Graduate thesis

NTNU
Norwegian University of Science and Technology
Faculty of Social and Educational Sciences
Department of Psychology

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Digital insomnia behavioral therapy for insomnia in people with chronic pain

A secondary moderation analysis of a large scale randomized controlled trial

Graduate thesis in Clinical Psychology
Supervisor: Alexander Olsen
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Digital insomnibehandling kan redusere insomni hos pasienter, men behandlingseffekt og etterlevelse varierer. Å undersøke mulige moderatorer av behandlingsutfall kan gi oss mer kunnskap om slik variasjon. Formålet med hovedoppgaven var å undersøkte om selvrapportert kronisk smerte ved baseline modererte forholdet mellom dCBT-I og grad av insomni. Sekundære analyser ble gjort på et stort norsk randomisert-kontrollert studie (RCT) som evaluerte effekten av en helautomatisert dCBT-I kalt Sleep Healthy Using the Internet (SHUTi). Et utvalg på 1721 norske deltakere med klinisk relevant insomni ble randomisert til SHUTi eller aktiv kontroll i form av pasientinformasjon om søvn (PE). Selvrapportert tilstedeværelse av kronisk smerte ved baseline ble brukt til å dele utvalget i undergrupper med og uten kronisk smerte. Sekundære utforskende statistiske analyser ble gjort på longitudinelle data fra fire måletidspunkter: baseline og oppfølging etter ni uker, seks måneder og 24 måneder. En Linear Mixed Model (LMM) fant ingen statistisk signifikante interaksjoner mellom måletidspunkt, intervensjon og kronisk smerte. Resultatene indikerer at deltakere både med og uten kronisk smerte hadde nytte av insomnibehandlingen både på kort og lang sikt. Det konkluderes med at digital insomnibehandling kan forbedre søvn hos individer med komorbid kronisk insomni og kronisk smerte. Samtidig viser litteraturen at kronisk smerte kan forverre insomni og derfor burde behandles parallelt. Fremtidige lignende studier bør inkludere kontinuerlige utfallsvariabler for kronisk smerte og flere variabler for søvn- og funksjonsutfall.

Abstract

Though digital cognitive behavioral therapy for insomnia (dCBT-I) effectively improves insomnia, there is individual variation in treatment adherence and response. Moderators of treatment effect should be identified to improve treatment applicability and maximalise desired outcomes. Secondary exploratory analyses were performed using longitudinal data from a large randomised controlled trial (RCT) that compared the effects of Sleep Healthy Using the Internet (SHUTi) program with an active control on insomnia severity. The community-based Norwegian sample with self-reported clinically significant insomnia (N = 1721) was sub-grouped based on baseline self-reported presence of chronic pain. A linear mixed-effect model was run to examine the binary chronic pain variable as a putative moderator of the relationship between the dCBT-I and Insomnia Severity Index (ISI) scores. The covariates were main effects and two- and three-way interactions of assessment time (baseline and 9-week, 6-month, and 24-month follow-up), intervention group (dCBT-I vs. patient education about sleep), and baseline self-reported presence of chronic pain. The analysis was adjusted for age and gender. At baseline, individuals with chronic pain had significantly greater mean ISI scores compared to those without. Across follow-up times, chronic pain did not significantly moderate insomnia severity at the $p < .05$ level. dCBT-I was associated with significant decreases in insomnia severity among participants with and without chronic pain, with significantly better outcomes than control. However, the analyses were explorative, limiting external validity. Future studies should include continuous chronic pain measures that could more precisely track the relationship between chronic pain and chronic insomnia over time.

Acknowledgments

This thesis was long in the making and would not be possible without the help of talented people who know way more about sleep research (and the importance of maintaining a sleep schedule) than me.

Firstly, I would like to thank my supervisors, Simen B. Saksvik and Alexander Olsen. Thank you for your feedback and for guiding this ship to harbour (and for repeatedly reminding me of the dangers of perfectionism). Secondly, I want to give a huge thanks to Stian Lydersen, without whose experience and insights I would be even more adrift in the confusing waters of statistical analysis.

When working on a thesis like this, data is everything. I would therefore like to thank Vedaa and colleagues for their invaluable work on the digital insomnia treatment study from which I have benefited greatly. I also owe a lot to Håvard Kallestad and the rest of the NTNU sleep research group, from whom I first learned about the study that formed the basis for my thesis. Thanks to them, I got the chance to experience the ups and downs, the trials and tribulations of data collection and follow-up work. I learned a lot, and I now have more respect than ever for all those who do this on a daily basis in search of ways to make people's lives better.

Lastly, thanks to my family and friends who supported me along the way with love, hugs, advice, and reminders that there is a light beyond the tunnel of thesis writing. You guys rock, and I hope you're all blessed with a pain-free, good night's sleep.

Table of contents

Abbreviations and acronyms

CBT: Cognitive Behavioural Therapy

CBT-I: Cognitive Behavioural Therapy for Insomnia

CI: Confidence interval

CPain: chronic pain subgroup of individuals who self-reported chronic pain at baseline

dCBT-I: Digital Cognitive Behavioural Therapy for Insomnia

ISI: Insomnia Severity Index

LMM: Linear Mixed Model

nCPain: chronic pain subgroup of individuals who self-reported no chronic pain at baseline

PE: Patient education

RCT: Randomized Controlled Trial

SHUTi: Sleep Healthy Using the Internet

Introduction

Insomnia is the most common sleep disorder in the world, and there is an urgent need for non-pharmacological, scalable, and effective treatment (Baglioni et al, 2020). While both in-person and digital cognitive behavioral therapy for insomnia have been found to effectively improve insomnia severity, compliance and remission rates vary (Baglioni et al., 2020; Riemann et al., 2017). Identifying moderators of treatment effect can improve prediction models, patient targeting, and treatment effectiveness (Kraemer et al., 2002). Insomnia is highly comorbid medical, neurological, and psychiatric disorders (Khurshid, 2018; Sivertsen et al., 2021), and the bidirectional relationship between insomnia and such comorbidities can cause negative feedback loops that may complicate insomnia treatment and remission (Garland et al., 2018; Khurshid, 2018). This thesis uses pre-existing research data to examine whether the presence of chronic pain significantly impacted the effect of a digital and fully automated treatment program on insomnia severity.

Chronic Insomnia and Insomnia treatment

Insomnia is characterised by persistent difficulties of falling or staying asleep that result in daytime symptoms such as fatigue, irritability or depressed mood, and cognitive impairments (World Health Organization [WHO], 2022). The diagnosis depends less on the objective duration and quality of sleep than the subjective experience of sleep dissatisfaction. Insomnia is diagnosed as acute, caused by passing circumstances, or chronic, when symptoms recur several times a week for three months or longer (WHO, 2022). The latter is a great individual, societal, and economic burden, impairing educational and work-related productivity (Hysing, 2015; Hysing, 2016; Vedaa et al., 2019a), physical and mental health (Sivertsen et al., 2009; Sivertsen et al., 2014), and even life expectancy (Leger & Bayon, 2010; Laugsand et al., 2014; Li et al., 2023). It is estimated that one in ten adults satisfy the criteria for chronic insomnia (Baglioni et al., 2020; Morin & Jarrin, 2022), though it is likely under-reported (Torrens Darder et al., 2021). In Norway, surveys show that about 15% of the adult population experiences chronic insomnia, but 85% do not seek or receive insomnia treatment (Helsedirektoratet, 2017). When provided, treatment is most often in the form of hypnotics such as benzodiazepines or melatonin (Bjorvatn et al., 2020). The prescription rate of these drugs has increased alongside growing insomnia rates (Pallesen et al., 2014). This is concerning for several reasons. While hypnotics can improve acute and short-term sleep disruptions, regular long-term use is associated with risk of addiction and side effects such as

daytime fatigue, memory issues, increased risk of falling, and disruptions of sleep stages (De Crescenzo et al., 2022). Furthermore, chronic insomnia may be caused or maintained by actors that pharmacological interventions leave unaddressed, thereby omitting factors that could be crucial for successful long-term improvement (Sateia, 2014). In the wake of these discoveries, hypnotics are disadvised as a first and only treatment option. Instead, the focus has shifted non-pharmacological interventions.

Cognitive Behavioural Therapy for Insomnia

Based on existing research, the European guideline for the diagnosis and treatment of insomnia recommends cognitive behavioural therapy for insomnia (CBT-I) (Riemann et al., 2017). The same was concluded by a task force of the European Sleep Research Society and the European Insomnia Network (Baglioni et al., 2020). As mentioned, one of the drawbacks to sleep medication is that it does not directly target psychological or behavioural factors that may cause or contribute to insomnia symptoms and severity. CBT-I, on the other hand, is a structured and problem-oriented therapeutic approach inspired by the behavioural model of insomnia (Spielman, Caruso, & Glovinski, 1987; Spielman & Glovinsky, 1991). The treatment consists of learning about and practicing sleep hygiene, relaxation training, behavioural strategies for stimulus control and sleep restriction, and cognitive therapy focused on sleep and insomnia misconceptions (Riemann et al., 2017). In short, the goal of CBT-I is for the patient to learn to better manage their sleep, with the aid of a trained therapist. There are clear benefits to this approach. Whereas hypnotics mask insomnia symptoms, CBT-I directly targets maladaptive thoughts, feelings, and behaviours that may cause or contribute to such symptoms (Rossman, 2019). The effect of CBT-I on insomnia severity appears mildly to moderately higher than that of hypnotics and tends to last beyond the initial treatment period (Mitchell et al., 2012). A comparison of the sleeping agent zopiclone, CBT-I, and placebo among elderly Norwegian insomnia patients found that CBT-I was associated with better sleep, both subjectively experienced and objectively measured (Sivertsen et al., 2006). This effect was visible both immediately and six months after treatment. Meta-studies show that CBT-I has durable effects and can reduce insomnia severity up to a year after treatment (van der Zweerde et al., 2019).

Despite these benefits, there is a catch, and a large one at that: the CBT-I cost is high, the scalability low, and it is regrettably underutilized (Rossman, 2019). Considering the high insomnia prevalence versus the comparatively sparse number of CBT-I trained healthcare

personnel, such in-person therapy is very inaccessible to patients (Baglioni et al., 2020). Luckily, with the aid of technology, new treatment alternatives are emerging.

Digital Cognitive Behavioural Therapy for Insomnia

Digital CBT-I (dCBT-I), or internet-based CBT-I (iCBT-I), is an umbrella term for a group of technology-based alternatives to face-to-face insomnia therapy (Jackson, Meaklim, & Mason, 2023; van Straten & Lancee, 2020). There are several types of dCBT-I, such as video-based using programs for long-distance therapy sessions, and automated treatment programs in the form of websites or phone applications. The main arguments for a digitalized CBT-I are increased treatment availability and decreased time and costs compared to in-person therapy (Baglioni et al., 2020). So far, the treatment is effective, though slightly lower than in-person CBT-I (Cheng & Dizon, 2012; Seyffert et al., 2016; Ye et al., 2015; Zachariae et al., 2017; for a summary, see Riemann et al., 2017). This effect appears to extend across a range of psychiatric and medical comorbidities, such as depression (Lin et al., 2023), paranoia and hallucinations (Freeman et al., 2017), and chronic fatigue (Ramfjord et al., 2023). Digital CBT-I-related improvements in insomnia severity and other sleep measures appear to be durable, lasting for up to a year after treatment (Soh et al., 2020). It has therefore been suggested that dCBT-I should be promoted by national health care systems as a first level treatment for insomnia, before administering more costly in-person therapy (Baglioni et al., 2020). The hope is that dCBT-Is can be prescribed as an alternative to sleep medication, with similar scalability. A recent network meta-analysis comparing a specific government-authorized dCBT-I prescription, in-person CBT-I, and sleep medications reported greater improvements in insomnia severity and remission from the dCBT-I (Forma et al., 2022).

Chronic pain

Like insomnia, the diagnosis of pain is largely based on subjective experiences and reports. Chronic primary pain is defined as pain that persists or recurs for three months or longer, can cause significant emotional distress or functional disability, and cannot be explained by another chronic condition (Barke, Korwisi, & Rief, 2022). This contrasts secondary pain, in which a causal medical condition can be identified. A distinction has also been made between cancer-related malignant pain and non-malignant pain unrelated to cancer (Bennett et al., 2019). Overall, chronic pain is extremely prevalent, with global estimates ranging from ten to 50% (Zimmer et al., 2022). Norwegian surveys show that up to one in three adults report

some type of chronic pain (Steingrimsdottir, Nielsen, & Handal, 2023), though a recent comparison of survey and clinical examination data indicate that this is an under-representation of the actual chronic pain prevalence (Borchgrevink et al., 2022). Both globally and domestically, then, chronic pain should be regarded as a public health priority (Zimmer et al., 2022).

Insomnia-Pain comorbidity and treatment

Chronic insomnia and chronic pain are highly comorbid. About 75% of chronic non-cancer pain patients report clinically significant insomnia (Sun et al., 2021). A community-based study found a significant overlap between chronic insomnia and non-malignant chronic pain: 50% of participants with chronic insomnia reported chronic pain compared to 18% of insomnia-free participants, and 48% of those with chronic pain reported chronic insomnia compared to 17% of the pain-free participants (Taylor et al. (2007). Few other medical subgroups reported statistically higher insomnia severity.

