.18)	0.29	.36	2.10 (1.65)	0.58	.20	-1.31 (1.62)	0.36	.42	-0.94 (1.61)	0.26	.56	-0.48 (1.65)	0.13	.77	1.23 (2.28)	0.34	.59	1.22 (2.30)	0.33	.60	-0.89 (2.30)	0.24	.70
Hyperarousal																								
Pre-Sleep Arousal Scale - Somatic	1.15 (0.95)	0.46	.23	-0.76 (1.29)	0.31	.56	-0.50 (1.27)	0.20	.69	-1.07 (1.27)	0.43	.40	-0.98 (1.26)	0.39	.44	-0.35 (1.76)	0.14	.84	-0.08 (1.78)	0.03	.97	-0.15 (1.72)	0.06	.93
Pre-Sleep Arousal Scale - Cognitive	0.74 (1.55)	0.18	.64	-4.84 (2.10)	1.19	**.02**	-1.41 (2.07)	0.35	.50	-2.56 (2.07)	0.63	.22	-3.68 (2.06)	0.90	.08	4.17 (2.87)	1.02	.15	3.56 (2.91)	0.87	.22	6.46 (2.82)	1.58	**.02**
Arousal Predisposition Scale	-0.99 (1.09)	0.35	.36	1.60 (1.47)	0.57	.28	0.77 (1.45)	0.27	.60	2.64 (1.44)	0.94	.07	-0.45 (1.44)	0.16	.75	-1.58 (2.00)	0.56	.43	-2.90 (2.02)	1.03	.15	-0.84 (1.96)	0.30	.67
Hyper Arousal Scale	-1.29 (1.11)	0.45	.25	1.83 (1.51)	0.63	.23	1.94 (1.49)	0.67	.19	1.47 (1.48)	0.51	.32	-0.32 (1.47)	0.11	.83	-2.65 (2.05)	0.92	.20	-3.39 (2.08)	1.17	.11	-0.02 (2.01)	0.01	.99
Adult ADHD Self-Report Scale	-0.54 (0.79)	0.26	.49	0.53 (1.07)	0.26	.62	1.59 (1.05)	0.77	.13	-0.24 (1.05)	0.12	.82	-0.62 (1.05)	0.30	.55	-2.51 (1.46)	1.22	.09	-0.52 (1.47)	0.25	.73	0.09 (1.43)	0.04	.95
Mood and Affect																								
Anxiety (HADS)	-0.19 (0.51)	0.12	.71	-1.21 (0.71)	0.76	.09	0.81 (0.70)	0.51	.25	0.37 (0.70)	0.23	.60	0.24 (0.71)	0.15	.74	-0.27 (0.99)	0.17	.79	-0.70 (1.01)	0.44	.49	0.87 (0.99)	0.55	.38
Depression (HADS)	-0.12 (0.58)	0.07	.84	-1.11 (0.81)	0.62	.17	0.45 (0.79)	0.25	.57	-0.27 (0.80)	0.15	.74	-0.13 (0.81)	0.07	.87	0.07 (1.12)	0.04	.95	-0.19 (1.14)	0.10	.87	0.75 (1.13)	0.42	.51
Positive Affect (PANAS)	1.18 (1.25)	0.30	.35	0.28 (1.75)	0.07	.87	-1.99 (1.71)	0.51	.25	-1.98 (1.72)	0.51	.25	-2.38 (1.75)	0.61	.18	2.05 (2.41)	0.53	.40	2.87 (2.45)	0.74	.24	1.93 (2.43)	0.50	.43
Negative Affect (PANAS)	-0.07 (0.96)	0.02	.95	-2.76 (1.34)	0.93	**.04**	1.30 (1.31)	0.44	.32	1.45 (1.32)	0.49	.28	-0.28 (1.34)	0.10	.83	-0.28 (1.85)	0.10	.88	0.66 (1.88)	0.22	.73	2.90 (1.86)	0.98	.12
Temporal Experience of Pleasure	3.03 (1.70)	0.58	.08	-3.19 (2.38)	0.61	.18	-5.58 (2.32)	1.06	**.02**	-2.98 (2.34)	0.57	.20	-1.93 (2.38)	0.37	.42	6.31 (3.28)	1.20	.06	5.98 (3.34)	1.14	.07	3.29 (3.30)	0.62	.32
Quality of Life SF36																								
Physical Component Summary	-0.18 (1.26)	0.05	.89	0.36 (1.77)	0.09	.84	-0.53 (1.71)	0.14	.76	-0.65 (1.71)	0.17	.70	0.50 (1.76)	0.13	.77	0.14 (2.44)	0.04	.96	1.08 (2.46)	0.28	.66	-0.91 (2.47)	0.23	.71
Mental Component Summary	0.72 (1.74)	0.13	.68	2.57 (2.45)	0.48	.30	-3.46 (2.37)	0.64	.15	-1.50 (2.37)	0.28	.53	0.94 (2.43)	0.17	.70	1.90 (3.37)	0.35	.57	-0.25 (3.41)	0.05	.94	0.82 (3.41)	0.15	.81

The model intercept and main effects of ICBTI and any CT are not shown. Main effects for ICBTI and any CT were non significant, except for a significantly higher intercept for participants receiving ICBTI combined with Warm Baths on sleep diary WASO (β (SE) =88.12 (40.63), *P* = .03), a lower intercept for participants receiving Bright Light on Sleep Locus of Control (β (SE) = -3.48 (1.71), *P* = .04) and a higher intercept for participants receiving Physical Activity on Depression (HADS) (β (SE) = 2.48 (1.11), *P* = .03) and SF 36 Physical Component Summary (β (SE) = 3.61 (1.80), *P* = .05)

Abbreviations: SE, standard error of β; ICBTI, Internet-based Cognitive Behavioral Therapy for Insomnia; CT, Chronobiological Treatment; HADS, Hospital Anxiety and Depression Scale; PANAS, Positive Affect Negative Affect Scale; SF36, Short Form 36. Effect estimates were obtained from intent-to-treat mixed-effect regression analyses.

[a] Effect size is calculated by dividing the absolute effect estimate (β) by the residual standard deviation of the model

[b] Wake After Sleep Onset includes the time awake after final awakening, but before Lights On

Table 6. Estimated effects of time and treatment by time interactions on subjective and all outcome measures at T2 relative to T0

	T2 - T0			ICBTI x T2-T0			Bright Light x T2-T0			Physical Activity x T2-T0			Warm Baths x T2-T0			ICBTI x Bright Light x T2-T0			ICBTI x Physical Activity x T2-T0			ICBTI x Warm Baths x T2-T0		
Outcome measure	β (SE)	d[a]	*P* Value	β (SE)	d[a]	*P* Value	β (SE)	d[a]	*P* Value	β (SE)	d[a]	*P* Value	β (SE)	d[a]	*P* Value	β (SE)	d[a]	*P* Value	β (SE)	d[a]	*P* Value	β (SE)	d[a]	*P* Value
Sleep Diary																								
Sleep Efficiency (%) (Primary)	13.40 (2.25)	0.85	**<.001**	-6.48 (3.11)	0.41	**.04**	-4.06 (3.15)	0.26	.20	-6.38 (3.25)	0.40	.05	-5.10 (3.17)	0.32	.11	10.97 (4.37)	0.69	**.01**	12.85 (4.50)	0.81	**.005**	9.42 (4.43)	0.60	**.04**
Time in Bed (min)	-29.85 (8.83)	0.51	**.001**	7.52 (12.22)	0.13	.54	6.76 (12.31)	0.11	.58	9.85 (12.69)	0.17	.44	-0.75 (12.44)	0.01	.95	6.45 (17.15)	0.11	.71	-15.50 (17.60)	0.26	.38	13.71 (17.38)	0.23	.43
Sleep Onset Latency (min)	-18.40 (8.32)	0.30	**.03**	17.88 (11.51)	0.29	.12	6.09 (11.63)	0.10	.60	2.65 (12.01)	0.04	.83	3.29 (11.73)	0.05	.78	-27.75 (16.17)	0.45	.09	-31.18 (16.62)	0.51	.06	-22.16 (16.39)	0.36	.18
Wake After Sleep Onset (min)[b]	-58.53 (14.47)	0.54	**<.001**	45.70 (20.02)	0.42	**.02**	13.27 (20.25)	0.12	.51	1.47 (20.92)	0.01	.94	28.38 (20.39)	0.26	.17	-58.46 (28.13)	0.54	**.04**	-56.39 (28.92)	0.52	.05	-82.30 (28.51)	0.76	**.004**
Total Sleep Time (min)	35.34 (11.22)	0.41	**.002**	-17.95 (15.51)	0.21	.25	-7.39 (15.69)	0.09	.64	-16.01 (16.22)	0.19	.33	-20.68 (15.82)	0.24	.19	45.92 (21.80)	0.53	**.04**	42.27 (22.42)	0.49	.06	52.35 (22.11)	0.61	**.02**
Average Daytime Functioning	0.46 (0.16)	0.77	**.01**	-0.49 (0.23)	0.83	**.03**	-0.06 (0.23)	0.10	.80	-0.16 (0.24)	0.27	.49	-0.56 (0.23)	0.94	**.02**	0.26 (0.32)	0.43	.42	0.29 (0.33)	0.48	.39	1.05 (0.32)	1.76	**.001**
Difficulty Initiating Sleep	-0.35 (0.22)	0.25	.11	0.02 (0.30)	0.01	.95	-0.21 (0.31)	0.16	.48	0.22 (0.32)	0.16	.49	0.10 (0.31)	0.08	.74	0.06 (0.43)	0.05	.88	-0.51 (0.44)	0.37	.25	0.07 (0.43)	0.05	.88
Difficulty Maintaining Sleep	-1.00 (0.23)	0.72	**<.001**	0.28 (0.32)	0.20	.39	0.10 (0.32)	0.07	.77	0.14 (0.33)	0.10	.68	0.56 (0.33)	0.40	.09	-0.32 (0.45)	0.23	.48	-0.41 (0.46)	0.29	.38	-0.68 (0.46)	0.49	.14
Early Morning Awakening	-1.05 (0.23)	0.75	**<.001**	0.37 (0.32)	0.27	.24	-0.03 (0.32)	0.02	.92	0.14 (0.33)	0.10	.68	0.56 (0.32)	0.40	.08	-0.54 (0.44)	0.38	.22	-0.59 (0.45)	0.42	.19	-1.06 (0.45)	0.75	**.02**
Actigraphy																								
Sleep Efficiency (%)	2.62 (1.46)	0.34	.07	-0.28 (2.08)	0.04	.90	-1.59 (2.15)	0.20	.46	-0.45 (2.26)	0.06	.84	-2.88 (2.14)	0.37	.18	-0.23 (2.99)	0.03	.94	-0.41 (3.08)	0.05	.89	3.04 (3.00)	0.39	.31
Sleep Onset Latency (min)	-2.72 (2.55)	0.16	.29	0.94 (3.65)	0.05	.80	2.84 (3.76)	0.16	.45	5.23 (3.96)	0.30	.19	4.34 (3.75)	0.25	.25	0.73 (5.25)	0.04	.89	1.01 (5.40)	0.06	.85	-0.59 (5.26)	0.03	.91
Wake After Sleep Onset (min)[b]	-5.97 (5.45)	0.18	.28	-8.85 (7.80)	0.27	.26	3.69 (8.04)	0.11	.65	-1.16 (8.49)	0.04	.89	-0.07 (8.01)	0.00	.99	5.38 (11.22)	0.16	.63	9.19 (11.55)	0.28	.43	8.67 (11.24)	0.26	.44
Total Sleep Time (min)	-18.88 (8.96)	0.33	**.04**	5.10 (12.84)	0.09	.69	0.26 (13.25)	0.00	.98	12.46 (14.01)	0.22	.38	-4.53 (13.19)	0.08	.73	-1.53 (18.48)	0.03	.93	-20.23 (19.04)	0.36	.29	13.34 (18.51)	0.23	.47
Average Sleep Bout Duration (min)	0.98 (9.80)	0.03	.92	14.97 (13.85)	0.50	.28	1.72 (14.00)	0.06	.90	-1.61 (14.50)	0.05	.91	-0.58 (14.22)	0.02	.97	7.36 (19.67)	0.25	.71	-8.72 (20.06)	0.29	.66	-15.29 (19.81)	0.51	.44
Average Wake Bout Duration (min)	-0.04 (0.06)	0.10	.53	-0.11 (0.08)	0.30	.18	-0.06 (0.09)	0.16	.50	0.03 (0.09)	0.07	.78	0.02 (0.08)	0.04	.85	0.12 (0.12)	0.34	.30	0.08 (0.12)	0.21	.53	0.05 (0.12)	0.13	.69
Sleep related surveys																								
Insomnia Severity Index	-5.06 (1.01)	1.68	**<.001**	-0.20 (1.39)	0.07	.88	-1.96 (1.39)	0.65	.16	0.91 (1.44)	0.30	.53	-0.39 (1.39)	0.13	.78	1.91 (1.93)	0.64	.32	-2.18 (1.97)	0.72	.27	1.92 (1.93)	0.64	.32
Dysfunctional Beliefs and Attitudes	-13.88 (2.54)	1.85	**<.001**	3.63 (3.46)	0.49	.30	-0.02 (3.49)	0.00	.99	3.37 (3.62)	0.45	.35	4.13 (3.47)	0.55	.24	0.33 (4.82)	0.04	.94	-7.75 (4.95)	1.04	.12	-5.17 (4.83)	0.69	.29
Glasgow Sleep Effort Scale	-1.92 (0.50)	1.29	**<.001**	-0.67 (0.69)	0.45	.33	-0.01 (0.69)	0.01	.99	-0.16 (0.72)	0.11	.83	0.87 (0.69)	0.58	.21	1.23 (0.96)	0.83	.20	0.95 (0.98)	0.64	.34	0.69 (0.96)	0.46	.48
Sleep Locus Of Control	3.12 (1.12)	0.95	**.01**	-3.04 (1.52)	0.92	**.05**	-0.54 (1.53)	0.16	.73	-2.59 (1.59)	0.79	.11	-0.92 (1.53)	0.28	.55	2.50 (2.12)	0.76	.24	4.84 (2.18)	1.47	**.03**	3.18 (2.13)	0.97	.14
Sleep Self-Efficacy Scale	5.23 (1.26)	1.40	**<.001**	-0.16 (1.72)	0.04	.93	2.27 (1.73)	0.61	.19	-2.09 (1.79)	0.56	.25	-2.83 (1.73)	0.76	.10	-4.06 (2.40)	1.09	.09	0.84 (2.46)	0.22	.73	0.74 (2.40)	0.20	.76
Hyperarousal																								
Pre-Sleep Arousal Scale - Somatic	-0.30 (1.12)	0.10	.79	1.18 (1.52)	0.40	.44	-1.22 (1.50)	0.42	.41	0.73 (1.53)	0.25	.63	-0.01 (1.57)	0.00	1.00	-0.22 (2.04)	0.07	.92	-2.80 (2.16)	0.95	.20	-1.85 (2.12)	0.63	.39
Pre-Sleep Arousal Scale - Cognitive	-0.90 (1.35)	0.26	.51	-0.48 (1.83)	0.14	.79	-0.76 (1.80)	0.22	.67	-0.84 (1.85)	0.24	.65	-3.74 (1.88)	1.06	**.05**	-0.70 (2.46)	0.20	.78	-1.33 (2.60)	0.38	.61	3.19 (2.56)	0.91	.21
Arousal Predisposition Scale	-2.98 (1.10)	1.05	**.01**	1.86 (1.48)	0.65	.21	2.99 (1.46)	1.05	**.04**	3.50 (1.50)	1.23	**.02**	1.56 (1.53)	0.55	.31	-1.69 (1.99)	0.59	.40	-2.46 (2.11)	0.87	.24	-2.45 (2.07)	0.86	.24
Hyper Arousal Scale	-0.20 (1.00)	0.08	.84	-0.36 (1.35)	0.14	.79	-0.67 (1.33)	0.26	.61	-0.17 (1.36)	0.07	.90	-1.72 (1.39)	0.67	.22	0.23 (1.81)	0.09	.90	-0.99 (1.92)	0.38	.61	0.58 (1.89)	0.22	.76
Adult ADHD Self-Report Scale	-0.31 (0.85)	0.14	.71	-0.71 (1.15)	0.32	.54	0.24 (1.13)	0.11	.83	-0.57 (1.16)	0.26	.63	-0.90 (1.19)	0.40	.45	0.61 (1.55)	0.27	.70	0.62 (1.63)	0.28	.71	2.29 (1.61)	1.03	.16
Mood and Affect																								
Anxiety (HADS)	-1.29 (0.59)	0.72	**.03**	-0.08 (0.83)	0.05	.92	0.76 (0.83)	0.42	.36	0.37 (0.86)	0.21	.67	0.74 (0.82)	0.41	.37	-0.12 (1.16)	0.07	.92	-0.75 (1.21)	0.42	.53	0.18 (1.16)	0.10	.88
Depression (HADS)	-1.20 (0.69)	0.58	.08	0.14 (0.96)	0.07	.89	0.03 (0.95)	0.01	.98	0.13 (0.99)	0.06	.89	-0.15 (0.95)	0.07	.88	0.32 (1.34)	0.15	.81	-0.85 (1.40)	0.41	.54	0.57 (1.34)	0.28	.67
Positive Affect (PANAS)	3.77 (1.43)	0.87	**.01**	-3.89 (2.00)	0.90	.05	-1.77 (1.99)	0.41	.37	-2.21 (2.06)	0.51	.28	-3.67 (1.98)	0.85	.07	3.77 (2.79)	0.87	.18	6.74 (2.89)	1.55	**.02**	6.11 (2.79)	1.41	**.03**
Negative Affect (PANAS)	-1.97 (1.07)	0.61	.07	-1.48 (1.50)	0.46	.33	3.26 (1.49)	1.01	**.03**	0.53 (1.55)	0.16	.73	1.17 (1.48)	0.36	.43	-1.68 (2.09)	0.52	.42	1.66 (2.17)	0.51	.45	0.83 (2.09)	0.26	.69
Temporal Experience of Pleasure	5.26 (1.76)	0.99	**.003**	-4.94 (2.46)	0.93	.05	-3.21 (2.44)	0.60	.19	-3.86 (2.54)	0.73	.13	-4.36 (2.43)	0.82	.08	3.81 (3.42)	0.72	.27	6.47 (3.56)	1.22	.07	4.18 (3.43)	0.79	.22
Quality of Life SF36																								
Physical Component Summary	0.25 (1.23)	0.07	.84	-1.61 (1.70)	0.43	.34	0.16 (1.71)	0.04	.93	0.17 (1.77)	0.05	.92	-0.59 (1.70)	0.16	.73	2.10 (2.38)	0.56	.38	1.71 (2.44)	0.46	.48	0.76 (2.38)	0.20	.75
Mental Component Summary	3.10 (1.61)	0.64	.06	0.67 (2.22)	0.14	.76	-1.65 (2.24)	0.34	.46	-3.04 (2.33)	0.62	.19	0.37 (2.23)	0.08	.87	-0.73 (3.12)	0.15	.81	3.85 (3.20)	0.79	.23	1.71 (3.12)	0.35	.59

The model intercept and main effects of ICBTI and any CT are not shown. Main effects for ICBTI and any CT were non significant, except for a significantly higher intercept for participants receiving ICBT in week 1-4 combined with Warm Baths on sleep diary WASO (b (SE) =88.64 (41.31), *P* = .03) and a higher intercept for participants receiving Physical Activity on Depression (HADS) (b (SE) = 2.25 (1.07), *P* = .04) and SF 36 Physical Component Summary (β (SE) = 3.62 (1.74), *P* = .04)

Abbreviations: SE, standard error of β ; ICBTI, Internet-based Cognitive Behavioral Therapy for Insomnia; CT, Chronobiological Treatment; ISI, Insomnia Severity Index. Effect estimates were obtained from intent-to-treat mixed-effect regression analyses.

