The effect of bright light on sleep in nursing home patients with dementia

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Scientific environment

The work presented in this thesis has been conducted and written at the Department of Clinical Psychology, Faculty of Psychology, University of Bergen, and the Department of Health and Care, City of Bergen. The Ph.D. training programme was conducted through the Graduate School of Clinical and Developmental Psychology at the University of Bergen and the Norwegian Research School in Neuroscience. The Ph.D. candidate was affiliated with the Bergen Research Group for Innovation, Growth, Health, and Technology, and the Bergen Clinical Psychology Research Group, both at the Department of Clinical Psychology, and the Bergen Sleep and Chronobiology Network. In addition, the candidate has participated in meetings held by the Norwegian Competence Center for Sleep Disorders.

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Abstract

Background: Up to 70% of nursing home patients with dementia suffer from disrupted sleep, often characterized by multiple awakenings at night and excessive daytime sleep. Sleep disruption may have negative effects on the cognition, mood, behaviour, and well-being of nursing home patients, while also representing a challenge for nursing home staff. However, few sleep scales are developed and validated specifically for the nursing home setting.

Sleep problems among nursing home patients are frequently treated by medications, which are associated with severe side effects, including daytime sleepiness, and an increased risk of falls. Thus, there is a need for non-pharmacological interventions to improve sleep in this population. Bright light treatment (BLT) may represent such an intervention, providing increased light exposure aiming to impact sleep, circadian rhythmicity, mood, and/or behaviour.

Light is the most important zeitgeber to the circadian system, and consequently has a significant impact on sleep-wake behaviour. Unfortunately, studies have reported low indoor light levels in nursing homes, which in combination with dementia-related neuropathology and age-related reductions in light sensitivity, are likely to contribute to sleep problems in this population. The aim of this thesis was to investigate whether increasing daytime light exposure, by means of BLT, can improve sleep in nursing home patients with dementia, and also to address methodological challenges in this field of research.

Methods: Paper 1 is a systematic review of the literature, focusing on the methodological features of the included studies, in addition to their findings. Paper 2 and 3 are based on data from the DEM.LIGHT trial; a cluster-randomized placebo-controlled trial conducted in Norwegian nursing homes, including 69 patients. The intervention comprised a diurnal cycle of ambient light with a maximum of 1,000 lux and 6,000 Kelvin (K) from 10:00-15:00, administered using light emitting diode (LED) light. Before and after this interval, the light levels gradually increased/decreased in lux and K. In the placebo condition, standard light levels were

maintained at 150-300 lux and approximately 3,000 K throughout the day. The intervention and placebo lights were installed in the common rooms of the included nursing home units. Outcomes were measured at baseline and at follow-up at week 8, 16, and 24. Paper 2 was a validation study of a proxy-rated sleep scale, using the baseline data from the DEM. LIGHT trial. Actigraphy was used as the reference standard. Paper 3 reported on the sleep outcomes of the trial, which were the primary outcomes.

Results: Paper 1 found that there are promising, though inconsistent, results regarding the effect of BLT on sleep and circadian rhythmicity in dementia. Large heterogeneity in terms of interventions, study designs, population characteristics, and outcome measurement tools may explain some of the inconsistencies of results across studies. Paper 2 showed that the proxy-rated Sleep Disorder Inventory (SDI) had satisfactory internal consistency and convergent validity. Using actigraphy as the reference standard, the SDI was termed clinically useful, and we suggested a cut-off score of five or more as defining disrupted sleep in nursing home patients with dementia. These results should be interpreted keeping in mind that actigraphy have some important weaknesses, such as underestimating wake time. Paper 3 evaluated the effects of the BLT on sleep and found an improvement in sleep according to the SDI scores in the intervention group, as compared to the control group, from baseline to week 16 and baseline to week 24. There was no effect in terms of sleep measured by actigraphy.

Conclusion: In summary, this thesis found that the evidence for an effect of BLT on sleep in nursing home patients with dementia is promising, but equivocal. Importantly, the research field faces some important methodological challenges, such as accurately measuring sleep. The SDI may represent a valid tool to measure sleep in the nursing home setting, which may be used both by researchers and by practitioners. Although the results of this thesis are not conclusive regarding the effect of BLT on sleep in nursing home patients with dementia, it may represent a step forward in understanding the potential value of BLT in this population, and may lay the ground for further investigation. The lack of an improvement on the SDI at week 8 indicates that the effect of BLT may take a long time to manifest in this population.

Samandrag på norsk

Bakgrunn: Opp til 70% av personar med demens i sjukeheim har forstyrra søvn, ofte karakterisert av hyppige oppvakningar om natta og mykje søvn på dagtid. Søvnforstyrringar har negative konsekvensar for kognisjon, humør, åtferd og livskvalitet hos pasientane, og symptoma er krevjande å handtere for personalet. Likevel finst det få kartleggingsinstrument som er utvikla og validert spesifikt for bruk i sjukeheim.

Søvnproblem hos sjukeheimspasientar blir ofte behandla medikamentelt, men slik behandling er assosiert med alvorlege biverknader, inkludert søvnigheit på dagtid og auka fallrisiko. Det er difor behov for å finne ikkje-medikamentelle intervensjonar for å betre søvn i denne populasjonen. Lysbehandling, eller 'bright light treatment' (BLT), kan vere eit slikt behandlingsalternativ. BLT inneber å auke lyseksponering for å påverke søvn, døgnrytme, humør og/eller åtferd.

Lys er den viktigaste stabiliserande faktoren for døgnrytmen, og er difor avgjerande for regulering av søvn-vaken-syklusen. Forskarar har funne lave nivå av innandørs lys på sjukeheimar. I kombinasjon med demensrelatert nevropatologi og aldersrelatert reduksjon i sensitiviteten for lys, bidreg dette venteleg til den høge førekomsten av søvnproblem i denne populasjonen. Målet med denne avhandlinga var å undersøke om ein kan betre søvn hos personar med demens i sjukeheim ved å auke lyseksponering på dagtid, samt å sjå nærare på dei metodologiske utfordringane i dette forskingsfeltet.

Metode: Artikkel 1 er ein systematisk litteraturgjennomgang der vi fokuserte på metodologiske trekk ved dei inkluderte studiane, i tillegg til studiane sine resultat. Artikkel 2 og 3 var basert på data frå DEM.LIGHT-studien; ein klynge-randomisert placebo-kontrollert studie gjennomført på norske sjukeheimar, som inkluderte 69 pasientar. Intervensjonen bestod av takmontert LED-lys, som gav ein syklus av lys med maksimalt nivå på 1,000 lux og 6,000 Kelvin (K) frå kl. 10:00 til kl. 15:00. Før og etter dette intervallet vart lyset gradvis auka/dempa i lux og K. Kontrollgruppa hadde standard lys på 150-300 lux og rundt 3,000 K gjennom heile dagen. Intervensjonen og placebo-lyset vart installert i daglegstova til dei inkluderte sjukeheimsavdelingane.

Utfalla vart målt på baseline og ved oppfølging i veke 8, 16 og 24. Artikkel 2 var ein validerings-studie av ein søvnskala, basert på baseline-data frå DEM.LIGHT-studien. Aktigrafi vart brukt som referanse. Artikkel 3 rapporterte søvnutfalla (primærutfall) frå DEM.LIGHT-studien.

Resultat: Artikkel 1 viste at det finst lovande, men inkonsistente funn om effekten av BLT på søvn og døgnrytmeforstyrringar hos personar med demens. Vi fann store skilnader i val av intervensjonar, design, karakteristikkar ved studiepopulasjonen og mellom utfallsmål, som kan forklare dei ulike resultata på tvers av studiar. Artikkel 2 viste at søvnskalaen Sleep Disorder Inventory (SDI), utfylt av sjukeheimspersonale, hadde tilfredsstillande indre konsistens og konvergent validitet. Samanlikna med aktigrafi som referanse, fann vi at SDI var klinisk nyttig, og vi foreslo ein skår på fem eller meir som cut-off for å definere forstyrra søvn hos personar med demens i sjukeheim. Desse resultata må tolkast i lys av at aktigrafi har nokre viktige ulemper, til dømes at dei kan underestimere vakentid på natta. Artikkel 3 evaluerte effekten av BLT på søvn og fann ei betring av SDI i intervensjonsgruppa frå baseline til veke 16 og frå baseline til veke 24, samanlikna med kontrollgruppa. Det var ingen effekt på søvn målt med aktigrafi.

Konklusjon: Oppsummert viste denne avhandlinga at effekten av BLT på søvn hos personar med demens i sjukeheim er lovande, men ikkje eintydig. Forskingsfeltet har nokre viktige metodologiske utfordringar, mellom anna nøyaktige mål for søvn. SDI kan representere et valid verktøy for bruk i sjukeheimar og kan nyttast både av forskarar og i klinisk praksis. Sjølv om resultata av denne avhandlinga ikkje er konkluderande om effekten av BLT på søvn hos personar med demens i sjukeheim, representerer dei eit steg framover i å forstå den potensielle verdien av BLT for denne populasjonen, og kan bidra til vidare forsking. Manglande betring av SDI i veke 8 tyder på at effekten av BLT kjem først etter ei stund i denne populasjonen.

List of Publications

Hjetland, G. J., Pallesen, S., Thun, E., Kolberg, E., Nordhus, I. H., & Flo, E. (2020). Light interventions and sleep, circadian, behavioral, and psychological disturbances in dementia: A systematic review of methods and outcomes. Sleep Medicine Reviews, 101310.

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Hjetland, G. J., Kolberg, E., Pallesen, S., Thun, E., Nordhus, I. H., Bjorvatn, B., Flo-Groeneboom, E. (*Manuscript submitted for publication*). Ambient bright light treatment improved subjectively measured sleep but not sleep measured by actigraphy in nursing home patients with dementia: A placebo-controlled randomized trial.

Abbreviations

ADL	Activities of Daily Living
ANOVA	Analysis of Variance
AUC	Area Under the Curve
BLT	Bright Light Treatment
BPSD	Behavioural and Psychological Symptoms of Dementia
CCI	Charlson Comorbidity Index
CCT	Correlated Colour Temperature
CSDD	Cornell Scale of Depression in Dementia
EEG	Electroencephalogram
FAST	Functional Assessment Staging
GABA	γ-Aminobutyric Acid
ipRGC	Intrinsically Photosensitive Retinal Ganglion Cells
K	Kelvin
LED	Light Emitting Diode
MMSE	Mini Mental State Examination
MOBID-2	Mobilization-Observation-Behaviour-Intensity-Dementia 2
NIF	Non-Image Forming
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory-Nursing Home Version
NREM	Non-Rapid Eye Movement
PSG	Polysomnography
RCT	Randomized Controlled Trial
REM	Rapid Eye Movement
ROC	Receiver Operating Characteristic
SAD	Seasonal Affective Disorder
SCN	Suprachiasmatic Nucleus
SD	Standard deviation
SDI	Sleep Disorder Inventory
SE	Sleep Efficiency

SWS	Slow Wave Sleep
TST	Total Sleep Time
VLPO	Ventrolateral Preoptic Area
WASO	Wake After Sleep Onset

Contents

1. Introduction and background

Life expectancy has increased during the last decades, and it has been estimated that one in six people will be over the age of 65 by 2050 [1]. Although epidemiological studies have demonstrated an increase in the number of healthy years in old age [2], the relative increase in older people in the global population, implies an increased number of people with dementia [3] and a growing need of continuous care. The demand for nursing home places is consequently likely to escalate. Disrupted sleep is one of the central challenges related to nursing home patients with dementia [4]. Sleep is essential for good health, and many of the symptoms and challenges associated with dementia, such as impaired cognition, depression, anxiety, agitation, and psychotic symptoms [5], seem to be exacerbated by severely disrupted sleep [6–10].

Unfortunately, assessing sleep in nursing home patients is particularly challenging in dementia. Patients may not retain experiences of their own sleep and may have lost their ability to communicate. Further, treating sleep disturbances in this population is complicated due to multimorbidity, and pharmacological treatments often cause side effects such as sedation and increased risk of falling [11, 12]. Thus, adequate non-pharmacological treatments are warranted.

One promising non-pharmacological intervention is Bright Light Treatment (BLT), where patients are exposed to bright light during the day. Light exposure plays a key role in regulating sleep and wakefulness [13]. Alas, several studies have reported suboptimal light levels in nursing homes [14–17], and insufficient light exposure seems to contribute to sleep problems among nursing home patients with dementia [14, 18]. Some studies have shown promising effects of BLT on sleep in people with dementia [e.g., 19, 20], but there is a general lack of rigorous clinical trials including this population.

1.1 Purpose and scope of the dissertation

The main aim of this thesis was to investigate the effect of BLT on sleep in nursing home patients with dementia. In order to achieve this goal, we first performed a

systematic review of relevant literature (Paper 1). To get a broader and clinically meaningful sense of the use of BLT as a treatment option for people with dementia, we included studies evaluating the effect on sleep and circadian rhythmicity, and also Behavioural and Psychological Symptoms of Dementia (BPSD), such as depression agitation, functional status, and quality of life. Further, the use of different valid measures of sleep may be a prerequisite to reach an approximation of the actual sleep pattern in people with dementia. Hence, we addressed the challenges of measuring sleep in people with dementia and investigated the validity of a sleep scale designed for use in this population (Paper 2). Lastly, we evaluated the effect of a BLT intervention on sleep in nursing home patients with dementia by means of a cluster-randomized placebo-controlled trial (Paper 3).

The following background section will present key research on sleep and sleep-wake regulation, including the role of light in sleep-wake regulation. Following this, the nursing home context and sleep in this context will be presented. Then, previous studies evaluating the effect of BLT on sleep problems in dementia will be reviewed, and finally, some central challenges pertaining to BLT research will be outlined.

1.1.1 Current research and development

A systematic literature search was conducted in June 2016, covering medical subject headings (MeSH) terms and free text phrases synonymous with “nursing home”, “bright light treatment” and “dementia”. We searched Medline, Embase, PsycINFO, Cochrane library, CINAHL, and Web of Science. Updated searches were performed in 2018 and 2019. These searches became the basis of Paper 1 and updated searches performed in 2020, last performed in August 2020, provided literature for the present thesis.

1.2 Sleep

Humans spend approximately one third of their lives sleeping [21]. Although there are still many undiscovered mechanisms related to our need for sleep, considerable evidence suggest that sleep serves several essential functions, such as brain restitution

[e.g., 22], and metabolic and hormone regulation [e.g., 23]. In addition, sleep is essential to cognitive functions such as learning and memory [24, 25]. Prolonged sleep problems have consequently been shown to have severe health consequences. For example, one recent meta-analysis including more than 5 million participants, reported that short sleep duration (less than six hours each night) is associated with an increased risk of diabetes mellitus, cardiovascular disease, and obesity [26]. Also long sleep duration (more than eight hours each night) has been linked to poor health outcomes [27]. Longitudinal studies of humans have shown that sleep problems and circadian disturbances at baseline are associated with an increased risk of developing cognitive impairment and dementia [28, 29].

Sleep is a reversible state that is characterized by reduced responsiveness, motor activity, and metabolism [30]. While sleeping, people are normally lying down, immobile, and with their eyes closed. At the same time, sleep is a highly complex behavioural and physiological state, with characteristic brain and body activity (see below) [31]. Human sleep normally occurs at night, and adults on average report sleeping for about 7 hours [32]. However, sleep timing and duration varies significantly across individuals and across nights [31, 33]. With aging, sleep quality and quantity are affected [34], and even more so in dementia [4, 35]. Basic research on sleep is most often performed on young adults, and the following description of sleep and sleep-wake regulation (section 1.2 and 1.3) refers to sleep as it typically presents itself in a healthy young adult. How sleep is affected by aging and dementia is described in section 1.4 and 1.5.1.