Intuitively, it should come as no surprise that constant pain makes rest and sleep difficult. There appears to be a negative feedback loop where a lack of sleep can increase feelings of pain, and pain can impair sleep. Some research indicates that the impact of insomnia on pain is stronger than that of pain on sleep (Finan, Goodin, & Smith, 2013). A prospective study following elderly Hong Kong residents with multimorbidity over time found that chronic musculoskeletal pain predicted insomnia severity (Sit et al., 2021). The authors concluded that pain management could be an important preventive measure for insomnia. On the other hand, insomnia and short sleep duration have been identified as key risk factors for developing increased pain sensitivity (Generaal et al., 2017). In experimental studies, sleep deprivation in otherwise healthy participants results in increased sensitivity to painful stimuli (Schrimpf et al., 2015). Outside experimental settings, this bidirectional relationship can increase disability (Sivertsen et al., 2015). For example, patients with fibromyalgia commonly present with chronic sleep disturbances that decrease their pain threshold, which in turn can worsen their overall health (Landis, 2011). A recent study using longitudinal survey data reported a bidirectional insomnia-pain relationship where insomnia symptoms had greater impact on pain than vice versa (Arnison et al., 2022). Together, this research tells us that sleep must be considered in chronic pain treatment. For people with

comorbid chronic insomnia and pain, the benefit of insomnia treatment might be two-fold, breaking a negative feedback loop.

Applicability of CBT-I and dCBT-I for chronic insomnia-pain comorbidity

The efficacy of CBT-I compared to sleep medication has been assessed for comorbidities such as depression, PTSD, and alcohol dependency, with favourable outcomes (Hertenstein et al., 2022). CBT-I effects on chronic pain are inconsistent, but tend to favour functional measures over pain severity (Finan et al., 2014; McCrae et al., 2019). In other words, while the experienced level of pain stays the same after treatment, the ability to perform daily activities and tasks improves. In a study where patients with chronic neck and back pain were randomized to either CBT-I or control, CBT-I was associated with significant improvements in sleep measures and pain interference on daily functioning (Jungquist et al., 2010). However, there were no significant between-group differences in pain severity. A recent systematic review and meta-analysis evaluating CBT-I on self-reported sleep, pain, and other health outcomes found significant improvements of post-treatment pain, as well as both post-treatment and follow-up sleep (Selvanathan et al., 2021). The authors estimated a pain improvement probability of 58% at post-treatment and 57% at follow-up – in other words, that over half of those who received CBT-I could expect longer-term reductions in pain severity. This suggests that, for some, CBT-I might at least 'take the edge off' their pain or help them deal better with their pain symptoms. For patients who struggle with sleep as well as pain, CBT-I might be the most effective treatment option (Enomoto et al., 2022). However, it has been suggested that patients with comorbid insomnia and pain should receive a hybrid CBT-I that incorporates aspects of CBT for pain management (Tang, 2022). Pain-focused CBT, both in-person and online, is associated with significant reductions in pain intensity (Knoerl, Smith & Weisberg, 2016).

While CBT-I does not directly target pain, it may improve overall well-being by alleviating comorbid sleep problems. Compared to CBT, fewer studies have assessed the applicability of its digital counterpart to patients with comorbid chronic insomnia and chronic pain. In a proof-of-concept, multiple baseline study targeting adult women with chronic migraines, 94% of participants were satisfied with the dCBT-I treatment; 65% saw reductions in insomnia severity; and 34% experienced a change from chronic to episodic pain (Crawford et al., 2020). In a recent RCT comparing brief internet-based CBT-I to applied relaxation, the former was associated with a more rapid decline in insomnia symptoms compared to the latter (Wiklund et al., 2022). No pain-related improvements were reported by either group,

though the authors speculated that patients with chronic pain could benefit from a combined treatment approach.

In sum, the relationship between chronic insomnia and chronic pain symptoms is bidirectional, and investing in better sleep may also be an investment in reducing pain related suffering. However, more studies are needed on the applicability of dCBT-I for comorbid chronic insomnia and chronic pain. One ongoing clinical trial of interest compares app-delivered CBT with usual care for Norwegian insomnia patients with comorbid musculoskeletal pain (Norwegian University of Science and Technology [NTNU], NCT05572697). The results may shed further light on the relationship between chronic insomnia, chronic pain, and dCBT-I. However, to the author's knowledge, no studies have examined whether simply having comorbid chronic pain affects the effectiveness of dCBT-I.

Hypothesis

In this thesis, the following hypotheses are tested:

> H_0: The presence of baseline chronic pain does not significantly moderate the relationship between the dCBT-I and insomnia severity. The treatment effect is homogeneous between participants with and without chronic pain.
>
> H_1: The presence of baseline chronic pain significantly moderates the relationship between the dCBT-I and insomnia severity. The treatment effect is heterogeneous between participants with and without chronic pain.

Answering these hypotheses could provide insights into the effects and applicability of dCBT-I for a common insomnia subgroup. If participants with chronic pain benefit less from the dCBT-I compared to people without chronic pain, it could indicate a need for treatment tailoring. Conversely, if participants with chronic pain benefit from the treatment similarly to participants without chronic pain, it can provide further support for the applicability of dCBT-I.

Methods

The following sections provide a summary of the trial method in Vedaa et al.'s (2020) RCT. For the full trial protocol, see Kallestad et al. (2018).

Trial design

Ethical considerations

The trial followed CONSORT guidelines for a parallel-group, superiority RCT. The trial protocol was registered with ClinicalTrials.gov (NCT02558647) and approved by the Regional Committees for Medical and Health Research Ethics in South-East Norway (2015/134). All participants provided written consent as part of the screening procedure and could opt out at any time. Personal data were de-identified to preserve anonymity during statistical analyses. Data storage and post-processing was done using the Service for Sensitive Data (TSD), developed and maintained by the University of Oslo IT Department (USIT), in line with the Norwegian Personal Data Act and the Health Research Act. In order to remotely access data and perform secondary analyses for the present thesis, the author registered a TSD user with two-step verification measures. No adverse trial events were reported (Vedaa et al., 2020).

Participant recruitment

A community-based volunteer sample was recruited between February 26th, 2016, and July 1st, 2018. Study information was distributed in the form of posters in general health practitioners' clinics, waiting areas, and health facilities, alongside digital advertising across relevant health institution websites and social media. The posters listed a publicly available website where those interested in participating could learn more and apply for the study. Information was also digitally advertised by the Norwegian University of Science and Technology (NTNU), the Norwegian Institute of Public Health (NIPH), and the Central Norway Regional Health Authority. Research team members were interviewed by local and national newspapers to further boost public awareness of the trial.

Eligibility criteria

Participant eligibility was determined through online screening using the same publicly available website mentioned above. Inclusion criteria were age ≥ 18 years, Insomnia Severity Index (ISI) score ≥ 12 indicating clinically significant insomnia (Filosa et al., 2021), and

regular internet access. Exclusion criteria were Epworth sleepiness score > 10 (indicating excessive daytime sleepiness or hypersomnia); self-reports of regular snoring or breathing problems during sleep with daytime difficulties staying awake (indicating sleep apnoea); self-reports of medical conditions contraindicating CBT-I (e.g., epilepsy, bipolar disorder, schizophrenia and psychotic disorders, recent heart surgery); and night-time shift work. Participants were informed that the trial was text-based and required them to set aside sufficient time to partake in the study. Those who accepted and electronically signed the consent form were provided with personal login details to access the baseline assessment questionnaires. Among the 5349 individuals who partook in the online screening process, 1497 were ineligible or declined to participate, while 2131 discontinued the screening process, leaving 1721 participants who satisfied the criteria. Figure 1 shows a flowchart of the eligibility assessment and participation process.

Interventions

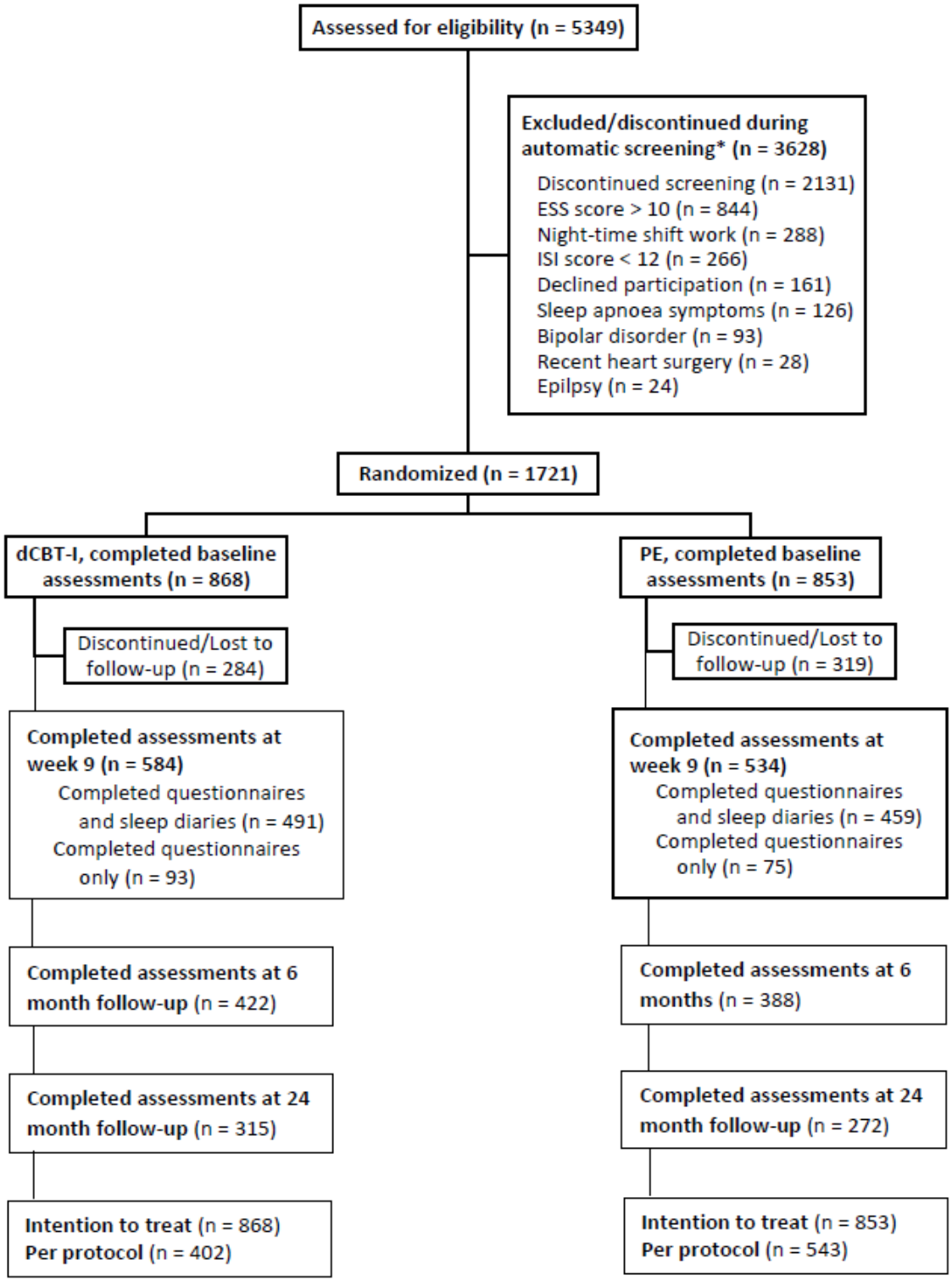
Upon completing baseline assessments, participants were randomly allocated (1:1) to receive either the experimental intervention or the active control. The randomization process was fully automated to ensure double blinding. Both trial conditions were administered through the website described in the eligibility section above.

Treatment intervention: Sleep Healthy Using the Internet (SHUTi)

The dCBT-I intervention consisted of a Norwegian translated version of the fully automated, interactive, and tailored web-based treatment program Sleep Healthy Using the Internet (SHUTi), developed at the University of Virginia (Thorndike et al., 2008). SHUTi consists of six sequential CBT-I based treatment cores designed to be completed within nine weeks. Each core consisted of objectives, activity review, feedback, updated content, and homework. To provide individually tailored treatment, participants filled out sleep diaries and self-reported treatment goals. Previous evaluations of the efficacy and availability of SHUTi have found that most participants report clinically meaningful short- and long-term sleep improvements and rate the program as convenient, understandable, and useful (Moloney et al., 2020; Ritterband et al., 2012; Ritterband et al., 2017; Ritterband et al., 2022). Similar results have been found in RCTs using a Norwegian version of SHUTi (Hagatun et al. 2019; Vedaa et al., 2019b; Vedaa et al., 2020). Table 1 shows more detailed descriptions of the SHUTi treatment cores.

Figure 1

CONSORT flowchart of participants for the Norse 3 RCT, from Vedaa et al. (2020).



Note. ESS = Epworth Sleepiness scale. ISI = Insomnia Severity Index. dCBT-I = digital Cognitive Behavioural Therapy for Insomnia. PE = Patient Education.

* One participant was deemed ineligible due to more than one inclusion/exclusion criterion.

Table 1

Description and completion rates of SHUTi sessions during the intervention period, from Vedaa et al (2020).