[a] Effect size is calculated by dividing the absolute effect estimate (β) by the residual standard deviation of the model

[b] Wake After Sleep Onset includes the time awake after final awakening, but before Lights On

Table 7. Means and Standard Deviations for Sleep Parameters[a]

	week 1 - 4	Inactive Ionizer		Bright Light		Physical Activiy		Warm Baths		Inactive Ionizer + ICBTI		Bright Light + ICBTI		Physical Activity + ICBTI		Warm Baths + ICBTI		
	week 6 - 9	ICBTI		ICBTI		ICBTI		ICBTI		no treatment								All
Variable		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
									Sleep Diary										
Sleep Efficiency (%) - Primary Outcome																			
T0		20	67.77 (15.00)	24	71.10 (11.66)	24	72.29 (12.14)	20	75.09 (11.39)	21	66.98 (11.96)	21	71.28 (10.64)	21	64.32 (24.02)	24	66.42 (17.81)	175	69.41 (15.00)
T1		19	73.79 (13.71)	22	76.99 (10.78)	22	73.01 (13.07)	20	77.32 (13.61)	21	79.32 (9.66)	21	83.15 (7.24)	20	79.16 (18.03)	22	78.58 (17.89)	167	77.68 (13.50)
T2		19	81.60 (11.11)	20	81.34 (9.12)	17	79.50 (8.56)	20	83.21 (8.31)	21	73.95 (14.58)	21	85.11 (5.81)	19	79.10 (17.71)	19	76.08 (19.90)	156	80.01 (12.93)
Time in Bed (min)																			
T0		20	479.24 (47.59)	24	483.75 (37.61)	24	471.06 (48.25)	20	470.20 (33.15)	21	482.22 (48.80)	21	458.11 (42.59)	21	485.58 (52.03)	24	473.98 (39.59)	175	475.57 (43.98)
T1		19	473.31 (45.68)	22	488.07 (57.00)	22	484.63 (63.56)	20	465.28 (39.81)	21	443.10 (39.71)	21	429.75 (41.33)	20	454.43 (40.15)	22	453.66 (42.21)	167	461.66 (50.02)
T2		19	451.80 (44.23)	20	460.50 (35.93)	17	452.12 (43.51)	20	438.84 (46.44)	21	460.14 (40.85)	21	448.93 (31.34)	19	455.85 (38.82)	19	465.52 (39.38)	156	454.19 (40.05)
Sleep Onset Latency (min)																			
T0		20	43.45 (36.96)	24	35.61 (27.55)	24	37.03 (48.86)	20	34.60 (33.11)	21	44.50 (27.54)	21	38.88 (34.06)	21	72.68 (78.98)	24	59.88 (104.91)	175	45.82 (56.90)
T1		19	44.21 (48.22)	22	33.90 (25.74)	22	35.54 (39.35)	20	33.50 (35.17)	21	28.20 (26.42)	21	21.46 (15.41)	20	37.73 (35.26)	22	34.32 (66.74)	167	33.47 (39.11)
T2		19	25.45 (27.30)	20	23.36 (19.09)	17	23.87 (23.56)	20	19.25 (17.34)	21	43.85 (41.00)	21	16.70 (11.16)	19	38.46 (41.87)	19	45.56 (95.27)	156	29.55 (42.80)
Wake After Sleep Onset (min)[b]																			
T0		20	129.40 (90.37)	24	111.35 (65.37)	24	123.59 (80.44)	20	89.56 (59.01)	21	116.20 (43.09)	21	108.44 (50.98)	21	157.24 (151.90)	24	165.51 (199.81)	175	125.77 (108.17)
T1		19	126.95 (100.89)	22	85.49 (53.67)	22	114.84 (73.21)	20	97.00 (79.95)	21	69.42 (38.56)	21	51.63 (27.91)	20	73.07 (91.55)	22	97.76 (126.42)	167	89.30 (81.61)
T2		19	71.05 (64.15)	20	62.23 (43.22)	17	71.13 (33.08)	20	60.32 (39.10)	21	103.47 (79.80)	21	50.41 (22.50)	19	75.11 (89.52)	19	114.89 (182.08)	156	75.97 (84.34)
Total Sleep Time (min)																			
T0		20	328.09 (79.03)	24	343.75 (60.47)	24	339.76 (55.49)	20	353.11 (52.24)	21	323.55 (59.65)	21	325.77 (56.82)	21	311.72 (113.57)	24	312.85 (87.94)	175	329.82 (73.10)
T1		19	348.27 (64.46)	22	376.82 (55.52)	22	351.83 (82.66)	20	356.64 (58.60)	21	351.17 (47.09)	21	356.49 (38.16)	20	359.62 (91.60)	22	358.64 (90.99)	167	357.63 (67.95)
T2		19	366.80 (45.85)	20	374.92 (45.03)	17	359.46 (53.98)	20	365.91 (54.83)	21	341.29 (82.68)	21	381.65 (38.82)	19	359.32 (80.17)	19	355.86 (96.56)	156	363.25 (64.88)
Average Daytime Functioning[c]																			
T0		20	4.54 (0.75)	24	4.35 (0.50)	24	4.57 (0.85)	20	4.55 (0.75)	21	4.63 (0.75)	21	4.77 (0.72)	21	4.79 (0.67)	24	4.43 (0.92)	175	4.57 (0.75)
T1		19	4.67 (0.90)	22	4.63 (0.75)	22	4.63 (0.86)	20	4.44 (0.74)	21	4.65 (0.78)	21	4.82 (0.84)	20	4.98 (0.79)	22	4.67 (0.86)	167	4.69 (0.81)
T2		19	4.97 (0.77)	20	4.78 (0.84)	17	5.05 (0.84)	20	4.46 (0.74)	21	4.59 (0.81)	21	4.93 (0.81)	19	4.94 (0.73)	19	4.89 (0.98)	156	4.82 (0.82)
Difficulty Initiating Sleep[d]																			
T0		20	3.26 (1.00)	24	3.56 (1.01)	24	3.10 (1.27)	20	3.17 (1.09)	21	3.60 (1.24)	21	3.32 (1.23)	21	3.50 (1.41)	24	3.20 (1.23)	175	3.34 (1.18)
T1		19	3.05 (0.86)	22	3.30 (1.04)	22	3.09 (1.26)	20	2.94 (0.91)	21	3.18 (1.11)	21	2.96 (0.96)	20	2.96 (1.20)	22	2.88 (0.98)	167	3.05 (1.04)
T2		19	2.90 (0.78)	20	2.94 (0.78)	17	2.82 (0.93)	20	2.90 (0.85)	21	3.27 (1.18)	21	2.84 (0.92)	19	2.82 (1.30)	19	3.06 (0.95)	156	2.95 (0.97)
Dificulty Maintaining Sleep[d]																			
T0		20	4.96 (0.77)	24	4.77 (1.30)	24	4.97 (0.94)	20	4.81 (0.73)	21	4.85 (0.87)	21	4.83 (1.03)	21	4.49 (1.28)	24	4.70 (1.16)	175	4.80 (1.03)
T1		19	4.20 (0.97)	22	4.06 (1.23)	22	4.52 (1.40)	20	4.22 (0.86)	21	4.17 (0.92)	21	4.01 (0.78)	20	3.62 (1.28)	22	4.05 (1.22)	167	4.11 (1.11)
T2		19	3.90 (0.89)	20	3.90 (1.30)	17	4.01 (1.16)	20	4.36 (0.99)	21	4.13 (1.29)	21	3.88 (0.82)	19	3.53 (1.37)	19	3.93 (1.01)	156	3.96 (1.12)
Early Morning Awakening[d]																			
T0		20	4.58 (0.96)	24	4.66 (1.21)	24	4.46 (1.08)	20	4.46 (0.95)	21	4.37 (1.25)	21	4.60 (1.11)	21	4.49 (1.18)	24	4.72 (1.08)	175	4.55 (1.09)
T1		19	4.05 (1.12)	22	3.68 (1.34)	22	3.81 (1.35)	20	4.05 (1.02)	21	3.94 (1.10)	21	3.61 (0.89)	20	3.42 (1.21)	22	3.84 (1.20)	167	3.80 (1.16)
T2		19	3.52 (0.85)	20	3.56 (0.92)	17	3.36 (0.85)	20	3.94 (1.06)	21	3.70 (1.26)	21	3.35 (1.04)	19	3.34 (1.15)	19	3.62 (1.21)	156	3.55 (1.05)

(continued)

Actigraphy																		
Sleep Efficiency (%)																		
T0	20	79.57 (5.48)	23	81.04 (8.37)	21	80.40 (5.73)	18	80.87 (4.49)	20	78.10 (8.23)	21	79.87 (6.62)	21	81.79 (7.54)	22	79.90 (5.56)	166	80.21 (6.62)
T1	19	79.42 (8.72)	19	80.00 (8.61)	19	80.86 (6.95)	20	82.30 (4.62)	21	79.81 (8.42)	21	81.70 (7.20)	18	84.93 (6.09)	22	84.10 (3.87)	159	81.65 (7.10)
T2	19	82.14 (7.52)	17	82.41 (8.76)	14	82.59 (7.21)	18	80.38 (8.17)	20	79.02 (10.29)	19	80.54 (8.72)	18	83.39 (5.95)	18	82.62 (4.09)	143	81.56 (7.78)
Sleep Onset Latency (min)																		
T0	20	10.10 (9.65)	23	10.00 (11.78)	21	10.90 (9.29)	18	12.39 (10.28)	20	15.64 (19.63)	21	8.54 (8.67)	21	13.48 (12.08)	22	9.72 (10.22)	166	11.28 (11.82)
T1	19	9.70 (7.11)	19	10.23 (8.67)	19	17.13 (16.43)	20	10.55 (9.75)	21	15.85 (11.98)	21	9.13 (5.13)	18	8.92 (6.26)	22	10.35 (6.89)	159	11.50 (9.88)
T2	19	7.49 (6.62)	17	9.28 (7.61)	14	13.46 (12.98)	18	13.92 (18.02)	20	16.62 (19.26)	19	10.70 (7.64)	18	18.40 (15.93)	18	12.77 (12.77)	143	12.86 (13.65)
Wake After Sleep Onset (min) [b]																		
T0	20	69.20 (29.48)	23	64.37 (24.04)	21	64.47 (25.92)	18	64.77 (16.92)	20	78.76 (34.78)	21	71.76 (28.17)	21	60.02 (26.60)	22	71.44 (26.13)	166	68.06 (26.95)
T1	19	73.32 (38.28)	19	67.42 (22.97)	19	60.87 (26.86)	20	56.11 (13.59)	21	67.27 (29.04)	21	61.46 (22.34)	18	53.25 (25.58)	22	53.41 (14.93)	159	61.57 (25.52)
T2	19	63.68 (32.48)	17	63.73 (30.09)	14	57.10 (20.51)	18	59.19 (23.50)	20	69.29 (33.45)	19	64.10 (34.59)	18	51.74 (21.05)	18	62.08 (20.88)	143	61.60 (27.77)
Total Sleep Time (min)																		
T0	20	409.33 (45.87)	23	419.08 (34.19)	21	398.09 (41.49)	18	403.64 (35.82)	20	404.64 (47.01)	21	397.30 (53.88)	21	419.45 (57.10)	22	406.12 (34.25)	166	407.41 (44.21)
T1	19	406.85 (52.08)	19	419.89 (60.23)	19	405.66 (36.72)	20	408.31 (38.19)	21	372.19 (45.01)	21	369.91 (38.28)	18	402.00 (40.12)	22	393.20 (39.82)	159	396.78 (46.49)
T2	19	392.93 (45.60)	17	400.28 (52.36)	14	392.71 (47.87)	18	377.91 (55.46)	20	383.51 (58.98)	19	382.01 (51.62)	18	396.70 (34.91)	18	401.05 (34.40)	143	390.55 (48.02)
Average Sleep Bout Duration (min)																		
T0	20	14.47 (4.79)	23	14.19 (4.90)	21	16.13 (14.23)	18	13.13 (3.02)	20	14.07 (3.75)	21	13.63 (4.36)	21	15.40 (5.55)	22	18.27 (19.51)	166	14.96 (9.48)
T1	19	14.12 (4.68)	19	13.30 (3.90)	19	40.96 (90.91)	20	33.83 (63.01)	21	21.61 (17.88)	21	21.32 (28.47)	18	19.20 (15.39)	22	14.55 (5.52)	159	22.32 (41.09)
T2	19	15.49 (5.61)	17	16.79 (16.52)	14	15.46 (4.78)	18	13.50 (3.32)	20	29.50 (49.16)	19	38.43 (106.24)	18	21.05 (16.94)	18	18.36 (23.41)	143	21.49 (44.40)
Average Wake Bout Duration (min)																		
T0	20	1.20 (0.27)	23	1.15 (0.31)	21	1.08 (0.25)	18	1.11 (0.28)	20	1.32 (0.53)	21	1.28 (0.68)	21	1.16 (0.48)	22	1.27 (0.36)	166	1.20 (0.42)
T1	19	1.19 (0.35)	19	1.09 (0.21)	19	1.11 (0.31)	20	1.01 (0.21)	21	1.31 (0.48)	21	1.05 (0.27)	18	1.06 (0.31)	22	1.17 (0.35)	159	1.13 (0.33)
T2	19	1.17 (0.29)	17	1.06 (0.17)	14	1.08 (0.17)	18	1.10 (0.38)	20	1.18 (0.27)	19	1.18 (0.71)	18	1.06 (0.32)	18	1.21 (0.33)	143	1.13 (0.37)
Sleep-related scales																		
Insomnia Severity Index																		
T0	20	16.00 (4.74)	24	16.92 (3.20)	24	15.13 (4.61)	20	16.50 (3.44)	21	16.76 (4.31)	21	15.81 (3.30)	21	16.95 (3.92)	24	16.79 (4.23)	175	16.35 (3.98)
T1	19	14.37 (4.68)	21	16.10 (3.60)	22	15.00 (4.96)	20	14.90 (4.22)	20	11.90 (5.10)	21	11.05 (4.61)	19	10.11 (4.32)	21	12.43 (4.48)	163	13.26 (4.86)
T2	17	10.94 (4.15)	19	9.63 (3.90)	16	10.38 (5.18)	20	11.05 (4.24)	20	11.40 (5.47)	20	10.40 (3.36)	19	10.37 (5.19)	19	13.26 (4.68)	150	10.94 (4.57)
Dysfunctional Beliefs and Attitudes about Sleep																		
T0	20	62.75 (13.06)	24	62.96 (14.60)	24	59.25 (15.48)	20	58.40 (12.60)	21	63.76 (15.00)	21	57.24 (9.63)	21	68.95 (13.34)	24	59.92 (15.37)	175	61.62 (14.01)
T1	18	61.67 (12.11)	21	61.67 (15.02)	22	58.91 (14.30)	20	56.55 (12.79)	20	55.35 (14.74)	21	47.86 (12.10)	19	55.95 (16.08)	21	50.62 (12.31)	162	55.99 (14.23)
T2	17	47.76 (15.30)	19	48.79 (15.95)	16	47.25 (15.50)	20	48.65 (11.97)	20	53.65 (13.89)	20	47.10 (12.12)	19	53.74 (17.88)	19	49.21 (11.48)	150	49.59 (14.23)
Glasgow Sleep Effort Scale																		
T0	20	5.15 (2.94)	24	4.58 (2.67)	24	5.25 (3.43)	20	3.70 (1.89)	21	5.19 (2.56)	21	4.14 (1.90)	21	4.95 (3.06)	24	4.83 (3.28)	175	4.74 (2.79)
T1	18	4.44 (2.68)	21	4.52 (2.60)	22	4.64 (3.08)	20	3.95 (2.56)	20	2.85 (2.62)	21	2.95 (2.06)	19	2.89 (1.79)	21	3.38 (3.04)	162	3.71 (2.64)
T2	17	3.06 (2.22)	19	2.89 (2.16)	16	2.44 (2.06)	20	2.65 (2.23)	20	2.45 (2.19)	20	2.75 (2.17)	19	3.05 (2.09)	19	3.84 (2.95)	150	2.89 (2.26)
Sleep Locus of Control																		
T0	20	24.10 (5.14)	24	20.63 (5.25)	24	24.75 (6.37)	20	23.65 (6.52)	21	22.86 (6.03)	21	23.76 (5.40)	21	22.67 (5.38)	24	22.38 (4.54)	175	23.06 (5.62)
T1	19	25.05 (5.46)	21	20.90 (5.37)	22	24.18 (5.53)	20	23.90 (5.75)	20	23.15 (7.19)	21	26.14 (5.96)	19	25.53 (6.82)	21	25.14 (5.53)	163	24.23 (6.05)
T2	17	27.24 (6.16)	19	23.00 (5.80)	16	24.25 (6.65)	20	25.85 (6.93)	20	22.80 (6.99)	20	25.80 (6.71)	19	25.05 (7.32)	19	24.79 (5.58)	150	24.83 (6.55)
Sleep Self-Efficacy Scale																		
T0	20	26.65 (6.91)	24	24.33 (4.93)	24	26.46 (6.37)	20	27.20 (5.33)	21	24.19 (6.20)	21	26.48 (4.82)	21	26.71 (5.20)	24	25.54 (5.77)	175	25.91 (5.71)
T1	19	27.68 (5.87)	21	24.10 (5.64)	22	26.41 (6.77)	20	27.80 (5.72)	20	27.20 (6.41)	21	29.57 (4.70)	19	30.21 (4.78)	21	26.90 (5.73)	163	27.44 (5.90)
T2	17	31.88 (5.77)	19	31.74 (6.89)	16	30.19 (5.14)	20	29.60 (5.62)	20	29.10 (6.77)	20	30.05 (4.51)	19	30.58 (4.82)	19	28.42 (6.22)	150	30.16 (5.76)

Abbreviations: ICBTI, Internet-based Cognitive Behavioral Therapy for Insomnia.

[a] Raw means (SDs) are presented.