1.2.1 Characteristcs of sleep-wake patterns

The discovery of the electric activity of the brain and the invention of the electroencephalogram (EEG) represent the start of the modern scientific study of sleep [36]. The EEG records the electric activity of the brain, producing distinct wave patterns when measured by electrodes placed on the scalp. Today, the gold standard of sleep monitoring is polysomnography (PSG), a technique encompassing EEG, electrooculography (recording eye movements), and electromyography (recording muscle activity), followed by a manual analysis of the recordings [37]. Clinical PSG

additionally include electrocardiography, and recordings of respiration, activity of the musculus tibialis, and oxygen saturation. By recording the changes in the electrical activity of the brain throughout the sleep episode, different sleep stages have been identified. In humans, sleep is broadly classified into Non-Rapid Eye Movement (NREM) sleep and Rapid Eye Movement (REM) sleep, which occur in cycles of approximately 90 minutes throughout the sleep episode [31]. Traditionally, NREM sleep has been divided in four substages based on the EEG activity [38]. In 2007, the NREM sleep stages were redefined by the American Academy of Sleep Medicine into three stages of successively deeper sleep (N1-N3) [39] (see Table 1). N3 is characterized by high-amplitude slow waves, or slow-wave activity, and is also referred to as slow-wave-sleep (SWS).

Table 1: An overview of the sleep stages [31, 37, 39].

	AASM classification	**Traditional stages**	**EEG characteristics**	**Approximate distribution of sleep stages in one sleep episode**
Non-REM sleep	N1	Stage 1	Slowing of the EEG wave pattern	2-5%
	N2	Stage 2	Characteristic EGG waveforms of sleep spindles and K-complexes	45-55%
	N3	Stage 3-4	Scored when at least 20% of the epochs (30 sec) are slow-wave activity; slow waves with high-amplitude called delta waves. N3 is also referred to as slow-wave sleep.	13-23% (3-8% in Stage 3 and 10-15% in Stage 4)
	R	REM sleep	The EEG pattern resembles the activity during wakefulness (low amplitude, high frequency).	20-25%

AASM= American Academy of Sleep Medicine, EEG= Electroencephalogram, REM= Rapid-eye-movement.

The proportion of NREM and REM sleep changes in a predictable pattern across the sleep period, as initially documented by Dement and Kleitman [40], and that has been confirmed in later studies [e.g., 41]. Following sleep onset into NREM sleep, sleep becomes gradually deeper, and approximately 30 minutes are spent in N3 during the

first sleep cycle (approximately 90 minutes in total). Subsequently, sleep becomes 'lighter', moving rapidly through N3 and N2, followed by REM sleep. During REM sleep, visual dreams often occur, and the subject displays saccadic eye movements [42, 43]. REM sleep is also accompanied by muscle atonia, which is detected by electromyography [37]. Following the first REM episode, sleep again becomes gradually deeper and the process is repeated. The longest SWS episodes occurs during the first third of the night, while REM sleep and N2 dominate the last third. The approximate distribution of sleep stages are given in Table 1.

1.2.2 The neurobiological and neurophysiological basis of sleep

Sleep is an active process that is generated by brain areas mainly located in the brainstem, thalamus, hypothalamus, and the basal forebrain [44]. The transitions between sleep and wakefulness are driven by a reciprocal inhibition between the circuits involved in sleep and those involved in wake and arousal. The transition has been compared to a flip-flop switch, where the activity of one system inhibits the activity of the other [45].

Wakefulness is induced by the activity of multiple neurochemical systems originating in the brainstem and forebrain, projecting to the thalamus and/or the neocortex, resulting in widespread cortical activity [46]. The thalamus, located above the brainstem, act as a relay station between sensory input and the cerebral cortex, where sensory inputs are processed and interpreted.

During the transition to drowsiness, sleep-promoting neurons inhibit the arousal systems [47]. The evidence suggests that GABAergic neurons (i.e., neurons releasing the neurotransmitter γ-Aminobutyric Acid, GABA) located in the ventrolateral preoptic area (VLPO) and in the median preoptic nucleus of the hypothalamus, are largely responsible for initiating and maintaining sleep [47]. During sleep onset, these sleep-promoting neurons are activated by excitatory input from the suprachiasmatic nucleus (SCN) of the hypothalamus and from the neurotransmitter adenosine [46]. The SCN is responsible for the circadian 24 hour rhythm of the sleep-wake cycle (see below), and activates the VLPO when it is time to sleep [46]. Adenosine is a waste

product of brain activity that accumulates during wakefulness and activates the sleep-promoting neurons of the VLPO. The activity of sleep-promoting neurons inhibit the activity of systems involved in wakefulness [46]. Thus, the thalamus and the cerebral cortex are quiet during SWS, tuning out the outside world. Conversely, the sleep-promoting GABAergic neurons are inhibited by the neurotransmitters involved in wakefulness [48].

The transition from SWS to REM sleep involves inhibitory interaction between "REM-on" neurons and "REM-off" neurons located in the midbrain and hindbrain. In transitioning to REM sleep, the cholinergic neurochemical system becomes active, while serotonergic and noradrenergic neurons become inhibited [49]. The cerebral cortex, thalamus, and basal forebrain are active, while neurons from the "REM-on" neuronal centres project to the spinal cord and cause muscle atonia [46].

1.3 Sleep-wake regulation

1.3.1 The two-process model

One highly influential model for describing sleep regulation is the two-process model, initially presented by Borbély in the early 1980s [50]. According to the model, sleep timing and structure are the products of i) a build-up of sleep pressure following wakefulness, termed the homeostatic process, and ii) endogenously generated near-24-hour rhythms in sleep and arousal, termed the circadian process. Since the model was proposed by Borbély [50], it has been revised and inspired other models of sleep regulation [51]. However, the two-process model remains highly influential and serves as a guide to understanding sleep regulation.

The homeostatic process

The homeostatic sleep drive increases during wakefulness and decreases during sleep [52]. Slow-wave EEG activity is regarded the principal marker of the homeostatic sleep drive. The magnitude of slow-wave activity increases after prolonged wakefulness, signalling the build-up of sleep pressure, and diminishes during sleep.

Adenosine is a key mediator of the homeostatic process, where the accumulation of adenosine in the basal forebrain accompanies the build-up of sleep pressure [53].

The circadian process

Circadian rhythms are near-24-hour rhythms in cellular activity, protein expression, and finally behaviour, evident in rhythms of sleep and wakefulness, core body temperature, metabolic function, hormone production, and a range other biological processes [54]. These rhythms are produced by a molecular clockwork present in most cells [55].

The SCN of the hypothalamus has been identified as the "master clock" or circadian pacemaker, which synchronizes, or orchestrates, the different rhythms throughout the body [56], ensuring that the brain and body are prepared to carry out functions appropriate to the time of day/night. Two prominent circadian rhythms are the daily fluctuations of melatonin secretion and core body temperature, which are often used to assess circadian phase. Melatonin is a hormone secreted by the pineal gland inducing sleepiness, which increases during the evening, reaches its peak levels during the night, and shows low levels during the day. Core body temperature, on the other hand, reaches its minimum (nadir) approximately two hours prior to habitual wake-up time [57]. Because the internal rhythm of the circadian pacemaker for most people is slightly longer than 24 hours [54, 58], the circadian pacemaker depends on exposure to environmental time signals (zeitgebers) to synchronize to geophysical time [54]. The most important zeitgeber is the light/dark cycle [54] (see section 1.3.2). Although light and darkness are the most potent zeitgebers, other non-photic events, such as changes in temperature, physical activity, or food consumption, may also act as entraining signals [59–62].

Importantly, the homeostatic and circadian processes affect each other [63, 64]. For example, while homeostatic sleep pressure increases with wakefulness and decreases with sleep, its contribution to sleep timing is restricted by the oscillation of the circadian rhythm, which is normally entrained to the 24-hour day [52]. Thus, following the same amount of time spent awake, sleep onset latency and the quality of

the sleep, depend on when the person goes to bed. Conversely, sleep restriction or advancing/delaying the sleep episode changes the activity of the circadian system [65].

In addition to the homeostatic and circadian processes, ultradian rhythms (shorter than 24 hours) are aspects of sleep-wake regulation. One example is the 90 min NREM-REM cycles [66]. There is also some ultradian rhythmicity in waking EEG, with a period of 3-4 hours, with accompanying variations in vigilance and alertness [67]. In sum, sleep is produced by a complex interaction of homeostatic and circadian processes [63, 64, 66, 68], as well as ultradian rhythms [52, 69].

Environmental/behavioural influences on sleep

Under ideal circumstances, the rhythms of sleep-wake, metabolism, hormone secretion, and other rhythms throughout the body are synchronized in a temporal order securing optimal functioning [57]. However, people frequently behave in ways that misaligns the sleep-wake cycle from the light dark-cycle. Perhaps the most prominent example is shift work, where people work during the night and go to sleep in the morning. Consequently, behaviour is a major factor in sleep-wake regulation, where people advance, delay, or shorten their sleep episode. This behaviour may also affect how much light a person is exposed to, and the timing of exposure.

1.3.2 Light and entrainment of circadian rhythms

As light exposure is the most important zeitgeber to the circadian system [54], it is fundamentally implicated in sleep and circadian rhythm entrainment [13]. Light information is projected directly from the retina to the SCN by a group of ganglion cells in the retina, called intrinsically photosensitive retinal ganglion cells (ipRGCs) [70, 71]. The ipRGCs are intrinsically photosensitive as they contain the photopigment melanopsin [72], and are maximally sensitive to short wavelength light of about 480 nm, corresponding to blue light [73, 74]. There are five subtypes of ipRGCs [75], which in addition to projecting to the SCN and entraining circadian rhythms, have a widespread pattern of projection to areas such as the VLPO and the lateral hypothalamus, areas implicated in the regulation of sleep, wakefulness/alertness, and mood [72]. All of these “non-visual” effects of light, including circadian effects, are

collectively termed “non-image-forming” (NIF) functions [72]. While the ipRGCs are sufficient to drive circadian responses to light, rods and the three kinds of cone photoreceptors (the “classical” photoreceptors involved in image-forming functions) also contribute to NIF responses [76, 77].

The “optimal” dose of daily light exposure in terms of timing, intensity, and spectral composition has not been established [78]. However, research have demonstrated how these aspects of light impact the circadian system. Firstly, the effect of light exposure on the circadian system depends on the circadian phase in which the light is delivered, a phenomenon referred to as phase-response curves [79, 80]. Phase-response curves estimate the direction and magnitude of phase shifts following light exposure at specific times. Exposure to bright light following nadir (the time of the lowest point of the temperature rhythm) advances the circadian rhythm (i.e., shifts the rhythm to an earlier time), while bright light prior to nadir delays the rhythm (i.e., shifts the rhythm to a later time) [79, 81, 82]. The magnitude of the circadian response to a light stimulus may be expressed as how much the phase of the circadian rhythm is delayed or advanced, where the largest phase shifts occur close to nadir [57]. Importantly, the human circadian system is sensitive to light input throughout the day, and phase advances may be invoked by bright light for up to 8 hours after habitual waking [81, 83]. Bright light at midday has been shown to advance the phase of the melatonin rhythm and increase nocturnal plasma melatonin [84]. Light exposure during the evening and night may significantly disrupt circadian rhythms [85, 86].

In addition to the timing of light exposure, the physiological response to light partly depends on the level of illumination [87]. Illuminance is a commonly used measure that refers to how much the incident light illuminates a surface [88]. Traditionally, the most widely used photometric unit for illuminance is lux [89]. This metric, however, is weighted by the spectral sensitivity of cones (peak sensitivity at ~555 nm), and not ipRGCs (peak sensitivity at ~480 nm). Given that NIF responses are largely driven by ipRGCs, lux inadequately predicts NIF responses to light [89]. Lucas and colleagues [90] developed a toolbox for quantifying the activation of each photoreceptor (equivalent “α-opic” illuminance), including a metric quantifying the activation of

melanopsin, the ‘equivalent melanopic lux’. Building on this work, the International Commission on Illumination (CIE S 026/E:2018) recently developed a toolbox offering metrics compliant to the International System of Units [91]. The CIE developed the metric “melanopic equivalent daylight illuminant” (melanopic EDI), closely reflecting the “equivalent melanopic lux” presented by Lucas et al. [90]. In recent years, researchers have increasingly used these metrics, which are superior in predicting the circadian response to a light stimulus, compared to photopic illuminance (lux) [90, 92]. Yet others have used the metric “circadian stimulus”, quantifying the circadian effectiveness of a light stimulus in terms of melatonin suppression [93–95]. However, as these developments are fairly recent, the majority of BLT studies involving people with dementia to date have reported lux.

One of the first demonstrations of the physiological effects of light showed that at least 1,000 lux of polychromatic white light was needed to suppress melatonin in humans [96]. Daylight illumination can typically range from 13,500 lux (overcast) to 63,000 lux (clear sky), and can reach a maximum level of over 100,000 lux [97]. Later, Brainard et al. [98] demonstrated that much lower light intensities (3-7 lux) of monochromatic (single wavelength) light of 509 nm and could cause a significant reduction in nocturnal plasma melatonin in humans when the pupil was artificially dilated. Under normal circumstances, with normal pupil constriction, higher illuminance is needed. One study demonstated that daytime exposure to 200 lux, i.e., typical indoor illumination, was not sufficient to maintain circadian phase at 24 hours [99]. In contrast, daytime exposure to 1,000 lux entrained the circadian rhythm [99].

The physiological response to light also depends on spectral composition, i.e., which wavelengths the light consists of [87, 100]. Since the ipRGCs are maximally sensitive to short wavelength light, short wavelength light has a stronger impact on the circadian system than light of longer wavelengths [101, 102]. The spectral composition of light is often expressed as the correlated colour temperature (CCT) of the light, reported in Kelvin (K). Sunlight contains all visible wavelengths (it is polychromatic), including high amounts of blue light. The CCT of daylight lies around 6,000 Kelvin (K),

depending on weather conditions [103]. Typical indoor light is about 200 lux and 2,700-4,000 K [16, 17].

In addition, the response to light, in terms of NIF responses, also depends on the duration of exposure and on previous light exposure, or light history. Generally, the phase shifting properties of light is stronger when the duration of exposure is increased [104], although phase shifts can also occur in response to very short light bursts [105]. Further, exposure to bright light decreases the sensitivity of the ipRGCs. One study demonstrated that exposure to blue-white light in the morning reduced the phase-shifting response to evening light exposure [106]. Conversely, limiting daytime light exposure to dim light only, has been shown to increase melatonin suppression in response to nocturnal light exposure [107, 108], and hence increase the risk of circadian disruption. Thus, sufficient daytime light exposure seems to protect against circadian disruption caused by evening/nocturnal light. In conditions with extremely weak or absent zeitgebers, circadian rhythms decouple from geophysical time and 'free-run' according to the intrinsic oscillation of the circadian pacemaker [54].

Importantly, bright light exposure also has well-demonstrated effects on alertness; indirectly through suppressing melatonin, and directly by stimulating the arousal system [109–111]. Thus, light may shift the timing of sleep through its effect on the circadian system, and also by suppressing sleepiness and enhance alertness.

The consequences of non-optimal light exposure

Due to the intimate relationship between the circadian system and the light-dark cycle, changes in the light dark-cycle often lead to circadian dysregulation, including the disruption of the sleep-wake rhythm [72]. Common causes of circadian dysregulation is shift work and travelling across time zones [112], which misaligns the main sleep episode from the light-dark cycle. This often results in sleep deprivation and sleep fragmentation [113], and misaligns sleep from other circadian rhythms. Such internal misalignment of different circadian rhythms may in itself be detrimental to health and well-being [114].

Modern life often entails spending the majority of time indoors, largely cut off from daylight, as well as using electrical light and light-emitting devices in the evening. This life style diminishes the amplitude of the light-dark cycle [115]. As mentioned above, the circadian system is more susceptible to night-time light exposure in the absence of a robust light input during the day. Research suggests that a robust light-dark cycle promote a stable rhythm, and standard indoor light levels seem to be insufficient to maintain a stable circadian rhythm [99]. As will be elaborated in section 1.5, this may be particularly relevant in nursing homes.