	Session description	**n***
Core 1: Overview	Reviews the nature of insomnia and how the program works; identify sleep problems and set personal treatment goals.	748 (86%)
Core 2: Behaviour and sleep 1	How behavioural changes can improve sleep, with special emphasis on sleep restriction.	641 (74%)
Core 3: Behaviour and sleep 2	How behavioural changes can improve sleep, with special emphasis on stimulus control.	563 (65%)
Core 4: Sleep and thoughts	Addressing and changing beliefs and thoughts that might impair sleep (e.g., excessive worrying about the possible consequences of insomnia).	503 (58%)
Core 5: Sleep hygiene	Lifestyle and environmental factors that might interfere with sleep (e.g., caffeine and nicotine intake, electronic media use in bed).	448 (52%)
Core 6: Relapse prevention	Integrating the behavioural, educational, and cognitive components from the former core to develop strategies to avoid future episodes of poor sleep from developing into full-blown chronic insomnia.	402 (46%)

Note. No data were available for the number of participants in the patient education control group who read the content in its entirety. SHUTi = Sleep Healthy Using the Internet.

* Number of participants who completed the session (n = 868).

Active control: Patient education about sleep (PE)

Online patient education (PE) about sleep was used as an active control intervention. PE included non-tailored and fixed information about insomnia symptoms, impact, causes, and prevalence; basic lifestyle, environmental and behavioural strategies to manage these symptoms; and advice about when to seek medical care. Participants were given the option to download and fill out sleep diaries, but no feedback was provided. Instead, they were encouraged to read the insomnia information accessible through the website and implement the suggested strategies into their daily lives. Control participants could access this

information at any point during the trial period. This specific PE content has been compared with SHUTi in previous RCTs (Hagatun et al., 2019; Ritterband et al., 2017).

Data extraction

Data were extracted from four assessment times: baseline, nine-week post randomization, and six- and 24-month follow-up assessments.

Outcome measure: the Insomnia Severity Index (ISI)

A Norwegian translated version of the ISI questionnaire was used as a continuous outcome variable to assess treatment effect as well as remission and intervention response. ISI is a seven-item self-report instrument that uses a five-point (0-4) Likert scale. The total ISI score ranges from 0 to 28, where higher scores indicate greater insomnia severity (Bastien et al., 2001). Insomnia treatment effect is measured by the difference in mean ISI scores across groups and assessment times. Insomnia remission is indicated by an ISI score < 8, and intervention response as an ISI score reduction ≥ 8 from baseline (as per Morin, 1993). The ISI is recommended by the European guideline for the diagnosis and treatment of insomnia (Riemann et al., 2017), and is a validated and reliable staple in insomnia research (Cerri et al., 2023; Manzar, Jahrami, & Bahammam, 2021; Morin et al., 2011; Sommer, Lavigne, & Ettlin, 2015). This includes web-based administration (Thorndike et al., 2011). The Norwegian version of the ISI was translated by sleep experts from the Norwegian Competence Centre for Sleep Disorders. It is widely used in Norwegian insomnia research and clinical practice, though there has not yet been a formal validation of its internal consistency. A cross-sectional study using Norwegian participants ($n = 232$) found good-to-very-good validity for ISI-based insomnia diagnoses (Filosa et al., 2021).

Operationalization of chronic pain

Self-reported presence of chronic pain was assessed at baseline and at 24-month follow-up. The assessment was based on whether participants answered affirmatively on a single categorical item: “In the past year, have you been bothered by muscular and joint pain and/or stiffness that has lasted for at least three continuous months?” (author’s translation). The specified duration of three months or longer is in line with the criterion for chronic pain duration listed in the most recent edition of the International Classification of Diseases (ICD-11; Treede et al., 2015; WHO, 2022).

Statistical analyses

Preparations

All statistical analyses were performed using SPSS version 29.0 (IBM Corp., 2022). The de-identified dataset was structured in a "long" VARSTOCAS (variables to cases) format. Repeated ISI score measures were specified by the continuous variable "isi". Baseline and the three follow-up times were represented by the "time" variable (coded as 1 = baseline, 2 = 9 weeks, 3 = 6 months, 4 = 24 months). In preparation for the main analysis, separate time variables were created to add follow-up times as dichotomous covariates: 9 weeks = "t2", 6 months = "t3", and 24 months = "t4" (all coded as 0 = no response and 1 = response at given time). Trial intervention group was specified by the "intervention" variable (coded as PE = 0, SHUTi = 1). Presence of baseline chronic pain was specified by the "pain" variable (coded as 0 = no chronic pain, 1 = chronic pain). Note that SPSS uses the highest number as the reference group.

Moderation criteria

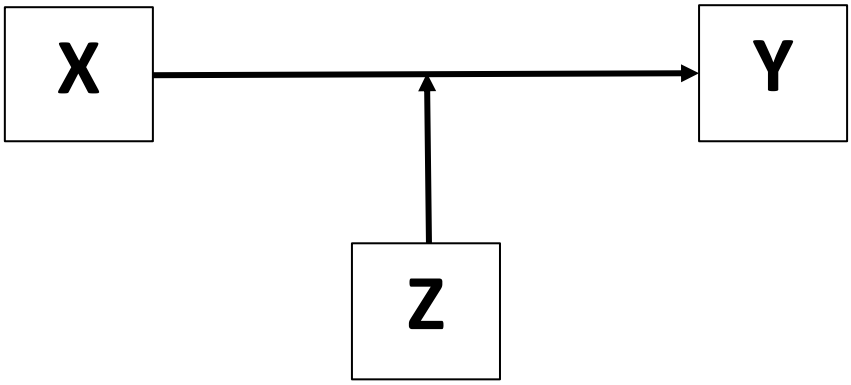
Moderation analysis examines whether an independent variable (Z) strengthens or weakens the correlation between another independent (X) and dependent (Y) variable (Figure 4). A moderator variable must satisfy certain eligibility and analytical criteria: it must precede and be uncorrelated with the treatment (eligibility); and it must show treatment effect heterogeneity across levels of the grouping variable (analytic) (Chmura Kraemer et al., 2008). The nature of the RCT ensured that baseline characteristics, chronic pain included, satisfied the eligibility criteria. In order to satisfy the analytic criterion, individuals with and without chronic pain had to show a statistically significant difference in treatment effect.

Planned analyses

Baseline descriptive statistics were reported as means and standard deviations. In line with CONSORT guidelines for RCTs, no tests for significant differences in baseline demographics were performed, as a lack of such systematic differences is assumed (de Boer et al., 2015; Lydersen, 2020a; Moher et al., 2010). Independent samples *t*-test was used to compare baseline mean ISI scores of participants with and without chronic pain. Pearson chi-square test was used to compare the proportions of participants with and without chronic pain who completed the dCBT-I. Cross-tabulation was used to find ISI completion rates from baseline to follow-up.

Figure 2

Illustrative example of moderation on the relationship between two variables.



Note. The independent variable X affects the dependent variable Y. Another independent variable, Z, is a moderator if it affects the strength of the relationship between X and Y.

Because of the longitudinal RTC design, a linear mixed-effects model (LMM) was deemed appropriate for moderation analysis (Lydersen, 2023; Shek & Ma, 2011). The model was run with ISI scores as the dependent variable. Treatment effect was estimated as the difference in follow-up mean ISI scores compared to baseline mean ISI scores (Wang & Ware, 2014). Individual participants ("id") were added as a random effect and random intercept. The fixed effects included the categorical follow-up time variables of "t2, "t3", and "t4", the "intervention" variable, and the baseline "pain" variable as dichotomous covariates as follows: main effects of time and pain, two-way interactions of time×intervention, time×pain, and three-way interactions of intervention×pain×time. Because of the RCT design, baseline ISI values were expected to be very similar across the randomized interventions. Following the recommendations of Twisk et al. (2018), the model omitted a systematic main effect of intervention group (at baseline) and the interaction intervention×pain (at baseline). This was done to adjust for baseline values of the outcome variable, which improves the estimates of longitudinal RCT data (Lydersen, 2022a). The three-way interaction terms were used to evaluate the estimated mean difference in follow-up outcome values between treatment and control and chronic or no chronic pain. This was estimated for the intervention groups in terms of the coefficient of the corresponding interaction term intervention×time. Adjustments for gender and age were done by including them as covariates. The model was fitted with a variance components (VC) covariance structure. The results are reported in line with the recommendations of Meteyard & Davies

(2020) and S. Lydersen (personal communication, October 27th, 2023). As per Meteyard and Davies' (2020) recommendations for transparency, the SPSS syntax and its explanation are provided in the Appendix and Table A1, formatted after Shek & Ma (2011) and Bauer, Sterba & Hallfors (2008).

Normal distribution of residuals was confirmed by visual inspection of the Q-Q-plot. Statistical significance is reported as two-sided $p \leq .05$. However, as *p*-values should be interpreted with caution (Greenland et a., 2016; Ioannidis, 2005; Nuzzo, 2014; Wasserstein & Lazar, 2016), the 95% confidence intervals (CIs) and effect sizes are included in the results and discussion (Greenland et al., 2016). Between-group effect sizes (Cohen's *d*) were calculated by dividing the estimated mean score difference by the pooled baseline SD. In the moderation analysis, effect sizes were provided for the two-way but deemed irrelevant for the three-way interactions (Lydersen, 2020b).

Missing values

Missing values are common in longitudinal RCT data and can reduce statistical power, cause bias in estimates, reduce sample representativeness, and complicate analyses and treatment effect estimates (Bell et al., 2014; Kang, 2013). Missing values and participant attrition were expected for each follow-up time. The main analysis was performed under the missing at random (MAR) assumption, for which mixed effect models are considered unbiased and robust (Chakraborty & Gu, 2009). Restricted maximum likelihood method (REML) was used to estimate model fit (S. Lydersen, personal communication, October 27th, 2023).

Results

Baseline characteristics

The trial sample (N = 1721) had a mean age of 45 years (range 18-90, *SD* = 13,9). Most participants were women (73%, n = 1251) and married or cohabiting (62%, n = 1074). The mean ISI score was 19.4 (range 8-28, *SD* = 3.9) indicating moderate insomnia. The trial sample was skewed towards chronic pain (63%, n = 1076). One participant had missing chronic pain data. Note that 31 (1.8%) of the participants had a baseline ISI score below 12, meaning their insomnia severity had decreased below the eligibility threshold since the screening process. The difference in baseline mean ISI scores of participants with chronic pain (*M* = 19.7, *SD* = 3.9) and without chronic pain (*M* = 18.9, *SD* = 4.0) was statistically significant: *t* (1717) = -3.94, *p* < .001, Cohen's *d* = -.20. Table 2 summarizes selected baseline characteristics. Figure 3 shows the ISI score distribution across individuals with and without chronic pain at baseline.

Table 2

A selection of baseline characteristics, presented as mean (SD) or % (n).

	CPain (n=1076)		nCPain (n=644)	
Intervention	SHUTi (n=532)	PE (n=544)	SHUTi (n=335)	PE (n=309)
Age (years)[a]	45.8 (13.8)	46,8 (14.1)	41.7 (14.1)	40.9 (12.5)
Sex[b]				
Female	80% (423)	76% (414)	67% (225)	61% (189)
Male	20% (109)	24% (131)	33% (110)	39% (120)
Married	42% (221)	42% (229)	39% (130)	40% (125)
Sleepmed				
Yes	61% (325)	62% (336)	51% (170)	59% (183)
No	39% (207)	38% (208)	49% (165)	41% (126)
ISI[c]	19,4 (3.8)	20,0 (3.9)	18,7 (3.9)	19.2 (3.9)

Note: CPain = reported chronic pain at baseline. nCPain = reported no chronic pain at baseline. SHUTi = Sleep Healthy Using the Internet. PE = patient education about sleep. Sleepmed = sleep medication. ISI = Insomnia Severity Index.