[b] Wake After Sleep Onset includes time awake after final awakening, but before Lights On

[c] 1 = very poor, 2 = poor, 3 = somewhat poor, 4 = not good, not poor, 5 = somewhat good, 6 = good, 7 = very good

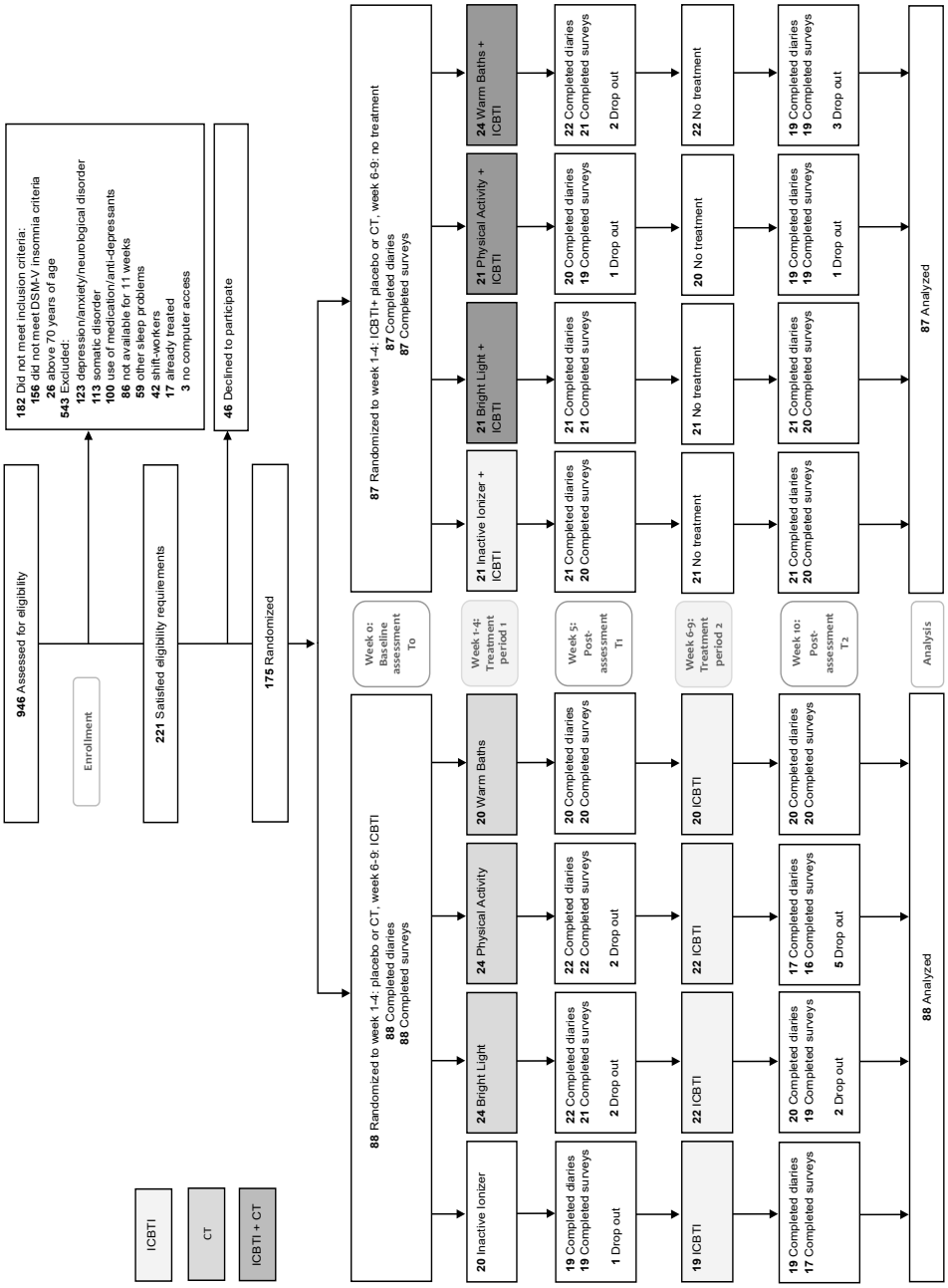
[d] 1 = very good, 2 = good, 3 = somewhat good, 4 = not good, not bad, 5 = somewhat bad, 6 = bad, 7 = very bad

Table 8. Means and Standard Deviations for Mood, Affect, Arousal and Quality of Life Parameters[a]

	week 1 - 4	Inactive Ionizer		Bright Light		Physical Activiy		Warm Baths		Inactive Ionizer + ICBTI		Bright Light + ICBTI		Physical Activity + ICBTI		Warm Baths + ICBTI			
	week 6 - 9	ICBTI		ICBTI		ICBTI		ICBTI		no treatment								All	
Parameter		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Mood and Affect																			
Anxiety (HADS)																			
T0		20	6.60 (3.52)	24	6.79 (3.64)	23	6.61 (3.17)	20	6.05 (1.99)	21	7.43 (3.60)	21	7.00 (3.30)	19	7.47 (2.74)	24	7.38 (3.49)	172	6.92 (3.21)
T1		19	6.47 (3.04)	22	7.50 (3.86)	22	6.73 (4.42)	20	6.10 (2.99)	20	6.20 (3.35)	21	6.14 (3.04)	19	5.89 (2.87)	22	7.18 (3.02)	165	6.55 (3.35)
T2		18	5.17 (2.92)	19	6.37 (3.83)	16	4.69 (1.99)	20	5.50 (3.20)	19	6.16 (4.06)	20	6.10 (2.88)	17	6.06 (3.03)	19	6.63 (2.83)	148	5.86 (3.15)
Depression (HADS)																			
T0		20	3.05 (2.95)	24	4.79 (3.40)	23	5.30 (4.76)	20	4.80 (4.36)	21	4.71 (3.55)	21	4.33 (3.54)	19	4.53 (3.85)	24	4.08 (3.23)	172	4.47 (3.72)
T1		19	3.05 (2.39)	22	5.00 (4.06)	22	4.59 (4.73)	20	4.55 (5.13)	20	3.40 (3.28)	21	3.62 (3.57)	19	2.79 (2.35)	22	3.55 (2.84)	165	3.85 (3.70)
T2		18	1.89 (2.47)	19	3.21 (2.99)	16	2.63 (2.96)	20	3.45 (4.63)	19	3.63 (3.53)	20	3.50 (3.22)	17	2.59 (2.37)	19	3.53 (3.01)	148	3.08 (3.22)
Positive Affect (PANAS)																			
T0		20	32.90 (7.68)	24	33.42 (6.22)	23	31.35 (8.45)	20	30.95 (7.53)	21	32.43 (7.39)	21	29.86 (5.43)	20	31.25 (5.76)	24	30.79 (7.03)	173	31.63 (6.96)
T1		19	33.79 (5.79)	22	33.09 (7.04)	22	31.41 (7.63)	20	29.75 (7.92)	20	33.70 (5.89)	21	31.38 (5.84)	19	33.79 (6.82)	22	32.41 (6.95)	165	32.39 (6.79)
T2		18	36.50 (6.80)	19	35.63 (5.57)	16	34.56 (7.83)	20	31.05 (7.41)	19	31.84 (5.86)	20	31.85 (6.49)	17	35.47 (6.21)	19	33.79 (6.92)	148	33.75 (6.78)
Negative Affect (PANAS)																			
T0		20	17.25 (4.84)	24	17.17 (6.32)	23	17.57 (6.83)	20	16.20 (4.67)	21	19.71 (8.65)	21	17.52 (6.07)	20	17.30 (4.77)	24	17.58 (5.84)	173	17.54 (6.10)
T1		19	17.32 (5.50)	22	18.41 (7.37)	22	18.64 (8.12)	20	15.85 (6.42)	20	17.15 (7.06)	21	15.71 (4.88)	19	16.32 (5.47)	22	17.59 (5.59)	165	17.16 (6.37)
T2		18	15.22 (4.83)	19	18.53 (6.87)	16	14.25 (4.51)	20	15.40 (7.34)	19	16.58 (6.95)	20	15.50 (5.85)	17	16.00 (4.91)	19	15.47 (3.69)	148	15.90 (5.79)
Temporal Experience of Pleasure																			
T0		20	75.85 (12.33)	24	77.29 (10.62)	23	75.13 (8.92)	20	74.30 (10.83)	21	73.43 (7.77)	21	75.62 (9.68)	20	76.00 (7.67)	24	76.29 (8.17)	173	75.53 (9.47)
T1		19	78.68 (11.04)	22	74.50 (11.75)	22	76.05 (9.14)	20	75.40 (15.26)	20	73.00 (8.52)	21	76.19 (9.82)	19	79.21 (7.12)	22	78.32 (8.40)	165	76.38 (10.37)
T2		18	80.72 (8.66)	19	79.00 (10.86)	16	77.25 (8.93)	20	75.20 (14.83)	19	73.53 (5.91)	20	76.35 (9.23)	17	78.76 (8.15)	19	76.95 (8.58)	148	77.16 (9.79)
Hyperarousal																			
Arousal Predisposition Scale																			
T0		16	36.56 (5.60)	22	35.95 (6.46)	20	36.85 (6.29)	18	35.11 (4.61)	20	36.10 (7.83)	20	34.40 (6.18)	19	36.42 (5.35)	21	37.38 (7.32)	156	36.10 (6.26)
T1		15	35.60 (5.83)	17	35.76 (5.40)	19	38.47 (6.84)	18	33.67 (5.24)	16	35.94 (9.14)	17	33.88 (5.82)	15	36.33 (6.50)	20	36.95 (5.86)	137	35.87 (6.42)
T2		14	33.64 (7.37)	17	36.00 (5.68)	16	36.13 (6.38)	14	33.71 (6.94)	16	33.56 (6.40)	19	34.47 (5.76)	13	35.69 (6.21)	17	35.65 (7.17)	126	34.88 (6.38)
Hyper Arousal Scale																			
T0		16	36.56 (6.57)	22	38.09 (7.46)	20	40.30 (6.95)	18	37.44 (5.01)	20	37.40 (8.09)	20	36.20 (6.68)	19	38.32 (5.61)	21	37.67 (6.99)	156	37.78 (6.72)
T1		15	35.33 (7.78)	17	38.47 (7.80)	19	40.00 (7.57)	18	35.83 (5.52)	16	37.31 (8.38)	17	36.06 (7.13)	15	37.33 (6.06)	20	37.90 (6.62)	137	37.35 (7.11)
T2		14	36.14 (7.30)	17	36.94 (9.34)	16	38.25 (7.43)	14	35.57 (6.85)	16	35.75 (7.30)	19	34.84 (6.09)	13	36.85 (5.47)	17	36.47 (8.06)	126	36.33 (7.22)
Adult ADHD Self-Report Scale																			
T0		16	9.94 (5.12)	22	10.14 (4.70)	20	10.05 (3.95)	18	11.00 (4.65)	20	9.90 (3.78)	20	9.55 (3.32)	19	9.63 (3.34)	21	9.67 (3.69)	156	9.97 (4.02)
T1		15	9.20 (4.84)	17	11.00 (4.89)	19	9.21 (3.49)	18	9.83 (4.94)	16	9.31 (3.96)	17	8.47 (3.48)	15	8.93 (3.17)	20	9.25 (4.58)	137	9.41 (4.18)
T2		14	9.29 (5.06)	17	9.88 (4.55)	16	8.50 (3.71)	14	10.14 (5.10)	16	8.38 (3.90)	19	9.21 (4.30)	13	8.92 (4.27)	17	9.88 (4.58)	126	9.28 (4.36)
Pre-Sleep Arousal Scale - Somatic																			
T0		16	16.69 (6.93)	22	15.41 (5.11)	20	15.70 (6.22)	18	14.56 (4.79)	20	16.10 (5.48)	20	15.30 (4.94)	19	15.16 (4.94)	21	14.95 (4.28)	156	15.46 (5.26)
T1		15	17.20 (5.83)	17	15.12 (4.17)	19	14.84 (5.38)	18	14.72 (5.48)	16	15.94 (6.53)	17	14.12 (3.55)	15	14.33 (4.03)	20	14.40 (3.27)	137	15.04 (4.83)
T2		14	15.71 (6.90)	17	13.06 (3.27)	16	14.56 (5.63)	14	14.50 (5.14)	16	16.50 (5.77)	19	14.58 (3.86)	13	14.08 (5.56)	17	14.18 (3.49)	126	14.63 (4.95)
Pre-Sleep Arousal Scale - Cognitive																			
T0		16	20.00 (7.21)	22	21.18 (7.64)	20	23.45 (8.25)	18	21.78 (6.54)	20	24.45 (7.34)	20	21.60 (6.86)	19	21.95 (7.67)	21	23.43 (6.91)	156	22.29 (7.29)
T1		15	21.67 (7.88)	17	19.65 (8.18)	19	21.47 (8.70)	18	18.83 (6.90)	16	20.25 (8.44)	17	19.88 (5.94)	15	18.73 (6.57)	20	22.15 (8.63)	137	20.38 (7.66)
T2		14	19.36 (6.33)	17	18.59 (6.95)	16	20.69 (8.48)	14	17.14 (6.33)	16	22.50 (7.87)	19	18.47 (6.41)	13	17.69 (6.21)	17	21.76 (7.45)	126	19.60 (7.11)
Quality of Life SF 36																			
Physical Component Summary																			
T0		20	44.16 (7.65)	24	47.22 (6.13)	24	47.78 (6.15)	20	46.66 (6.12)	21	46.79 (5.95)	21	46.16 (6.50)	21	47.70 (5.67)	24	48.89 (5.85)	175	46.99 (6.27)
T1		19	43.87 (7.41)	22	46.93 (4.85)	22	46.90 (6.99)	20	46.99 (5.84)	19	47.58 (4.38)	21	45.95 (6.61)	19	48.11 (4.83)	21	48.24 (4.98)	163	46.83 (5.86)
T2		18	44.71 (7.10)	19	47.84 (5.16)	16	47.42 (5.12)	20	46.32 (6.34)	20	45.91 (4.87)	20	47.57 (4.56)	19	48.00 (3.24)	19	47.45 (4.54)	151	46.90 (5.21)
Mental Component Summary																			
T0		20	47.84 (7.35)	24	44.14 (9.85)	24	44.23 (12.57)	20	45.36 (11.82)	21	44.98 (9.16)	21	47.99 (8.88)	21	45.31 (9.90)	24	42.30 (11.28)	175	45.17 (10.24)
T1		19	48.32 (7.35)	22	41.33 (11.84)	22	44.73 (10.80)	20	47.02 (9.04)	19	48.07 (9.40)	21	49.72 (7.80)	19	47.39 (11.85)	21	48.05 (9.62)	163	46.74 (9.99)
T2		18	50.81 (8.05)	19	46.36 (11.46)	16	47.97 (10.08)	20	48.82 (11.25)	20	48.89 (8.58)	20	49.60 (7.69)	19	50.46 (7.21)	19	49.00 (8.43)	151	49.00 (9.09)

Abbreviations: ICBTI, Internet-based Cognitive Behavioral Therapy for Insomnia; HADS, Hospital Anxiety and Depression Scale; PANAS, Positive Affect Negative Affect Scale; SF36, Short Form 36.

[a] Raw means (SDs) are presented.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Enrollment
182 Did not meet inclusion criteria:
156 did not meet DSM-V insomnia criteria
26 above 70 years of age
543 Excluded:
123 depression/anxiety/neurological disorder
113 somatic disorder
100 use of medication/anti-depressants
86 not available for 11 weeks
59 other sleep problems
42 shift-workers
17 already treated
3 no computer access
221 Satisfied eligibility requirements
46 Declined to participate
175 Randomized
ICBTI
CT
ICBTI + CT
88 Randomized to week 1-4: placebo or CT, week 6-9: ICBTI
88 Completed diaries
88 Completed surveys
87 Randomized to week 1-4: ICBTI+ placebo or CT, week 6-9: no treatment
87 Completed diaries
87 Completed surveys
Week 0: Baseline assessment T0
Week 1-4: Treatment period 1
Week 5: Post-assessment T1
Week 6-9: Treatment period 2
Week 10: Post-assessment T2
Analysis
20 Inactive Ionizer
24 Bright Light
24 Physical Activity
20 Warm Baths
21 Inactive Ionizer + ICBTI
21 Bright Light + ICBTI
21 Physical Activity + ICBTI
24 Warm Baths + ICBTI
19 Completed diaries
19 Completed surveys
1 Drop out
22 Completed diaries
21 Completed surveys
2 Drop out
22 Completed diaries
22 Completed surveys
2 Drop out
20 Completed diaries
20 Completed surveys
21 Completed diaries
21 Completed surveys
20 Completed diaries
19 Completed surveys
1 Drop out
22 Completed diaries
21 Completed surveys
2 Drop out
19 ICBTI
22 ICBTI
22 ICBTI
20 ICBTI
21 No treatment
21 No treatment
20 No treatment
22 No treatment
19 Completed diaries
17 Completed surveys
20 Completed diaries
19 Completed surveys
2 Drop out
17 Completed diaries
16 Completed surveys
5 Drop out
20 Completed diaries
20 Completed surveys
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1 Drop out
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3 Drop out
88 Analyzed
87 Analyzed

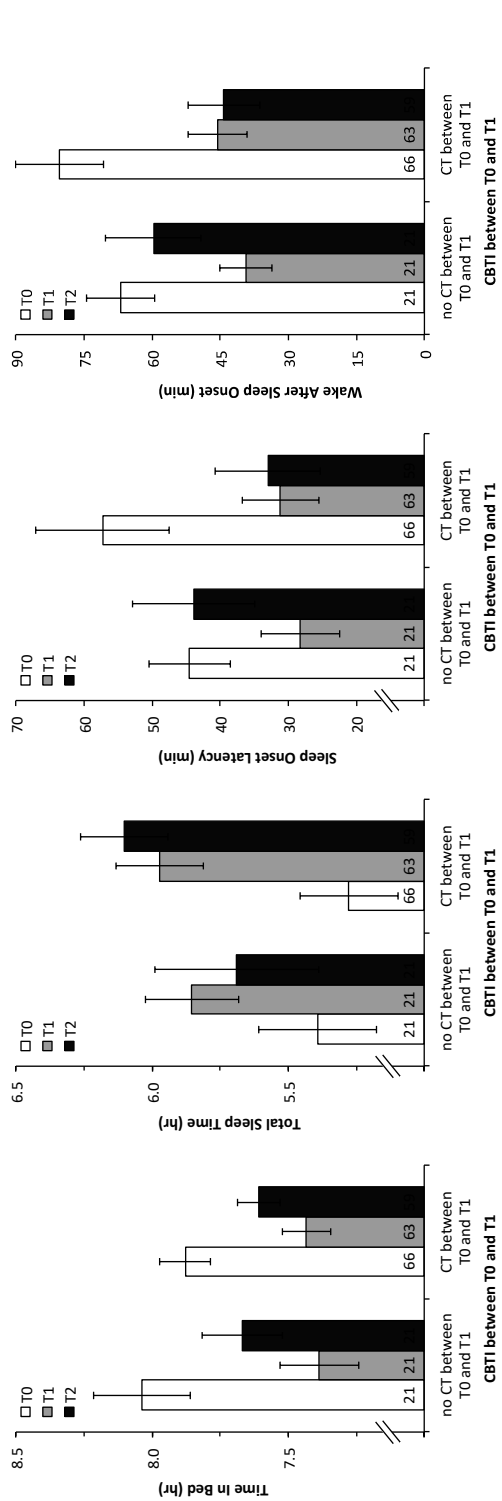

Figure 2. Secondary Sleep Outcomes.

From left to right, panels show the secondary outcome measures Time in Bed, Total Sleep Time, Sleep Onset Latency and Wake after Sleep Onset. Bars indicate baseline (T0, white), week 5 (T1, light grey) and week 10 (T2, dark gray) for the groups that received ICBTI in week 1-4 (between T0 and T1) either without CT (three bars on the left-hand side in each panel) or with CT (three bars on the right-hand side in each panel). Numbers in bars indicate the sample size of participants included at in each condition at each time point. Comparison of the light and dark grey bars shows little effect of adding CT on Total Sleep Time, Sleep Onset Latency and Wake after Sleep Onset immediately after CBTI. Only at follow-up it shows that adding CT has been of value, by promoting maintenance of the initial responses of these variables to ICBTI.

CHAPTER 4: HOW PERSONALITY PROFILE SIMILARITY CAN IMPROVE COMPARABILITY BETWEEN ASSESSMENT FORMATS: AN EXAMPLE OF THE MINI-IPIP AND IPIP-NEO-120 IN A DUTCH COMMUNITY SAMPLE.

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PsyArXiv, 21 Nov. 2018. Web.

ABSTRACT

Background There is a growing interest to unravel the genetic and brain structural underpinnings of personality by pooling data for mega- and meta-analyses within international consortia. Consequently, it is of increasing importance to evaluate the consistency of personality traits across assessment formats and languages. In this study, we evaluated the profile similarity framework as a means to compare personality profiles assessed using different inventories.

Methods We first assessed the psychometric properties of the Dutch translations of the 20-item Mini-IPIP and 120-item IPIP-NEO-120, both completed by 822 volunteers. We then applied the profile similarity framework to compare the personality factors and profiles obtained using the Mini-IPIP and the IPIP-NEO-120.

Results. The psychometric properties and factor structure of the Dutch translations resembled the original English questionnaires well. The correlations between the personality profile scores were shown to be more robust and less format-dependent than the correlations between personality factors. This improvement was maintained when accounting for profile normativeness.

Conclusions These findings show the way to more consistent personality factors and profiles obtained across different assessment formats and languages. The method promises increased sensitivity and reliability in large-scale international collaborative studies on the underlying mechanisms of the five-factor personality model.