1.4 Sleep and aging

With increasing age, some well-documented changes in sleep timing and structure also occur. Firstly, circadian rhythms become less robust [116]. The output from the SCN is altered, with a reduced amplitude of hormone-secretion, electrophysiological activity, and gene expression [117]. Also, there is some evidence that sleep homeostasis becomes less robust, with diminished sleep pressure with increasing age [118, 119]. By the age of 60, total sleep time, sleep efficiency (SE; the percentage of time spent asleep while in bed), SWS, and REM sleep decrease, and there is commonly an increase in the time spent awake after sleep onset, sleep onset latency (the time it takes to fall asleep), time spent in sleep stages N1 and N2 (i.e., lighter sleep), and more arousals from sleep [34, 120]. Beyond 60 years, the amount of time spent in N1 increases and SE decreases further, while other sleep parameters remain stable [34]. However, this stability of sleep parameters beyond 60 years of age pertain to healthy adults and not those with medical issues. Somatic diagnoses and their treatment, such as hypertension, heart disease, and diabetes, seem to contribute to sleep disturbances [121–124]. These conditions are more common in older populations [125].

With increasing age, the amount of light reaching the retina is reduced due to lens yellowing and pupil constriction [126–128], which may contribute to sleep disturbances. Brøndsted, Lundeman, and Kessel [129] measured the transmission of light through donor lenses and calculated that the ability of photoentrainment

decreases by 0.6-0.7% for each year of life because yellowing of the lens increasingly absorbs short wavelengths. Tuner and Mainster [128] calculated the age-related decline in circadian photoreception based on both lens yellowing and senescent miosis (age-related decline in pupil size). According to their calculations, a 45-year old have roughly half the circadian photoreception of a 10-year old, and 80- and 90-year olds retain only about 10% of the circadian photoreception of a 10-year old. Indeed, such changes may contribute to sleep disturbances in older adults. Clinically, lens yellowing is associated with more subjectively reported sleep disturbances and sleep medication use [130]. In addition, the sensitivity of the SCN to photic input may also decrease with age [131]. Duffy and colleagues [132] reported that older adults (65 or older) were less sensitive to low-to-moderate light levels (50-1,000 lux) than young adults in terms of the delaying effect of evening light exposure on the circadian rhythm. Herljevic and colleagues [133] found a smaller suppression of melatonin following light exposure in older adults compared to younger adults. There is some evidence for compensatory mechanisms preserving the melatonin response to light [127], and diminished responses to light seem to be more pronounced at low-to-moderate light levels, while the responses to very bright light (8,000-10,000 lux) is largely preserved by age [132, 134, 135]. These changes in light sensitivity implies that older adults are particularly dependent on a robust light-dark cycle to retain a stable circadian rhythm.

1.5 Sleep in the nursing home

Nursing homes are the largest institutions in Norway, and 32,234 people were registered with long-term placement in 2018 [136]. In Norway, long-term placement is offered primarily to older people who are no longer able to live at home [137]. In other words, to be eligible for nursing home placement, the person has to be in need of continuous care beyond what can be offered by visits at home [138]. Hence, the average age of long term nursing home residents is relatively high (84 years) [138], 80% suffer from dementia [125, 139, 140], and many have poor somatic health [125]. Coronary disease, congestive heart failure, cerebrovascular disease, and diabetes are common, where one study found prevalences at admission to the nursing home of

25%, 21%, 24%, and 15%, respectively [125]. Consequently, nursing home patients represent a frail group with multiple somatic and psychological needs [138]. Unfortunately, findings from a Norwegian study indicated a lack of sufficient competence among staff to meet the complex needs of nursing home patients [141], which may lead to insufficient patient care and distress among staff. Among physicians, a Norwegian report found that there was high turnover and little continuity, where most were engaged in part time positions [142]. There is on average one registered nurse per 11 patients, one licensed practical nurse per seven patients, and one unskilled nurse per 16 patients during the day shift [143]. During the night, these numbers are 24, 20, and 23, respectively. Numbers may vary across municipalities and depending on the nursing home, the number of patients per nurse may be even higher. Not surprisingly, sleep problems, in particular agitation and confusion during the night, can be difficult to handle for a small night staff.

Sleep disruption is common among nursing home patients, with prevalences of 25-67% [144–148], and studies have reported that up to 50% use hypnotics [149–151]. Dementia is a major contributor to sleep disruption among nursing home patients, and the following section wil describe dementia and the impact of dementia on sleep.

1.5.1 Dementia – Diagnoses, symptoms, and sleep regulation

Among people of 60 years of age or more, 5-7% suffer from dementia [152]. Dementia is associated with significant economic costs related to medical treatment and formal and informal care. The total costs make up between 0.2 and 1.4% of the gross domestic product in low- and high-income countries, respectively, and the World Health Organization have recognized dementia as a social health priority [153]. In Norway, it is estimated that between 80,000-100,000 people suffer from dementia, and this number is expected to double by 2050 [3].

Dementia is caused by progressive neurodegenerative and/or vascular damage to the brain that result in cognitive impairment, behavioural and psychological changes, and the loss of ability to perform everyday tasks [153]. In the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), dementia, or major neurocognitive

disorder, is now subsumed in the broader category of "neurocognitive disorders", alongside delirium and mild neurocognitive disorder. The term 'dementia' is still frequently used [154]. These diseases are progressive in nature and ultimately fatal [155]. Each of the dementia subtypes are associated with specific underlying brain pathology, with changes in brain structure, function, and chemistry [156]. Importantly, people often have brain abnormalities corresponding to more than one type of dementia. Post-mortem autopsies have shown that about half of the presumed Alzheimer's disease cases involve additional pathology associated with other dementias [156]. Thus, patients with the same diagnosis may differ significantly in underlying pathology and also on how this pathology translates to function, behaviour, and well-being. Additionally, dementia is under-diagnosed in Norwegian nursing homes, likely due to resource limitations and advanced dementia with mixed pathologies [125]. As such, studies in nursing homes often include all patients with likely dementia.

Dementia subtypes

The most common dementia subtypes in old age includes Alzheimers disease, vascular dementia, dementia with Lewy-Bodies, frontotemporal dementia, and Parkinsons disease dementia [156]. AD is the most common cause of neurodegenerative dementia, causing roughly 60% of dementia cases [157]. Alzheimer's disease is recognized by an insidious onset and a gradual progression, with memory and learning impairments as typical early symptoms [156]. The aggregation of the proteins amyloid-β and tau in the brain into amyloid plaques and neurofibrillary tangles, are the hallmark pathophysiological characteristics of Alzheimer's disease, causing neuronal dysfunction, neuronal death, and atrophy (schrinkage) of the brain [158]. Alzheimer's disease neuropathology arises 10-20 years prior to the clinical manifestation of the disease. Following initial diagnosis, the average life expectancy of Alzheimer's disease patients range from 3-12 years [159].

Vascular dementia is regarded as the second most common subtype of dementia in old age, making up approximately 15% of dementia cases [157, 160]. The cognitive changes associated with vascular dementia are variable and depend on the location of

the vascular pathology in the brain [160]. Vascular dementia may arise from different vascular events, such as stroke, small-vessel disease, or multiple cortical infarcts. In contrast to Alzheimer's disease, vascular dementia does not necessarily include memory impairment. Rather, it is commonly associated with deficits in information processing, attention, and executive functioning due to subcortical pathology [160]. Following initial diagnosis, life expectancy of people with vascular dementia is 3-5 years [159]. Importantly, only 5-10% of people with dementia have vascular damage alone, as vascular changes are more common in combination with Alzheimer's disease pathology [161, 162].

Dementia with Lewy-Bodies make up 4-5% of dementia cases [163]. It resembles Alzheimer's disease as it is characterized by progressive cognitive impairment, however, with early change observed in executive functions and complex attention tasks, rather than memory and learning [154]. Lewy-bodies are aggregations of the alpha-synuclein protein in neurons, causing dementia with Lewy-bodies when they develop in the cortex [156].

Frontotemporal dementia accounts for almost 3% of dementia cases among people older than 65 [164]. Frontotemporal dementia is a pathologically heterogeneous group of dementias that are associated with shrinkage of the frontal and temporal lobes [156]. Typical symptoms include behavioural impairments such as apathy and disinhibition, resulting in socially inappropriate behaviour and a lack of insight, and/or difficulties with language production or comprehension. Cognitive decline often presents itself later in the course of the disease, mainly dominated by executive impairment [156].

Parkinson's disease dementia accounts for approximately 3-4% of dementia cases [165]. People with Parkinson's disease may develop dementia as the disease progress, on average 8-10 years after an initial diagnosis of Parkinson's disease. In Parkinson's disease dementia, cognitive decline develop due to pathophysiological processes either similar to dementia with Lewy-Bodies or similar to Alzheimer's disease [156].

Behavioural and psychological symptoms of dementia

The diagnostic criteria for dementia mainly focus on cognitive domains, however, dementia is typically also characterized by a range of non-cognitive symptoms. These "Behavioural and Psychological Symptoms of Dementia" (BPSD) include depression, agitation, anxiety, hallucinations, apathy, and disrupted sleep, among other symptoms [5]. Up to 90% of people with dementia develop one or more BPSD during the course of their disease [166]. The individual symptoms may have a fluctuating course, and very few symptoms are continuously present across time [167]. BPSD are associated with high levels of distress for the afflicted person, as well as for informal (family members) and formal caregivers (nursing home staff, in-home assistance) [168]. Some symptoms may be associated with specific dementias. For example, apathy, depression, anxiety, and emotional lability are more common in vascular dementia compared to Alzheimer's disease [169, 170]. Importantly, the clinical presentation of BPSD vary substantially both within dementia subtypes and within each individual [5].

Sleep and circadian rhythm disruption in dementia

Sleep problems are considered one aspect of BPSD [5]. Many of the brain areas and neural systems that are involved in sleep and circadian regulation are affected by the pathological brain changes seen in Alzheimer's disease and other dementias, and are often increasingly affected as neurodegeneration progresses [171]. Alzheimer's disease is also associated with pathological changes in the retina and the optic nerve, including the loss of ipRGCs [172]. In addition, other ocular changes associated with Alzheimer's disease, such as glaucoma, macular degeneration, pupillary dysfunction, and reduction in optical nerve fibre thickness may disrupt circadian regulation [173]. Thus, dementia increase the risk of disrupted sleep, beyond the impact of environmental influences and somatic conditions. Irregular sleep-wake rhythm disorder is common, which is characterized by fragmentation of the sleep-wake rhythm, with multiple sleep and wake episodes throughout the day and night [174]. Observational studies have demonstrated extremely fragmented sleep among nursing home patients with dementia, where patients rarely spent one full hour asleep or awake [175, 176]. One recent meta-analysis reported that 70% of nursing home patients with dementia had disrupted sleep as measured by actigraphy [4]. Different dementia

subtypes are associated with specific underlying neuropathology and consequently different patterns of sleep disturbances may occur [177].

Subtypes of dementia and sleep

In Alzheimer's disease, sleep and circadian disturbances often debut early in the disease, even prior to the onset of cognitive symptoms, and may contribute to the pathogenesis of Alzheimer's disease [178]. Alzheimer's disease is characterized by severely disturbed sleep at night and excessive napping during the day [7, 179–181]. The neurodegeneration in Alzheimer's disease includes the SCN, and as a consequence, there is a general disturbance of all circadian rhythms [182]. The daytime EEG pattern is characterized by more slow-wave activity compared to older people without dementia [183], and the nocturnal EEG pattern by less SWS [183]. Around 25% of people with mild to moderate Alzheimer's disease and 50% of people in moderate to severe stages suffer from disrupted sleep [183, 184].

In vascular dementia, the frequency of disrupted sleep has been shown to be two times the frequency in Alzheimer's disease [7]. Particularly, vascular dementia is associated with a high frequency of sleep disordered [7]. Sleep disturbances are also more prevalent in people with Lewy-Body dementia, compared to Alzheimer's disease, with more movement disorders and daytime sleepiness [185, 186]. Up to 80% suffer from REM sleep behaviour disorder, where the absence of muscle atonia, which normally accompanies REM sleep, results in vocalization and motor activity while dreaming [187]. In people with frontotemporal dementia, one study found a fragmented sleep pattern that varied considerably across days, but with a general increase in activity during the night and lower activity during the morning compared to healthy controls [188]. Compared to Alzheimer's disease, patients with frontotemporal dementia develop sleep disturbances even earlier in the course of the disease [189]. Sleep problems are highly prevalent in people with Parkinson's disease, with one study showing that 98% experienced sleep problems [190], manifested as a wide range of sleep disturbances [191]. Factors such as coughing, cold/heat sensations, and pain, which are more common in PD, may contribute to the disturbed sleep [192].

Other factors contributing to disrupted sleep in the nursing home

Importantly, the aetiology of sleep disturbances among nursing home patients is multifactorial and a range of different factors contribute to disrupted sleep beyond dementia [193], such as medical conditions, pain [194, 195], and psychiatric conditions [144]. Further, multimorbidity is often accompanied by taking multiple medications, referred to as polypharmacy, which also increase the risk of sleep problems [144]. Polypharmacy is often defined as taking five or more drugs daily [196]. Further, sleep problems may be exacerbated by nursing home routines that are at odds with recommendations for good sleep hygiene. For example, Norwegian studies of nursing homes have found a mean time in bed (bedtime to rise time) of more than 12 hours, not including time in bed during the day [197, 198]. Other examples are little daytime activity [199], noise during the night [200], and diminished light input [14].

Thus, the risk of developing sleep disturbances is high among nursing home patients, due to dementia, multimorbidity, polypharmacy, and poor sleep hygiene [193] (summarized in Figure 1).

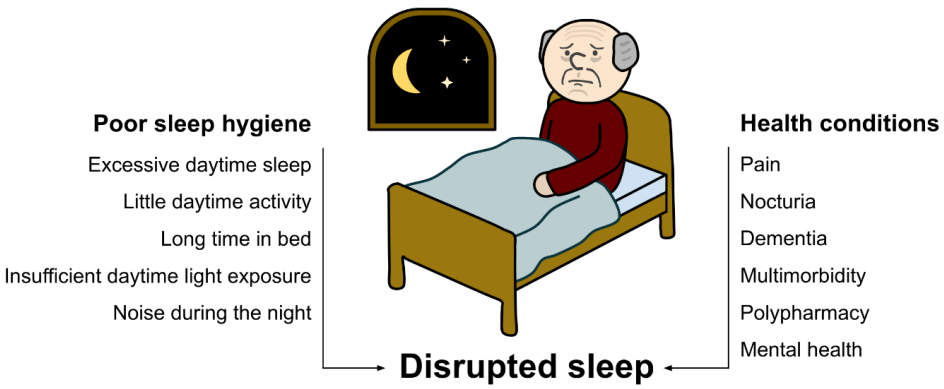

Figure 1: A schematic overview of factors that may contribute to sleep disturbances in nursing home patients.

Consequences of sleep disturbances

Importantly, disrupted sleep in people with dementia add to the impairment caused by the underlying neuropathology, such as reduced memory and concentration, slowed

response time, and increased risk of falls [201]. In severe dementia, the consequences of poor sleep, such as impaired cognitive function, agitation, and depressive symptoms, may be interpreted as part of the dementia [122], but are more prevalent among those with sleep disturbances compared to those without [6–10, 169, 202]. A study by Anderson and colleagues found that older people with abnormal sleep-wake cycles had over 3 times the risk of death over a two-year period, compared to elderly with a normal sleep-wake cycle [8].

In the community, sleep disruption causes significant distress for the caregiver [203], and is an important cause of institutionalization [204]. In the nursing home context, sleep disturbances are disruptive for the staff [205]. For example, one study found that patients were more likely to be agitated when awakening during the night than during the day [206]. In a qualitative study, nursing home staff described patients getting up at night, moving around the common areas and into other residents' rooms [207]. Patients may even attempt to leave the nursing home during the night, and make noise that disturb other patients. Further, the nursing home staff described how poor nocturnal sleep caused the patients to be more agitated the following day. The staff experienced it as difficult to care for patients with sleep disturbances, particularly if they woke up other residents [207].