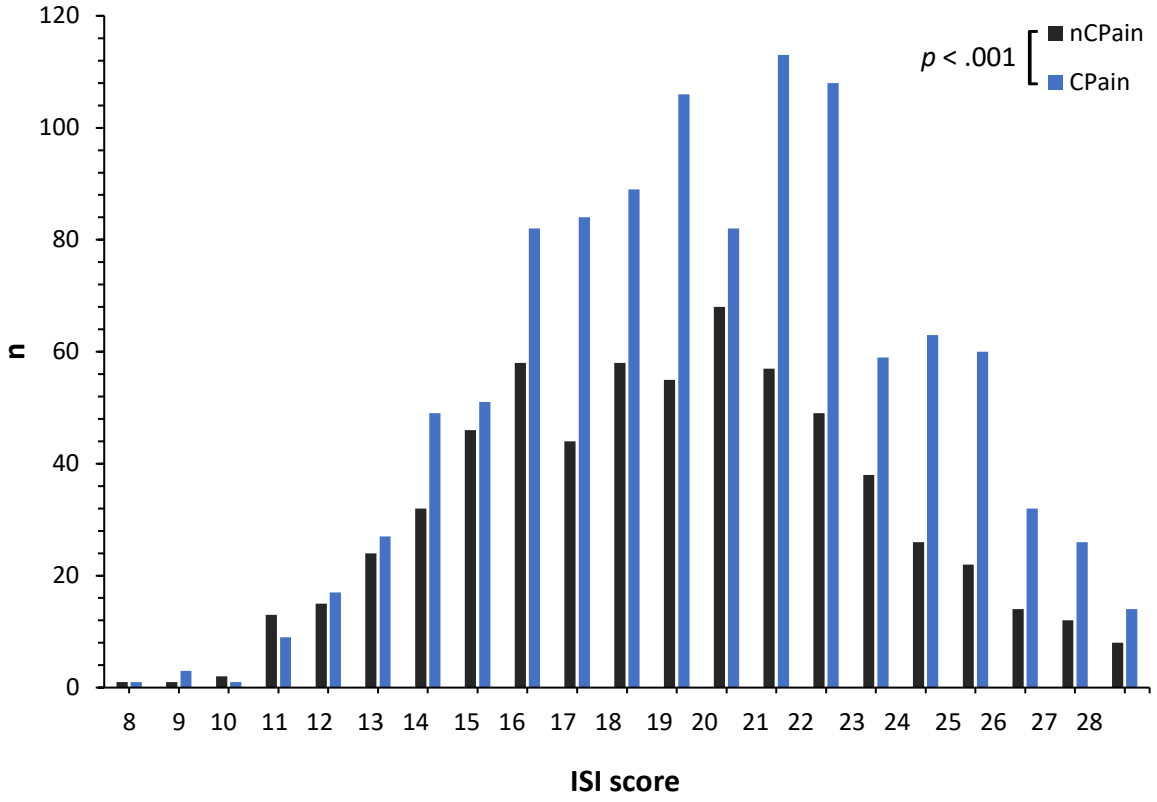
[a] 1 missing (<1%)

[b] 1 missing (<1%)

[c] 2 missing (<1%)

Figure 3

Baseline ISI score distributions stratified by chronic pain subgroups.



Note: The chronic pain subgroup differences in insomnia severity were statistically significant at the $p < .001$ level. CPain = reported chronic pain at baseline. nCPain = reported no chronic pain at baseline. n = number of participants. ISI = Insomnia Severity Index.

Chronic pain prevalence

Percentage wise, compared to the prevalence of chronic pain in the baseline trial sample (63%, n = 1076), there was a small reduction at 24-month follow-up (59%, n = 343). Eight of the participants who reported chronic pain at baseline no longer reported chronic pain two years later.

Adherence and attrition

Treatment cores

Among the 1076 participants with chronic pain, 532 were randomized to SHUTi. The first treatment core was completed by 86% (n = 459), while all six cores were completed by 49% (n = 262). Among the 644 participants without chronic pain, 335 were randomized to SHUTi.

The first core was completed by 86% (n = 288), while all six cores were completed by 41% (n = 139). There was a small and statistically insignificant difference in treatment adherence between participants with and without chronic pain: $X^2 = 1.72$, $p = .189$. Attrition could not be measured for the participants who were randomized to the active control, as they received immediate access to all of the patient education information following randomization.

Insomnia Severity Index

From the baseline total of participants with chronic pain (n = 1076), ISI was completed by 65% (n = 695) at nine-week, 46% (n = 500) at six-month, and 33% (n = 351) at 24-month follow-up. This gives respective attrition rates of 35%, 54%, and 67%.

Table 3 shows follow-up ISI completion rates stratified by chronic pain and intervention subgroups. At the 9-week follow-up, ISI was completed by 1116 participants *(M* = 46 years, *SD* = 13.8, 74% female). Among them, 62% (n = 695) had baseline chronic pain, and were randomized to SHUTi (52.5%, n = 365) or PE (47.5%, n = 330). At the 6-month follow-up, 807 participants (*M* = 45 years, *SD* = 13.8, 73% female) completed the ISI. Among them, 62% (n = 500) had baseline chronic pain, and were randomized to SHUTi (51.2%, n = 256) or PE (48.8%, n = 244). At the 24-month follow-up, 587 participants (*M* = 42.7 years, *SD* = 13.8, 70% female) completed the ISI. Among them, 60% (n = 351) had baseline chronic pain, and were randomized to SHUTi (49.6%, n = 174) or PE (50.4%, n = 177).

Table 3

ISI completion rates (n, %) from baseline to 24-month follow-up, stratified by chronic pain and intervention subgroups.

	CPain		nCPain	
Intervention	SHUTi	PE	SHUTi	PE
Baseline	532 (100%)	544 (100%)	335 (100%)	309 (100%)
9 weeks	365 (69%)	330 (61%)	225 (67%)	196 (63%)
6 months	256 (48%)	244 (45%)	164 (49%)	143 (46%)
24 months	174 (33%)	177 (33%)	129 (39%)	107 (35%)

Note. Response rates reported as percentages compared to baseline. CPain = reported chronic pain at baseline. nCPain = reported no chronic pain at baseline. SHUTi = Sleep Healthy Using the Internet. PE = Patient education.

Insomnia severity

At baseline, the meanDecreases in mean ISI scores from baseline to 24-month follow-up were reported in all stratifications of intervention and chronic pain subgroups (CPain×SHUTi, CPain×PE, nCPain×SHUTi, and nCPain×PE). The greatest baseline to final follow-up mean difference was reported by nCPain×SHUTi (-9.7), and the smallest by CPain×PE (-5.9). At the 9-week and 6-month follow-ups, the mean scores of the CPain×SHUTi and nCPain×SHUTi subgroups indicated successful treatment (ISI score reduction ≥ 8 compared to baseline). At the 24-month follow-up, only the nCPain×SHUTi subgroup mean satisfied the treatment effect criterion. In contrast, the CPain×SHUTi subgroup reported a mean ISI score increase of .07 compared to the 6-month assessment. The mean ISI scores across subgroups and assessment times are reported in Table 4 and visualized in Figure 4.

Moderator analysis

Results of the Linear Mixed Model showed significant fixed effects of all follow-up times and the presence of baseline chronic pain on insomnia severity (Table 5). However, the analysis reported no statistically significant three-way interaction between chronic pain, intervention, and follow-up times. Chronic pain was associated with significantly elevated mean ISI scores compared to the overall intercept, but did not significantly affect the

Table 4

ISI scores at baseline and 9-week, 6-month, and 24-month follow-ups, presented as mean (SD), stratified by chronic pain and intervention subgroups.

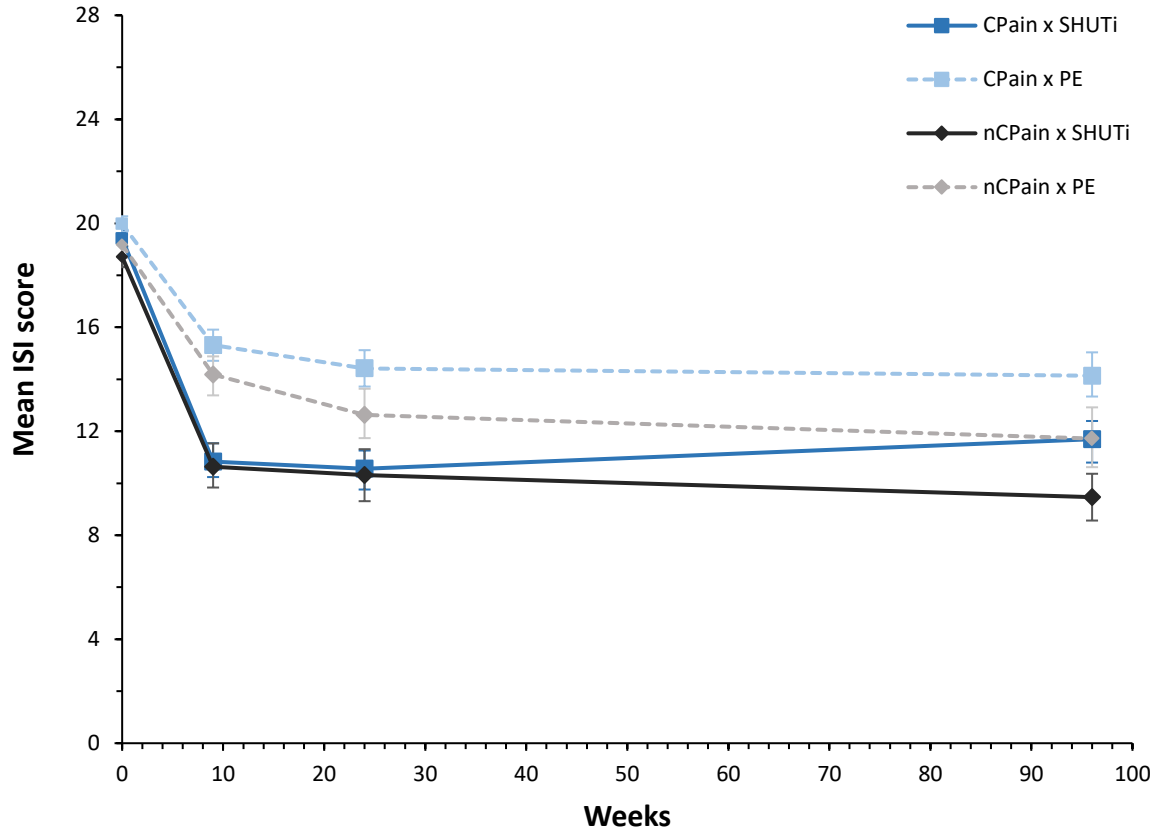
	CPain		nCPain	
Intervention	SHUTi	PE	SHUTi	PE
ISI*				
Baseline	19.4 (3.8)	20.0 (3.9)	18.7 (3.9)	19.2 (3.9)
9 weeks	10.8 (6.2)	15.3 (5.5)	10.6 (6.4)	14.2 (5.4)
6 months	10.6 (6.1)	14.4 (5.7)	10.3 (6.7)	12.6 (5.6)
24 months	11.7 (6.0)	14.1 (5.9)	9.5 (5.2)	11.7 (5.9)

Note. CPain = reported chronic pain at baseline. nCPain = reported no chronic pain at baseline. SHUTi = Sleep Healthy Using the Internet. PE = Patient education about sleep. ISI = Insomnia Severity Index. ISI score reduction ≥ 8 from baseline indicated treatment effect.

* 2 missing.

Figure 4

Mean ISI scores and 95% CIs from baseline to 24-month follow-up, stratified by chronic pain and intervention subgroups.



Note. Mean regression slopes for intervention and chronic pain subgroups, with corresponding 95% confidence intervals. Baseline and first, second, and final follow-ups were at week number 0, 9, 24 and 96, respectively. ISI = Insomnia severity index. CPain = Participants who reported chronic pain at baseline. nCPain = participants who reported no chronic pain at baseline. SHUTi = Sleep Healthy Using the Internet. PE = Patient education about sleep.

relationship between dCBT-I and ISI scores at any follow-up time. Adjusting for gender and age did not significantly affect the model. Repeating the analysis with a recoded chronic pain variable (0 → 1, 1 → 0) yielded the same results.

The fixed effect of all follow-up times were associated with significant decreases in insomnia severity in the overall trial sample ($p < .001$). In contrast, the fixed effect of chronic pain was associated with a significant increase in insomnia severity compared to the intercept (95% CI [.23, 1.25], $p = .005$).

Table 5

Estimated from the Linear Mixed Model analysis with REML fitting, adjusted for gender and age.

Parameter	b	95% CI		*p*	Cohen's d
		LL	UL		
Intercept ISI	18.25	17.31	19.20	**<.001**	-
Fixed effects					
t2	-4.62	-5.30	-3.93	**<.001**	-
t3	-6.13	-6.92	-5.35	**<.001**	-
t4	-7.33	-8.22	-6.45	**<.001**	-
Pain	.74	.23	1.25	**.005**	-
Age	.01	.00	.03	.166	-
Gender	.18	-.28	.64	.447	-
Interactions					
Intervention×t2	-3.59	-4.48	-2.71	**<.001**	.53
Intervention×t3	-2.25	-3.27	-1.22	**<.001**	.42
Intervention×t4	-1.66	-2.83	-.50	**.005**	.32
CPain×t2	.21	-.66	1.08	.632	-.09
CPain×t3	1.19	.20	2.18	**.019**	-.13
CPain×t4	1.56	.43	2.68	**.007**	-.31
Intervention×CPain×t2	-.66	-1.78	.47	.251	-
Intervention×CPain×t3	-1.25	-2.55	.05	.060	-
Intervention×CPain×t4	-.08	-1.6	1.43	.922	-

Note. The mean estimated differences are products of the baseline-adjusted linear mixed model. Bold values denote statistical significance at the $p < .05$ level. Negative values favour dCBT-I, indicating reduction in insomnia severity. REML = Restricted maximum likelihood. b = unstandardized regression coefficient; CI = confidence interval; *LL* = lower limit; *UL* = upper limit. ISI = Insomnia Severity Index. CPain = baseline self-reported chronic pain (0 = no pain, 1 = pain). Intervention = randomized trial condition (0 = control, 1 = SHUTi). t2 = 9-week follow-up. t3 = 6-month follow-up. t4 = 24-month follow-up. All time covariates were coded as 0 = no response and 1 = response at given time. Note that for linear mixed models, SPSS uses the highest number code as reference. Effect size reported as Cohen's *d.*

The two-way interactions of intervention group and follow-up times showed that dCBT-I significantly decreased insomnia severity at the 9-week (95% CI [-4.48, -2.71], Cohen's $d = .53$, $p < .001$), 6-month (95% CI [-3.27, -1.22], Cohen's $d = .42$, $p < .001$,), and

24-month follow-up (95% CI [-2.82, -.50], Cohen's d = .32, p = .005). Effect sizes ranged from small to moderate.