Keywords: Personality Assessment, Personality Profile, Profile Similarity, Five Factor Model, Big Five

INTRODUCTION

Personality traits have been of interest for a long time in studies on mental development and disorders, such as intelligence,[174] social functioning,[175] addiction,[176] depression[177] and other mental diseases.[178] Moreover, personality traits have also been associated with the development of, and response to, physical health problems.[179,180] More recently, data from large cohorts have been pooled and used in mega- and meta-analyses, like Genome-Wide Association Studies (GWAS), to unravel the genetic underpinnings of personality.[181-183]

Many models on personality traits have been proposed,[184] of which the five-factor model (FFM), representing the domains of Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Openness, is the most dominant.[185] Within each of these domains, different personality 'facets' have moreover been suggested, that have been shown to explain substantially more variance and predict certain behaviors better.[186] The facets are therefore considered to reflect essential parts of the structure of personality.[187]

In order to facilitate international cooperation in refining measures of personality, Goldberg [184] created the International Personality Item Pool (IPIP): a large database of 3,320 freely available items. Using these items, more than 250 compositions have been constructed, many of which were based on the FFM. Consequently, even when focusing solely on the dominant five factor model of personality, many different assessment formats are available. In addition, many of these compositions have been translated, together in over 40 languages (see http://ipip.ori.org/newItemTranslations.htm). Given this wide variety in assessment formats and languages, it is of importance to be able to meaningfully compare scores assessed by different inventories.[188] This is especially true in the case where data is pooled across different cohorts, as is done in meta-analyses and in international collaborative studies of large-scale consortia employing genome wide association studies (GWAS) or neuroimaging data.

A framework that could be specifically suitable to compare personality assessed using different inventories is profile similarity.[189] Instead of comparing the raw scores on each of the five personality factors individually, profile similarity takes a more comprehensive approach by comparing the profile of scores on all assessed personality factors. The framework has previously been used to assess

personality profile similarity in domains of self-other agreement,[190] marital similarity,[191] behavioral consistency,[192] and temporal profile stability.[193-195] We propose to use the profile similarity framework to compare within-subject consistency of personality, assessed using two different formats.

In this study, we evaluated whether the profile similarity framework could improve the within-subject comparability of personality factors and profiles assessed using different inventories. Specifically, we focused on a short (Mini-IPIP[196]) and longer (IPIP-NEO-120[197]) questionnaire to assess the dominant and culturally robust [198] five-factor personality trait model.[199] In order to do so, we first translated both questionnaires into Dutch and evaluated their psychometric properties.

METHODS

PARTICIPANTS

Participants were volunteers of the Netherlands Sleep Registry (NSR),[135] an on-line platform to assess insomnia and a wide variety of traits in a general population. Participants anonymously fill out the available questionnaires at their convenience. We included participants older than 18 years without probable insomnia, indicated by an Insomnia Severity Index score below 8,[120] and selected the participants that completed the Mini-IPIP (*N*=987, 692 (70%) females; 54 ± 15 years) and/or the IPIP-NEO-120 (*N*=842, 591 (70%) females; 54 ± 15 years). Both questionnaires were completed by a subgroup of *N*=822 (577 (70%) females) of these participants, referred to as the NSR sample, that covered an age range of 18 to 86 years (54 ± 15 years). The questionnaires were filled out between September 2nd 2016 and August 30th 2017. The Medical Ethical Committee of the Academic Medical Center of the University of Amsterdam (29 September 2009, 09.17.1396) as well as the Central Committee on Research Involving Human Subjects (CCMO, 14 December 2011, CCMO11.1813/GK/jt), The Hague, The Netherlands, approved unsigned informed consent since no interventions or behavioral constraints are applied and participation is voluntary and anonymous.

RESEARCH MATERIALS

Mini-IPIP. The Mini-IPIP [196] is a 20-item questionnaire. Participants rate how well brief statements describe themselves using a 5-point Likert scale, ranging from 1 (very inaccurate) to 5 (very accurate). The original English Mini-IPIP shows acceptable psychometric properties: Internal consistencies as well as convergent, discriminant, and criterion-related validity are comparable to other, longer questionnaires that aim to assess the FFM [196].

IPIP-NEO-120. The 120-item IPIP-NEO-120[197] assesses both the five FFM factors and 30 personality facets, which represent the 30 NEO-PI-R facets.[27] Like the Mini-IPIP, participants rate brief statements on a 5-point Likert scale. The original English IPIP-NEO-120 shows acceptable reliability and validity and is an appealing and relatively short tool to measure all thirty personality facets similar to those in the 300-item IPIP-NEO.[184]

Translation. Both questionnaires were first translated into Dutch by EVS, and then back-translated into English by KD. Subsequently TB independently evaluated all items and their translations. Any divergence was discussed until consensus was reached. Next, a panel of two professional translators of Dutch origin with a MSc in English, who had no knowledge of the original English version, translated the Dutch items back into English. Discrepancies were discussed until consensus was reached.

Statistical Analyses

The statistical analyses served two purposes: to evaluate the psychometric properties and factor structure of the Dutch translations of the Mini-IPIP and the IPIP-NEO-120 in order to ultimately evaluate within-subject similarity of personality profiles obtained using either the short or longer version.

Psychometric properties of the Dutch translation

First, we compared the psychometric properties (Cronbach's alpha reliability and absolute intercorrelations of the scales) and factor structure of the Dutch Mini-IPIP and IPIP-NEO-120 to those reported in their respective original English versions: properties of the Mini-IPIP are reported for three college samples (N=2,663, N=329 and N=216); and properties of the IPIP-NEO-120 are

available for a Eugene-Springfield community sample (*N*=501) and two internet samples (*N*=307,313 and *N*=619,150), of which the larger internet sample, hereafter referred to as Johnson's Internet sample, is publicly available (https://osf.io/tbmh5/).

To evaluate the consistency of the factor structures we adopted the methodologies used in the original studies, thereby following the recommendation of Hopwood and Donnellan (2010) to "judge the quality of a particular factor solution against findings from previous research on the same inventory being evaluated". Accordingly, we repeated a confirmatory factor analysis (CFA) using Maximum Likelihood estimation on the Dutch Mini-IPIP and inspected the modification indices to identify possible sources of misfit. For the IPIP-NEO-120, we repeated a principal component analysis, extracting five components using varimax rotation with Kaiser normalization. Availability of Johnson's Internet sample allowed us to compare the factor solution in the NSR sample to that of Johnson's Internet sample by computing Tucker's congruence coefficients on the Procrustes rotated factor loadings matrix.[200] Interestingly, Johnson's Internet sample contains *N*=2,847 individuals who identified themselves as Dutch, allowing us to compare the NSR's sample factor structure to a more culturally matched subset. In addition, we compared the factor structures in more detail by visualizing the correlation structures of the IPIP-NEO-120 in the NSR sample and in Johnson's Internet sample in an association network. In this network, the personality facets are shown as 'nodes' and the correlations among the facets as 'edges', where green edges indicate positive relations and red edges indicate negative correlations.[201] This visualization might help to understand and compare the complex co-variations among the personality facets in both samples.[202]

Similarity across assessment formats

Second, to evaluate the within-subject consistency of the personality factors obtained using either the short or longer version, we computed Pearson's correlations between the five personality factors measured with each of the questionnaires. Since a few items overlap in both questionnaires, we also computed the adjusted correlations, leaving out the overlapping items from the IPIP-NEO-120 when calculating the personality factors. Subsequently, aiming to improve the comparison of personality across assessment formats, we used the *profile similarity framework.*[189] Within this framework, not

the personality factors separately, but the *profile* of personality factors relative to one another are compared across assessment formats. Furthermore, the framework takes the potential confound of *normativeness* into account. That is, since an individual's profile is likely to be similar to the average profile (e.g., most participants generally report low Neuroticism relative to Agreeableness), this may artificially inflate within-subject similarity of the two profiles. Following the framework, each individual has a *raw profile* on both assessment formats, see Figure 1a. The correlations among the two raw profiles of each individual, called the *overall similarities*, represent individuals' similarities of their personality profiles obtained using the two questionnaires, potentially confounded by normativeness. To take the normativeness into account, the personality profiles are decomposed into a *normative profile*, reflecting the mean personality profile of the sample, and *distinctive profiles*, reflecting the deviation of each individual to the normative profile. The correlation among the two normative profiles, called *generalized normative similarity*, reflects the similarity of the average personality profiles across assessment formats, see Figure 1b. Finally, the correlations among the two distinctive profiles for each individual, the *distinctive similarities*, represent individuals' personality profile similarities across assessment formats, while taking normativeness into account.

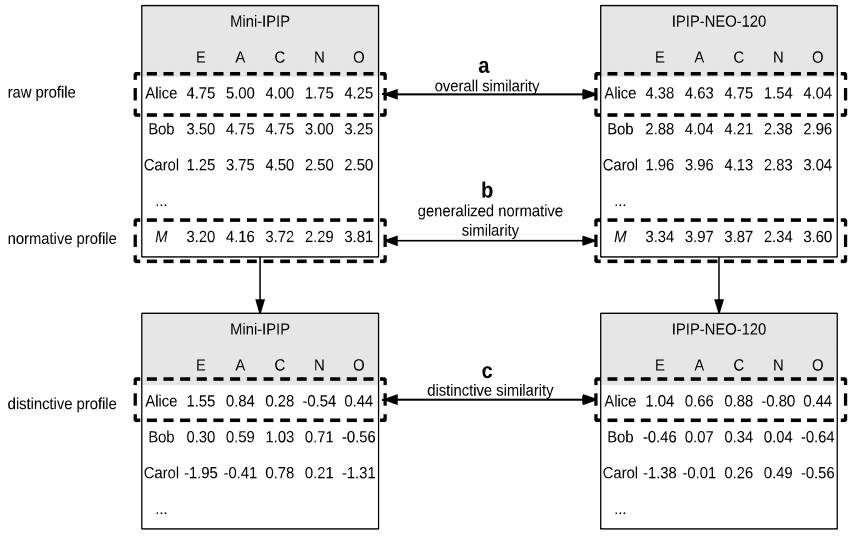

Figure 1. Profile similarity framework visualized: (a) the overall similarity, which is the correlation between the two raw profiles of an individual; (b) the generalized normative similarity, which is the correlation between two normative profiles; and (c) the distinctive similarity, the correlation between the two distinctive profiles of an individual.

Last, in the case when separate personality factors are of interest, we build upon the profile similarity framework and evaluated whether the individual personality factor scores would be more alike across assessment formats when taking into account an individual's profile. That is, for each individual we computed the deviation of each personality factor to the individual's average factor scores on that assessment format and called these the distinctive factor scores. This way, the separate distinctive factor scores incorporate the individual's scoring norm on a particular assessment format and reflect deviations from this norm. We then computed the mean absolute error in personality factor scores across assessment formats for the unadjusted scores and for the distinctive factor scores. Note that although this does not affect the correlations between the personality scores and profiles assessed using different formats (i.e., it does not adjust the distinctive similarity nor does it adjust the correlation between personality factors), it *can* affect the absolute differences in scores obtained using different assessment formats, since the profile is taken into account in the individual distinctive scores.

All analyses were performed in the open-source programming language R (version 3.4.1) using the statistical packages 'lavaan'(version 0.5-20),[203] 'psych'(version 1.6.6),[204] 'vegan'(version 2.4-4),[205] and 'qgraph'(version 1.3.4).[201]

RESULTS

MINI-IPIP

Consensus was reached for the translation of all items, which can be accessed online (http://ipip.ori.org/DutchMini-IPIP.htm). Table 1 (left panel) shows the mean, standard deviations, Cronbach's alpha reliability coefficients and scale intercorrelations for the current sample. All

Cronbach's alpha scale reliabilities were sufficient; all .70 or higher[206] except for Openness, and the average absolute intercorrelations ($\bar{r}$ = .12, SD = .08) were similar to those reported by Donnellan, Oswald, Baird, Lucas [196] (Study 1: $\bar{r}$ = .13, SD = .08; study 2: r = .14, SD = .08). The factor structure and the fit measures of the Dutch Mini-IPIP, shown in supplementary Table S1, were similar to the original English Mini-IPIP [196]. The modification indices, shown in supplementary Table S2, indicate that the largest misfit originates from the Openness personality factor. Specifically, the modification indices showed that the Openness factor might best be represented as two separate factors: one that captures both 'imagination' questions (item 5 and 20), and another that consists of both 'intellect' questions (item 10 and 15).

IPIP-NEO-120

Consensus was reached for the translation of all items and can be accessed online (http://ipip.ori.org/DutchIPIP-NEO-120.htm). Table 1 (right panel) shows the means and standard deviations, scale reliabilities and scale intercorrelations for the five FFM personality factors measured by the IPIP-NEO-120 in the NSR sample. Cronbach's alpha reliabilities, reported in supplementary Table S3, were good for the personality factors (all >.80), and acceptable (>.60) to good (>.70) for all but three personality facets, similar to those reported for the English IPIP-NEO-120. The congruence coefficients for most factors exceed .95 (Extraversion = .98; Agreeableness = .98; Conscientiousness = .98; Neuroticism = .97; Openness = .94), indicating that the factors can be considered equal.[207] When comparing the factor structure to the self-identified Dutch subset, only the Openness congruence coefficient increased to .96. The component loadings for each of the thirty personality facets in our current sample are shown in supplementary Table S4.

Figure 2 visualizes the correlation structure among the thirty personality facets for our NSR sample (left panel) and for the complete internet sample of Johnson (right panel). The global correlation structure is very similar across the samples. For example, in both samples the Extraversion facets are strongly and negatively correlated to the Neuroticism facets. The network visualization further shows that the personality factors differ considerably with respect to the strength of the correlations among

their facets. In both samples, the weakest relationships are observed among the Openness facets, while the Neuroticism facets are the most strongly related.

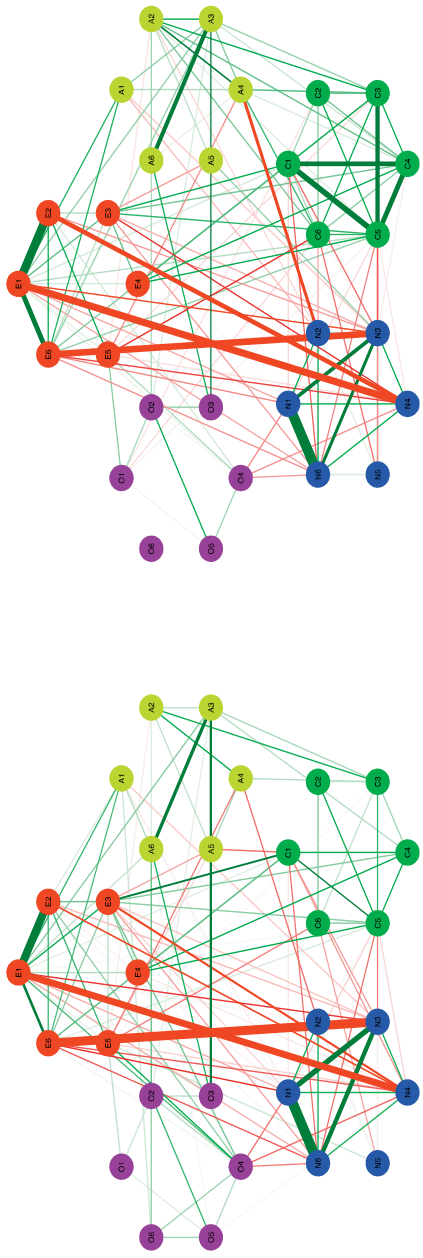

Figure 2. Correlation structure between the thirty personality facets of the IPIP-NEO-120 in the current, Dutch (left) and Johnson's (2014) English-speaking (right) internet samples ($N = 842$ and $N = 619{,}150$, respectively). Nodes represent personality facets and edges represent correlations between personality facets. Only correlations larger than .25 in absolute values are shown. Positive correlations are shown in green and negative correlations in red. A cut-off of .50 is used to scale the edges in width and color saturation. As a result, edges with absolute weight above (below) .50 have a stronger (weaker) color intensity and become wider (smaller) the stronger (weaker) they are.

Similarity between the Mini-IPIP and IPIP-NEO-120 personality profiles

The main objective was to apply the profile similarity framework to compare the within-subject personality profiles using either the short Mini-IPIP or the longer IPIP-NEO-120. The raw and adjusted (i.e., excluding overlapping items) Pearson's correlation coefficients between each of the personality factors are moderate (Extraversion: r = .71 (.68); Agreeableness: r = .51 (.48); Conscientiousness: r = .71 (.68); Neuroticism: r = .73[1]; Openness: r = .62 (.55)).

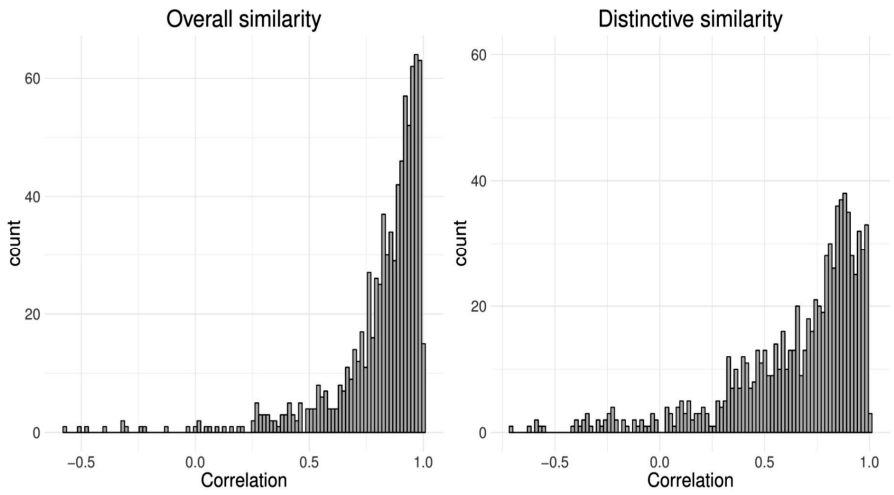

Figure 3. Histogram of the prevalence of within-subject correlation strengths (shown in 100 bins) for (a) subject's *overall* personality profiles and (b) subject's *distinctive* personality profiles obtained using either the Mini-IPIP or the IPIP-NEO-120.

The *overall similarities*, i.e., the correlations between the raw profiles of each individual, are shown in Figure 3 (left panel). The median overall similarity of .87 (M = .81, SD = .22) indicates that, for most individuals, the raw personality profiles are highly similar across assessment formats, which can be confounded by the generalized normative similarity.

[1] No items overlapped between the two inventories on Neuroticism

The normative profiles of the Mini-IPIP and the IPIP-NEO-120 are shown in Figure 4. The correlation between the two normative profiles, the *generalized normative similarity*, was 0.97 ($t(3) = 7.28$, $p = .005$).

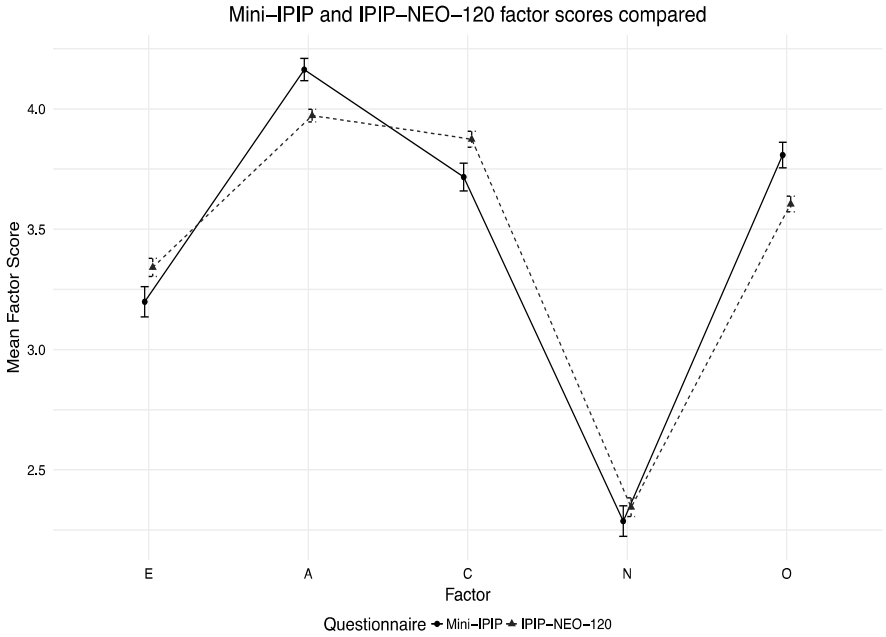

Figure 4. Normative profiles of the Mini-IPIP and IPIP-NEO-120 factor scores compared.