1.5.2 Light conditions in nursing homes

The lowered sensitivity to light in old age and dementia suggests that they need a strong light input during the day to stimulate the circadian system and increase alertness. Unfortunately, field studies in nursing homes and in the homes of people with dementia have reported low light intensities [14–17, 208]. These studies used different standards for indoor illumination. One standard is the European Lighting Standard EN 12464-1 [209], which states that areas used for writing, reading, and similar activities should have an illuminance of 500 lux, measured horizontally on the task surface. This and other standards emphasize visual focus and comfort, but focus less on the non-visual effects of light. De Lepeleire et al. [15] added 55% to the EN 12464-1 standard to account for the decline in light sensitivity associated with increasing age, amounting to an illuminance of 775 lux. In their study, they found that

the percentage of measurements that met this adapted standard varied considerably across nursing homes and across outdoor light conditions (sunny, cloudy, at dusk, and during darkness). When it was sunny outside, 20% to 60% of the measurements made in eight nursing homes met the adjusted standard, while only 13% of the measurements met the adjusted standard during darkness. These findings hints that during winter in high-latitude countries such as Norway, with few hours of daylight, indoor light availability is poor.

Sinoo et al. [16] measured light levels in 59 common rooms and corridors. They found that 65-96% of the measurements were below the chosen 750 lux reference, varying across nursing homes, while the median CCT values varied from 3,300-4,500 K. Further, even close to the window, 70% of measurements fell below 750 lux, while 100% of the measurements fell below this threshold at the back of the rooms. Similar findings have been reported by Konis et al. [17].

We conducted a field study measuring the light levels in dementia unit common rooms in Bergen, Norway [210]. During the winter, measurements at midday did not significantly differ from measurements made after dark. The daytime illuminance during winter had a median of 125 lux (range 63-185), when measured in the middle of the room, vertically at 1,2 m above the floor and facing away from the windows. Facing the windows, the median value was 176 lux (range 49-507).

Some early studies continuously measured light exposure among nursing home patients using actigraphs with a light sensor. Ancoli-Israel et al. [18] reported that nursing home patients with severe dementia spent less time in >1,000 lux and had a lower mean lux exposure during the day compared to those with mild and moderate dementia. Forty-seven percent of the patients with severe dementia spent no time in illuminations above 1,000 lux. Importantly, this was also the case for 20% of those with mild to moderate dementia. Shochat et al. [14] continuously measured light exposure and activity in 77 nursing home patients (96% had dementia), and found a mean daytime light exposure of 485 lux, and a median light exposure of 52 lux. The participants spent a median of 10 minutes in light of above 1,000 lux and a median of

2 minutes in more than 2,000 lux. Seventeen percent of the participants were never exposed to light levels of more than 1,000 lux across the three days of measurement. They also found that higher light exposure was associated with fewer night-time awakenings. Mishima et al. [211] reported diminished nocturnal melatonin secretion and a low amplitude of the melatonin rhythm among those with low levels of light exposure. In home-dwelling seniors with dementia, Figueiro and colleagues [212] found lower light exposure and more circadian disruption during the winter months, compared to the summer months.

These findings suggest that insufficient light exposure may represent a factor that exacerbates sleep problems in nursing home patients. Thus, reintroducing a strong light input during the day, by means of BLT, may ameliorate sleep problems in this population.

1.6 Treatment of sleep problems in nursing home patients and people with dementia

Sleep problems among nursing home patients are frequently treated by pharmacological means, using psychotropic drugs such as benzodiazepines, atypical antipsychotics, z-hypnotics, sedating antidepressants, melatonin, and antihistamines [11, 213–215]. There is generally a lack of evidence regarding the effect of pharmacological sleep aids in people with dementia [214, 216]. The evidence for a beneficial effect of exogenous melatonin on sleep in Alzheimer's disease patients is equivocal, but no adverse effects have been reported [11, 214]. There is limited evidence for the effectiveness of hypnotics on sleep in people with Alzheimer's disease [11], and hypnotics and sedatives are associated with the highest increase in fall risk, where the risk increase with higher dosages and in combination with other psychotropics [12]. Further, antidepressants may cause nausea, drowsiness, and sedation [217], while antipsychotics and atypical antipsychotics are associated with severe cardiac side effects [11] and an increased risk of mortality [218]. Patients may already use many of these medications when they are admitted to the nursing home, and discontinuing them may be challenging.

Considering the severe side effects associated with pharmacological treatment of sleep disturbances in dementia, the evaluation and implementation of non-pharmacological interventions should be prioritized in this population. A range of non-pharmacological treatments for sleep problems among nursing home patients exist [219, 219], including interventions such as individualized social activities [220] and physical resistance strength training [221]. Although such treatments have shown some positive results in terms of improved sleep [222], they require a high level of staff involvement and can be challenging in terms of implementation [219]. Thus, identifying interventions that are feasible and effective in the nursing home context, without the side-effects associated with pharmacological treatment, is of great interest. Importantly, the essential role of light exposure in regulating sleep may represent an opportunity in this regard.

1.6.1 Bright ligh treatment (BLT) for treating sleep problems in dementia

BLT may be defined as an enhanced indoor electrical light scheme aimed at impacting NIF responses including mood, behaviour, sleep, and/or circadian rhythmicity. BLT research may be placed in the broader fielt of "daylight research", encompassing research on the effectiveness of daylight and electrical light in promoting general health and quality of life [78]. Bright light was initially used to treat Seasonal Affective Disorder (SAD), where lengthening the photoperiod by means of daily exposure to 2,500 lux for three hours at dusk and at dawn for two weeks, had an antidepressant effect on patients [223]. Subsequent research has refined the treatment and BLT is today the first-line therapy for SAD [224]. The antidepressant effect is thought to be caused by stabilizing the circadian rhythm and/or by increasing synaptic serotonin [225]. Several studies have evaluated the effect of BLT on depression and agitation in dementia, with mixed results [226]. Due to the impact of light on sleep and wakefulness, BLT has also been used to treating sleep disturbances, including sleep disturbances in people with dementia [226, 227]. The following section will provide an overview of this research.

There is no commonly accepted gold standard for the timing, duration, spectral composition, illumination, or method of delivery of BLT for treating sleep and/or BPSD in people with dementia. The standard practice in treating SAD has been to provide daily light exposure of between 2,500 and 10,000 lux white light (around 4,000 K) for 30 minutes (when using 10,000 lux) and two hours (when using 2,500 lux), delivered using light boxes [228]. Light boxes are devices that deliver light of high illumination, often polychromatic white light.

Similar approaches have been used with people with dementia, and based on the latest systematic search, 11 studies evaluating the effect of BLT on sleep and circadian rhythmicity in people with dementia using light boxes were identified [19, 20, 198, 229–236]. Six of these were Randomized Controlled Trials (RCTs) [19, 20, 229–231, 233], and are summarized in Table 2. RCTs are considered the gold standard for evaluating the effect of interventions [237].

Bright light treatment using light boxes

Ancoli-Israel et al. [229] completed a RCT including 77 nursing home patients with dementia. The study compared two BLT conditions, either two hours of 2,500 lux white light in the morning (09:30-11:30) or in the evening (17:30-19:30), with a dim light control condition. The treatment lasted for 10 days. They found no effects on sleep during the night or activity during the day, as measured by actigraphy. In a subsequent study using the same protocol but only including people with Alzheimer's disease, the same researchers found an increase in the length of nocturnal sleep bouts from baseline to follow-up in the two BLT groups, but not in the dim light group [20]. A RCT by Burns and colleagues, including 48 nursing home patients, delivered two hours of 10,000 lux from 10:00-12:00 for two weeks [230]. That study found no changes in sleep duration, either observed sleep or sleep measured by actigraphy. In 67 home-dwelling participants with dementia, McCurry et al. [19] found a decrease in total wake time at night in the treatment group following two months of evening BLT (2,500 lux for 1 hour), compared to a control group. Several smaller pre-post studies (comparing the same patients before and after treatment, also called open clinical trials) have reported improved sleep following BLT using light boxes [198, 231–234,

236]. One Norwegian study found improvements on several sleep outcomes measured by actigraphy from baseline to follow-up after two weeks of 6,000-8,000 lux in the morning [238]. The improvement in sleep efficiency lasted for four weeks after treatment termination and the decrease in sleep onset latency lasted for 12 weeks. Thus, there are some indications that BLT using light boxes may cause improvements in sleep among people with dementia, as shown in RCTs [19, 20] and pre-post studies [198, 231–234, 236], some even long-lasting [238].

Bright light treatment using ambient light

Using light boxes may however not be feasible in the context of dementia. Dementia patients may not adhere to the treatment protocol unless they are reminded or motivated to stay in front of the light box and face the light. As a consequence, studies using light boxes have had staff accompanying the patients during BLT to ensure adherence [198, 230–233], which is time consuming for the staff. Additionally, it is possible that the increased staff presence (i.e., increased social contact) may have impacted the results. Therefore, BLT using ambient ceiling-mounted light, where the light condition in entire areas or rooms can be manipulated, may represent a more feasible treatment option, which also may increase the internal validity of studies. This approach has been used in studied of shift work [239, 240]. Ambient room illumination allows for people to be exposed to bright light while engaging in their normal activities. This approach has been increasingly utilized in studies on the effect of BLT in dementia, enabled by a rapid development of light emitting diode (LED) technology [241]. These advances have also allowed for the manipulation of the spectral composition of light [242]. Thus, several of the more recent studies have used light with high CCT and a more modest lux compared to light boxes, and with low CCT and illumination during the evening.

Using a systematic search, twelve studies that used ambient light were identified [106, 243–253], where three were RCTs [244, 247, 252] (Table 2). In the randomized cross-over study (all patients receive both the intervention and the control) by Sloane et al. [244], including 17 home-dwelling people with dementia, they evaluated the effect of six weeks of ambient light of 13,000 K and 400 lux on sleep. The treatment was

compared to a low-CCT placebo condition of 2,700 K and 400 lux. In addition to the ambient light, participants had a light box delivering monochromatic blue light of 470 nm in the high-CCT condition and red light of 638nm in the low-CCT condition. The two conditions were separated by a four-week wash-out. Sleep efficiency measured using a sleep scale improved during treatment compared to standard light, but not compared to the control low-CCT condition. There was no effect on daytime sleepiness or on sleep or circadian rhythmicity measured by actigraphy. In another randomized cross-over study, Figueiro et al. [252] evaluated the effect of a tailored light intervention in 47 nursing home patients with dementia. The intervention comprised floor luminaires, light boxes, and light tables, each providing between 350-750 lux and 5,000-7,000 K, all day (until 18:00) for four weeks. The placebo condition administered low illumination and CCT using the same equipment. Proxy-rated sleep, and also intradaily variability (circadian rhythm fragmentation) improved from baseline to follow-up in the intervention condition compared to the placebo condition.

Table 2: An overview of RCTs assessing the effect of bright light treatment in dementia

Study	Population	Intervention	Short summary of results (sleep and/or circadian rhythm)
Ancoli-Israel et al. [229]	77 NH patients, mixed dementias	10 days, 2 hours in the morning (09:30-11:30) or evening (17:30-19:30). Light box delivering 2,500 lux. Control dim red light.	No significant change in sleep or activity parameters (actigraphy). Within-group increase in mean activity level (mesor) and a delay of acrophase in the morning BLT group. Amplitude ns.
Ancoli-Israel et al. [20]	92 NH patients with AD	10 days, 2 hours in the morning (09:30-11:30) or evening (17:30-19:30). Light box delivering 2,500 lux. Control dim red light.	There was a within-group increase in the duration of the longest sleep bouts, as measured by actigraphy. Mean wake bout length decreased from end of treatment to post treatment in the evening treatment group. Other actigraphy sleep outcomes ns. Rhythmicity improved in the evening treatment group. Other circadian actigraphy outcomes ns.

Burns et al. [230]	48 NH patients, mixed dementias	Two weeks, 2 hours in the morning (10:00-12:00). Light box delivering 10,000 lux. Control dim light.	No effect on sleep duration measured by actigraphs or by nurses. At follow up, the BLT group had lower mean activity level compared to the control group.
Figueiro et al.* [252]	46 NH patients, Alzheimer's disease	Four weeks, 10-12 hours (from between 06:00-08:00 to 18:00). Floot luminaires (6,000 lux and 5,000 K or 550 lux and 7,000 K), light box (350 lux and 6,000 K) and light table (750 lux and 5,000 K)	Proxy-rated sleep (PSQI) improved and intradaily variability (actigraphy) reduced (improved) from baseline to follow-up compared to the control condition. Other actigraphy outcomes ns.
Graf et al. [254]	23 NH patients, mixed dementias	10 days, 2 hours in the afternoon/evening (17:00-19:00). Light box delivering 3,000 lux. Control dim light.	The intervention induced a phase delay of nadir of the axillary body temperature.
Lyketsos et al. [231]*	15 NH patients, mixed dementias	Four weeks, 1 hour in the morning (unknown time). Light box delivering 10,000 lux. Control low-frequency blinking light.	There was a within-group increase in sleep time at night. Between-groups ns.
McCurry et al. [19]	67 home-dwelling seniors with AD.	Two months, 1 hour before bedtime. Light box delivering 2,500 lux. Control care as usual.	Total wake time at night decreased at follow-up compared to the control group. Proxy-rated sleep (SDI) ns.
Mishima et al., [233]*	22 NH patients with AD and VD.	Two weeks, 2 hours in the morning (09:00-11:00). A set-up of light bulbs around the patients face delivering 5,000-8,000 lux. Control dim light.	There was a decrease in night-time activity in the VD group during BLT compared to dim light. Total activity and daytime activity ns. AD patients ns.
Sloane et al. [244]*	17 home-dwelling seniors,	Six weeks, all-day light (wake-up until 18:00).	Proxy-rated sleep sleep efficiency (PSQI) improved after the intervention compared to standard light, but not

	mixed dementias	Ambient light delivering 13,000 K and 400 lux, and also a LED light box delivering blue light. Control 2,700 K and 400 lux (ambient), and a light box delivering red light.	compared to placebo. There was no effect on sleep or circadian rhythmicity in the BLT group compared to the control group.
Van Hoof et al. [247]*	22 NH patients, mixed dementias	4 days, all-day light (08:00-18:00). Ceiling-mounted above a table delivering a maximum of 12,500 K and 400-500 lux. Control light of 2,700 K and 400-500 lux.	No change in tympanic temperature/circadian rhythm.

Note: For a more detailed overview of the populations, interventions, study procedures, and results, see Paper 1.
AD= Alzheimer's Disease, K= Kelvin, LED= Light Emitting Diode, NH= Nursing home, ns= not significant, PSQI= Pittsburgh Sleep Quality Index, RCT= Randomized Controlled Trial, SDI= Sleep Disorder Inventory, VD= Vascular Dementia.
*RCT with cross-over

Three meta-analyses have summarized the results of BLT studies including people with dementia [226, 227]. One Cochrane meta-analysis from 2014 including 13 RCTs concluded that "there is insufficient evidence to justify the use of bright light therapy in dementia" [226, p. 2]. Van Maanen et al. [227] conducted a meta-analysis of BLT for a range of sleep disorders, of which eleven RCTs and open clinical trials studied people with dementia. They reported a significant positive effect of BLT on sleep problems in people with dementia, specifically for objectively measured sleep onset latency, total sleep time, time in bed, sleep efficiency, and for sleep quality evaluated by questionnaires. Circadian outcomes (melatonin or core body temperature), bedtime and wake-time, and sleepiness/alertness had been examined by too few studies to do analyses on these outcomes. Non-significant effects were found for wake-after-sleep-onset and early morning awakenings [227]. Chiu et al. [255] included six RCTs assessing the effect on sleep and found an effect on total sleep time at night. Importanly, these meta-analyses also included studies using daylight and dawn-dusk simulation, in addition to electric light.