The two-way interactions of chronic pain and follow-up times showed that chronic pain significantly increased insomnia severity at the 6-month (95% CI [.20, 2.18], p = .019, Cohen's d = -.13) and 24-month (95% CI [.43, 2.68], p = .007, Cohen's d = -.31) follow-up. Effect sizes were small.

The LMM included individual participants as random effect and random intercept. Estimates of covariance parameters were provided for the residual (b = 15,30, SE = .42, p < .001) and intercept (b = 11.20, SE = .61, p < .001). The p-values were well below the specified α-level of .05, indicating that the random term significantly affected the response, and that the covariance structure suited the model. The within-person effect of the individual participants appeared to be strong.

Discussion

In order for chronic pain to be a moderator of the relationship between dCBT-I and insomnia severity, the mean difference in ISI scores of individuals with and without chronic pain had to be statistically significant. However, as shown in Table 5, the linear mixed model showed no statistically significant three-way interaction between intervention group, chronic pain, and follow-up assessment times. The treatment was associated with short and long term reductions in insomnia severity both in individuals with and without comorbid chronic pain. The results indicate that chronic pain does not moderate the treatment effect of dCBT-I on insomnia severity. This further supports the usefulness of dCBT-I for individuals with chronic insomnia and comorbid conditions (Soh et al., 2020).

At baseline, the individuals with chronic pain reported significantly stronger insomnia severity compared to the pain-free participants. The average baseline ISI score of participants with and without chronic pain was 19.7±3.9 and 18.9±4.0 respectively, which corresponds to moderate to severe insomnia (Bastien et al., 2001).

The adherence rates for individuals with and without chronic pain were 49% and 41%, giving respective non-completion rates of 51% and 59%. This difference was not statistically significant (p = .189). The non-completion of the chronic pain subgroup was comparable to the 54% non-completion rate of the overall trial sample (Vedaa et al., 2020) and average dCBT-I non-completion rates of 35.2±19.4% (Soh et al., 2020).

As expected, there was considerable participant loss to follow-ups. The trial sample had a nine-week attrition of 33%, while the chronic pain subgroup showed attrition rates of 35% at nine-week, 54% at six-month, and 67% at 24-month follow-up. The final follow-up attrition rate was the same for chronic pain participants randomized to dCBT-I and patient education. Considerable loss to follow-up is reported across dCBT-I studies, with an average one-year attrition rate of 21.6±16.9% for dCBT-I and 15.6±12.0% for control (Soh et al., 2020).

As shown in Figure 4, mean insomnia severity initially declined but then slowly increased in the subgroup with chronic pain who received dCBT-I. At the 24-month follow-up, their average insomnia severity was comparable to that of the pain-free participants who received patient education. In the cross-sectional analyses of follow-up data, the only subgroup that reported long-term treatment effect (ISI reduction > 8 compared to baseline) was the participants without chronic pain who received the dCBT-I. However, this finding

was not statistically significant. Cross-sectional analyses showed increases in standard deviations and standard errors over time, indicating increased response variation. This demonstrates the limitations of descriptive data analyses and the biasing effect of missing participant data. It might be that, for people with comorbid chronic insomnia and chronic pain, dCBT-I does not fully negate the sleep impairments commonly associated with chronic pain. This is only speculative, however, and more studies are needed to assess long-term interactions between chronic insomnia, chronic pain, and dCBT-I.

The trial sample appeared to be representative of the population of adult individuals with chronic insomnia and chronic pain. For example, the skew towards women is in line with global insomnia trends (Aernout et al., 2021). In 73% percent women in the chronic pain is in line with research reporting gender differences in pain risk, where women are more likely to experience chronic, stronger, and longer-lasting pain compared to men (Bartley & Fillingim, 2013). However, in the trial sample, baseline mean insomnia severity did not significantly differ between women and men. Adjusting for gender in the moderation analysis did not significantly impact the results, indicating that the participants benefited similarly from the dCBT-I treatment regardless of gender.

Strengths and limitations

The longitudinal RCT of Vedaa et al. (2020) is one of the largest of its kind and provides valuable insights into the use and effects of dCBT-I in a Norwegian community-based sample. The design allows for examination of participant data up to two years post-trial. This is crucial to assess the durability of the treatment effects and potential variation across intervention (and other) subgroups. The longitudinal data analyses reported here gives a clearer picture of the durability of the dCBT-I effects on insomnia severity for a common insomnia subgroup. From a public health perspective, the dCBT-I is an effective insomnia treatment with increased scalability and costs reduction compared to CBT-I and reduced adverse side effects compared to sleep medication (Baglioni et al., 2020; Forma et al., 2022). The main limitation concerns the generalizability of the findings. First, the sampling method was non-probability and convenience based. While the trial sample of Norwegian citizens with clinical insomnia was large and randomly assigned to treatment and control, they were not randomly selected from the population of interest. Instead, they were self-selected and volunteered to participate based on publicly distributed trial information. Convenience

sampling is common in clinical research but increases the risk of sampling bias and undermines the generalizability of the results from the trial to the target population (Staines, 2008).

The digital CBT-I was given in the form of the Sleep Healthy Using the Internet (SHUTi) treatment program. Luik et al. (2019) recommend caution in generalizing clinical evidence from specific dCBT-I programs onto other programs. However, SHUTi has been extensively studied, and the number of clinical trials assessing the Norwegian translated version is growing (Hagatun et al. 2019; Vedaa et al., 2019b; Vedaa et al., 2020). Note that SHUTi may go under the name Somryst in more recent literature (e.g., Morin, 2020).

The present data were assumed to be missing-at-random (MAR) (Vedaa et al., 2020), and there was considerable participant loss over time. While participants were randomly assigned to intervention and control, systematic differences in baseline characteristics may have contributed to dropout and attrition. Therefore, intervention and control groups can not be assumed to be equivalent in analyses of the follow-up data (Herbert, Kasza & Bø, 2018). While this biases the results of simple cross-sectional analyses, the linear mixed effect model is considered robust and unbiased for MAR data, as it includes subjects with missing values (Chakraborty & Gu, 2009). The linear mixed effect model is also a better for analysis of longitudinal RTC data compared to traditional repeated analysis of variance (ANOVA) (Lydersen, 2022c). Note that the robustness of the LMM is limited to the covariates that are included in the model (Herbert, Kasza & Bø, 2018). There are alternative methods that handle MAR data, such as multiple imputation (Herbert, Kazsa, & Bø, 2018; Lydersen, 2022b). This analytic method can be considered for future secondary analyses and longitudinal RTCs. For the sake of transparency, the SPSS syntax of the linear mixed effect model is included in the Appendix and explained in Table A1.

This thesis uses the Insomnia Severity Index as the outcome variable. While ISI is a subjective measure, it is widely used, standardized, and recommended for insomnia research (Riemann et al., 2017). It has been found reliable and valid for insomnia assessment, including in studies on insomnia-pain comorbidity (Sommer, Lavigne, & Ettlin, 2015). However, participants were not assessed for sleep difficulties other than insomnia and sleep apnoea, which could have masked comorbid sleep problems. Assessment of other sleep difficulties should be included in future studies.

Self-reports were also used for the clinical diagnosis of chronic pain, including subjective pain experience and required pain duration of three months or longer (WHO, 2022). However, chronic pain assessments should include continuous measures of pain severity as well as the means to distinguish between different types of chronic pain. The ICD-11 includes sub-categories such as primary, post-surgical, and neuropathic chronic pain (WHO, 2022). The relationship between insomnia severity, chronic pain, and dCBT-I may vary depending on the specific In the present data, it was not possible to distinguish between pain conditions and diagnoses,

Recommendations

Several recommendations can be made for further secondary and exploratory analyses of the data collected by Vedaa and colleagues (2020) or the conduction of similar RTC.

In order to improve external validity and simplify cross-study result comparisons, RCTs should include standardized measures used in previous similar studies (Stuart & Rhodes, 2016). In addition to ISI, baseline and follow-up assessment should include secondary outcomes like sleep diary measures. These measures include sleep onset latency, wake time after sleep onset, early morning awakenings, total sleep time, time spent in bed, and sleep efficiency. In studies assessing CBT-I for comorbid medical and psychiatric conditions, durable treatment effects on subjective sleep quality have been reported using ISI and sleep diary measures (Geiger-Brown et al., 2015). Another secondary outcome measure of interest is the Bergen Insomnia Scale (BIS; Pallesen et al., 2008). Other secondary health measures used by Vedaa et al. (2020) included the Hospital Anxiety and Depression Scale (HADS), the Chalder Fatigue Questionnaire (CFQ), and the Short-Form Health Survey (SF-12), which provide estimates of daytime functioning. Previous studies indicate that, while dCBT-I does not reduce pain severity, it has been linked to some improvement in functional pain factors (Finan et al., 2014). Assessing daytime functioning for the chronic pain subgroup before and after the trial period could be of interest for follow-up studies.

The present use of a broad definition of chronic pain may have masked more specific or comorbid chronic pain types that could help better explain the observed variation in insomnia severity, treatment adherence, and follow-up attrition. A closer look at a more specific chronic pain and insomnia relationship might therefore be of interest for future secondary analyses. In the recent Norwegian HUNT Pain Examination Study, it was reported

that most of the chronic pain population have musculoskeletal pain and more than one chronic pain condition, the most prevalent being nonspecific lower back and neck pain (Borchgrevink et al., 2022). The present trial sample were assessed for anatomical pain location(s), but this was not included in the analyses reported here. Another pain subgroup of interest could be individuals with fibromyalgia, which was reported by 6.2% (n = 107) of the trial sample. A study on patients with comorbid chronic insomnia and fibromyalgia found that baseline pain intensity moderated the impact of CBT-I on sleep onset latency and total wake time (McCrae et al., 2019). The fibromyalgia patients with moderate to severe pain benefited more from CBT-I compared to those with low baseline pain. A systematic review and meta-analysis of studies assessing CBT-I for individuals with comorbid insomnia and fibromyalgia showed significant improvements in sleep and pain symptoms compared to other therapeutical treatments (Climent-Sanz et al., 2021). However, the studies were few, and the evidence quality was low, showing a need for more research. Few if any dCBT-I studies have assessed the applicability of dCBT-I to comorbid insomnia and fibromyalgia.

At baseline, the trial participants were assessed for the presence of chronic pain, but not pain intensity or quality. Future studies examining chronic insomnia, dCBT-I and chronic pain should include continuous self-reports of pain intensity and other pain qualities in addition to binary presence of chronic pain. Access to continuous insomnia *and* pain measures would allow for more accurate estimates of their correlation and relation to digital insomnia treatment. The assessment of chronic pain is more complex than that of acute pain, but several measurement tools are commonly used in research (Breivik et al., 2008). A simple and effective way to assess pain intensity is through numeric rating scales (NRS) with a 0-10 range. The Brief Pain Inventory (BPI) and The Pain Disability Index could also be used to assess pain-related disability and pain interference with daily functioning (e.g., Hølen et al., 2008; Soer et al., 2013). The Pain-Related Beliefs and Attitudes about Sleep (PBAS) scale can be used to assess maladaptive and inflexible beliefs about sleep-pain interactions, which are common in patients chronic pain and insomnia (Afolalu et al., 2016).

Need for parallel treatment?

A prospective study following elderly Hong Kong residents with multimorbidity over time found that chronic musculoskeletal pain predicted insomnia severity (Sit et al., 2021). The authors concluded that pain management could be an important preventive measure for

insomnia. Contrary to earlier distinctions between a primary and secondary insomnia, current guidelines use no such differentiation, instead opting for an 'insomnia disorder' umbrella term (WHO, 2022). This is because insomnia often prevails after treatment of the disorder believed to contribute to or cause the insomnia symptoms. Therefore, if an insomnia patient presents with comorbid health conditions, parallel treatment is recommended. For example, a patient with depression and insomnia should receive specific treatment for their insomnia symptoms alongside depression therapy (Riemann et al., 2017; Bjorvatn et al., 2018). Similarly, patients with comorbid chronic insomnia and chronic pain benefit from parallel treatment, such as dCBT-I with applied relaxation (Wiklund et al., 2022). In the present thesis, it was not known whether the individuals with chronic pain received pain treatment in parallel with or after the dCBT-I, or in what form. Future studies should include baseline and follow-up assessments of pain medication or other pain treatment.

Conclusions and Relevance

Insomnia symptoms are present in many psychiatric and medical conditions, and dCBT-I should be applicable across such comorbidities. The secondary analyses presented in this thesis support the applicability of dCBT-I to individuals with comorbid chronic insomnia and chronic pain. Compared to patient education about sleep, dCBT-I was associated with significant short- and long term reductions in insomnia severity. Self-reported baseline chronic pain did not significantly moderate the treatment effect. Individuals with chronic pain reported slightly but significantly stronger insomnia severity compared to pain-free participants. However, they also reported significant short and long term insomnia improvements. In conclusion, digital and fully automated insomnia treatment can improve sleep in individuals with comorbid chronic insomnia and chronic pain. However, more research on insomnia-pain relationships with dCBT-I is needed. Such research should include measures of chronic pain intensity.