The right panel of Figure 3 shows the *distinctive similarities*, indicating whether someone's distinctive profile according to the Mini-IPIP is similar to someone's distinctive profile according to the IPIP-NEO-120. The median distinctive similarity of .76 ($M = .65$, $SD = .32$) indicates that an individual's distinctive profile according to the Mini-IPIP is, for most people, fairly similar to the distinctive profile according to the IPIP-NEO-120.

Last, across assessment formats, the difference in the raw personality factor scores (Extraversion: M=.53, SD=.41; Agreeableness: M=.50, SD=.36; Conscientiousness: M=.47, SD=.41; Neuroticism:

M=.50, *SD*=.36; Openness: *M*=.52, *SD*=.39) were significantly higher than the differences between the distinctive personality scores (Extraversion: *M*=.42, *SD*=.32; Agreeableness: *M*=.38, *SD*=.31; Conscientiousness: *M*=.45, *SD*=.34; Neuroticism: *M*=.43, *SD*=.32; Openness: *M*=.43, *SD*=.35), except for Conscientiousness (all four $t(821) > 8.1$, all $p < .001$). This indicates that within-subject standardization of the personality factors improves the correspondence of the factor scores using different assessment formats.

DISCUSSION

In order to support the increasing need of personality trait data pooling across cohorts and studies and measured in different assessment formats, the present investigation focused on the comparability of personality assessed using different questionnaires. Moreover, we evaluated the psychometric properties of the translations of two personality questionnaires, the Mini-IPIP[196] and the IPIP-NEO-120.[197] Both investigations showed that personality is robust, across languages and assessment formats.

Both the Dutch Mini-IPIP and the Dutch IPIP-NEO-120 resembled their respective original English versions in terms of scale-reliabilities, discriminant validity, and factor structures. The acceptable to good scale-reliabilities are satisfactory especially given the minimal scale length of only four items for the Mini-IPIP personality factors and the IPIP-NEO-120 personality facets [208]. For both questionnaires, the largest misfit (Mini-IPIP) and the largest discrepancy in factor interpretation (IPIP-NEO-120), was located at the Openness factor. For the Mini-IPIP, it was shown that the Openness factor may consist of the two related but separable factors ‘Intellect’ and ‘Imagination’. This finding corroborates a longstanding debate on the Openness factor e.g.,[209]. Alternatively, it has been suggested that the Openness personality factor has a different meaning in Dutch and is better interpreted as an “Autonomy” factor.[210] Interestingly, comparing our Dutch NSR sample to the Dutch subset of Johnson’s Internet sample indeed increased the similarity in interpretation of the Openness factor.

In order to find geniting underpinning and brain structural correlates for personality by assembling surveys from many samples, comparability of personality factors and profiles assessed with different assessment formats is essential. Our results showed that simply correlating the personality factors between the Dutch Mini-IPIP and the Dutch IPIP-NEO-120, provides moderate comparability. However, the more satisfactory profile similarity scores show that accuracy may be gained when assessing the personality profiles, rather than the raw individual factor scores. First of all, the two normative profiles are highly similar, which indicates that on a group level, personality profiles measured by these two questionnaires are almost interchangeable. This underlines the robustness of the five-factor model. Additionally, both the overall profile similarities and distinctive similarities are substantive, and for the majority of individuals higher than the simple correlations between the factors. This again indicates that the personality factors are even more comparable between assessment formats when assessed in context of the other personality factors, than when assessed separately. Even when a single personality factor is of interest, we showed that the distinctive scores, an extension of the personality profile framework, are preferable over the commonly used raw factor scores. Multiple-cohort studies (i.e. GWAS or meta-analyses) assessing traits other than personality, that are measured in more than one factor, may also benefit from calculating profile similarity.

In sum, our study contributes to the growing international need of personality trait phenotype pooling by (i) introducing the psychometrically consistent Dutch translations of the Mini-IPIP and the IPIP-NEO-120 and showing that they are both comparable to the original English questionnaires; (ii) underlining the robustness of the five-factor model across assessment formats and languages; and (iii) indicating that it may be more desirable to use the personality profiles when pooling data across cohorts or studies.

CHAPTER 5: INSOMNIA AND PERSONALITY – A NETWORK APPROACH

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Brain Sciences 2017; 7(3):28

ABSTRACT

Background Studies on personality traits and insomnia have remained inconclusive about which traits show the most direct associations with insomnia severity. It has moreover hardly been explored how traits relate to specific characteristics of insomnia.

Methods We here used network analysis in a large sample (*N*=2089) to obtain an integrated view on the associations of personality traits with both overall insomnia severity and different insomnia characteristics, while distinguishing direct from indirect associations.

Results We first estimated a network describing the associations among the five factor model personality traits and overall insomnia severity. Overall insomnia severity was associated with Neuroticism, Agreeableness, and Openness. Subsequently, we estimated a separate network describing the associations among the personality traits and each of the seven individual items of the Insomnia Severity Index. This revealed relatively separate clusters of daytime and nocturnal insomnia complaints, that both contributed to dissatisfaction with sleep, and were both most directly associated with Neuroticism and Conscientiousness.

Conclusion The approach revealed the strongest direct associations between personality traits and the severity of different insomnia characteristics and overall insomnia severity. Differentiating them from indirect associations identified the targets for improving CBT-I with the highest probability of effectively changing the network of associated complaints.

Keywords: Network analysis, Insomnia, Five factor model personality traits, Daytime complaints, Neuroticism

INTRODUCTION

Insomnia is a common burden in the general population.[59,211] Insomnia Disorder can be diagnosed if subjective problems with initiating sleep, maintaining sleep or waking up too early occur at least three nights a week, persist for at least three months and are accompanied by at least one form of subjective daytime impairments like fatigue, malaise or difficulties with concentration.[6] The diagnosis of Insomnia Disorder thus requires the presence of both nocturnal and daytime complaints. Although the causes of insomnia are still poorly understood,[212] a prevailing theory suggest the involvement of three types of factors Spielman, Caruso, Glovinsky [22]: premorbid predispositions, precipitating factors and perpetuating factors. It has been suggested that certain personality traits may predispose to insomnia.[25,28,213-215]

The dominant model of personality is the Five factor model (FFM), or the Big Five, and is based on a substantive body of evidence that found a five-factor solution to the correlations among personality characteristics.[27] The five personality traits are Extraversion, Agreeableness, Conscientiousness, Neuroticism and Openness. The study of personality traits in insomnia may provide clues about the underlying brain circuits involved in insomnia, because individual differences in personality traits are associated with individual differences in brain structure and brain function.[216-218] Some of the reported associations indeed seem relevant to insomnia, for example, both sleep vulnerability and introversion have been linked to low gray matter density in the orbitofrontal cortex.[94,219,220]

Even though the association between personality traits and insomnia has been studied extensively,[25,28-30,214,221-228] there is no conclusive consistency about which of the personality traits are most strongly associated with insomnia in a general adult population. Within the framework of the prevailing Five Factor model (FFM) of personality,[198] the most consistently reported finding in insomnia disorder is high Neuroticism.[25,29,30,214,222,226,227] Several studies also suggested insomnia disorder to be associated with low Conscientiousness, but showed that when all personality traits were simultaneously evaluated in a single regression model,[29,30,221,222] this association appeared to be secondary to the inverse association of Conscientiousness with Neuroticism. Multi-collinearity of personality traits thus has to be considered in efforts to understand the complexity of direct and indirect relations between insomnia and personality traits.

A relatively unexplored aspect is whether *specific symptoms* of insomnia may be associated differentially with personality traits. Previous studies focused mostly on nocturnal symptoms of insomnia,[29,221,222] or on a compound score.[30,221] Since insomnia is defined by both nocturnal and daytime aspects, it may be that some personality traits relate to nocturnal complaints, whereas others relate to daytime complaints. It could be more informative to perform an integrated analysis on how different symptoms of insomnia are associated with different personality traits.

Such an integrated analysis of how traits and symptoms are associated has shown to be feasible using *network analysis.* This method can simultaneously estimate partial correlations between all variables included - in our case all personality traits and insomnia symptoms measured - and visualizes them in a so-called *concentration network* graph. The graph shows all variables as nodes, and their partial correlations as connecting edges.[202] The relative strength of partial correlations can be represented by the length, color saturation and width of the edges between each of the nodes. Network analysis has recently been introduced for psychometric data,[201] including personality traits,[202,229] and has found increasing popularity over the years.[230]

The present study is, as far as we know, the first to apply network analyses on the data of a large sample of volunteers to obtain an integrated view on the associations of personality traits with overall insomnia severity as well as with different symptoms of insomnia. We estimated and visualized two concentration networks: one including the five personality traits and the Insomnia Severity Index (ISI) summary score; the other including the five personality traits and each of the seven individual ISI items.

MATERIALS AND METHODS

PARTICIPANTS

The data were obtained through the Netherlands Sleep Registry (NSR).[135] The NSR is an internet platform that aims to asses a wide variety of traits across the general population, both good and bad sleepers,[135] in order to create a psychometric database to facilitate research on traits that distinguish insomniacs from good sleepers. Participants of the NSR are unpaid volunteers that anonymously fill out as many different questionnaires as they wish, at a self-chosen place and time. Participants fill out each of the questionnaires once. Commitment is supported by online feedback, newsletters and occasional voucher lotteries. For the present study, we included all participants that completed both the Insomnia Severity Index (ISI),[120] the Mini-International Personality Item Pool (Mini-IPIP)[196] and a questionnaire on demographics including age and sex. Participants younger than 18 were excluded. This resulted in a cross-sectional sample of 2,089 volunteers (1,573 females, 75.3%), with an age range of 18 to 84 years of age (M = 51.7, SD = 13.6). The questionnaires were filled out between May 2012 and October 2016. The median time difference between filling out ISI and Mini-IPIP was 7.4 months. The Medical Ethical Committee of the Academic Medical Center of the University of Amsterdam as well as the Central Committee on Research Involving Human Subjects (CCMO), The Hague, the Netherlands, approved of unsigned informed consent, because of the voluntary and anonymous nature of participation and lack of any intervention or behavioral constraint.

MATERIALS

Mini-IPIP The 20-item Mini-IPIP[196] assesses the Big Five personality traits Neuroticism, Conscientiousness, Agreeableness, Extraversion and Openness to experiences. Participants are asked

to rate how accurate brief statements describe themselves, using a 5-point Likert scale ranging from 1 (very inaccurate) to 5 (very accurate). The Mini-IPIP has recently been translated into Dutch with satisfactory psychometric properties.[31]

ISI The Insomnia Severity Scale (ISI) is a 7-item scale that addresses aspects of insomnia.[120] Each question uses a 5-point Likert scale, ranging from 0 to 4. The first 3 questions assess the three main sleep complaints: difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS) and early morning awakening (EMA). Question 4 to 7 assess respectively dissatisfaction with sleep (Dissat), interference with daily functioning (IDF), how noticeable sleep problems impair quality of life (NIQoL) and worry about sleep (Worry). The compound score is a simple sum score of all items, resulting in a score ranging from 0 to 28.

STATISTICAL ANALYSIS

To estimate and visualize the concentration network of associations between the five personality traits and the Insomnia Severity Index (ISI) summary score, partial correlations were calculated between each of the six variables. The partial correlation among two variables represents the strength of the direct association between these variables, while taking all the other variables into account. The networks of the partial correlations thus represent the unique association between any two variables, that cannot be explained by their common associations with other variables.[202] As such, the network structure highlights possible pathways of influence: unrelated variables cannot directly influence each other, while the presence of a direct association indicates a potential causal pathway between two variables. To minimize spurious associations due to sampling error, we applied Least Absolute Shrinkage and Selection Operator (LASSO) regularization. This procedure controls for false-positive associations and retrieves only the most robust associations. Therefore, the included associations are very likely to play an important role in the network architecture (see Epskamp, Fried [231] for more information).

To visualize the concentration networks, each of the six variables is shown as a node, connected by edges. The edges in the network represent the partial correlations between variables that were estimated by the network model using LASSO regularization.[202] Green edges correspond to positive partial correlations, while red edges correspond to negative partial correlations. In addition, both the edge width and color saturation are scaled to the strength of the association: wider edges and more saturated colors represent stronger associations. The Fruchterman, Reingold [232] algorithm was used to topographically place the nodes in the network: variables with many strong connections were placed in the center of the network and variables with weaker connections are placed more at the periphery of the network.[232]

The same approach was applied to estimate and visualize the concentration network of associations between the five personality traits and the seven individual Insomnia Severity Index (ISI) item scores,

providing a more detailed investigation of how personality traits are associated with different aspects of insomnia. We used polychoric correlations for the correlations involving ISI items to take the Likert-scale type variables into account.

To facilitate interpretation of the networks, we determined the 'shortest paths' between all nodes. The shortest path between two nodes depends on the strength of the partial correlations between these two nodes, both directly – when present – and indirectly. The shortest path is defined as the 'easiest' route through edges representing strong partial correlations.[233] As such, the shortest path between two nodes can be indirect, even when they are directly related. In addition, we determined centrality measures: strength, closeness and betweenness.[202] The strength of a node is the sum of its absolute partial correlation coefficients. It summarizes the strength of the associations of the node with all its direct neighboring nodes. Closeness and betweenness in addition take also indirect relations of a node into account. The closeness of a node corresponds to the average 'distance' between a node and all other nodes in the network.[202] The stronger the partial correlation between two nodes, the smaller their distance. Thus, the higher the closeness of a node, the stronger the average partial correlations to all other nodes. Betweenness represents the number of shortest paths that pass a node. The centrality measures give an idea of how strong the variance in a certain variable is associated with variance in the other variables. For example, if two persons have different scores on a very 'central' variable, it is likely that their scores differ on most other variables as well. If these two persons have different scores on a variable that is less central, they may still have similar scores on the other variables.

RESULTS

DATA DESCRIPTION

Table 1 summarizes the measures of central tendency and dispersion for each of the variables. Table 2 provides the simple Pearson correlation coefficients among the personality traits and between each personality trait and the ISI sum score. All personality traits correlated significantly with each other, except for a lack of association of Extraversion with Conscientiousness, and of Agreeableness with Neuroticism. In agreement with previous reports, the simple Pearson correlations suggested that the ISI sum score was positively associated with Neuroticism. In addition, unlike previous findings, both Agreeableness and Openness were significantly associated with ISI sum score. In our sample, there was no significant correlation between Conscientiousness and ISI sum score.

Table 3 shows the polychoric correlation coefficients between the personality traits and the individual ISI items. Neuroticism, Agreeableness and Openness were significantly associated with all ISI items. Extraversion and Conscientiousness had significant associations with only some of the ISI items (Table 3), which corresponds to the absence of a significant association with the ISI sum score (Table 2).

Table 1. Mean (M), standard deviation (SD) and observed range for the five personality traits,the ISI sum score and the separate ISI items. Abbreviations: DIS = Difficulty Initiating Sleep, DMS = Difficulty Maintaining Sleep, EMA = Early Morning Awakening, Dissat = Dissatisfaction with sleep, IDF = Interference with Daily Functioning, NIQoL = Noticeability of Impaired Quality of Life, Worry = Worry about sleep.

	M ± *SD*	Range
Personality (IPIP-mini)		
Extraversion	12.45 ± 3.66	4 – 20
Agreeableness	16.94 ± 2.70	4 – 20
Conscientiousness	14.56 ± 3.43	4 – 20
Neuroticism	11.25 ± 4.03	4 – 20
Openness	14.89 ± 3.13	5 – 20
Insomnia (ISI)		
ISI sum	10.61 ± 7.20	0 – 28
DIS	1.19 ± 1.30	0 – 4
DMS	1.80 ± 1.49	0 – 4
EMA	1.42 ± 1.37	0 – 4
Dissat	2.10 ± 1.25	0 – 4
IDF	1.60 ± 1.29	0 – 4
NIQoL	1.14 ± 1.09	0 – 4
Worry	1.36 ± 1.25	0 – 4

Table 2. Pearson correlation coefficients and corresponding p-values for the correlations among the five personality traits and between the five personality traits and the ISI sum score. Significant correlations are in shown in **bold** font.

	Extraversion		Agreeable-ness		Conscientious-ness		Neuroticism		Openness	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Extraversion										
Agreeableness	**0.24**	$< 10^{-26}$								
Conscientiousness	0.02	.31	**0.15**	$< 10^{-11}$						
Neuroticism	**-0.17**	$< 10^{-15}$	0.03	.13	**-0.15**	$< 10^{-11}$				
Openness	**0.20**	$< 10^{-20}$	**0.13**	$< 10^{-8}$	**-0.11**	$< 10^{-6}$	**-0.08**	$< 10^{-4}$		
ISI sum	-0.04	.07	**0.12**	$< 10^{-7}$	-0.03	.17	**0.38**	$< 10^{-72}$	**-0.10**	$< 10^{-4}$

Table 3. Polychoric correlation coefficients and corresponding p-values for the correlations between each of the five personality traits and each of the individual ISI items. Abbreviations: DIS = Difficulty Initiating Sleep, DMS = Difficulty Maintaining Sleep, EMA = Early Morning Awakening, Dissat = Dissatisfaction with sleep, IDF = Interference with Daily Functioning, NIQoL = Noticeability of Impaired Quality of Life, Worry = Worry about sleep. Significant correlations are shown in **bold** font.

	Extraversion		Agreeable-ness		Conscientious-ness		Neuroticism		Openness	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
DIS	0.01	.80	**0.11**	$< 10^{-7}$	-0.02	.30	**0.29**	$< 10^{-40}$	**-0.09**	$< 10^{-4}$
DMS	-0.02	.34	**0.14**	$< 10^{-10}$	**0.06**	.01	**0.28**	$< 10^{-38}$	**-0.10**	$< 10^{-4}$
EMA	-0.03	.20	**0.09**	$< 10^{-4}$	0.03	.18	**0.25**	$< 10^{-30}$	**-0.08**	$< 10^{-3}$
Dissat	**-0.04**	.05	**0.11**	$< 10^{-6}$	-0.04	.06	**0.36**	$< 10^{-64}$	**-0.10**	$< 10^{-5}$
IDF	**-0.09**	10^{-4}	**0.11**	$< 10^{-6}$	**-0.10**	$< 10^{-5}$	**0.42**	$< 10^{-89}$	**-0.06**	.01
NIQoL	**-0.05**	.01	**0.06**	.01	**-0.09**	$< 10^{-4}$	**0.34**	$< 10^{-57}$	**-0.06**	.01
Worry	-0.03	.20	**0.11**	$< 10^{-6}$	**-0.05**	.03	**0.38**	$< 10^{-71}$	**-0.08**	10^{-3}
	Extraversion		Agreeable-ness		Conscientious-ness		Neuroticism		Openness	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
DIS	0.01	.80	**0.11**	$< 10^{-7}$	-0.02	.30	**0.29**	$< 10^{-40}$	**-0.09**	$< 10^{-4}$
DMS	-0.02	.34	**0.14**	$< 10^{-10}$	**0.06**	.01	**0.28**	$< 10^{-38}$	**-0.10**	$< 10^{-4}$
EMA	-0.03	.20	**0.09**	$< 10^{-4}$	0.03	.18	**0.25**	$< 10^{-30}$	**-0.08**	$< 10^{-3}$
Dissat	**-0.04**	.05	**0.11**	$< 10^{-6}$	-0.04	.06	**0.36**	$< 10^{-64}$	**-0.10**	$< 10^{-5}$
IDF	**-0.09**	10^{-4}	**0.11**	$< 10^{-6}$	**-0.10**	$< 10^{-5}$	**0.42**	$< 10^{-89}$	**-0.06**	.01
NIQoL	**-0.05**	.01	**0.06**	.01	**-0.09**	$< 10^{-4}$	**0.34**	$< 10^{-57}$	**-0.06**	.01
Worry	-0.03	.20	**0.11**	$< 10^{-6}$	**-0.05**	.03	**0.38**	$< 10^{-71}$	**-0.08**	10^{-3}
	Extraversion		Agreeable-ness		Conscientious-ness		Neuroticism		Openness	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
DIS	0.01	.80	**0.11**	$< 10^{-7}$	-0.02	.30	**0.29**	$< 10^{-40}$	**-0.09**	$< 10^{-4}$
DMS	-0.02	.34	**0.14**	$< 10^{-10}$	**0.06**	.01	**0.28**	$< 10^{-38}$	**-0.10**	$< 10^{-4}$
EMA	-0.03	.20	**0.09**	$< 10^{-4}$	0.03	.18	**0.25**	$< 10^{-30}$	**-0.08**	$< 10^{-3}$
Dissat	**-0.04**	.05	**0.11**	$< 10^{-6}$	-0.04	.06	**0.36**	$< 10^{-64}$	**-0.10**	$< 10^{-5}$
IDF	**-0.09**	10^{-4}	**0.11**	$< 10^{-6}$	**-0.10**	$< 10^{-5}$	**0.42**	$< 10^{-89}$	**-0.06**	.01
NIQoL	**-0.05**	.01	**0.06**	.01	**-0.09**	$< 10^{-4}$	**0.34**	$< 10^{-57}$	**-0.06**	.01
Worry	-0.03	.20	**0.11**	$< 10^{-6}$	**-0.05**	.03	**0.38**	$< 10^{-71}$	**-0.08**	10^{-3}

NETWORK ANALYSIS OF PERSONALITY TRAITS AND ISI SUM SCORE

Figure 1 shows the concentration network of partial correlations of the five personality traits and the ISI sum score. Shortest paths are shown in solid lines, the rest in dashed lines. Neuroticism and ISI showed the strongest partial correlation, even stronger than the partial correlation between any two personality traits. This indicates that Neuroticism has a stronger association with insomnia severity than with any other personality trait. Conscientiousness and Extraversion were only indirectly related to insomnia via Neuroticism. Neuroticism, Extraversion and Agreeableness scored high on the three centrality measures (Figure 2), and Neuroticism emerged as most central in the associations among personality traits and the ISI sum score.