In summary, previous studies evaluating the effect of BLT on sleep in dementia populations show promising, albeit mixed effects. Importantly, previous studies vary in terms of intervention strategies, using different methods of delivering light (light box, ambient light), light values (lux, CCT), duration of daily exposure, and duration of treatment. Few RCTs have been completed, and most studies have few participants and short treatment durations (days or weeks). In general, open clinical trials tend to find favourable results, while controlled studies (comparing the intervention group to a control group not receiving the intervention) are less consistent. Thus, there is a need for more high-quality studies, i.e., RCTs including more participants and with a longer duration of treatment.

1.7 Challenges in studying the effect of light in nursing home patients with dementia

Studying the effect of BLT in nursing home patients with dementia entails some specific challenges.

1.7.1 Measuring light

Illumination levels vary significantly depending on the direction of measurement [246, 247, 256]. When measuring light received by a ceiling-mounted light source, the highest light values are obtained when measuring light horizontally, e.g., the amount of light hitting a horizontal surface. Another approach is to measure light positioning the photometer vertically, which more closely reflects the amount of light entering the eye [91, 256] (Figure 2).

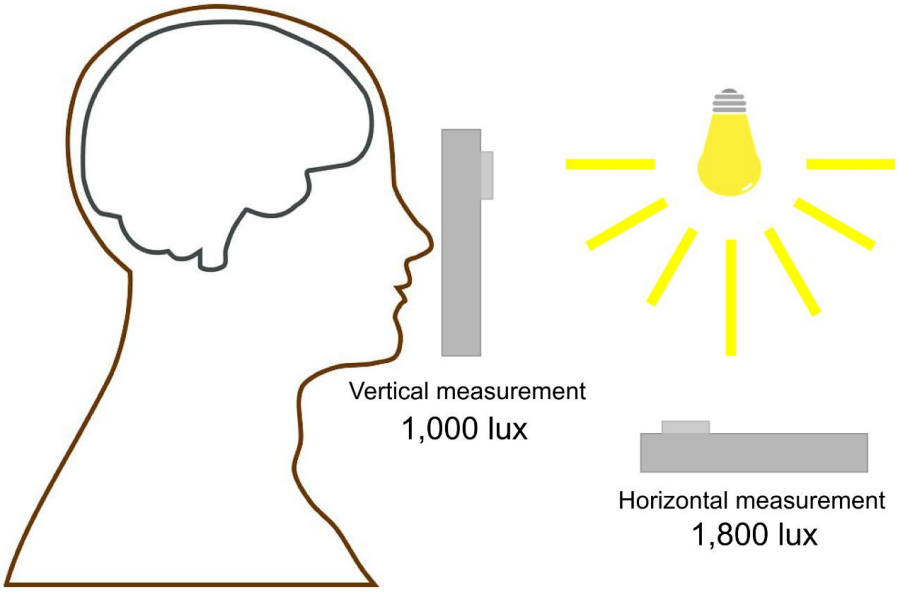

Figure 2: A schematic figure of vertical vs horizontal measurements using a photometer. Approximate lux values based on van Hoof et al. [246].

The rapid technological and theoretical developments of the field of BLT research means that no established standard for measuring and reporting light characteristics are consistently used by researchers. Previous studies vary in terms of the level of detail regarding light measurement, complicating the interpretation and comparison of results.

1.7.2 Estimating light exposure

Securing adherence to treatment is challenging when including people with dementia. When using light boxes, staff have to motivate patients to sit in front of the box, preventing them from wandering off or turning away from the light source. Using ceiling-mounted light, and thus providing BLT in entire rooms, reduces the need for supervision. However, measuring the exact amount of light received by each patient is challenging. Some studies have estimated light exposure based on data from wrist-worn devices [e.g., 249, 257]. While such devices may provide continuous data on light exposure, light levels at the wrist may deviate significantly from light exposure at eye level [258]. Also, the device may be covered by clothing or blankets during the day. Some studies have used a light meter (Daysimeter) worn as a pendant [248, 252,

253]. This also requires that the device is not covered by clothes or blanckets, and may not be tolerated by people with severe dementia. Other researchers have estimated light exposure by averaging light measurements at eye level made in intervals during treatment [246, 247]. While this approach may produce more accurate estimates of actual light exposure, it requires the presence of research staff to do the measurements and it may represent a disturbance in the nursing home environment. Another approach is to measure light at predetermined locations frequently occupied by residents. While this represents a systematic way of measuring light levels, a range of factors may impact the exact amount of light each participant is exposed to, such as the time spent in the BLT room, head position, and if their eyes are closed or open. The latter is a problem regardless of how light exposure is measured.

1.7.3 Assessing sleep in the nursing home and in people with dementia

Although disrupted sleep is common among nursing home patients, no optimal tool to assess sleep in this population exists to date. Measuring sleep in people with dementia by PSG is often not feasible, as it entails multiple electrodes and wires, which may not be tolerated by people with dementia [11, 259]. Further, it may be difficult to distinguish between wake and sleep, as the EEG pattern during wakefulness has been observed to contain slow EEG activity in this population [260, 261]. Another objective sleep measurement is activity-monitors, such as actigraphs. Actigraphs are small accelerometers, commonly worn on the wrist, that measure activity over days or weeks [20]. These are frequently used in dementia populations as they are non-intrusive and generally well tolerated. Actigraphs have an agreement rate with PSG of 72-97% (i.e., the percentage of observations scored identically by PSG and actigrapy), with a sensitivity of 87-99% (accurate detection of sleep) and a specificity of 28-67% (accurate detection of wake) [262]. Poor wake detection means that actigraphy may overestimate sleep. Further, the accuracy of actigraphy has been shown to decline with lower sleep efficiencies [263].

Sleep diaries and self-report questionnaires are important clinical tools in sleep research, however, they may be unfeasible and unreliable in the context of dementia.

People with dementia, particularly those with severe dementia, have significantly impaired abilities to communicate and may not remember how they slept. Thus, proxy-rated questionnaires, completed either by a cohabiting relative or by nursing home staff, are widely used in the clinical context [4]. A major challenge with proxy-rated questionnaires is that they might not be sensitive enough to detect sleep problems, especially when the rater does not share bed with the person with dementia. For example, one recent meta-analysis reported a pooled prevalence of sleep disturbances of 70% among institutionalized dementia patients when sleep was measured by actigraphy, while the prevalence was 20% when sleep was assessed using validated questionnaires [4]. Hoekert et al. [264] found that compared to actigraphy, nursing staff overestimated sleep time by an average of 1.5 hours. Blytt et al. [197] found that proxy-raters underreported sleep disturbances using sleep items from two commonly used BPSD assessment scales, as compared to actigraphy. One possible reason for the discrepancy between proxy-rated and actigraphy-assessed sleep, is that nursing home staff may not observe that someone is awake during the night. Conversely, validated questionnaires may provide important clinical information that is not registered by actigraphy, such as snoring or the impact of the disturbances on daytime function, on carers, or other residents [4].

Importantly, few sleep scales have been validated for people with dementia and for the nursing home context specifically [4]. Considering the negative impact of disrupted sleep, identifying a reliable and easy-to-administer sleep scale for the use in the nursing home context would be of great clinical value.

1.7.4 Ethical challenges

Some unique ethical dilemmas and consequences need to be considered in depth when planning to include people with dementia in research. People with dementia may not have the capacity to provide informed consent to participate due to diminished decision-making capacity [134]. Informed consent means that a potential participant provide voluntary consent after being informed about the study and about their right to refuse participation or to withdraw at any time, as stated in the *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* [265].

Assessing decision-making capacity generally involves the assessment of four abilities: i) the ability to communicate a choice of participation, ii) the ability to understand relevant information, iii) the ability to appreciate the medical consequences of their choice, and iv) the ability to reason about choices [266]. A diagnosis of dementia should not, however, necessarily be presumed to indicate a lack of capacity to provide informed consent. Some may retain the capacity to provide informed consent for participation in a study, however, many may not, particularly in the later stages [267]. In order to improve dementia care and prevention, it may in many cases be necessary to include them in clinical trials. The effect of BLT on sleep in healthy adults and older people, for example, may not translate to people with dementia, due to dementia-related neuropathology [171]. When a potential participant is deemed not to have the capacity to provide informed consent, a legal guardian may provide presumed consent to participate on behalf of the patient [265], by asking them to consider what the person in question would have wanted. To respect the autonomy and dignity of the patient, researchers should additionally aim to adapt the information about the study, convey this, and seek consent from the individual with dementia [268]. Interventions that improve medical, behavioural, or psychological symptoms could have a significant impact on the quality of life of nursing home patients and on the burden of care taken on by family and nursing home staff.

1.8 Rationale for this thesis

Based on the evidence, as summarized above, the DEM.LIGHT trial and this thesis were based on the following:

i) Sleep disruption is common among nursing home patients with dementia, and detecting and treating disrupted sleep should be a priority in the nursing home setting.
ii) There is a need for easy-to-administer scales that can reliably identify sleep problems in nursing home patients with dementia.
iii) Light exposure during the day is inherently important for optimal human functioning, including sleep-wake behaviour.

iv) Most nursing homes provide insufficient light exposure to sustain stable circadian rhythms, promote alertness during the day, and consolidate sleep during the night. Thus, sleep problems seen in dementia are hypothesized to, in part, be caused or exacerbated by the lack of a robust light input during the day.

v) Reintroducing a robust photic zeitgeber during the day by means of ceiling-mounted ambient bright light may improve nocturnal sleep and reduce daytime napping.

2. Aims

The overall aim of this thesis was to investigate whether BLT can improve sleep in nursing home patients with dementia. This entailed: i) an investigation of previous studies of BLT in dementia, highlighting methodological issues in the field (Paper 1), ii) an assessment of the validity of a proxy-rated sleep scale for use in nursing home patients with dementia (Paper 2), and finally, iii) an evaluation of the efficacy of a BLT intervention on sleep in nursing home patients with dementia (Paper 3).

The aim of Paper 1 was to synthesize previous research on BLT in people with dementia in a systematic review of the literature. The aim was to provide a detailed overview of the research field, including non-RCT studies. The paper focused on the differences between studies in terms of population characteristics, intervention strategies (delivery method, timing, duration, light levels), study designs, and outcome measures, and aimed to explore how these differences might have influenced study results.

The aim of Paper 2 was to validate the proxy-rated Sleep Disorder Inventory (SDI), a short-form questionnaire exclusively measuring sleep, against actigraphy.

The aim of Paper 3 was to evaluate the effects of a ceiling-mounted dynamic ambient BLT solution on sleep in nursing home patients with dementia by means of a cluster-randomized placebo-controlled trial, controlling for known confounding variables.

3. Methods

Paper 1 was based on a systematic search of the literature (PROSPERO CRD42017051004). Paper 2 and 3 used data from the DEM.LIGHT trial (*Therapy Light Rooms for Nursing Home Patients with Dementia – Designing Diurnal Conditions for Improved Sleep, Mood, and Behavioural Problems*, ClinicalTrials.gov Identifier: NCT03357328). The trial was approved by the Regional Committee for Medical and Health Research Ethics South East Norway (REC 2016/2246).

As the main study of this thesis was the DEM.LIGHT trial, the following section will present the methods of this trial, followed by the methods specific to each of the papers 1, 2, and 3.

3.1 The DEM.LIGHT trial

3.1.1 Design

Paper 2 and 3 were based on the dataset from the DEM.LIGHT trial, which was a 24-week cluster-randomized placebo-controlled trial. Data were collected at baseline and at follow-up at week 8, 16, and 24. The trial included eight nursing home units that constituted one cluster each.

3.1.2 Participants and setting

The DEM.LIGHT trial took place in Bergen, Norway between September 2017 and April 2018. Bergen municipality has 284,208 inhabitants (1st quarter, 2020, [269]), and the nursing homes are located across the city, suburbs, and more rural areas. In preparation of the study, the principal investigator had meetings with the Department of Health and Care, City of Bergen and the municipal agency for elderly and nursing homes, and presented the DEM.LIGHT trial on several occasions to the managers of the nursing homes in Bergen. The municipal agency provided a list of 14 eligible nursing homes (had a designated dementia unit, did not participate in other trials or quality of care projects), and the managers of these nursing homes were contacted directly by the research team via e-mail. The managers that were interested in participating in the study provided a candidate unit, and the researchers (Eirin Kolberg,

EK and Gunnhild Johnsen Hjetland, GJH) made on-site visits. A short presentation was given to the management, and staff and we assessed whether it was possible to install new light fixtures in the ceiling of the common room. When we had achieved the required number of nursing home units, we did not invite more units. One dementia unit had twice as many patients as the other units, and was excluded. Four units declined to participate, and one unit signalled their interest after we had finished recruitment. The eight recruited units were located in nursing homes in diverse locations (near the city centre or more rural areas) of different sizes (small and large nursing homes), and were located in old and new buildings.

One of the units was included about six months before the study commenced. The intervention was piloted for four weeks and adapted in collaboration with the staff to optimize the intervention strategy. Following this, the LED light sources were programmed to deliver standard light for two months until the study started. In the remaining nursing home units in the intervention group, the LED units were installed during the months prior to baseline data collection. Until the baseline data collection was completed, the light was set to standard light levels of approximately 100 lux (measured vertically in the middle of the room 1,2 m above the floor) and 3,000 K during the day.

When the units were included, we discussed the inclusion and exclusion criteria with the resident physician (see Table 3). The aim of the DEM.LIGHT trial was to assess the effect of BLT in nursing home patients with dementia. Although sleep and circadian rhythmicity were the primary outcomes, important secondary outcomes were BPSD and function. Therefore, we used wide inclusion criteria, where participants had to have *either* disrupted sleep, circadian disturbances, clinically significant BPSD, or severely reduced activities of daily living (ADL).

Table 3: The inclusion and exclusion criteria of the DEM.LIGHT trial

Participants were eligible if they:	Patients were not included in the study if they:
- were ≥60 years and in long-term care (>4 weeks) - had dementia in accordance with DSM-5 - had either sleep/circadian rhythm disturbances, BPSD as identified by NPI-NH, or severely reduced ADL function - provided written informed consent if the participant had capacity or, if not, a written proxy informed consent from a legally authorized representative	- were blind or might otherwise not benefit from light - took part in another trial - had a condition contra-indicated to the intervention - had an advanced, severe medical disease/disorder and/or expected survival less of than 6 months or other aspects that could interfere with participation - were psychotic or had a severe mental disorder

ADL=Activities of Daily Living, BPSD=Behavioural and Psychological Symptoms of Dementia, DSM-5=Diagnostic and Statistical Manual of Mental Disorders-5, NPI-NH=Neuropsychiatric Inventory-Nursing Home Version.

GJH and EK performed the data collection while in continuous contact with the research group.

3.1.3 The intervention

The intervention consisted of a light-emitting diode (LED) ceiling-mounted bright light solution that was installed in the common rooms of four intervention units. The light setup was delivered by Glamox, using a number of square LED units (Glamox, 1 x C95 48 CCT 6,500 K MP 47 W / 4,702 lm). Glamox engineers calculated the number of LED-units needed to provide the target light levels in each common room, accounting for the number and direction of windows. The LED units were programmed to provide 400 lux and 3,000 K (measured vertically) from 07:00-10:00, 1,000 lux and 6,000 K from 10:00 to 15:00, 400 lux and 3,000 K from 15:00-18:00, and 100 lux and 2,500 K from 18:00-21:00 (Figure 3). Light values gradually changed across 30 minutes. Figure 4 illustrates the contrast between standard light levels and light of 6,000 K.