References

Aernout, E., Benradia, I., Hazo, J. B., Sy, A., Askevis-Leherpeux, F., Sebbane, D., & Roelandt, J. L. (2021). International study of the prevalence and factors associated with insomnia in the general population. *Sleep Medicine*, *82*, 186-192. doi:10.1016/j.sleep.2021.03.028

Afolalu, E. F., Moore, C., Ramlee, F., Goodchild, C. E., & Yang, N. K. Y. (2016). Developments of the Pain-Related Beliefs and Attitudes about Sleep (PBAS) Scale for the Assessment and Treatment of Insomnia Comorbid with Chronic Pain. *Journal of Clinical Sleep Medicine*, *12*(9), 1269-1277. doi:10.5664/jcsm.6130

Arnison, T., Schrooten, M. G., Hesser, H., Jansson-Fröjmark, M., & Persson, J. (2022). Longitudinal, bidirectional relationships of insomnia symptoms and musculoskeletal pain across adolescence: The mediating role of mood. *Pain*, *163*(2), 287-298. doi: 10.1097/j.pain.0000000000002334

Baglioni, C., Altena, E., Bjorvatn, B., Blom, K., Bothelius, K., Devoto, A., Espie, C. A., Frase, L., Gavriloff, D., Tuuliki, H., Hoflehner, A., Högl, B., Holzinger, B., Järnefelt, H., Jernelöv, S., Johann, A. F., Lombardo, C., Nissen, C., Palagini, L, … & Riemann, D. (2020). The European Academy for Cognitive Behavioural Therapy for Insomnia: An initiative of the European Insomnia Network to promote implementation and dissemination of treatment. *Journal of Sleep Research, 29*(2), e12967. doi:10.1111/jsr.12967

Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep medicine*, *2*(4), 297-307. doi:10.1016/S1389-9457(00)00065-4

Barke, A., Korwisi, B., & Rief, W. (2022). Chronic Pain in the ICD-11: New Diagnoses That Clinical Psychologists Should Know About. *Clinical Psychology in Europe*, *4*(Spec Issue). doi:10.32872/cpe.9933

Bartley, E. J., & Fillingim, R. B. (2013). Sex differences in pain: a brief review of clinical and experimental findings, *BJA: British Journal of Anaesthesia*, *111*(1), 52–58. doi:10.1093/bja/aet127

Bauer, D. J., Sterba, A. K., & Hallfors, D. D. (2008). Evaluating Group-based Interventions When Control Participants Are Ungrouped. *Multivariate Behavioral Research, 43*(2). doi:10.1080/00273170802034810

Bell, M. L., Fiero, M., Horton, N. J., & Hsu, C. H. (2014). Handling missing data in RCTs; a review of the top medical journals. *BMC medical research methodology, 14*(1), 1-8. doi:10.1186/1471-2288-14-118

Bennett, M. I., Kaasa, S., Barke, A., Korwisi, B., Rief, W., & Treede, R. D. (2019). The IASP classification of chronic pain for ICD-11: chronic cancer-related pain. *Pain, 160*(1), 38-44. doi:10.1097/j.pain.0000000000001363

Bjorvatn, B., Waage, S., & Pallesen, S. (2018). The association between insomnia and bedroom habits and bedroom characteristics: an exploratory cross-sectional study of a representative sample of adults. *Sleep Health*, *4*(2), 188-193. doi:10.1016/j.sleh.2017.12.002

Bjorvatn, B., Sivertsen, B., Waage, S., Holsen, F., & Pallesen, S. (2020). *Nasjonal anbefaling for utredning og behandling av insomni.* Helse Bergen. Retrieved November 20, 2023, from https://www.helse-bergen.no/49cddc/siteassets/seksjon/sovno/documents/nasjonal-anbefaling-for-utredning-og-behandling-av-insomni.pdf

Borchgrevink, P. C., Glette, M., Woodhouse, A., Butler, S., Landmark, T., Romundstad, P., Dale, O., Stiles, T. C., Bonaa, K. H., Thorsvik, D., Thünte, S., & Kaasa, S. (2022). A Clinical Description of Chronic Pain in a General Population Using ICD-10 and ICD-11 (The HUNT Pain Examination Study). *The Journal of Pain, 23*(2), 337-348. doi:10.1016/j.jpain.2021.08.007

Cerri, L. Q., Justo, M. C., Clemente, V., Gomes, A. A., Pereira, A. S., & Marques, D. R. (2023). Insomnia Severity Index: A reliability generalisation meta-analysis. *Journal of Sleep Research*, e13835. doi:10.1111/jsr.13835

Chakraborty H, Gu H. A. (2009). Mixed Model Approach for Intent-to-Treat Analysis in Longitudinal Clinical Trials with Missing Values [Internet]. Research Triangle Park (NC): RTI Press. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538904/ doi:10.3768/rtipress.2009.mr.0009.0903

Cheng, S. K. and Dizon, J. (2012). Computerised cognitive behavioural therapy for insomnia: a systematic review and meta-analysis. *Psychother. Psychosom.*, *81*, 206–216. doi:10.1159/000335379

Chmura Kraemer, H., Kiernan, M., Essex, M., & Kupfer, D. J. (2008). How and why criteria defining moderators and mediators differ between the Baron & Kenny and MacArthur approaches. *Health Psychology*, *27*(2S), S101. doi:10.1037/0278-6133.27.2(Suppl.).S101

Climent-Sanz, C., Valenzuela-Pascual, F., Martinez-Navarro, O., Blanco-Blanco, J., Rubi-Carnacea, F., Garcia-Martinez, E., Barallat-Gimeno, E., & Gea-Sanchez, M. (2022). Cognitive behavioral therapy for insomnia (CBT-i) in patients with fibromyalgia: a systematic review and meta-analysis. *Disability and Rehabilitation*, *44*(20), 5770-5783. doi:10.1080/09638288.2021.1954706

Crawford, M. R., Luik, A. I., Espie, C. A., Taylor, H. L., Burgess, H. J., Jones, A. L., ... & Ong, J. C. (2020). Digital cognitive behavioural therapy for insomnia in women with chronic migraines. *Headache: the journal of head and face pain*, *60*(5), 902-915. doi:10.1111/head.13777

de Boer, M. R., Waterlander, W. E., Kujiper, L. D. J., Steenhuis, I. H. M., & Twisk, J. W. R. (2015). Testing for baseline differences in randomized controlled trials: an unhealthy research behaviour that is hard to eradicate. *International Journal of Behavioural Nutrition and Physical Activity, 12(*4). doi:10.1186/s12966-015-0162-z

De Crescenzo, F., D'Alò, G. L., Ostinelli, E. G., Ciabattini, M., Di Franco, V., Watanabe, N., ... & Cipriani, A. (2022). Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. *The Lancet*, *400*(10347), 170-184. doi:10.1016/S0140-6736(22)00878-9

Enomoto, K., Adachi, T., Fujino, H., Kugo, M., Tatsumi, S., & Sasaki, J. (2022). Comparison of the effectiveness of cognitive behavioral therapy for insomnia, cognitive behavioral therapy for pain, and hybrid cognitive behavioral therapy for insomnia and pain in individuals with comorbid insomnia and chronic pain: A systematic review and network meta-analysis. *Sleep Medicine Reviews*, 101693. doi:10.1016/j.smrv.2022.101693

Filosa, J., Omland, P. M., Langsrud, K., Hagen, K., Engstrøm, M., Drange, O. K., ... & Sand, T. (2021). Validation of insomnia questionnaires in the general population: The Nord-Trøndelag Health Study (HUNT). *Journal of Sleep Research*, *30*(1), e13222. doi:10.1111/jsr.13222

Finan, P. H., Buenaver, L. F., Runko, V. T., & Smith, M. T. (2014). Cognitive-Behavioral Therapy for Comorbid Insomnia and Chronic Pain. *Sleep Medicine Clinics*, *9*(2), 261-274. doi:10.1016/j.jsmc.2014.02.007

Finan, P. H., Goodin, B. R., & Smith, M. T. (2013). The association of sleep and pain: an update and a path forward. *The journal of pain*, *14*(12), 1539-1552. doi:10.1016/j.pain.2013.08.007

Forma, F., Pratiwadi, R., El-Moustaid, F., Smith, N., Thorndike, F., & Velez, F. (2022). Network meta-analysis comparing the effectiveness of a prescription digital therapeutic for chronic insomnia to medications and face-to-face cognitive behavioral therapy in adults. *Current Medical Research and Opinion*, *38*(10), 1727-1738. doi:10.1080/03007995.2022.2108616

Freeman, D., Sheaves, B., Goodwin, G. M., Yu, L-M., Nickless, A., Harrison, P. J., Emsley, R., Luik, A. I., Foster, R. G., Wadekar, V., Hinds, C., Gumley, A., Jones, R., Lightman, S., Jones, S., Bentall, R., Kinderman, P., Rowse, G., Brugha, T., … & Espie, C. A. (2017). The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. *The Lancet Psychiatry*, *4*(10), 749-758. doi:10.1016/S2215-0366(17)30328-0

Garland, S. N., Vargas, I., Grandner, M. A., & Perlis, M. L. (2018). Treating insomnia in patients with comorbid psychiatric disorders: A focused review. *Canadian Psychology/Psychologie canadienne*, *59*(2), 176. doi:10.1037/cap0000141

Generaal, E., Vogelzangs, N., Penninx, B. W., & Dekker, J. (2017). Insomnia, sleep duration, depressive symptoms, and the onset of chronic multisite musculoskeletal pain. *Sleep*, *40*(1), zsw030. doi:101093/sleep/zsw030

Hagatun, S., Vedaa, Ø., Nordgreen, T., Smith, O. R., Pallesen, S., Havik, O. E., ... & Sivertsen, B. (2019). The short-term efficacy of an unguided internet-based cognitive-behavioral therapy for insomnia: a randomized controlled trial with a six-month

nonrandomized follow-up. *Behavioral sleep medicine*, *17*(2), 137-155. doi:10.1080/15402002.2017.1301941

Helsedirektoratet (2017). Søvn og søvnvansker [nettdokument]. Oslo: Helsedirektoratet (last updated January 16th, 2017, read September 14, 2023). Retrieved from https://www.helsedirektoratet.no/tema/sovn/sovn-og-sovnvansker

Herbert, R. D., Kasza, J., & Bø, K. (2018). Analysis of randomised trials with long-term follow-up. *BMC Medical Research Methodology*, *18*, 1-9. doi:10.1186/s12874-018-0499-5

Hertenstein, E., Trinca, E., Wunderlin, M., Schneider, C. L., Züst, M. A., Fehér, K. D., ... & Nissen, C. (2022). Cognitive behavioral therapy for insomnia in patients with mental disorders and comorbid insomnia: A systematic review and meta-analysis. *Sleep medicine reviews*, *62*, 101597. doi:10.1016/j.smrv.2022.101597

Hysing, M., Haugland, S., Stormark, K. M., Boe, T., & Sivertsen, B. (2015). Sleep and school attendance in adolescence: results from a large population-based study. *Scand J Public Health*, *43*(1), 2-9. doi:10.1177/1403494814556647

Hysing, M., Harvey, A. G., Linton, S. J., Askeland, K. G., & Sivertsen, B. (2016). Sleep and academic performance in later adolescence: results from a large population-based study. *J Sleep Res*. doi:10.1111/jsr.12373

Hølen, J. C., Lydersen, S., Klepstad, P., Loge, J. H., & Kaasa, S. (2008). *The Clinical Journal of Pain, 24*(3), 219-225. doi:10.1097/AJP.0b013e31815ec22a

IBM Corp (2023, April 18). *SPSS Statistics 29.0.0*. IBM. Retrieved October 5, 2023, from https://www.ibm.com/docs/en/spss-statistics/29.0.0

Ioannidis, J. P. A. (2005). Why Most Published Research Findings Are False. *PLOS Medicine, 2*(8), e124. doi:10.1371/journal.pmed.1004085

Jackson, M.L., Meaklim, H., Mason, E.C. (2023). Digital Therapies for Insomnia. In: Passos, I.C., Rabelo-da-Ponte, F.D., Kapczinski, F. (eds.) *Digital Mental Health*. Springer, Cham. doi:10.1007/978-3-031-10698-9_6

Jungquist, C. R., O'Brien, C., Matteson-Rusby, S., Smith, M. T., Pigeon, W. R., Xia, Y., ... & Perlis, M. L. (2010). The efficacy of cognitive-behavioral therapy for insomnia in

patients with chronic pain. *Sleep medicine, 11*(3), 302-309. doi:10.1016/j.sleep.2009.05.018

Kang, H. (2013). The prevention and handling of the missing data. *Korean Journal of Anesthesiology, 64*(5), 402-406. doi:10.4097/kjae.2013.64.5.402

Kallestad, H., Vedaa, Ø., Scott, J., Morken, G., Pallesen, S., Harvey, A. G., ... & Sivertsen, B. (2018). Overcoming insomnia: protocol for a large-scale randomised controlled trial of online cognitive behaviour therapy for insomnia compared with online patient education about sleep. *BMJ open*, *8*(8), e025152. doi:10.1136/bmjopen-2018-025152

Khurshid, K. A. (2018). Comorbid insomnia and psychiatric disorders: an update. *Innovations in clinical neuroscience*, *15*(3-4), 28-32. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5906087/