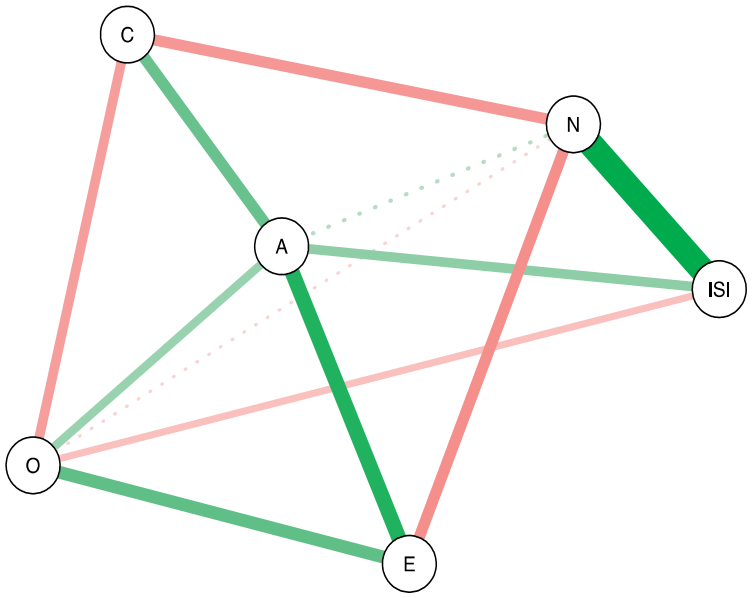

Figure 1. Concentration network of personality traits and the Insomnia Severity Index (ISI) sum score. Green lines indicate positive partial correlations; red lines indicate negative partial correlations. Solid lines indicate shortest paths, the other partial correlations are shown as dashed lines. The color saturation, thickness and length of the edges represent the strength of the association. Abbreviations: A = Agreeableness, C = Conscientiousness, E = Extraversion, N = Neuroticism, O = Openness. Neuroticism, Agreeableness and Openness show direct relations to ISI, while Conscientiousness and Extraversion are indirectly related to ISI. The partial correlation between Neuroticism and ISI is stronger than any of the other associations.

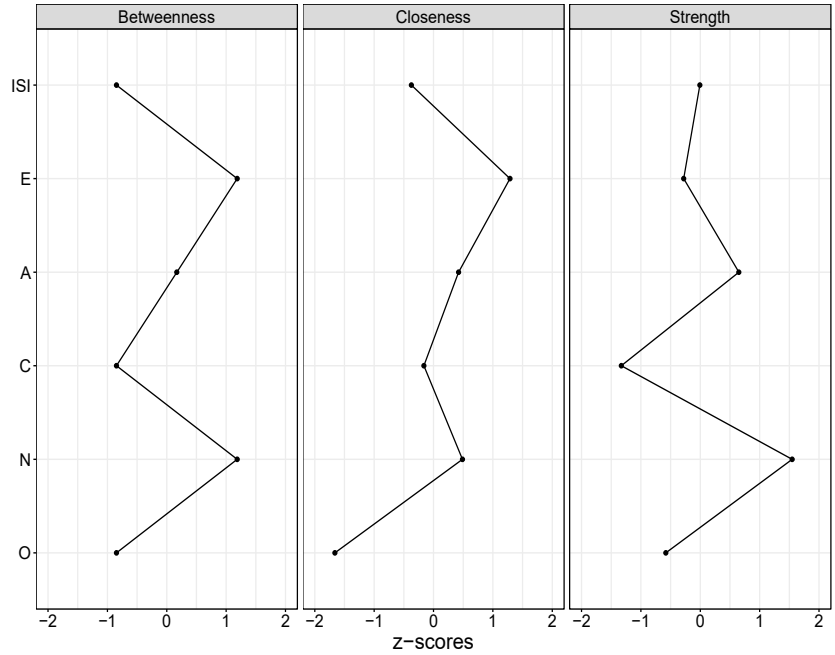

Figure 2. Standardized scores on the centrality measures of personality traits and the Insomnia Severity Index (ISI) sum score. Abbreviations: A = Agreeableness, C = Conscientiousness, E = Extraversion, N = Neuroticism, O = Openness. The plots show that the personality traits Neuroticism and Extraversion are highest on all three centrality measures. Extraversion lies on the shortest path between two other nodes most often (Betweenness), and has the smallest overall distance to all other nodes (Closeness), while Neuroticism is connected the strongest to its direct neighbors (Strength).

Network analysis of personality traits and ISI items

Figure 3 shows the concentration network of partial correlations of the five personality traits and each of the 7 ISI items. Panel A shows all partial correlations after the LASSO regularization, panel B highlights the shortest paths. Most partial correlations among ISI items were much stronger than the partial correlations between the ISI items and the personality traits. The ISI items DIS, DMS and EMA, which represent the nocturnal complaints of insomnia, clustered together. Likewise, the daytime complaints, items IDF, NIQoL and Worry also clustered together. The shortest paths between the nocturnal complaints to the daytime complaints were all through their common associations with dissatisfaction with sleep. Nocturnal and daytime complaints thus emerge as two smaller clusters within the network of associations, and are bridged by Dissat, suggesting that nocturnal and daytime complaints separately feed dissatisfaction. Dissatisfaction thus gets a central role in the network of nocturnal and daytime insomnia characteristics measured by the ISI (Figure 4). Within the cluster of nocturnal complaints, DMS and DIS are most strongly associated with parts of the network representing personality trait association: DMS with Conscientiousness and DIS with Neuroticism.

Within the cluster of daytime complaints, IDF is most strongly associated with parts of the network representing personality trait association through its associations with, once more, Conscientiousness and Neuroticism. A high betweenness, closeness and strength for ISI items IDF and DMS (Figure 4) suggests that individuals that are more alike with respect to these two insomnia characteristics, are also more likely to resemble each other with respect to personality traits. Since ISI items DIS, EMA and NIQoL scored low on all three centrality measures, such matching personality is less likely for subjects that resemble each other on these insomnia characteristics.

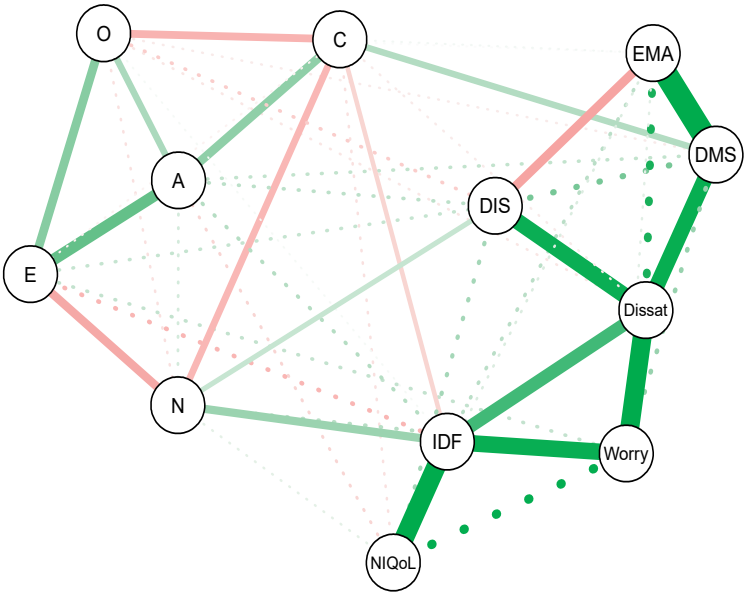

Figure 3. Concentration network of personality traits and Insomnia Severity Index (ISI) items. Green lines indicate positive partial correlations; red lines indicate negative partial correlations. Solid lines indicate shortest paths, the other partial correlations are shown as dashed lines. The color saturation, thickness and length of the edges represent the strength of the association. Abbreviations: DIS = Difficulty Initiating Sleep, Dissat = Dissatisfaction with sleep, DMS = Difficulty Maintaining Sleep, EMA = Early Morning Awakening, IDF = Interference with Daily Functioning, NIQoL = Noticeability of Impaired Quality of Life, Worry = Worry about sleep, A = Agreeableness, C = Conscientiousness, E = Extraversion, N = Neuroticism, O = Openness. The graph shows two main clusters of related variables, corresponding to a personality cluster and an insomnia cluster. The insomnia cluster can be further divided into a cluster of daytime symptoms (NIQoL, IDF and Worry) and a cluster of nocturnal symptoms (DIS, DMS, EMA) that are connected via Dissat. The shortest

paths that connect the personality and insomnia cluster contain Neuroticism, Conscientiousness, IDF, DMS, and DIS.

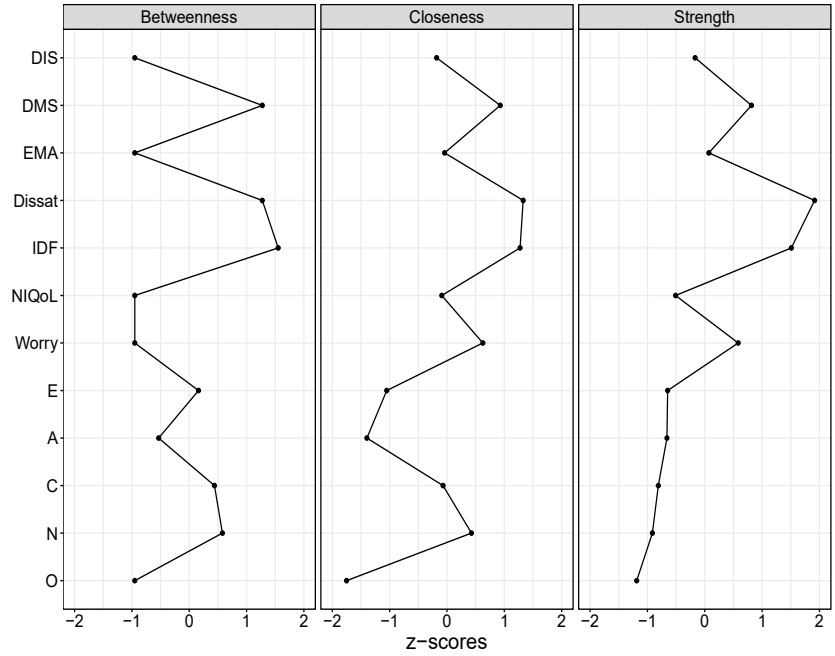

Figure 4. Standardized scores on the centrality measures of the personality traits and the ISI item scores. Abbreviations: Worry = Worry about sleep, NIQoL = Noticeability of Impaired Quality of Life, IDF = Interference with Daily Functioning, Dissat = Dissatisfaction with sleep, EMA = Early Morning Awakening, DMS = Difficulty Maintaining Sleep, DIS = Difficulty Initiating Sleep, A = Agreeableness, C = Conscientiousness, E = Extraversion, N = Neuroticism, O = Openness. The plots show that the ISI items Dissat and IDF are the highest on the centrality measures. IDF lies on the shortest path between two other nodes most often (Betweenness), while Dissat has the smallest overall distance to all other nodes (Closeness), and is connected the strongest to its direct neighbors (Strength).

Whereas the shortest paths of the ISI *sum* score with personality traits involved Neuroticism Agreeableness and Openness (Figure 1), a different picture emerged for the shortest paths between individual ISI *items* and personality traits. Neuroticism was the only trait that consistently connected the cluster of personality traits both with overall insomnia severity as well as with the cluster of individual insomnia complaints. However, the shortest paths between individual ISI *items* and personality traits now also included Conscientiousness, rather than Agreeableness and Openness.

DISCUSSION

The aim of this study was to obtain an integrated view on the associations between the five factor model personality traits and insomnia, both at the level of overall insomnia severity as well as at the level of individual symptom severities. In line with previous results, the simple Pearson correlations suggested that the personality traits Neuroticism and Agreeableness were positively related to insomnia severity.[25,29,30,214,222,226,227] Unlike previous studies, simple Pearson correlations also suggested a negative association between Openness and insomnia severity, and no significant association between Conscientiousness and insomnia severity. Most personality traits showed highly significant, small to moderately sized correlations with each other. This multi-collinearity makes it difficult to discriminate direct and indirect associations of insomnia severity with the individual personality traits. Therefore, we here applied a network approach to distinguish between direct and indirect associations.

We first estimated the network of partial correlations between personality traits and the overall insomnia severity as measured with the ISI summary score. Similar to the simple correlations, insomnia severity was most strongly and directly related to Neuroticism and secondarily as well to Openness and Agreeableness, and not directly related to Extraversion and Conscientiousness. In addition to the simple correlations, the network indicates possible pathways of influence that extent further than just two variables. For example, although Extraversion is not directly related to insomnia, it is strongly associated to Neuroticism and Agreeableness, which in turn are related to insomnia. Thus, by evaluating and visualizing the associations as a network provides insight into possible pathways across multiple variables.

We subsequently estimated a network of the partial correlations between personality traits and different insomnia complaints, as measured by individual ISI *items*. Evaluating the item-level networks provided a number of important insights, both on the association between insomnia complaints and personality and on the associations between insomnia complaints.

First, consistent with the previous analyses, Neuroticism was directly related to insomnia complaints. Item-level analyses indicated that the strongest direct associations to personality concerned difficulty initiating sleep and interference with daily functioning. Interestingly, unlike the lack of a direct association of Conscientiousness with *overall* insomnia severity, this personality trait did show direct associations *specifically* with the insomnia complaints of difficulty maintaining sleep and of interference with daily functioning. Notably, while the partial correlation between Conscientiousness and interference with daily functioning was negative, the partial correlation between Conscientiousness and difficulty maintaining sleep was positive. This suggests that while highly conscientious people are more likely to experience difficulty maintaining sleep, they are less likely to

report that sleep problems interfere with their daily functioning. The inverse associations cancel out with the use of an overall insomnia severity measure, underscoring the value of item-level analyses.

Second, the network approach revealed that daytime and nocturnal insomnia complaints seem organized in two separable clusters, that both contributed to dissatisfaction. This indicates that a summary score may dilute possible specific daytime or nocturnal insomnia severity. The finding could moreover have consequences for the treatment of choice for insomnia, which is cognitive behavioral therapy (CBTI).[164] There could be additive effects of combining interventions that address nocturnal complaints with interventions that promote coping with daytime complaints. A second possibility is that interventions that specifically promote coping with dissatisfaction could ameliorate both daytime and nocturnal complaints. Indeed, CBTI encompasses components focusing on managing expectations and beliefs regarding sleep, improving nocturnal sleep and coping with daytime complaints.[71]

The direction of influences between the insomnia complaints cannot be derived from the current cross-sectional assessment: future studies may consider repeated assessments, both during the development of insomnia as well as during intervention studies. By studying the effect of CBT-I on the individual insomnia complaints, strengths and weaknesses of the intervention could be identified and efficacy may be improved.

Both network analyses showed that Neuroticism is strongly and directly related to insomnia. This is in line with previous literature.[25,29,30,214,222,226,227] Assessing Neuroticism may allow for early detection of premorbid predisposition of insomnia, the first of Spielman's 3P's.[22] Coping with Neuroticism has been shown feasible using both cognitive and cognitive behavioral interventions.[234-236] Moreover, knowledge about the personality traits that are characteristic of insomnia may provide clues on underlying causes of vulnerability to develop insomnia. For example, individual differences in personality traits are associated with individual differences in brain structure and brain function.[216-218]

A few limitations of this study should be mentioned. First of all, participants filled out the questionnaires in an uncontrolled setting and at a self-chosen time. This resulted in a median of 7.4 months between filling out the ISI and the Mini-IPIP. However, since the Mini-IPIP assesses personality traits that are not assumed to change over time, the personality traits can be expected to be the same at the time the participants filled out the ISI. Another limitation, that has already been mentioned, is the cross-sectional set-up of this study. Whereas the current cross-sectional approach has revealed the strongest direct associations between constructs of personality and insomnia complaints, it requires longitudinal studies to address possible changes in the associations between ISI items. We recommend longitudinal and intervention studies to not only report on ISI summary scores, but also to investigate the network of associations between items.

In summary, using network analysis in a large sample, we obtained an integrated view on the associations of personality traits with both overall insomnia severity and individual insomnia complaints. We found that examining the individual insomnia complaints provides additional information on the direct and indirect associations both between personality traits and insomnia, as well as between the different insomnia complaints. The approach allowed us to discriminate direct associations from indirect relations and thereby identified possible targets for improving CBTI with the highest probability of effectively changing the network of associated complaints.

CHAPTER 6: DISCUSSION

Insomnia Disorder is a highly prevalent disorder,[32] that is defined by persistent nocturnal sleep complaints – trouble falling or maintaining sleep – and impaired daytime functioning.[6] People suffering from insomnia often experience impairments in many aspects of their daytime functioning, among which: memory problems, difficulty concentrating, increased error and accident proneness and headaches. This can result in higher medical costs and more work absenteeism. Insomnia Disorder places a tremendous burden on health and society.[45] Therefore, adequate treatment is important. The recommended treatment for insomnia is cognitive behavioral therapy for insomnia (CBTI).[7] A wide body of evidence shows its effectiveness.[7] However, the remission rate is only 56%,[54] leaving room for improvement. Another group of treatments for Insomnia Disorder, known as chronobiological treatment (CT), is far less studied but seems promising in alleviating insomnia complaints,[159] either as a stand-alone treatment, or combined with CBTI.

Perhaps finding or combining new treatment protocols is not the only opportunity to improve the treatment of Insomnia Disorder. Personality traits have been shown to be related to Insomnia Disorder.[28] It still remains inconclusive, however, which personality traits are most directly associated to which insomnia complaints. Investigating these associations may open a door to more personalized treatment of Insomnia Disorder.