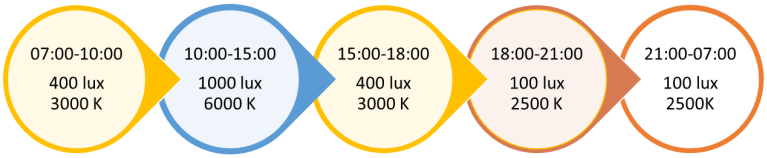

Figure 3: An illustration of the intervention light sequence. The light changed gradually across 30 minutes between each condition. The staff at each unit could choose if they wanted to maintain the light at 100 lux and 2,500 K through the night or if they wanted it to turn off.

Figure 4: An illustration of the contrast between the spectral composition of standard light (left, 3,000 K) and the spectral composition used in the intervention (right, 6,000 K). The photos show one of the units in the intervention group. Source: Photos provided by Glamox, reprinted with permission.

Following the installation of the LED units and activation of the light sequence, we measured light levels in all eight units, using the GL Spectis 1.0 T Flicker spectrometer (GL Optic). Measurements were made at predetermined locations vertically 1,2 m above the floor. Illumination, CCT, and equivalent melanopic illuminance were calculated using the Lucas et al. 2014 toolbox [90]. Unfortunately, the maximum light level was too low in one of the units (mean 722 lux, range 641-796; 5,641 K, range 5,478-5,723), however, still substantially higher than the control units (see Table S1 in Paper 3). The LED units were installed prior to the start of the

study and light levels were maintained at standard levels so that staff and participants could get used to the new light fittings. The intervention light sequence was switched on immediately following the baseline data collection. The control panel for the light was locked with a personal identification number only known to the researchers. The contact information of the researchers (GJH and EK) was provided in case of any problems with the light setup.

3.1.4 The placebo condition

The placebo control condition was created by replacing the light sources of the existing light fittings in all control common rooms with conventional light sources of 3,000 K (CFL AURA UNIQUE-D/E LL 18W/830 G241-2 in three common rooms and CFL AURA UNIQUE-L LL 18W/830 2G11 in one). Light sources were replaced immediately following the baseline data collection.

3.1.5 Estimating time spent in the common room

At week 8, 16, and 24, we estimated when, and how long, each participant had been present in the common room (where the intervention/placebo was installed) during the preceding eight weeks. This was measured by means of a short questionnaire completed by the nursing staff. They were asked to estimate the approximate time the patient had spent in the living room in different epochs of the day during the preceding eight weeks. The epochs corresponded to the light cycle, so that the day was split into time epochs of 07:00-10:00, 10:00-15:00, 15:00-18:00, and "after 18:00". The staff provided a time estimate for each epoch in hours and minutes. They were also instructed to report the number of days when the patient was not present in the common room, and that these days should not be included in the above-mentioned estimate.

3.1.6 Assessments used in DEM.LIGHT

The primary outcomes were sleep and circadian rhythmicity measured by actigraphy and a proxy-rated sleep scale. The secondary outcomes were neuropsychiatric symptoms, activities of daily living, quality of life, pain, cognitive impairment, clinical impression of change, and care demand. The patients received a thorough medical and

psychological examination and testing. Not all measurements were used in this thesis. See Table 4 for a complete overview of the assessment tools used in the DEM.LIGHT trial.

Table 4: Assessment tools used in the DEM.LIGHT trial and how they are used in paper 2 and 3.

Assessment tool	What the tool measures	Characteristics	How the instrument was used in this thesis
		Sleep assessments	
Actigraphy†: SE	The percentage of time spent asleep in the rest interval	The percentage of time spent asleep in the rest interval from 22:00 to 06:00. Mean across a minimum of five days.	Paper 2: Outcome. Paper 3: Outcome and baseline correlation.
Actigraphy†: WASO	Time spent awake after sleep onset	The time (in minutes) spent awake after sleep onset. Mean across a minimum of five days.	Paper 2: Outcome. Paper 3: Outcome and correlation analysis at baseline.
Actigraphy†: TST in the rest interval	Sleep duration during the night	The time (in minutes) spent asleep in the rest interval. Mean across a minimum of five days.	Paper 2: Outcome. Paper 3: Outcome.
Actigraphy†: TST 24h	The amount of sleep across 24 hours	The time (in minutes) spent asleep across 24 hours. Mean across a minimum of five days.	Paper 2: Not used. Paper 3: Outcome and correlation analysis at baseline.
Actigraphy†: TST in the daytime interval	The amount of sleep during the day	The time (in minutes) spent asleep during the day interval from 10:00 to 18:00. Mean across a minimum of five days.	Paper 2: Not used. Paper 3: Outcome and correlation analysis at baseline.
Actigraphy†: Fragmentation index	A measure of sleep fragmentation across 24 hours	A higher number represents a more severe fragmentation of the sleep-wake rhythm. Mean across a minimum of five days.	Paper 2: Outcome. Paper 3: Not used.
SDI*† [203]	Sleep-wake behaviour	Assesses seven sleep-related behaviours observed the preceding two weeks. A higher score (range 0-84) indicates poorer sleep.	Paper 2: Outcome. Paper 3: Outcome and correlation analysis at baseline.
		Other assessments	

ADL*† [270]	Activities of daily living	Assesses the patient's ability to perform six activities. A higher score (range 0-30) indicate poorer function.	Paper 2: Not used. Paper 3: Patient characteristic at baseline and a potential covariate.
CCI*† [271]	Comorbid burden	Seventeen comorbidities are weighted with a score from 1-6. A higher score indicates a higher comorbid burden.	Paper 2: Patient characteristic at baseline. Paper 3: Patient characteristic at baseline, correlation analysis at baseline, and a potential covariate.
CMAI*† [272]	Agitation	Assesses 29 behaviours. A higher score (range 29-203) indicate more agitation.	Outcome in the DEM.LIGHT trial not used in this thesis.
CSDD*† [273, 274]	Depression	Assesses 19 symptoms of depression. A higher score (range 0-38) indicate more depressive symptoms.	Outcome in the DEM.LIGHT trial not used in this thesis.
FAST*† [275]	Severity of dementia	Assesses the severity of dementia, rated in seven stages.	Paper 2: Patient characteristic at baseline. Paper 3: Patient characteristic at baseline, correlation analysis at baseline, and a potential covariate.
MMSE† [276]	Cognitive impairment	Assesses the level of cognitive impairment using 30 items. A lower score (range 0-30) indicates more severe impairment.	Paper 2: Patient characteristic at baseline. Paper 3: Patient characteristic at baseline, correlation analysis at baseline, and a potential covariate.
MOBID-2*† [277, 278]	Pain in people with severe dementia	Pain is scored according to the patient's pain behaviour during standardized, guided movements and according to observed pain behaviours prior to assessment	Outcome in the DEM.LIGHT trial not used in this thesis.
NPI-NH*† [279, 280]	BPSD	Assesses twelve symptoms observed in the preceding four weeks. A higher score (range 0-144) indicates more severe symptoms.	Paper 2: Patient characteristic at baseline. Sleep item used as outcome. Paper 3: Patient characteristic at baseline.

Telemetric core-temperature monitoring [281]	Core body temperature	A measure of circadian phase using core body temperature across 24 hours. An ingestible capsule measures temperature in 1-minute intervals.	Outcome in the DEM.LIGHT trial not used in this thesis.
QUALID*† [282]	Quality of life in late-stage dementia	Assesses 11 observable behaviours and emotional expressions. A lower score (range 11-55) indicate a higher quality of life.	Outcome in the DEM.LIGHT trial not used in this thesis.

*Proxy rated instrument, † Validated for use in people with dementia.
ADL= Activities of daily living, CCI= Charlson Comorbidity Index, CMAI= Cohen-Mansfield Agitation Inventory, CSDD= Cornell Scale of Depression in Dementia, FAST= Functional Assessment Staging, MMSE= Mini Mental Status Examination, MOBID-2= Mobilization-Observation-Behaviour-Intensity-Dementia-2, NPI-NH= Neuropsychiatric Inventory- Nursing Home version, QUALID= Quality of Life in late-Stage Dementia Scale, SDI= Sleep Disorder Inventory, SE= sleep efficiency, TST= total sleep time, WASO= wake after sleep onset.

In the following, the assessment tools used in this thesis are described.

Sleep outcomes

Actigraphy

The *Actiwatch II (Philips Respironics)* was used for actigraphy measurement. In accordance with previous studies in this population [197, 283, 284], the actigraphs were placed on the dominant wrist. The staff were informed about the purpose of the actigraphs so that they could inform the patient if they had any questions while we were not present. The staff were instructed to help patients remove the actigraph if necessary (if a patient gave any sign of wanting to remove the device).

The epoch length was set to 1 minute, and each epoch was scored as sleep or wake by the *Actiware 6.0.9 (Philips Respironics)* software. The threshold for wakefulness was set to medium. Epochs were scored based on the activity count of the epoch in question, in addition to the two preceding and to following epochs (Figure 5). The epoch was scored as sleep if the sum of the activity counts of these five epochs (weighted by .04 for the most distant epochs and .20 for the closest epochs) was at or below a threshold (medium= 40).

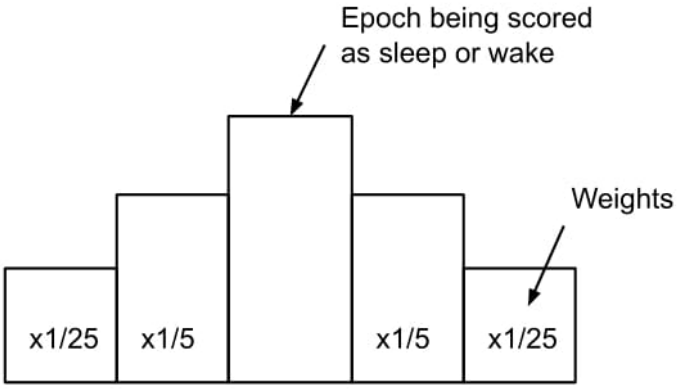

Figure 5: An epoch is scored as sleep if the sum of the activity counts are at or below the threshold. The activity counts of the epochs preceding and following the epoch is weighted by 1/25 or 1/5. Figure adapted from the Actiware user manual.

Actiware requires the definition of a rest interval from where to estimate periods of sleep. In accordance with previous studies, the rest interval was set from 22:00 to 06:00 [9, 18, 229, 284]. Relevant only to Paper 3, a fixed interval was also set for daytime, from 10:00 to 18:00, in line with another study on dementia [180]. Sleep intervals were automatically set by Actiware within the rest interval. After the start of each rest interval, the start of each sleep interval (sleep onset) was set to the first epoch of ten subsequent epochs (1 epoch=1 minute) where all except one epoch were scored as sleep. Before the end of each rest interval, the end of each sleep interval was set to the last epoch of ten subsequent epochs where all except one epoch were scored as sleep.

The participants wore the actigraphs for seven days, with five nights as a required minimum to be included in the analyses. All actigraphy outcomes represent means across a minimum of five nights. In Paper 2, we used actigraphy as the reference against which a sleep scale was validated. In Paper 3, actigraphy was used as a primary outcome.

Sleep Disorder Inventory (SDI)

In addition to actigraphy, sleep was assessed by the staff. Because people with cognitive impairment may be unable to provide estimates of their own sleep or may provide unreliable estimates [181], nursing home staff served as proxy-raters,

assessing the patients' sleep using the SDI [203]. Few proxy-rater tools for people with dementia exist, and the SDI was chosen because it is relatively short and straightforward. The SDI was developed and validated for the use in people with dementia living at home, using in-living relatives as proxy-raters [203]. The scale was adapted to the nursing home context and translated to Norwegian for the purpose of the DEM.LIGHT trial.

The SDI evaluates sleep-related behaviour during the two weeks preceding test administration [203]. The SDI is based on the sleep item of the Neuropsychiatric Inventory (NPI) [279], which evaluates the frequency, severity, and caregiver distress of several BPSDs, including disturbed sleep. Each item of the NPI is elaborated with subquestions, and the SDI was developed by assigning a frequency (0-4), severity (0-3), and caregiver distress (0-5) score to each subquestion of the NPI sleep item [203].

In Paper 2, the SDI was validated against actigraphy. In Paper 3, the SDI was used as a primary outcome.

Other outcomes

Activities of Daily Living (ADL)

To assess ADL, the instrument by Lawton and Brody was used [270]. This scale includes six items. The total score ranges from 0-30, where a lower value indicates better functioning and independence. In Paper 3, the ADL was used as a baseline patient characteristic and as a potential covariate.

Charlson Comorbidity Index (CCI)

The CCI [271] is a measure of comorbid burden, where 17 comorbidities are weighted with a score ranging from 1-6. A higher score indicates a higher risk of mortality and a total score of ≥5 has been associated with a 1-year mortality of 85% (63). The CCI was used as a baseline patient characteristic in Paper 2 and 3, and also as a potential covariate in Paper 3.

Functional Assessment Staging (FAST)

The FAST [275] is a measure of the severity of dementia, rated in seven stages. Patients receiving a score of 1-2 are considered to have normal cognition, 3 indicates

mild dementia, 4-5 moderate dementia, and 6-7 severe dementia. The FAST has documented good validity and reliability [275]. FAST was used as one of the measures for potential dementia while screening patients for the DEM.LIGHT trial, as a baseline patient characteristic in Paper 2 and Paper 3, and also as a potential covariate in Paper 3.

Medical records

The research team had permission to extract data from a centralized journal system used in all nursing homes in Bergen. To limit the workload on the nursing home staff, information about blood pressure, heart rate, height, weight, registered diagnoses, and medications was extracted from the patients' medical records prior to each visit. The total number of medications, number of psychotropic medications (all drugs coded as N in the ATC system), and the number of sedatives (N05C drugs, including z-hypnotics) were used as baseline patient characteristics in Paper 2 and Paper 3, and the number of psychotropic medications was used as a potential covariate in Paper 3.

Mini Mental Stage Examination (MMSE)

The MMSE assesses the level of cognitive impairment [276]. The total score ranges from 0-30, where a low score indicates worse cognitive function [276]. The MMSE was used as one of the measures for potential dementia while screening patients for the DEM.LIGHT trial, and as a baseline patient characteristic in Paper 2 and Paper 3, and also as a potential covariate in Paper 3.

Neuropsychiatric Inventory – Nursing Home Version (NPI-NH)

The NPI-NH [279, 280] is a proxy-rated tool that assesses BPSD by assigning frequency and severity ratings to 12 symptoms (delusion, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night-time behaviour, and eating disturbance). The NPI-NH was used as a baseline patient characteristic in both Paper 2 and Paper 3. In Paper 2, the sleep item of the NPI-NH was used to assess the convergent validity of the SDI.

3.1.7 Data collection procedure

On each unit, we established contact with one or two nurses, and scheduled our visits with them. All questionniares were completed by daytime staff, either the same week as the patients wore an actigraph or the following week. We assisted the nurses as they completed the questionnaires in order to aid them in completing the assessment tools. As the nurses became familiar with the questionnaires, they completed them independently, allowing them to complete the questionnaires at times most convenient to them.

3.1.8 Sample size

Using G-power [285, 286], the power-analysis showed that we needed 64 patients when including eight clusters in order to detect differences between conditions, expecting moderate effect sizes (Cohen's d= .50) for the actigraphy outcomes, a .05 alpha level (two-tailed), and the power set to .80. We expected a 20% dropout, and thus the aim was to recruit 80 participants from eight nursing home units (clusters).

3.1.9 Randomization

The clusters were randomized by EF and EK to the intervention condition (1) or the control condition (0) using random group assignment in *SPSS for Windows, version 25.0*.

3.1.10 Blinding

The DEM.LIGHT trial was single-blinded, aiming to blind the participants and the nursing home staff to group allocation. However, staff and participants could not be kept completely blind to the intervention, as the light setup comprised an obvious change in the common room. Therefore, we installed new light sources in the control units, in order to mimic an intervention and to ensure similar lighting across the control units. All included units were located at different nursing homes to minimize threats to internal validity in terms of performance and detection bias [237].