Knoerl, R., Lavoie Smith, E. M., & Weisberg, J. (2016). Chronic pain and cognitive behavioral therapy: An integrative review. *Western journal of nursing research*, *38*(5), 596-628. doi:10.1177/0193945915615869

Kraemer, H. C., Wilson, G. T., Fairburn, C. G., & Agras, W. S. (2002). Mediators and moderators of treatment effects in randomized clinical trials. *Archives of general psychiatry*, *59*(10), 877-883. doi:10.1001/archpsyc.59.10.877

Landis, C. A. (2011). Chapter 39 – Sleep, pain, fibromyalgia, and chronic fatigue syndrome. *Handbook of Clinical Neurology, 98,* 613-637. doi:10.1016/B978-0-444-52006-7.00039-3

Laugsand, L. E., Strand, L. B., Vatten, L. J., Janszky, I., & Bjørngaard, J. H. (2014). Insomnia symptoms and risk for unintentional fatal injuries—the HUNT study. *Sleep, 37*(11), 1777-1786. doi:10.5665/sleep.4170

Leger, D., & Bayon, V. (2010). Societal costs of insomnia. *Sleep Medicine Reviews, 14*(6), 379-389. doi:10.1016/j.smrv.2010.01.003

Li, H., Qian, F., Han, L., Feng, W., Zheng, D., Guo, X., & Zhang, H. (2023). Association of healthy sleep patterns with risk of mortality and life expectancy at age of 30 years: a population-based cohort study. *QJM: An International Journal of Medicine,* hcad237. doi:10.1039/qjmed/hcad237

Lin, W., Li, N., Yang, L., & Zhang, Y. (2023). The efficacy of digital cognitive behavioral therapy for insomnia and depression: a systematic review and meta-analysis of randomized controlled trials. *PeerJ, 11*, e16137. doi:10.7717/peerj.16137

Luik, A. I., van der Zweerde, T., van Straten, A., & Lancee, J. (2019). Digital Delivery of Cognitive Behavioral Therapy for Insomnia. *Current Psychiatry Reports, 21*(50). doi:10.1007/s11920-019-1041-0

Lydersen, S. (2020a). Avoid significance tests for background variables in randomised controlled trials. *Tidsskriftet Den Norske Legeforening,* doi:10.4045/tidsskr.19.0684

Lydersen, S. (2020b). Is the effect large or small? *Tidsskriftet Den Norske Legeforening.* doi:10.4045/tidsskr.19.0665

Lydersen, S. (2022a). Adjustment for baseline value in longitudinal randomized trials. *Tidsskriftet Den Norske Legeforening.* doi:10.4045/tidsskr.21.0824

Lydersen, S. (2022b). Multiple imputation for missing data. *Tidsskriftet Den Norske Legeforening.* doi:10.4045/tidsskr.21.0772

Lydersen, S. (2022c). Analysis of longitudinal data. *Tidsskriftet Den Norske Legeforening.* doi:10.4045/tidsskr.21.0740

Lydersen, S. (2023, October 1). Constrained longitudinal analysis of repeated measurements in an RCT: How to handle subgroups. *Norwegian Journal of Epidemiology, 31* (1, Suppl. 1). Retrieved 05.12.23 from https://www.ntnu.no/ojs/index.php/norepid/issue/archive

Manzar, M. D., Jahrami, H. A., & Bahammam, A. S. (2021). Structural validity of the Insomnia Severity Index: A systematic review and meta-analysis. *Sleep medicine reviews*, *60*, 101531. doi:10.1016/j.smrv.2021.101531

McCrae, C. S., Williams, J., Roditi, D., Anderson, R., Mundt, J. M., Miller, M. B., ... & Robinson, M. E. (2019). Cognitive behavioral treatments for insomnia and pain in adults with comorbid chronic insomnia and fibromyalgia: clinical outcomes from the SPIN randomized controlled trial. *Sleep*, *42*(3), zsy234. doi:10.1093/sleep/zsy234

Meteyard, L., & Davies, R. A. (2020). Best practice guidance for linear mixed-effects models in psychological science. *Journal of Memory and Language*, *112*, 104092. doi:10.1016/j.jml.2020.104092

Mitchell, M. D., Gehrman, P., Perlis, M., & Umscheid, C. A. (2012). Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC family practice*, *13*(1), 1-11. doi:10.1186/1471-2296-13-40

Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., Devereaux, P. J., ... & Altman, D. G. (2010). CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 340: c869. doi: org/10.1136/bmj. C869.

Moloney, M. E., Dunfee, M., Rutledge, M., & Schoenberg, N. (2020). Evaluating the feasibility and acceptability of internet-based cognitive behavioral therapy for insomnia in rural women. *Women's Health Reports*, *1*(1), 114-122. doi:10.1089/whr.2020.0053

Morin CM. Insomnia: psychological assessment and management. New York: Guilford Press, 1993.

Morin, C. M., Belleville, G., Bélanger, L., & Ivers, H. (2011). The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*, *34*(5), 601-608. doi:10.1093/sleep/34.5.601

Morin, C. M. (2020). Profile of Somryst Prescription Digital Therapeutic for Chronic Insomnia: Overview of Safety and Efficacy. *Expert Review of Medical Devices, 17*(12), 1239-1248. doi:10.1080/17434440.2020.1852929

Morin, C. M. & Jarrin, D. C. (2022). Epidemiology of insomnia: Prevalence, Course, Risk Factors, and Public Health Burden. *Sleep Medicine Clinics*, *17*(2), 173-191. doi:10.1016/j.jsmc.2013.05.002

Norwegian University of Science and Technology (2022, October -). App-delivered cognitive behavioral therapy for insomnia among patients with comorbid musculoskeletal complaints and insomnia referred to 4-week inpatient multimodal rehabilitation: protocol for a randomized clinical trial. Identifier NCT05572697. Retrieved January 27th, 2024 from https://clinicaltrials.gov/study/NCT05572697?term=NCT05572697&rank=1

Nuzzo, R. (2014). Scientific Method: Statistical Errors. *Nature*, 506, 150–152. doi: 10.1038/506150a

Pallesen, S., Bjorvatn, B., Nordhus, I. H., Sivertsen, B., Hjørnevik, M. A. R. I., & Morin, C. M. (2008). A new scale for measuring insomnia: the Bergen Insomnia Scale. *Perceptual and motor skills*, *107*(3), 691-706. doi:10.2466/pms.107.3.691-706

Pallesen, S., Sivertsen, B., Nordhus, I. H., & Bjorvatn, B. (2014). A 10-year trend of insomnia prevalence in the adult Norwegian population. *Sleep medicine*, *15*(2), 173-179. doi:10.1016/j.sleep.2013.10.009

Ramfjord, L. S., Faaland, P., Scott, J., Saksvik, S. B., Lydersen, S., Vedaa, Ø., Kahn, N., Langsrud, K., Stiles, T. C., Ritterband, L. M., Harvey, A. G., Sivertsen, B., & Kallestad, H. (2023). Digital cognitive behaviour therapy for insomnia in individuals with self-reported insomnia and chronic fatigue: A secondary analysis of a large scale randomized controlled trial. *Journal of Sleep Research*, 32(5), e13888. doi:10.1111/jsr.12888

Riemann, D., Baglioni, C., Bassetti, C., Bjorvatn, B., Dolenc Groselj, L., Ellis, J. G., ... & Spiegelhalder, K. (2017). European guideline for the diagnosis and treatment of insomnia. *Journal of sleep research*, *26*(6), 675-700. doi:10.1111/jsr.12594

Ritterband, L. M., Bailey, E. T., Thorndike, F. P., Lord, H. R., Farrell-Carnahan, L., & Baum, L. D. (2012). Initial evaluation of an Internet intervention to improve the sleep of cancer survivors with insomnia. *Psycho-Oncology*, *21*(7), 695-705. doi:10.1002/pon.1969

Ritterband, L. M., Thorndike, F. P., Ingersoll, K. S., Lord, H. R., Gonder-Frederick, L., Frederick, C., ... & Morin, C. M. (2017). Effect of a Web-Based Cognitive Behavior Therapy for Insomnia Intervention With 1-Year Follow-up: A Randomized Clinical Trial. *JAMA psychiatry*, *74*(1), 68-75. doi:10.1001/jamapsychiatry.2016.3249

Ritterband, L. M., Thorndike, F. P., Morin, C. M., Gerwien, R., Enman, N. M., Xiong, R., ... & Maricich, Y. A. (2022). Real-world evidence from users of a behavioral digital therapeutic for chronic insomnia. *Behaviour Research and Therapy*, *153*, 104084. doi:10.1016/brat.2022.104084

Rossman, J. (2019). Cognitive-behavioral therapy for insomnia: an effective and underutilized treatment for insomnia. *American journal of lifestyle medicine*, *13*(6), 544-547. doi:10.1177/1559827619867677

Sateia, M. J. (2014). International classification of sleep disorders. *Chest, 146*(5), 1387-1394. 10.1378/chest.14-0970

Schrimpf, M., Liegl, G., Boeckle, M., Leitner, A., Geisler, P., & Pieh, C. (2015). The effect of sleep deprivation on pain perception in healthy subjects: a meta-analysis. *Sleep Medicine, 16*(11), 1313-1320. doi:10.1016/j.sleep.2015.07.022

Selvanathan, J., Pham, C., Nagappa, M., Peng, P. W., Englesakis, M., Espie, C. A., ... & Chung, F. (2021). Cognitive behavioral therapy for insomnia in patients with chronic pain–a systematic review and meta-analysis of randomized controlled trials. *Sleep medicine reviews*, *60*, 101460. doi:10.1016/j.smrv.2021.101460

Seyffert, M., Lagisetty, P., Landgraf, J., Chopra, V., Pfeiffer, P. N., Conte, M. L., & Rogers, M. A. (2016). Internet-delivered cognitive behavioral therapy to treat insomnia: a systematic review and meta-analysis. *PloS one*, *11*(2), e0149139. doi:10.1371/journal.pone.0149139

Shek, D. & Ma, C. (2011). Longitudinal Data Analyses Using Linear Mixed Models in SPSS: Concepts, Procedures and Illustrations. *The Scientific World Journal, 11*, 42-76. doi:10.1100/tsw.2011.2

Sivertsen, B., Krokstad, S., Overland, S., & Mykletun, A. (2009). The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. *Journal of Psychosomatic Research, 67*(2), 109-116. doi:10.1016/j.jpsychores.2009.05.001

Sivertsen, B., Lallukka, T., Salo, P., Pallesen, S., Hysing, M., Krokstad, S., et al. (2014). Insomnia as a risk factor for ill health: results from the large population-based prospective HUNT Study in Norway. *Journal of Sleep Research, 23*(2), 124-132. doi:10.1111/jsr.12102

Sivertsen, B., Lallukka, T., Petrie, K. J., Steingrimsdottir, O. A., Stubhaug, A., & Nielsen, C. S. (2015). Sleep and pain sensitivity in adults. *Pain, 156*(8), 1433-1439. doi:10.1097/j.pain.0000000000000131

Sivertsen, B., Hysing, M., Harvey, A. G., & Petrie, K. J. (2021). The Epidemiology of Insomnia and Sleep Duration Across Mental and Physical Health: The SHoT Study. *Frontiers in psychology*, *12*, 662572. doi:10.3389/fpsyg.2021.662572

Soer, R., Köke, A. J., Vroomen, P. C., Stegeman, P., Smeets, R. J., Coppes, M. H., & Reneman, M. F. (2013). Extensive validation of the pain disability index in 3 groups of patients with musculoskeletal pain. *Spine, 38*(9), E562-E568. doi:10.1097/BRS.0b013e31828af21f

Soh, H. L., Ho, R. C., Ho, C. S., & Tam, W. W. (2020). Efficacy of digital cognitive behavioural therapy for insomnia: a meta-analysis of randomised controlled trials. *Sleep medicine, 75*, 315-325. doi:10.1016/j.sleep.2020.08.020

Sommer, I., Lavigne, G., Ettlin, D. A. (2015). Review of self-reported instruments that measure sleep dysfunction in patients suffering from temporomandibular disorders and/or orofacial pain. *Sleep Medicine, 16*(1), 27-38. doi:10.1016/j.sleep.2014.07.023

Spielman, A.; Glovinsky P. (1991). The varied nature of insomnia. In P.J. Haun (Ed.). *Case studies in insomnia* (1-15). New York. Plenum Press.

Spielman, A. J., Caruso, L. S., & Glovinsky, P. B. (1987). A behavioral perspective on insomnia treatment. *Psychiatric Clinics of North America, 10*(4), 541–553.