The aim of the present thesis is to identify opportunities to improve the treatment of Insomnia Disorder. In order to do so, the thesis can be roughly divided into four parts. The first part is the introduction. In chapter 1, an elaborate overview is given of wat Insomnia disorder is and what factors influence the development and perpetuations of the disorder. The second part, chapter 2 and 3, is dedicated to a randomized clinical trial incorporating different combinations of non-pharmacological treatment methods. Chapter 2 describes an elaborate study protocol for this trial that was the first to evaluate, in a single design, the relative effectiveness of internet-supported cognitive behavioral therapy for insomnia (ICBTI), three types of chronobiological treatment (bright light, physical activity and warm baths) and the combination of ICBTI with CT. The primary outcome is the difference in sleep efficiency pre to post treatment. Sleep efficiency is calculated as the percentage of time spent asleep of the time spent in bed for sleep. Chapter 3 describes the results of this trial.

The third part of this thesis, chapter 4 and 5, addresses how personality profiles relate to insomnia complaints. Personality traits are hypothesized to be both predisposing and perpetuating factors for the development of insomnia disorder. Investigating the relationship between personality traits and insomnia complaints may provide relevant information for personalizing treatment, which may lead to better effectiveness of treatment.

This last chapter, the fourth part of the thesis, will first summarize the findings of the studies described in chapter 2 to 5. Subsequently, a few results from the RCT that were not within the confines of the hypotheses posed in chapter 3 will be discussed, zooming in on subtypes of insomnia.

These subtypes were published after writing Chapter 3 and indicated that the subtypes of insomnia have clinical relevance. We will relate our findings will to the results described in chapter 3 and 5, focusing on the effects of treatments on daytime complaints and the differences between individuals suffering from Insomnia Disorder. Finally, the implications of these combined results and recommendations for future research are discussed.

SUMMARY OF RESULTS

The main findings of the large RCT, as described in **chapter 2 and 3**, were that ICBTI improved diary-derived sleep efficiency, whereas none of the active CTs on their own elicited improvement compared to the placebo control condition. Adding CT to ICBTI did however have benefits that appeared only at follow-up. For participants that only received ICBTI, a part of the initial sleep efficiency improvement was lost during the month following completion of treatment. This is best illustrated by figure 1 of chapter 3. Those that received ICBTI in combination with any active CT better maintained their initial gain in sleep efficiency and moreover fell asleep more easily, slept longer and had less nocturnal wakefulness (see the supplementary figures of chapter 3). Immediate effects of ICBTI on sleep efficiency are at least partly driven by the reduced time in bed demanded by the sleep restriction intervention that is integral part of ICBTI. However, at follow-up, the participants that had combined ICBTI with CT experienced more sleep and less wake compared to those who only received ICBTI, while time in bed did not differ. Supported by additional benefits to complaints about early morning awakening and daytime functioning, the findings indicate that the addition of either bright light, physical activity or warm baths solidifies the sleep improvement induced by ICBTI. CT interventions are low in cost and risk, making them a valuable addition to consolidate ICBTI effects on sleep in Insomnia Disorder.

In **chapter 4** the psychometric properties of the Dutch translations of the IPIP-120-NEO and the mini-IPIP, that both measure the Big Five personality traits, were found to resemble the original English questionnaires well. The factor structures, scale-reliabilities and discriminant validity were similar to the original versions. The profile similarity framework, which is a theoretical framework that compares profiles of personality factors, rather than individual components, showed that the correlations between the personality profile scores were more robust and less format-dependent than the correlations between personality factors. These findings show the way to more consistent personality factors and profiles obtained across different assessment formats and languages.

The study described in **chapter 5** aimed to obtain an integrated view on the associations between the Big Five personality traits and insomnia, as measured by the Insomnia Severity Index (ISI), by using network analysis in a large sample. As expected, and often reported, neuroticism was directly related to insomnia complaints, most strongly with the nocturnal complaint of having difficulty initiating sleep and the daytime complaint of interference with daily functioning. These relationships were

positive, meaning highly neurotic people experience more difficulty initiating sleep and more interference with daily functioning. Interestingly, the personality trait conscientiousness showed a positive association with the nocturnal insomnia complaint of difficulty maintaining sleep and a negative association with daytime complaint of interference with daily functioning. This suggests that while highly conscientious people are more likely to experience difficulty maintaining sleep, they are less likely to report that sleep problems interfere with their daily functioning. These inverse associations of conscientiousness and insomnia complaints cancel out with the use of the overall insomnia severity measure. Since neuroticism was found to have only positive associations with insomnia symptoms, it is also related to the overall insomnia severity measure and therefore more easily associated to insomnia. The difference in findings between these two personality traits underscore the value of symptom-level analyses. The network approach allowed to discriminate direct associations from indirect relations and thereby identify possible targets for improving CBTI with the highest probability of effectively changing the network of associated complaints.

OPTIMIZING TREATMENT – COMBINING CBTI WITH CT

Chapter 3 of this thesis shows the beneficial effects of adding a form of chronobiological treatment to CBTI. We saw beneficial effects emerge only at follow-up, and not only on sleep efficiency, our primary outcome, but also sleep on onset latency, total sleep time, nocturnal wakefulness, complaints about early morning awakening and complaints about daytime functioning. To the best of our knowledge, this is the first study to show that adding CT to ICBTI helps people suffering from Insomnia Disorder maintain the initial benefits they experience caused by ICBTI after four weeks. To follow-up this study, many opportunities arise to investigate even further optimization of treatment. First of all, the treatment protocol of only 4 weeks was shorter than the often used 6 weeks. Within 6 weeks, the circadian clock may have more time to adjust to the enforced rhythm. In addition, since we found no difference in form of CT, it may be a next step to let participants choose the CT they feel will benefit them most, or the CT they feel they can easily incorporate in daily life. In this case, the placebo effect may help a little, but it will also most likely result in better compliance. Although average compliance was quite high, especially the warm baths and physical activity showed some room for improvement in terms of protocol and compliance to it. Compliance for warm baths was 21 out of 28 days and for physical activity it was 22 out of 28 days. The other two conditions had a compliance rate of 26 out of 28 days. Although this is a statistically significant difference between CT's, it is not lower than the compliance to ICBTI (on average 22 out of 28 days). The most heard complaint about the warm baths condition was that it is a waste of water and a burden on the environment. People who feel strongly about the environment would therefore probably prefer physical activity over warm baths. For physical activity, we saw that most people do comply, but not always in the set time window. This can be due to bad weather conditions or an unsafe feeling being

outside in the dark in winter. These people may prefer to take a warm bath. Moreover, it may even be more beneficial to combine two or more CTs. This may train the circadian clock more rigorously, although it may also become a bit harder to comply to. Importantly, combining ICBTI with one or more CTs is very feasible. CTs are low in cost and risk and are easy incorporate in everyday life, even more so if one can choose their preferred CT, since they can become part of the daily routineTo conclude this paragraph, whereas the benefit of ICBTI would otherwise weaken over time, the addition of CT helps to maintain the effect on sleep efficiency and moreover improves both nocturnal and daytime aspects of insomnia. CTs are low in cost and risk and therefore a promising addition to consolidate ICBTI effects on sleep in Insomnia Disorder, worth further investigation.

OPTIMIZING TREATMENT - INSOMNIA SUBTYPES AND PERSONALITY

Chapter 2 mentions another opportunity for the optimization of treatment, on top of combining ICBTI with CT. This opportunity is based on the idea that the people suffering from insomnia most likely represent a heterogeneous mix of subtypes, with different underlying causes and expected treatment response. These subtypes may not necessarily be distinguished by the type of sleep problems. Other factors such as personality traits, medical complaints and medical history, and the ability to perceive comfort, may differ between the proposed subtypes as well. Our research group commenced a large-scale study using web-based assessment of questionnaires to collect data on these variables (the Netherlands Sleep Registry, NSR, www.sleepregistry.org[135]). The use of latent class analysis on these data allowed for the data-driven detection of multivariate subtypes, the calculation of subtype probability and the development of the Insomnia Type Questionnaire (ITQ).[31] Blanken *et al.* (2019) thus found five well distinguished subtypes.[31] The RCT described in chapter 2 and 3 originally aimed to evaluate the possibility to optimize insomnia treatment along the principles of personalized and stratified medicine. We aspired to make the first step towards the development of a protocol for individualized optimal treatment for the mentioned subtypes of insomnia, which each may show different responsiveness to ICBTI and the different CT manipulations. The ITQ that can probe the above-mentioned subtypes of insomnia was only developed after data collection of the RCT was completed. Therefore, the insomnia subtype of the participants could only be determined after treatment and analyses fell outside the scope of this thesis. However, for sake of completion, we here concisely describe the results of the analyses performed on a subset of the participants in our RCT.

The distribution of the five insomnia subtypes in all treatment groups of the RCT was suboptimal and did not provide sufficient power to analyze treatment effect moderation of the subtypes within the RCT. There was an overrepresentation of two of the subtypes (type 2 and 4, 41% and 25% respectively) and an underrepresentation of type 3 (7%). See Blanken *et al.* (2019)[31] for details regarding the meaning and exact distributions of these subtypes. However, sufficient data were

available to elucidate that at least one effect of ICBTI differed for subtype 2 and 4. Of the participants of type 2 (*N*=43, mean (SD) age 50.8 (12.9) years, 88% females) 26 were in the group that received ICBTI in week 1-4 and 17 were in the group that did not receive ICBTI in week 1-4, the waitlist control group. Of the type 4 participants (*N*=25, mean (SD) age 53.2 (9.8) years, 96% females), 16 received ICBTI in week 1-4 and 9 were in the waitlist control group. Mixed model analyses on insomnia severity (ISI) scores in week 0 and 5 revealed that ICBTI differentially ameliorated insomnia severity in type 2 and 4 patients. As compared to waitlist control, ICBTI induced a strong decrease in insomnia severity (ISI) in subtype 2 (-5.5 (7.8) mean (SD), $P < 0.001$) and a reasonable decrease in insomnia severity in subtype 4 (-3.1 (7.3) mean (SD), $P=0.003$). As suggested in chapter 5 of this thesis, item-level analyses were performed and showed that ICBTI decreased difficulty initiating sleep more in type 2 than in type 4 (-0.8 (1.9) mean (SD), $P < 0.001$, *vs*. 0.1 (1.5) mean (SD), $P = 0.69$).

Given the small sample sizes, the results should be regarded preliminary. Also, since the subtypes were determined only after treatment, we cannot be sure that treatment did not alter the subtype of participants. However, these preliminary results indicate the clinical relevance of taking insomnia subtypes into account. Future research in a better-balanced sample could determine the stability of insomnia subtype across treatment and investigate treatment effect differences between subtypes. The insomnia subtypes are partly determined by personality traits, and the results in chapter 5 showed the different relationships with personality traits and insomnia symptoms. The preliminary results already indicated that subtype differences in the response of difficulty initiating sleep to ICBTI. In future clinical studies on treatment of Insomnia Disorder, it is therefore recommended to take the subtypes into account. One could aim to recruit a balanced sample of all five subtypes to attain optimal statistical power to investigate the response differences.

OPTIMIZING TREATMENT - IMPAIRED DAYTIME FUNCTIONING

The diagnosis of Insomnia Disorder includes the presence of impaired daytime functioning.[6] However, most interventions focus on improving (nocturnal) sleep complaints. In addition to the effects of combined CT and ICBTI on sleep efficiency and other nocturnal sleep parameters (SOL, WASO, TST), the analyses of the RCT data described in chapter 3 also showed delayed positive effects of the combination of ICBTI with a CT on average daytime functioning (see table 3 of chapter 3).

Additionally, the study described in chapter 5 underlines the importance of assessing the daytime symptoms of insomnia disorder. In this study both the personality traits of neuroticism and conscientiousness showed strong direct associations with the daytime complaint of interference with daily functioning (IDF) assessed by the ISI, but in opposite directions: neuroticism showed a positive

relationship with IDF and conscientiousness showed a negative relationship with IDF. Since the sample was evenly distributed over healthy sleepers and insomniacs, this result is not driven by a single group.

Taking the daytime symptoms into account, when evaluating different treatments of Insomnia Disorder, may open the opportunity to identify so far overlooked effects of the treatment. The daytime aspect of insomnia is generally seen as a consequence of the nocturnal complaints. However, both physical and mental complaints can be precipitating factors in the development of chronic insomnia. Therefore, it could be argued that alleviating these complaints could relieve the burden of the disease tremendously. This could even result in less worry about the bad sleep, which in turn may break the vicious circle of lying awake, worrying about lying awake.

RECOMMENDATIONS FOR FUTURE RESEARCH

This thesis shows that there is ample room for improvement of the treatment of insomnia. First, our RCT showed beneficial effects of combining CT with ICBTI. Interestingly, we found no difference between the three forms of CT. Since no difference was found between the treatments in this four-week protocol, it is of interest to study whether the treatments still perform equally in longer treatment protocols, giving the circadian clock more time to adapt. In addition, future studies may address possibilities to improve compliance to physical activity and warm baths. Another opportunity for future research is to combine different types of CT. The aim of all three forms of chronobiological treatment used in this thesis is to enhance the amplitude and control the timing of the circadian rhythm. Possibly, this effect is increased when combining the different forms of CT.

Second, it remains to be evaluated how insomnia subtypes differ in their treatment response. Chapter 5 of this thesis showed that the personality traits of neuroticism and conscientiousness are strongly and differently associated with insomnia complaints. Also, the additional results of the current chapter indicate different treatment response between insomnia subtypes. Since the personality traits are incorporated in the insomnia subtypes, adjusting the focus of treatment according to either personality profile or insomnia subtype, may be the next step towards more personalized and therefore optimized treatment of Insomnia Disorder. By finding the optimal (combination of) treatment for the five individual subtypes, the remission rates might be increased.

Third, and related to the previous point, it was also apparent from the RCT we conducted, and the subtype analysis performed afterwards, that our sample was not proportionally distributed over the insomnia subtypes. Therefore, it may very well not be a representative sample of the population of people with Insomnia Disorder. Since we recruited through common channels, it is very well possible that samples in other studies are equally unbalanced. Some subtypes may be more inclined to

participate and persist in participation of (clinical) studies. Some subtypes may be more likely to be excluded because of high scores on e.g. depression or anxiety rating scales. Future studies should take subtypes into account and recruit participants of all subtypes in the right proportions. This will lead to more representative samples. More representative samples will in turn allow for more thorough investigation of the treatment response of different insomnia subtypes.

Fourth, even though daytime functioning is a part of the diagnosis of insomnia disorder, it remains unclear how daytime functioning is improved by (I)CBTI, CT or their combinations. Future studies should focus on assessing if and how these treatments influence day to day life of people suffering from insomnia disorder. Hypothetically, even if the nocturnal insomnia complaints would not be improved by a treatment, if daytime functioning is fully restored, the diagnosis of Insomnia Disorder would no longer apply.

And last of all, to make an even greater step towards personalized and stratified treatment, both individual differences and both nocturnal and daytime aspects of Insomnia Disorder should be studied together. This will combine all opportunities described above. In my humble opinion, this is the true next step towards treating Insomnia Disorder to a satisfactory level of remission.

GENERAL CONCLUSION

CBTI is currently the recommended treatment for insomnia disorder.[7] The recent European guidelines indicate that CTs are promising but as yet under-studied.[7] Our results showed that combining four weeks of ICBTI with simultaneous CT, improves long-term effects on sleep efficiency over receiving only ICBTI, driven by longer sleep and less nocturnal wake. Similar effects were seen on daytime functioning. Additional analyses only described in the current chapter indicated that the people suffering from insomnia disorder have to be regarded as a heterogeneous mix of subtypes of insomnia. These subtypes are defined by non-sleep related traits, such as personality profiles, life experience, medical history et cetera. Preliminary results suggest that responses to ICBTI could differ between subtypes.

Personality traits have been proposed as both predisposing and perpetuating factors for insomnia. When zooming in on the individual insomnia complaints, we saw that conscientiousness and neuroticism are strongly related to insomnia. Highly neurotic and highly conscientious personalities have more difficulty maintaining sleep, a nocturnal complaint of insomnia disorder. Highly neurotic people also report much interference with daily functioning. In contrast, highly conscientious personalities report low interference with daily functioning.

Combining the findings in this thesis, we show that there are several opportunities to improve the effectiveness of treatment of Insomnia Disorder. First of all, we show that adding any form of CT to

ICBTI, can sustain the treatment effect of the latter for at least a month. This treatment effect was most apparent in sleep efficiency and other nocturnal aspects of sleep. However, similar improvements were noticeable in daytime complaints. Second, we show clear relations between personality traits and different complaints of insomnia. We also found an indication that insomnia subtypes respond differently to ICBTI. The improved treatment effect of combined treatment may therefore be moderated by individual differences such as personality profiles or insomnia subtypes. Possibly, treatment effects could be further improved by personalizing treatment based on personality traits or insomnia subtype.

A third opportunity of optimizing treatment is broadening the focus on improving daytime complaints of insomnia disorder with interventions. Relieving daytime symptoms of insomnia could perhaps also have beneficial effects on the nocturnal symptoms. When the burden on everyday life is decreased, the worry about, and pressure of, having a good night's sleep might also decrease. This can in turn lead to improved sleep.

In short, we recommend clinical investigations of Insomnia Disorder to (1) combine (I) CBTI with CT, (2) recruit a balanced sample of the five insomnia subtypes, (3) investigate the moderation effects of these subtypes and (4) asses both the nocturnal and daytime symptoms that together define Insomnia Disorder.

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SUMMARY

Insomnia Disorder is a highly prevalent disorder, that is defined by persistent nocturnal sleep complaints – trouble falling or maintaining sleep – and impaired daytime functioning. People suffering from insomnia often experience impairments in many aspects of their daytime functioning, among which: memory problems, difficulty concentrating, increased error and accident proneness and headaches. This can result in higher medical costs and more work absenteeism. Insomnia Disorder places a tremendous burden on health and society. Therefore, adequate treatment is important. The recommended treatment for insomnia is cognitive behavioral therapy for insomnia (CBTI). A wide body of evidence shows its effectiveness. However, the remission rate is only 56%, leaving room for improvement. Another group of treatments for Insomnia Disorder, known as chronobiological treatment (CT), is far less studies but seems promising in alleviating insomnia complaints, either as a stand-alone treatment, or combined with CBTI.

Perhaps finding or combining new treatment protocols is not the only opportunity to improve the treatment of Insomnia Disorder. Personality traits have been shown to be related to Insomnia Disorder. It still remains inconclusive, however, which personality traits are most directly associated to which insomnia complaints. Investigating these associations may open a door to more personalized treatment of Insomnia Disorder.

The thesis before you aims to identify opportunities to improve the treatment of Insomnia Disorder and optimize its effectiveness. In order to do so, our focus is threefold. First, we investigate different forms of treatment for insomnia. We conducted a randomized controlled trial (RCT) that evaluates the relative effectiveness of CBTI and three forms of CT (bright light, physical activity and warm baths) or their combination. Second, we focus on individual differences between people who suffer from insomnia, such as personality traits and subtypes of insomnia, and how these differences relate to insomnia symptoms and treatment effects. By increasing the understanding on how individual differences may influence how Insomnia Disorder presents and is affected by treatment, we pave the path towards more personalized treatment. Third, we discuss the importance to focus not only on nocturnal, but also on daytime symptoms of insomnia. Nocturnal complaints of insomnia are the inability to fall asleep, maintain sleep or waking up unrested. Daytime complaints are defined in the ICSD and DSM and range from headache and stomachache, to fatigue and tiredness, to the inability to concentrate and memory loss. Insomnia Disorder is defined by both types of symptoms. However, the effect of treatment on daytime symptoms is less studied than the effect on nocturnal symptoms. Shifting or broadening the focus to daytime complaints may provide more insight in the effectiveness of the treatments.

To achieve the aim of identifying opportunities to optimize the treatment of Insomnia Disorder, in **chapter 2** we elaborately describe a study protocol for an RCT that was the first to evaluate, in a single design, the relative effectiveness of internet-supported cognitive behavioral therapy for insomnia (ICBTI), three types of chronobiological treatment (bright light, physical activity and warm baths) and the combination of ICBTI with CT. The primary outcome is the difference in sleep efficiency pre to post treatment. Sleep efficiency is calculated as the percentage of time spent asleep of the time spent in bed for sleep. Chapter 2 discusses the rationale and treatment application, the procedure for recruiting and selecting participants and the trial execution and the statistical methods used to analyze the data.