3.1.11 Contributions

Elisabeth Flo-Groeneboom was the PI for the DEM.LIGHT trial. The data-collection was organized and data were collected by PhD-fellow Eirin Kolberg (EK) and the

candidate (GJH), with guidance and support by the main supervisor (EF) and co-supervisors (Ståle Pallesen, Inger Hilde Nordhus, and Eirunn Thun). Eirunn Thun also participated in parts of the data collection. Two research assistants, Kristin Stotesbury and Marianne Hvattum Løken, took part in the data collection and plotting of data at week 8 and 16.

3.1.12 Ethics

The DEM.LIGHT trial was planned and conducted in line with the Declaration of Helsinki [265]. The trial was approved by the Regional Committee for Medical and Health Research Ethics, Health Region South East (project no. 2016/2246). The trial was preregistered at clinicaltrials.gov (Identifier NCT03357328).

At each nursing home, we conferred together with the resident physician regarding the individual patient's capacity to provide informed consent. In most cases, the patients did not have the capacity to provide informed consent, and the legal guardians were thus contacted by phone and we explained the study protocol to them. Subsequently, they received a letter with comprehensive information about the study aims, proceedings, and time frame, and a presumed concent form to return with their signature. The legal guardians were asked to provide presumed consent if they thought that the patient would wish to participate in the study if they were able to give their own consent, in line with the Helsinki Declaration [265].

Regardless of consent capacity, we endeavoured to inform all participants about the study, adapting the information accordingly. We made a close assessment of their ability to understand study information when talking with the patients and administering the MMSE. During the study period, the patients' ability to provide active assent or dissent was respected. Thus, no patients were forced to complete any assessments that involved their active participation (MMSE, MOBID-2, actigraphy). The researchers were sensitive to any protests or expressions of discomfort from the participants; and considered this as withdrawal of consent to complete the assessment in question. Most of the data were collected using proxy-raters.

The data were stored using a solution for secure processing of sensitive personal data in research, offered by the University of Bergen (SAFE). Only the research team had access to the data, which were accessed via a secure desktop.

3.2 Methods of Paper 1

3.2.1 Systematic literature search

Protocol and registration

The protocol for the systematic review was pre-registered in PROSPERO (registration number CRD42017051004), which is an international prospective register of systematic reviews.

Eligibility criteria

Table 5 shows the inclusion and exclusion criteria used to select studies for the review. These criteria were applied to reduce the heterogeneity of the included studies, while including all studies of interest.

Table 5: Listing the inclusion and exclusion criteria applied in the systematic review.

Inclusion criteria	Exclusion criteria
- BLT was delivered as an enhanced indoor electrical light scheme - The intervention was aimed at impacting NIF responses, including mood, behaviour, sleep, and/or circadian rhythmicity - The interventions had to entail an increase in illumination (lux) and/or CCT compared to baseline or control conditions - Information about lux or equivalent unit - Studies had to implement BLT as an intervention using standard care group comparison, placebo group comparison, or a single group pre-post design - The included participants had dementia - Quantitative study design	- Qualitative studies - Case studies, chronicles, guidelines, protocols, non-systematic reviews, legal documents, conference abstracts, and other grey literature - Not published in English

BLT= Bright Light Treatment, CCT= Correlated colour temperature, NIF= Non-image forming

We defined BLT as an enhanced indoor electrical light scheme aimed at impacting NIF responses including mood, behaviour, sleep, and/or circadian rhythmicity. Further, the interventions had to entail an increase in illumination (lux) and/or CCT compared to baseline or control conditions. Studies using dawn-dusk simulation (low lux, low CCT) were excluded.

We only included studies encompassing participants with presumed dementia. A presumed dementia diagnosis could be based on medical records, diagnosed specifically for the study according to the Diagnostic and Statistical Manual for Mental Disorder (DSM) or the International Classification of Disorders (ICD) system, or on a MMSE cut-off. When both people with and without a dementia diagnosis were included, the study was included only if the results from the dementia participants were reported separately.

To provide a comprehensive description of the published research in the field and to capture important insights from all available studies, we chose to be inclusive with regard to study design. Thus, we did not restrict inclusion to RCTs. Included studies had to be quantitative and implement BLT as an intervention using standard care group comparison, placebo group comparison, or a single group pre-post design. Publications such as case studies, chronicles, guidelines, protocols, non-systematic reviews, legal documents, conference abstracts, and other grey literature, as well as non-English publications, were excluded. We also excluded studies where BLT was combined with other treatments.

Information sources and search strategy

In collaboration with a skilled university librarian, Regina Küfner Lein, systematic literature searches were conducted in relevant databases: CINAHL, Medline, PsychINFO, Embase, Web of Science, and Cochrane libraries. The initial systematic search was conducted in June 2016, with a follow up search in March 2019. The search covered MESH terms and free text phrases synonymous with “bright light treatment” (*phototherapy, *photo therap, dawn-dusk, dawn dusk, light*, illuminat*,

bright, therap*, treatment, box, visor*, exposure*, LED), “dementia” (alzheimer disease, frontotemporal lobar degeneration, lewy body disease, delirium, amnestic, cognitive disorders, dement*, Alzheimer*, lewy body disease), and “nursing home” (home* for the aged, hospice*). No time limit was set for the searches. A complete overview of the search strategy for each database is available as supplementary material to Paper 1.

Study selection

On the basis of the inclusion and exclusion criteria, potential manuscripts were screened at the abstract level by GJH and EF, after which the inclusion and exclusion criteria were used to assess selected full texts by GJH and EK. Any disagreements were discussed with the co-authors. The reference lists of the full-text publications were searched for potential additions to the review.

Data extraction process

The data extraction was a back-and-forth process involving the co-authors, following the PRISMA guidelines (“Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [287]. We agreed on the information of interest and developed a standardized form, which was piloted on a few of the included publications and amended in meetings with the research group. The following data items were extracted: Full reference, publication year, country, inclusion and exclusion criteria, type of setting (nursing home or home-dwelling), number of participants, participant characteristics (age, percentage female, type of dementia, and information about dementia severity), study design, intervention strategy (delivery method, illumination, CCT, duration of daily exposure, timing of daily exposure, duration of intervention period, and time of year) and control condition, time to follow-up, study setting, outcome measures, and study results.

Risk of bias in individual studies

The study quality was assessed using the Oxford Quality Scoring System [288], where quality is assessed in terms of randomization, descriptions of randomization procedures, double-blinding, descriptions of blinding procedure, and descriptions of

dropout. Studies were graded from zero to five, where a higher score reflects a more rigorous study. The included studies were rated independently by GJH and EK and subsequently compared. Any disagreements were discussed with EF and a consensus was reached.

Risk of bias in the review

In order to reduce risk of bias in terms of including publications in the review, potential manuscripts were screened at the abstract level by two authors (GJH and Elisabeth Flo-Groeneboom, EF), after which the inclusion and exclusion criteria were used to assess selected full texts by two authors (GJH and EK). Any disagreements were discussed in group meetings.

3.2.2 Synthesis of results

The included studies were systematized according to the PICO system (Population, Intervention, Comparison, and Outcome). The synthesis started with creating a descriptive summary of each included study, in the form of a table containing the extracted data items. Through discussions of this preliminary summary, we decided to group the studies according to which outcomes they had measured and according to the intervention strategy. To synthesize outcomes, the studies were systematized according to: 1) behavioural and psychological symptoms of dementia, 2) function and dementia severity, 3) sleep, and 4) circadian rhythmicity. To differentiate between types of interventions, BLT interventions with 1,000 lux or above, where the CCT was not manipulated, were categorized as “high illumination”. Interventions with high CCT compared to standard warm-white light, i.e., 5,000 K or more, were defined as “high CCT”. These categories were used to describe the different interventions.

Under each category of outcomes, we first summarized all results, and then the results from the high illumination studies and the high CCT studies separately. Important study characteristics were highlighted in the text, while more details were available in a supplementary table. The goal of the synthesis was to collate the findings of the included studies while considering the strength of the evidence, exploring if there were any consistent effects across studies, and exploring relationship between the

characteristics of single studies (study design, population characteristics, intervention strategy) and the reported findings. Potential confounders, and recommendations for futures studies were discussed.

3.3 Methods of Paper 2

3.3.1 Procedures

Paper 2 was a validation study of the SDI. This paper was based on baseline data from the DEM.LIGHT trial.

The SDI was adapted to the nursing home setting and translated to Norwegian. Item 4 ("awakening you during the night") was replaced with "awakening at night", in order to capture wake time during the night, but where the patient did not engage in the behaviours covered in the other items (e.g., getting out of bed or wandering). The translation process adhered to standard guidelines [289]. EF translated the SDI to Norwegian. GJH and EK back-translated the Norwegian version to english, and the back-translated version was compared to the original version by Inger Hilde Nordhus (IHN). Further refinements were made in a meeting between EF, EK, GH, and IHN. As some of the wording of the SDI was similar to the sleep item from the NPI-NH, which was already translated to Norwegian [280], we used existing translations when possible. Thus, five out of seven items were based on the Norwegian version of the NPI-NH.

Actigraphy was used as a reference standard in order to validate the SDI. The following outputs were extracted from *Actiware*: Sleep efficiency (SE; the percentage of time spent asleep in the rest interval), total sleep time (TST) in the rest interval, wake-after-sleep-onset (WASO; the time spent awake after sleep onset), and the 24 hour fragmentation index (indicates the overall disturbance of the sleep-wake rhythm across 24 hours, a higher score indicates a higher fragmentation). In addition to the SDI, the sleep item from the NPI-NH was also included in this study.

3.3.2 Statistical analyses

The statistical analyses for Paper 2 were conducted using *SPSS for Windows, version 25.0*. The analyses were performed by GJH, in close collaboration with the co-authors.

For the SDI, missing data were imputed using Expectation Maximization when questionnaires were missing <20% of items. In total 31 items from 11 patients (2.3% of all items) were imputed, while three participants were missing ≥20% and were excluded from the analyses. Normality of the data was assessed and non-normal data were analysed using non-parametric tests.

The internal consistency of the SDI was assessed using Cronbach's alpha. Internal consistency is one of the main aspects of the reliability of a scale and refers to inter-item correlations. This reflects if the items are measuring the same construct [290]. A Cronbach's alpha of above 0.7 is normally considered acceptable, but is also dependent on the number of items, where more items results in a higher alpha [291].

Convergent validity refers to how closely the scale in question is related to other measures of the same construct [292]. We assessed convergent validity by evaluating the strength of the relationship between the SDI and the NPI-NH sleep item and between the SDI and actigraphy outcomes, calculating Spearman correlation coefficients. To further evaluate the clinical utility of the SDI, receiver operating characteristic (ROC) curves were calculated. ROC curves require a dichotomous "gold standard" outcome of which the test in question is compared to [293]. An actigraphy-based cut-off defining the presence of disrupted sleep was set to sleeping less than six hours in the fixed rest interval. The ROC analysis produces an "area under the curve" (AUC) score, which reflects the discriminatory ability of the test (here the SDI). A test with a high rate of true positives and a low rate of false positives, yields a high AUC score. An AUC score of .75 or more is considered clinically useful [293].

The next step was to identify which total score on the SDI should be used as cut-off to represent clinically significant sleep problems. Thus, sensitivity (the rate of true positives), specificity (the rate of true negatives), and predictive values were calculated for different cut-offs on the SDI. In this context, the positive predictive value is the

probability that a person scoring on or above the SDI cut-off (i.e., a positive test) actually has disrupted sleep (as defined by the actigraphy reference), and the negative predictive value is the probability that a person scoring below the cut-off (i.e., a negative test) actually do not have disrupted sleep. Figure 6 shows how sensitivity, specificity, and positive and negative predictive values are calculated. The Youden's index (sensitivity + specificity - 1) is a common summary measure for ROC curve data, incorporating sensitivity and specificity, which may be used to determine the most appropriate cut-off value for a scale [294–296]. The cut-off that results in the highest Youden's index value is regarded as the "optimal/best" threshold value.

	Positive test	**Negative test**	**Measures**
Sick	**True positive** TP	**False negative** FN	**Sensitivity** $\frac{TP}{TP+FN}$
Healthy	**False positive** FP	**True negative** TN	**Specificity** $\frac{TN}{FP+TN}$
Measures	**Positive Predictive Value** $\frac{TP}{TP+FP}$	**Negative Predictive Value** $\frac{TN}{FN+TN}$	

Figure 6: A schematic overview of how sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of a test are calculated. Sick= Disrupted sleep according to actigraphy. Healthy= Not disrupted sleep according to actigraphy.

3.4 Methods of Paper 3

Paper 3 was based on sleep data (actigraphy and the SDI) from the DEM.LIGHT trial. The following actigraphy outputs were extracted: SE, WASO, TST in the rest interval, TST during the day, and 24 h TST. The SDI total score was calculated as the sum of the products of the frequency and severity of each item.

3.4.1 Statistical analyses

The statistical analyses for Paper 3 were partially conducted using *SPSS for Windows, version 25.0*. Baseline data were presented as means (standard deviation; SD) for normally distributed continuous data, medians (25^{th}-75^{th} percentile) for non-normal continuous data, and number of participants (%) for categorical variables.

The relationships between sleep outcomes and age, gender, eye disease, total number of drugs, number of psychotropic drugs, number of sedatives, MMSE, FAST, and CCI were assessed using correlation analysis for continuous data and by comparing groups for categorical data. Student's t-test was used for normally distributed data and Mann-Whitney U test for skewed data.

To compare the light levels of the intervention condition and the control condition, differences in light levels between the intervention and the placebo condition were evaluated using Mann-Whitney U test.

The effect of the intervention on sleep outcomes was analysed using multilevel regression modelling in "R" [297]. These analyses were completed by EK in close collaboration with GJH and the rest of the research group. Treatment effects on the primary outcomes were evaluated using linear mixed models, which incorporate the assessments from all time points (baseline, week 8, week 16, and week 24). There were some missing data because patients passed away or moved to another facility during the study (see Figure 2 in Paper 3). Mixed linear models use all available data while performing well in the presence of missing data. This model also estimates fixed effects while adjusting for correlation caused by repeated measurements of the same individuals [298, 299].

Linear mixed models using restricted maximum likelihood estimation were used to assess all outcomes for the impact of group (intervention and placebo), time (treated as categorical with levels baseline, 8 weeks, 16 weeks, and 24 weeks), and the group-by-time interaction. Fixed effects for time, the intervention, and their interaction were included in the models. The models were fitted with random intercepts at the

participant level to allow each participant to vary at baseline, and random slope was included if it improved model fit.

Covariates were also selected based on model fit. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) were examined, and log likelihood values were compared using analysis of variance (ANOVA). Covariates that improved the fit were added to the model. The following list of covariates were tested: Age, gender, number of psychotropic medications, CCI, FAST, MMSE, eye disease, whether the participants passed away or moved during the study (drop-out), and average time in the living room during the day (between 10:00 and 15:00). Because there was some variation in light levels within the intervention group and within the control group, the measured melanopic illuminance of each unit was also tested as a covariate.

The SDI data were transformed to achieve normal distribution, as preliminary analyses showed that the SDI data were highly skewed. The scores were transformed to achieve normal distribution by adding a constant of 0.5 and using a Box Cox transformation resulting in a lambda of 0.6.

4. Summary of results

4.1 Paper 1

- The systematic review included 31 publications from 24 studies.
- The results of the included studies were inconsistent, with a mixture of significant improvements, non-significant findings, and even negative results in terms of circadian rhythmicity, sleep, BPSD, function, and quality of life.
- The included studies varied widely regarding intervention characteristics, designs, outcome measures, and population characteristics, which may have affected the outcomes.
- Most of the studies had small samples with time-limited treatment durations. Longer treatment durations (≥eight weeks) appeared to be more effective on BPSD than shorter treatment durations (two weeks or less).
- No pattern emerged in terms of timing (time of day) of treatment. It might be that timing is less important than a general increase in light exposure, as this population is notoriously under-exposed to daylight.
- Studies using too intense placebo conditions (>400 lux) might have nullified potential differences between intervention and control conditions.
- Considering the long-lasting effects on sleep found in one study for up to 12 weeks post-treatment, there may have been carry-over effects in the studies using a cross-over design and with no wash-out or a short wash-out.
- There was some evidence that studies including only people with Alzheimer's disease had more favourable outcomes than studies including patients with multiple diagnoses, and that men might be more sensitive to light exposure than women.
- The review did not support the notion that light of higher illumination (above 2,500 lux) is more effective.
- Several studies reported that high-CCT ambient light (from 6,500 K and 1,200 lux to 13,000 K and 400 lux) had a negative impact on some outcomes, including depression and agitation. Keeping the light below 6,500K and 1,200

lux (measured vertically), but still as high as possible, could represent a viable solution.