Steingrímsdóttir Ó. A., Nielsen C. S., Odsbu I., Skurtveit S., Handal M. (2023). Langvarig smerte i Norge. *Folkehelserapporten - Helsetilstanden i Norge [web document]*. Oslo: Folkehelseinstituttet [updated March 14th, 2023; read September 13th, 2023]. Retrieved from https://www.fhi.no/he/folkehelserapporten/ikke-smittsomme/smerte/?term=#om-langvarig-smerte

Stuart, E. A. & Rhodes, A. (2016). Generalizing Treatment Effect Estimates From Sample to Population: A Case Study in the Difficulties of Finding Sufficient Data. *Evaluation Review, 41*(4). doi:10.1177/0193841X16660663

Sun, Y., Laksono, I., Selvanathanm J., Saripella, A., Nagappa, M., Pham., C., Englesakis, M., Peng, P., Morin, C. M., & Chung, F. (2021). Prevalence of sleep disturbances in patients with chronic non-cancer pain: A systematic review and meta-analysis. *Sleep Med Rev., 57*, 101467. doi:10.1016/j.smrv.2021.101467

Taylor, D. J., Mallory, L. J., Lichstein, K. L., Durrence, H. H., Riedel, B. W., & Bush, A. J. (2007). Comorbidity of chronic insomnia with medical problems. *Sleep, 30*(2), 213-218. doi:10.1093/sleep/30.2.213

Tang, N. K. Y. (2022). CBT-I Protocol for Insomnia Co-morbid with Chronic Pain. In Baglioni, C., Espie, C. A., & Riemann, D. (Eds.) *Cognitive Behavioral Therapy for Insomnia (CBT-I) Across the Life Span: Guidelines and Clinical Protocols for Health Professionals* (1st ed., 169-179). John Wiley & Sons Ltd. doi:10.1002/978119891192.ch15

Thorndike, F. P., Saylor, D. K., Bailey, E. T., Gonder-Frederick, L., Morin, C. M., & Ritterband, L. M. (2008). Development and perceived utility and impact of an internet intervention for insomnia. *E-journal of applied psychology: clinical and social issues*, *4*(2), 32. doi:10.7790/ejap.v4i2.133

Thorndike, F. P., Ritterband, L. M., Saylor, D. K., Magee, J. C., Gonder-Frederick, L. A., & Morin, C. M. (2011). Validation of the insomnia severity index as a web-based measure. *Behavioral sleep medicine*, *9*(4), 216-223. doi:10.1080/15402002.2011.606766

Torrens Darder, I., Argüelles-Vázquez, R., Lorente-Montalvo, P., Torrens-Darder, M. D. M., & Esteva, M. (2021). Primary care is the frontline for help-seeking insomnia patients. *European Journal of General Practice*, *27*(1), 286-293.doi:10.1080/13814788.2021.1960308

Treede, R. D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., ... & Wang, S. J. (2015). A classification of chronic pain for ICD-11. *Pain*, *156*(6), 1003. doi:10.1097/j.pain.0000000000000160

Twisk, J. W. (2013). *Applied longitudinal data analysis for epidemiology: a practical guide*. Cambridge university press.

Twisk, J., Bosman, L., Hoekstra, T., Rijnhart, J., Welten, M., & Heymans, M. (2018). Different ways to estimate treatment effects in randomised controlled trials. *Contemporary clinical trials communications*, *10*, 80-85. doi:10.1016/j.conctc.2018.03.008

van der Zweerde, T., Bisdounis, L., Kyle, S. D., Lancee, J., & van Straten, A. (2019). Cognitive behavioral therapy for insomnia: a meta-analysis of long-term effects in controlled studies. *Sleep medicine reviews*, *48*, 101208. doi:10.1016/j.smrv.2019.08.002

van Straten, A., & Lancee, J. (2020). Digital cognitive behavioural therapy for insomnia: the answer to a major public health issue? *The Lancet Digital Health*, *2*(8), e381-e382. doi:10.1016/S2589-7500(20)30167-9

Vedaa, O., Erevik, E. K., Hysing, M., Hayley, A. C., & Sivertsen, B. (2019a). Insomnia, sleep duration and academic performance: a national survey of Norwegian college and university students. *Sleep Med X, 1*, 100005. doi:10.1016/j.sleepx.2019.100005

Vedaa, Ø., Hagatun, S., Kallestad, H., Pallesen, S., Smith, O. R., Thorndike, F. P., ... & Sivertsen, B. (2019b). Long-term effects of an unguided online cognitive behavioral therapy for chronic insomnia. *Journal of Clinical Sleep Medicine*, *15*(1), 101-110. doi:10.5664/jcsm.7580

Vedaa, Ø., Kallestad, H., Scott, J., Smith, O. R., Pallesen, S., Morken, G., ... & Sivertsen, B. (2020). Effects of digital cognitive behavioural therapy for insomnia on insomnia severity: a large-scale randomised controlled trial. *The Lancet Digital Health*, *2*(8), e397-e406. doi:10.1016/S2589-7500(20)30135-7

Wang, R., & Ware, J. H. (2013). Detecting moderator effects using subgroup analyses. *Prevention science*, *14*, 111-120. doi:10.1007/s11121-011-0221-x

Wasserstein, R. L. & Lazar, N. A. (2016). The ASA Statement on *p*-Values: Context, Process, and Purpose. *The American Statistician, 70*(2), 129-133. doi:10.1080/00031305.2016.1154198

West, B. T., Welch, K. B., & Galecki, A. T. (2022). Linear Mixed Models: A Practical Guide Using Statistical Software (3rd ed.). CRC Press.

Wiklund, T., Molander, P., Lindner, P., Andersson, G., Gerdle, B., Dragioti, E. (2022). Internet-Delivered Cognitive Behavioral Therapy for Insomnia Comorbid With Chronic Pain: Randomized Controlled Trial. *J Med Internet Res, 24*(4):e29258 doi:10.2196/29258

World Health Organization (2022). International statistical classification of diseases and related health problems (11th ed.). Retrieved from https://icd.who.int/

Ye, Y. Y., Zhang, Y. F., Chen, J., Liu, J., Li, X. J., Liu, Y. Z., Lang, Y., Lin, L., Yang, X., & Jiang, X. J. (2015). Internet-based cognitive behavioral therapy for insomnia (ICBT-i)

improves comorbid anxiety and depression – A meta-analysis of randomized controlled trials. *PLoS ONE*, *10*(11): e0142258. doi:10.1371/journal.pone.0142258

Zachariae, R., Lyby, M. S., Ritterband, L. M., & O'Toole, M. S. (2016). Efficacy of internet-delivered cognitive-behavioral therapy for insomnia – A systematic review and meta-analysis of randomized controlled trials. *Sleep medicine reviews, 30,* 1-10. doi:10.1016/j.smrv.2015.10.004

Zimmer, Z., Fraser, K., Grol-Prokopczyk, H., & Zajacova, A. (2022). A global study of pain prevalence across 52 countries: examining the role of country-level contextual factors. *Pain, 163*(9), 1740-1750. doi:10.1097/j.pain.0000000000002557

Appendix A

SPSS syntax for the linear mixed model analysis

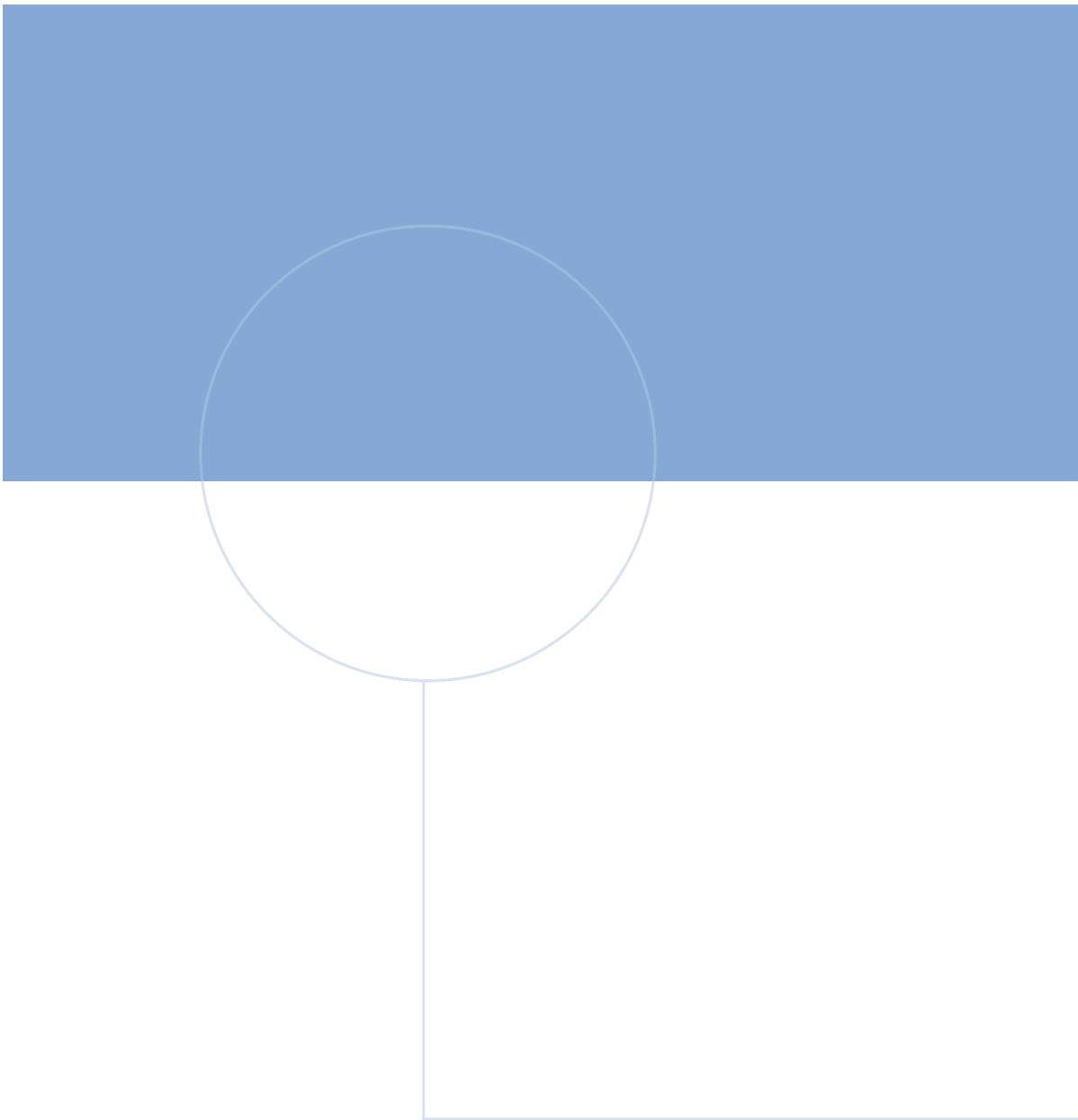
```
MIXED isi WITH intervention t2 t3 t4 cpain age gender
    /CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100)
    MXSTEP(10) SCORING(1) SINGULAR(0.000000000001)
    HCONVERGE(0.00000001, RELATIVE) LCONVERGE(0, ABSOLUTE)
    PCONVERGE(0, ABSOLUTE)
    /FIXED=t2 t3 t4 age gender cpain intervention*t2 intervention*t3 intervention*t4
    t2*cpain t3*cpain t4*cpain intervention*t2*cpain intervention*t3*cpain
    interventiont4*cpain | SSTYPE(3)
    /METHOD=REML
    /PRINT=SOLUTION
    /RANDOM=INTERCEPT | SUBJECT(id) COVTYPE(VC)
    /SAVED=RESID.

EXECUTE.
```

Table A1

Explanation of the SPSS syntax for the linear mixed model.

Command	Syntax	Interpretation
1	MIXED isi WITH intervention t2 t3 t4 cpain age gender	Requests the mixed-level analysis with covariates of randomized trial group (intervention), follow-up times (t2, t3, t4), and baseline presence of chronic pain (cpain). Age and gender were included as covariates for control.
2	/CRITERIA=DFMETHOD(SATTERTHWAITE) CIN(95) MXITER(100) MXSTEP(10) SCORING(1) SINGULAR(0.000000000001) HCONVERGE(0.00000001, RELATIVE) LCONVERGE(0, ABSOLUTE) PCONVERGE(0, ABSOLUTE)	Lists analysis criteria. Requests 95% confidence interval (CIN(95)); the default maximum number of iterations of 100 (MXITER(100)); the default step-halving per iteration of 10 (MXSTEP(10)); the Fisher scoring default up to iteration 1; the singularity for the default 10^{-12} value (SINGULAR(000000000001)). Requests that the Hessian convergence criteria (HCONVERGE(0.00000001, RELATIVE) is used, and that log-likelihood convergence criteria (LCONVERGE(0,ABSOLUTE)) and default convergence criterion for parameter estimates (PCONVERGE(0,ABSOLUTE)) are not used.
3	/FIXED=t2 t3 t4 cpain intervention*t2 intervention*t3 intervention*t4 t2*cpain t3*cpain t4*cpain intervention*t2*cpain intervention*t3*cpain intervention*t4*cpain | SSTYPE(3)	Specifies the fixed effects, two-way interactions, and three-way interactions. Specifies type III sum of squares method (SSTYPE(3)).
4	/METHOD=REML	Specifies the use of estimation method (REML).
5	/PRINT=SOLUTION	Requests the printed output with specific results (fixed-effect estimates, its standard errors, a t-test for the parameter, significance tests for the estimated variance components).
6	/RANDOM=INTERCEPT | SUBJECT(id) COVTYPE (VC)	Specifies the random effects (intercept). Specifies the classification variable (individual participants, id) and the error covariance structure type (VC).
7	/SAVED=RESID.	Requests saving the residuals for visual inspection of QQ-plots.
8	EXECUTE.	Executes the syntax command.

Note. The analysis was run using SPSS v.29.0. Table formatting based on Shek & Ma (2011) and Bauer, Sterba & Hallfors (2008).



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