Subsequently, in **chapter 3** we report the results of this RCT. The main results were that ICBTI improved diary-derived sleep efficiency, whereas none of the active CTs on their own elicited improvement compared to the placebo control condition. Adding CT to ICBTI did however have benefits that appeared only at follow-up. For participants that only received ICBTI, a part of the initial sleep efficiency improvement was lost during the month following completion of treatment. Those that received ICBTI in combination with any active CT better maintained their initial gain in sleep efficiency and moreover fell asleep more easily, slept longer and had less nocturnal wakefulness. Immediate effects of ICBTI on sleep efficiency are at least partly driven by the reduced time in bed demanded by the sleep restriction intervention that is integral part of ICBTI. However, at follow-up, the participants that had combined ICBTI with CT experienced more sleep and less nocturnal wake compared to those who only received ICBTI, while time in bed did not differ. Supported by additional benefits to complaints about early morning awakening and daytime functioning, the findings indicate that the addition of either bright light, physical activity or warm baths solidifies the sleep improvement induced by ICBTI. CT interventions are low in cost and risk, making them a valuable addition to consolidate ICBTI effects on sleep in Insomnia Disorder.

Chapter 4 is a methodological chapter that evaluates if the profile similarity framework can be used as a means improve the within-subject comparability of different assessment formats. The personality similarity framework is a theoretical framework that compares the profiles of personality factures, rather than individual components. In order to evaluate the profile similarity framework, we use two versions of the same personality questionnaire, namely the mini-IPIP and the IPIP-NEO-120 that measure the Big Five personality traits. Additionally, this study evaluates the psychometric properties of the Dutch translations of the mini-IPIP and the IPIP-NEO-120. We found that the psychometric properties of the Dutch translations of the IPIP-120-NEO and the mini-IPIP resembled the original English questionnaires well. The factor structures, scale-reliabilities and discriminant validity were similar to the original versions. The profile similarity framework showed that the correlations between the personality profile scores were more robust and less format-dependent than the correlations

between personality factors. These findings show the way to more consistent personality factors and profiles obtained across different assessment formats and languages.

The study described in **chapter 5** investigates how the different complaints of insomnia relate to personality traits. In this chapter, we show direct and indirect associations between the Big Five personality traits and insomnia, as measured by the Insomnia Severity Index (ISI), by using network analysis in a large sample. As expected, and often reported, neuroticism was directly related to insomnia complaints, most strongly with the nocturnal complaint of having difficulty initiating sleep and the daytime complaint of interference with daily functioning. These relationships were positive, meaning highly neurotic people experience more difficulty initiating sleep and more interference with daily functioning. Interestingly, the personality trait conscientiousness showed a positive association with the nocturnal insomnia complaint of difficulty maintaining sleep and a negative association with daytime complaint of interference with daily functioning. This suggests that while highly conscientious people are more likely to experience difficulty maintaining sleep, they are less likely to report that sleep problems interfere with their daily functioning. These inverse associations of conscientiousness and insomnia complaints cancel out with the use of the overall insomnia severity measure. Since neuroticism was found to have only positive associations with insomnia symptoms, it is also related to the overall insomnia severity measure and therefore more easily associated to insomnia. The difference in findings between these two personality traits underscore the value of symptom-level analyses. The network approach allowed to discriminate direct associations from indirect relations and thereby identify possible targets for improving CBTI with the highest probability of effectively changing the network of associated complaints.

In **chapter 6** all results are discussed and put into perspective. Additionally, we explain why not all intended analyses as described in the study protocol in chapter 2 were presented in chapter 3. The additional results are described in a paper that was outside the scope of this thesis. This study found five well distinguished subtypes of Insomnia Disorder. These subtypes are not only distinguished by sleep complaints, but also by other traits, such as personality, life history, medical history et cetera. Preliminary results show that different subtypes respond differently to ICBTI.

In conclusion, we identified three opportunities to optimize the treatment of Insomnia Disorder. First of all, the results of our RCT show that combining ICBTI with any form of CT sustains the initial benefits of the former treatment on sleep efficiency over a longer period, than when applying stand-alone ICBTI. Since this was a first study to show this, it leaves ample opportunity to further refine this combination of treatments to find the optimal combination.

Second, we found that personality traits have different associations with different symptoms of insomnia disorder. Additionally, our research group identified five distinct subtypes of insomnia and showed that these subtypes respond differently to ICBTI. The improved treatment effect of combined

treatment may therefore be moderated by individual differences such as personality profiles or insomnia subtypes. And treatment effect could be further improved by personalizing treatment based on personality traits and/or insomnia subtype.

And third, we identified the different relationships between personality traits and nocturnal and daytime symptoms of insomnia. Currently, most research focusses on the effect of treatments of insomnia on nocturnal symptoms. The rationale behind this is that nocturnal symptoms precede daytime symptoms of insomnia. However, some of the daytime symptoms, such as worry, can also be predisposing factors of insomnia. Relieving the daytime symptoms could perhaps release some of the burden of insomnia, which could lead to less rumination and better sleep. On top of this reversed effect, focusing on both relieving nocturnal and daytime symptoms of Insomnia Disorder will increase the effectiveness of treatment and lead to better results.

SAMENVATTING

Slapeloosheid, of insomnie, is een veel voorkomende aandoening, die wordt gedefinieerd door aanhoudende nachtelijke slaapklachten - problemen met in slaap vallen of blijven - en verstoord functioneren overdag. Mensen die lijden aan slapeloosheid ervaren vaak beperkingen in veel aspecten van hun dagelijks functioneren, waaronder: geheugenproblemen, concentratieproblemen, verhoogde kans op het maken van fouten en ongevallen en hoofdpijn. Dit kan resulteren in hogere medische kosten en meer ziekteverzuim. Slapeloosheid legt daarmee een enorme last op de gezondheid en de maatschappij. Daarom is een adequate behandeling belangrijk. De aanbevolen behandeling voor slapeloosheid is cognitieve gedragstherapie voor insomnie (CGTI). Een groot aantal wetenschappelijke studies toont de effectiviteit ervan. Het remissiepercentage is echter slechts 56%, waarmee er ruimte voor verbetering is. Een andere groep behandelingen voor slapeloosheid, bekend als chronobiologische behandeling (CB), is veel minder bestudeerd, maar lijkt veelbelovend bij het verlichten van slapeloosheidsklachten, hetzij als een zelfstandige behandeling, hetzij gecombineerd met CGTI.

Wellicht is het vinden of combineren van nieuwe behandelprotocollen niet de enige mogelijkheid om de behandeling van slapeloosheid te verbeteren. Van persoonlijkheidskenmerken is aangetoond dat ze verband houden met slapeloosheid. Het blijft echter onduidelijk welke persoonlijkheidskenmerken het meest direct verband houden met welke slapeloosheidsklachten. Onderzoek naar deze associaties kan een deur openen naar een meer gepersonaliseerde behandeling van slapeloosheid.

Het proefschrift dat voor u ligt heeft als doel om kansen te identificeren om de behandeling van slapeloosheid te verbeteren en de effectiviteit ervan te optimaliseren. Om dit te doen, is onze focus drieledig. Allereerst onderzoeken we verschillende vormen van behandeling voor slapeloosheid. We hebben een gerandomiseerde gecontroleerde trial (RCT) uitgevoerd die de relatieve effectiviteit van CGTI en drie vormen van CB (helder licht, fysieke activiteit en warme baden) of hun combinatie evalueert. Ten tweede richten we ons op individuele verschillen tussen mensen die lijden aan slapeloosheid, zoals persoonlijkheidskenmerken en subtypen van slapeloosheid, en hun relatie tot slapeloosheidssymptomen en behandelingseffecten. Door het inzicht te vergroten in hoe individuele verschillen van invloed kunnen zijn op hoe slapeloosheid zich voordoet en wordt beïnvloed door behandeling, effenen we de weg naar een meer gepersonaliseerde behandeling. Ten derde leggen we het belang uit van niet alleen te focussen op nachtelijke symptomen van slapeloosheid, maar ook op symptomen die zich overdag voordoen. Nachtelijke klachten van slapeloosheid zijn het onvermogen om in slaap te vallen of te blijven slapen of niet uitgerust wakker worden. Klachten overdag worden gedefinieerd in de ICSD en DSM en variëren van hoofdpijn en buikpijn tot slaperigheid en

vermoeidheid, tot het onvermogen om zich te concentreren en geheugenverlies. Slapeloosheid wordt gedefinieerd door beide typen symptomen. Het effect van de behandeling op de symptomen overdag is echter minder bestudeerd dan het effect op de nachtelijke symptomen. Het veranderen of verbreden van de focus naar de klachten overdag kan meer inzicht geven in de effectiviteit van de behandelingen.

Om het doel van het identificeren van kansen om de behandeling van slapeloosheid te optimaliseren te bereiken, beschrijven we in **hoofdstuk 2** uitvoerig een studieprotocol voor een RCT dat als eerste de relatieve effectiviteit evalueerde van internet-ondersteunde cognitieve gedragstherapie voor slapeloosheid (ICGTI), drie soorten chronobiologische behandelingen (helder licht, lichamelijke activiteit en warme baden) en de combinatie van ICGTI met CB. De primaire uitkomstmaat is het verschil in slaapefficiëntie vóór en na de behandeling. De slaapefficiëntie wordt berekend als het percentage tijd dat men slaapt van de tijd die in bed wordt doorgebracht om te slapen. Hoofdstuk 2 bespreekt de beredenering van het onderzoek en toepassing van de behandelingen, de procedure voor het werven en selecteren van deelnemers, de uitvoering van het onderzoek en de statistische methoden om de data te analyseren.

Vervolgens bespreken we in **hoofdstuk 3** de resultaten van deze RCT. De belangrijkste resultaten waren dat ICGTI de slaapefficiëntie berekend uit het slaapdagboek verbeterde, terwijl geen van de actieve CBs op zichzelf verbetering liet zien in vergelijking met de placebo-controleconditie. Het toevoegen van CB aan ICGTI had echter voordelen die pas bij follow-up duidelijk werden. Voor deelnemers die alleen ICGTI ontvingen, ging een deel van de initiële verbetering van de slaapefficiëntie verloren in de maand na voltooiing van de behandeling. Degenen die ICGTI kregen in combinatie met een van de actieve CBs behielden beter hun initiële winst in slaapefficiëntie en vielen bovendien gemakkelijker in slaap, sliepen langer en hadden minder nachtelijke waak. Onmiddellijke effecten van ICGTI op de slaapefficiëntie worden ten minste gedeeltelijk aangedreven door de kortere tijd in bed die wordt vereist door de slaaprestrictie interventie die een integraal onderdeel van ICGTI is. Bij de follow-up ervoeren de deelnemers die ICGTI met CB hadden gecombineerd echter meer slaap en minder nachtelijke waak dan degenen die alleen ICGTI kregen, terwijl de tijd in bed niet verschilde. Ondersteund door extra voordelen voor vroeg in de ochtend wakker worden en functioneren overdag, geven de bevindingen aan dat de toevoeging van ofwel helder licht, fysieke activiteit of warme baden de slaapverbetering, die veroorzaakt werd door ICGTI, vasthoudt. CB-interventies hebben lage kosten en een laag risico, waardoor ze een waardevolle toevoeging zijn om de effecten van ICGTI bij slapeloosheid te consolideren.

Hoofdstuk 4 is een methodologisch hoofdstuk dat evalueert of het raamwerk voor profielovereenkomst kan worden gebruikt als methode om de vergelijkbaarheid binnen personen van verschillende formats van vragenlijsten te verbeteren. Het raamwerk voor profielovereenkomst is een

theoretisch raamwerk dat de scores op de persoonlijkheidsfactoren vergelijkt als een profiel, in plaats van als individuele componenten. Om dit te illustreren, gebruiken we twee versies van dezelfde persoonlijkheidsvragenlijst, namelijk de mini-IPIP en de IPIP-NEO-120 die de Big Five-persoonlijkheidskenmerken meten. Bovendien evalueert deze studie de psychometrische eigenschappen van de Nederlandse vertalingen van de mini-IPIP en de IPIP-NEO-120. We vonden dat de psychometrische eigenschappen van de Nederlandse vertalingen van de IPIP-120-NEO en de mini-IPIP goed leken op de originele Engelse vragenlijsten. De factorstructuren, schaalbetrouwbaarheid en discriminantenvaliditeit waren vergelijkbaar met de originele versies. Het raamwerk voor profielovereenkomst toonde aan dat de correlaties tussen de scores van het persoonlijkheidsprofiel robuuster en minder formatafhankelijk bleken te zijn dan de correlaties tussen persoonlijkheidsfactoren. Deze bevindingen wijzen de weg naar meer consistente persoonlijkheidsfactoren en profielen die zijn verkregen met vragenlijsten van verschillende formats en talen.

De studie beschreven in **hoofdstuk 5** was bedoeld om een geïntegreerd beeld te krijgen van de associaties tussen de Big Five persoonlijkheidskenmerken en slapeloosheid, zoals gemeten door de Insomnia Severity Index (ISI), door netwerkanalyse te gebruiken in een grote steekproef. Zoals verwacht, en vaak gerapporteerd, was neuroticisme direct gerelateerd aan slapeloosheidsklachten, het sterkst met de nachtelijke klacht van moeite hebben met in slaap vallen en de klacht overdag van interferentie met dagelijks functioneren. Deze relaties waren positief, wat betekent dat zeer neurotische mensen meer moeite hebben met in slaap vallen en meer interferentie ervaren met het dagelijks functioneren. Interessant is dat het persoonlijkheidskenmerk nauwgezetheid (conscientiousness) een positieve associatie vertoonde met de nachtelijke slapeloosheidsklachten van moeite met in slaap blijven en een negatieve associatie met de klacht overdag van interferentie met dagelijks functioneren. Dit suggereert dat, hoewel zeer nauwgezette mensen meer moeite hebben met het in standhouden van slaap, ze minder snel melden dat slaapproblemen hun dagelijks functioneren verstoren. Deze omgekeerde associaties van nauwgezetheid en de twee slapeloosheidsklachten heffen elkaar op met het gebruik van de totale ISI-score. Aangezien neuroticisme alleen positieve associaties met slapeloosheidssymptomen bleek te hebben, is het ook gerelateerd aan de totale ISI-score en daarom sneller geassocieerd met slapeloosheid. Het verschil in bevindingen tussen deze twee persoonlijkheidskenmerken benadrukt de waarde van analyse op symptoomniveau. De netwerkbenadering maakte het mogelijk om directe associaties te onderscheiden van indirecte relaties en zo mogelijke doelen te identificeren voor het verbeteren van CGTI met de grootste waarschijnlijkheid om het netwerk van bijbehorende klachten effectief te veranderen.

In **hoofdstuk 6** worden alle resultaten besproken en in perspectief geplaatst. Ook leggen we uit waarom niet alle beoogde analyses die beschreven werden in het studieprotocol in hoofdstuk 2 ook konden worden uitgevoerd en gepresenteerd in hoofdstuk 3. De aanvullende resultaten worden

beschreven in een artikel dat buiten het bestek van dit proefschrift viel. Deze studie vond vijf goed onderscheiden subtypen van slapeloosheid. Deze subtypen onderscheiden zich niet alleen door slaapklachten, maar ook door andere eigenschappen, zoals persoonlijkheidskenmerken, levensgeschiedenis, medische geschiedenis, enzovoort. Voorlopige resultaten laten zien dat verschillende subtypen anders reageren op ICGTI.

Concluderend hebben we drie mogelijkheden geïdentificeerd om de behandeling van slapeloosheid te optimaliseren. Allereerst tonen de resultaten van onze RCT aan dat het combineren van ICGTI met vorm van CB de initiële voordelen van de eerste behandeling gedurende een langere periode in stand houdt, dan wanneer uitsluitend ICGTI wordt toegepast. Aangezien dit een eerste studie was die dit aantoonde, bieden deze resultaten voldoende gelegenheid om deze combinatie van behandelingen verder te verfijnen om de optimale combinatie te vinden.

Ten tweede vonden we dat persoonlijkheidskenmerken verschillende associaties hebben met verschillende symptomen van slapeloosheid. Bovendien identificeerde onze onderzoeksgroep vijf verschillende subtypen van slapeloosheid en toonde aan dat deze subtypen anders reageren op ICGTI. Het verbeterde behandelingseffect van de gecombineerde behandeling kan daarom worden gemodereerd door individuele verschillen, zoals persoonlijkheidskenmerken of subtypen van slapeloosheid. Daardoor zou het behandelingseffect verder kunnen worden verbeterd door de behandeling te personaliseren op basis van persoonlijkheidskenmerken en/of subtype van slapeloosheid.

En ten derde hebben we verschillende relaties geïdentificeerd tussen persoonlijkheidskenmerken en nachtelijke symptomen en symptomen overdag van slapeloosheid. Momenteel richt het meeste onderzoek naar het effect van behandelingen van slapeloosheid zich op nachtelijke symptomen. De reden hiervoor is dat men aanneemt dat nachtelijke symptomen voorafgaan aan symptomen van slapeloosheid overdag. Sommige van de symptomen overdag, zoals piekeren, kunnen echter ook predisponerende factoren van slapeloosheid zijn. Het verlichten van de symptomen overdag kan misschien de last van slapeloosheid verlichten, wat kan leiden tot minder piekeren en betere slaap. Bovenop dit omgekeerde effect zal de focus op zowel het verlichten van nachtelijke als dag symptomen van slapeloosheid de effectiviteit van de behandeling verhogen en tot betere resultaten leiden.

LIST OF ABBREVIATIONS

A	agreeableness;
APS	arousal predisposition scale;
ARSQ	Amsterdam resting state questionnaire;
ASRS	ADHD self-report scale;
BL	bright light treatment;
BW	body warming treatment;
C	conscientiousness;
CBS	central bureau for statistics;
CBT	cognitive behavioral therapy;
CBTI	cognitive behavioral therapy for insomnia;
CCMO	central committee of research involving human subjects;
CFA	confirmatory factor analysis;
CSD	consensus sleep diary;
CT	chronobiological treatment;
DBAS	dysfunctional beliefs and attitudes towards sleep;
DI	deactivated ionizer;
DIS	difficulty initiating sleep;
Dissat	dissatisfaction with sleep;
DMS	difficulty maintaining sleep;
DSISD	Duke's structured interview for sleep disorders;
DSM-V	diagnostic and statistical manual of mental disorders, 5th edition;
E	extraversion;
EMA	early morning awakening;
FFM	five-factor model;
GSES	Glasgow sleep efficiency scale;
GWAS	genome-wide association study;
HADS	hospital anxiety and depression scale;
HAS	hyper arousal scale;
HDNI	high density negative ionization;
ICBTI	internet-based cognitive behavioral therapy for insomnia;
ICC	intraclass correlation coefficient;
ICD-10	international statistical classification of diseases and related health problem, 10th edition;
ICSD-2	international classification of sleep disorders, 2nd edition;
ICSD3	international classification of sleep disorders, 3rd edition;
ID	insomnia disorder;
IDF	interference with daily functioning
II	inactive ionizer;
IPIP	international personality item pool;
ISI	insomnia severity index;
ISP	insomnia subtype probability;
ITQ	insomnia type questionnaire;
LASSO	least absolute shrinkage and selection operator;
N	neuroticism;
NIQoL	noticeability of impaired quality of life;

NSR	Netherlands sleep register;
NTR	Netherlands trial register;
O	openness;
OR	odds ratio;
PA	physical activity treatment;
PANAS	positive affect, negative affect scale;
PSAS	pre-sleep arousal scale;
RCT	randomized controlled trial;
RHT	retinohypothalamic tract;
SCN	suprachiasmatic nucleus;
SE	sleep efficiency;
SF-36	short form 36;
SLOC	sleep locus of control;
SOL	sleep onset latency;
SSES	sleep self-efficacy scale;
TEPS	temporal experience of pleasure scale;
TIB	time in bed;
TiC-P	Trimbos/iMTA questionnaire for costs associated with psychiatric illness;
TST	total sleep time;
WASO	wake after sleep onset;
Worry	worry about sleep.

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