4.2 Paper 2

- The internal consistency of the SDI was high, with a Cronbach's Alpha of .82 for the frequency ratings and .87 for the severity ratings.
- The SDI was tested using three different ways of calculating a total score. All three total scores had a high convergent validity, with moderate significant correlations with the actigraphy-based outcomes of TST in the rest interval (Spearman's rho, all correlations >.4, all p's <.01), and WASO in the rest interval (all correlations -.4). The SDI did not correlate significantly with the fragmentation index (p=.10).
- The ROC analyses showed that all three SDI total scores yielded an AUC score of .77 (95% CI about 65%-90%), using actigraphy as the reference standard (sleep disturbance defined as SE<75%). AUC scores of more than .75 are considered to be "clinically useful".
- The *SDI summed product score* (summarizing all item products, i.e., each scale item's frequency multiplied with its severity), using a cut-off of five or more, yielded the best sensitivity, specificity, and predictive values for predicting sleep disturbance. This total score and cut-off also had the highest Youden's Index of 0.49.
- The results indicate that even though the SDI was developed for home-dwelling people with dementia and their caregivers, the SDI may be used to identify of sleep disturbances when administered by daytime staff in a nursing home context. However, clinicians should be vigilant to any signs of poor sleep, as there is a risk of missing up to 30% of potential cases using the SDI.

4.3 Paper 3

- The intervention delivered significantly higher lux and CCT in the four intervention units (mean vertical lux 1,039 (SD 225); mean CCT 5,369 K (SD 275)) compared to the four control units (mean vertical lux 242 (SD 102), p=.001; mean CCT 3049 K (SD 470), p=.000), as measured at predetermined locations using a standardized protocol.
- The linear mixed model analyses for actigraphically measured sleep showed no statistically significant changes in the intervention group compared to the control group from baseline to week 8, 16, or 24.
- The linear mixed model analysis for sleep measured by the SDI showed a significant improvement in the intervention group compared to the control group from baseline to week 16 (regression coefficient -.06, p=.02) and from baseline to week 24 (regression coefficient -.05, p=.03).

5. Discussion

The overall aim of this thesis was to investigate whether BLT can improve sleep in nursing home patients with dementia and to highlight important methodological challenges in this field of research. Paper 1 reviewed previous studies on the effect of BLT in people with dementia, with a focus on the methodology of the included studies. Paper 1 demonstrated the diversity of the field, highlighting important methodological challenges that should be addressed in future studies. One of the findings was that the variety of measurement tools and operationalizations of outcomes (e.g., SE was calculated differently across studies), may explain some of the inconsistency of results across the included studies. Paper 2 complemented this finding by validating the proxy-rated sleep scale SDI against actigraphy, using baseline data from the DEM.LIGHT trial. The results showed that the SDI may be clinically useful to identify patients with potentially disrupted sleep in the nursing home context. Finally, Paper 3 reported on the sleep outcomes of the DEM.LIGHT trial, evaluating the effect of a dynamic ambient BLT intervention in nursing home patients with dementia. Here, we found that proxy-rated sleep measured by the SDI, improved in the intervention group compared to the control group from baseline to week 16 and from baseline to week 24. There were, however, no improvements in sleep measured by actigraphy.

5.1 Discussion of the results

In the following, the main aim of this thesis, i.e., whether BLT may represent an effective non-pharmacological treatment for sleep problems in nursing home patients with dementia, will be discussed. In order to do so, the findings from Paper 3 will be discussed first, followed by an overall discussion of this question. Subsequently, the use of the SDI as a measurement of sleep in the nursing home context will be discussed.

5.1.1 The findings from Paper 3

The discrepancy between actigraphy and the SDI outcomes reported in Paper 3 may have been caused by the most important difference between these outcome measures; namely that actigraphy measure activity, while the SDI taps into the observations made by the staff. As discussed in Paper 2, over 80% of the variability in the SDI score was not explained by TST measured by actigraphy. There is a lot more complexity to sleep than is measured by actigraphy, which ultimately is a measure of mobility/immobility. There was a high use of psychotropic drugs among the participants in the DEM.LIGHT trial. As reported in Paper 3, 97% were prescribed at least one psychotropic drug, which is higher than the numbers reported in other Norwegian studies [300, 301]. The mean number of psychotropic drugs was 2.7, which may have resulted in sedation [302]. The potentially high occurrence of quiet wakefulness as a result of sedation may have confounded the actigraphy outcomes, as quiet wakefulness is recorded as sleep by the actigraphs. Conversely, staff observations may capture a more comprehensive impression of the patients' sleep-wake behaviour and is not subject to these limitations. Although, as discussed in the discussion of the methods, proxy-rated instruments include other methodological issues which may have biased the results.

The findings of Paper 3 are similar to those in a recent study by Figueiro et al. [252], also using ambient light. In this RCT with a cross-over, they tailored a light intervention to each participant, according to where they spent the most time during the day. Light was administered for four weeks using floor luminaires (600 lux and 5,000 K or 550 lux and 7,000 K at eye level), light boxes (350 lux, 6,000 K), and light tables (750 lux and 5,000 K). Similar to the findings reported in Paper 3, the intervention resulted in improved proxy-rated sleep (using the Pittsburg Sleep Quality Index), compared to the placebo condition, but not sleep parameters measured by actigraphy. Three other RCTs also found no effect on sleep measured by actigraphy [229, 230, 244].

Meanwhile, the finding of paper 3 are in contrast to the findings by McCurry et al. [19], who reported an improvement of sleep measured by actigraphy, but not sleep

measured by the SDI, following two months of evening BLT using light boxes (2,500 lux). Also, Ancoli-Israel et al. [20] found improvements of sleep measured by actigraphy following only 10 days of BLT delivered using light boxes (2,500 lux), both when administered during the morning and when administered during the evening. Further, a recent open clinical trial by Van Lieshout-van Dal et al. [251], where they administered ambient light using floor-lamps, reported improvements of sleep (estimated based on an activity sensor in the participants' beds) during the intervention compared to standard light. The intervention comprised 1,100 lux and 6,500 K vertically at eye level from 10:00-14:00, and 600 lux and 1,800 K in the morning and evening, for three weeks.

There is a possibility that the lack of a robust effect of the intervention on sleep as reported in Paper 3 is related to issues regarding actual light exposure. Although we asked the nursing home staff to estimate the time each participant on average spent in the common room, these estimates may have been inaccurate. In addition, corneal light exposure is reduced when the observer is facing the floor or closing their eyes, which was not recorded. Thus, actual light exposure may have been lower than intended. This issue was exemplified in a recent study by Münch and colleagues [257]. Here, they used ceiling-mounted light and administered approximately 1,000 lux and 6,500 K from 11:00 to 16:00, with a gradual increase from 2,700 K in the morning and that reversed back to 2,700 K and below 200 lux in the evening. They found no effect of the intervention on sleep measured by actigraphy compared to the control group, however, found significant improvements in sleep when comparing groups based on individual light exposure (high vs. low light exposure), measured by light sensors on the actigraphs. It was not possible to evaluate individual light exposure based on light information from the actigraphs in the DEM.LIGHT trial, as the participants frequentlty wore clothing covering the device.

5.1.2 Is BLT an effective non-pharmacological treatment for sleep problems in nursing home patients with dementia?

Based on the findings from Paper 1 and Paper 3, the effectiveness of BLT in ameliorating sleep problems among nursing home patients with dementia is uncertain.

However, positive effects have been demonstrated, including our findings reported in Paper 3. As reported in Paper 1, we found that overall, the majority of studies assessing sleep and circadian rhythmicity using actigraphy found improvements in some of the parameters, but also several non-significant results. The lack of a robust effect may be explained by several factors. As will be elaborated in the discussion of the methods, both actigraphy and proxy-rated scales have some important weaknesses that may obscure the effect of BLT on sleep. Beyond the challenges of measuring sleep, other issues are relevant to discuss. First, effects of BLT may take a long time to manifest. Second, the response to BLT may depend on dementia diagnosis and/or severity. Third, polypharmacy and other factors associated with nursing home placement might counteract effects of BLT. Finally, the intervention strategy used in the studies included in Paper 1 and the DEM.LIGHT trial intervention might not have been optimal.

Long-term effects

One of the findings from Paper 1 was that 9 out of 23 included studies had short treatment durations of around 2 weeks, 11 studies had a treatment duration of 3-4 week, and a longer treatment duration (eight weeks or more) was recommended based findings regarding BPSD. The same conclusion may pertain to sleep, although one RCT found improvements of sleep following only 10 days of treatment, using 2,500 lux light boxes [20], and Figueiro et al. [252] found and improvement of proxy-rated sleep after four weeks of treatment. In contrast, the improvement in the SDI reported in Paper 3 was not seen until week 16 (and not in week 8), indicating that several weeks of exposure may be necessary to elicit a beneficial effect of BLT on sleep in people with severe dementia.

The effect may depend on diagnosis and/or severity of dementia

As highlighted in Paper 1, the included studies varied in terms of population characteristics. Some included people with Alzheimer's disease only, while others included people with different diagnoses. Ancoli-Israel et al. [20] repeated the protocol used in a study of people with different dementia diagnoses [229], including participants with Alzheimer's disease only. In the second study, they found within-

group improvements of sleep following BLT, while there were no significant effects on sleep when including people with different diagnoses [229]. Similarly, in their review of the literature, Mitolo et al. [303] suggested that people with mild to moderate Alzheimer's disease might benefit more from BLT than people with severe Alzheimer's disease and other dementias.

In the DEM.LIGHT trial, we included patients with different dementia diagnoses who on average had severe dementia. Ideally, we should have had enough participants to perform subgroup analyses based on dementia severity and diagnosis. However, the majority of the participants had severe dementia, as indicated by the median MMSE score of 4, prohibiting a separation of patients based on severity. Further, studies have shown that it is common for one patient to have several types of neuropathology corresponding to several types of dementia [161, 162]. This is increasingly common with higher age [304, 305], complicating a separation of patients based on dementia subtype in our population.

There is also a possibility that some people with dementia have too widespread neuropathology to benefit from BLT, where areas involved in sleep-wake regulation are affected to the point that efforts to improve sleep are ineffective. Alternatively, age- and dementia-related changes of eye physiology [306] may have progressed to the stage that the BLT was unable to adequately stimulate NIF responses in some patients, and consequently had no effect on sleep measured by actigraphy. In line with this, van Someren et al. [245] found an improvement of circadian rhythmicity only in participants with no eye pathology. Whether or not a participant had a diagnosed eye condition was a significant covariate for SE in Paper 3, indicating that eye disease affected the response to BLT. However, eye disease was not a significant covariate for the other sleep outcomes. Importantly, it is unlikely that extensive eye examinations aiming to assess light sensitivity are performed upon nursing home admission, and information regarding eye pathology may not have been accurate. Some previous studies have assessed eye health in relation to BLT [e.g., 244], and future studies should aim to implement such assessments.

Improving sleep in the nursing home context

Importantly, the are multiple causes of sleep disruption, and although light exposure is pivotal for a stable sleep-wake rhythm, other factors may significantly impact sleep. One obvious challenge related to nursing home patients is that they often spend a significant amount of time in bed, often more than 12 hours from bedtime to rise-time, excluding daytime naps [146, 197, 198]. Paradoxically, the first-line treatment for insomnia in otherwise healthy adults entail behavioural approaches such as restricting time in bed [307]. Although people with dementia may need more rest than otherwise healthy adults, spending more than 12 hours in bed and frequent daytime naps [146, 197, 198] will normally increase the risk of fragmented sleep significantly [308]. Similarly, other factors that are prevalent in nursing homes, such as reduced daytime activity [199] and/or a high sedative load resulting from polypharmacy [144] may counteract effects of BLT. Attempting to improve sleep in this context is perhaps futile, and it is perhaps not possible to fully delineate the effect of BLT on sleep unless the aforementioned practical issues are resolved.

Dementia is progressive in nature and as a consequence, deterioration in sleep quantity and quality over time is to be expected in this population. In Paper 3, the observed means and standard deviations of the SDI for the groups at each time point indicate that the significant treatment effect in week 16 and 24, as shown in the mixed linear model analysis, was caused by an improvement in the intervention group in combination with a worsening in the control group (see Table 6 in Paper 3). Importantly, the observed means do not account for drop-out during the course of the study. Thus, improving sleep in people with dementia may largely entail preventing or counteracting deterioration of sleep over time. This highlights the necessity of including a control group.

Was the intervention strategy optimal?

Several previous studies have provided the participants with BLT from 7:00 or 8:00 in the morning. This is appropriate if the aim is to advance the sleep-wake rhythm (i.e., wake up earlier, go to sleep earlier), and if the person has a normal circadian rhythm. However, nursing home patients may vary in the timing of their circadian phase [257].

Providing BLT early in the morning might actually delay the rhythm, as people might be exposed to light prior to nadir for core body temperature. Ideally, BLT should be tailored to each patients' circadian phase. However, when using ambient light in common rooms, this is not possible. By providing light from 10:00, we were confident that the light occurred after nadir for most patients. Importantly, people with dementia often struggle with sleep fragmentation (i.e., multiple sleep and wake episodes across the day and night) [174], rather than a delay or advance of the rhythm. Thus, the aim of the intervention was to consolidate sleep to the night and promote wakefulness/alertness during the day, both through the circadian effects and the acute alerting effects of light [13, 111]. Circadian effects occur even when bright light is provided several hours after wake-up [81, 83, 84]. Also, exposure to bright light during the day seem to protect against circadian disruption and alerting effects caused by evening/night-time light exposure [106].

It is possible that the light levels (lux and CCT) and duration of daily exposure used in the DEM.LIGHT trial were not sufficient to stimulate NIF responses due to age- and dementia-related deterioration of eye physiology. The optimal light levels to employ when delivering BLT as ambient light has not been established, as reflected in the wide variety of intervention strategies employed in previous studies, as summarized in Paper 1. Recently, knowledge regarding the light characteristics needed for optimal physiological and psychological well-being for people in general was also highlighted as a gap in the literature by Münch et al. [78], thus expanding beyond dementia research. In the DEM.LIGHT trial, we decided to use a peak light level of 1,000 lux and 6,000 K from 10:00 to 15:00, with lower light levels in the morning and afternoon/evening (see section 3.1.3). This strategy was based on previous studies, discussions with experts in the field, and on feedback from nursing home staff. In the DEM.LIGHT trial, we completed a pilot including one nursing home unit, where nursing home staff had the opportunity to provide feedback on the light settings. Following feedback from staff, we reduced the duration of the interval with the highest light levels (1,000 lux and 6,000 K), and reduced the illumination in the evening. There is a possibility that people with severe dementia may require much higher light levels in order to stimulate NIF responses than people without dementia.

Conversely, too high CCT and/or lux may have undesirable effects. As reported in Paper 1, three studies using ambient light reported negative outcomes following BLT with high CCT values. Van Hoof et al. [247] reported increased anxious and depressive behaviour using light with a CCT level of about 12,500 K, and a vertical lux level of 400-500, for the whole day. Another study reported increased apathetic behaviour following light of 6,500 K and 1,200 vertical lux delivered for the whole day [246]. One study used light of 6,500 K and 2,500 horizontal lux (corresponding to a somewhat lower vertical lux) and reported increased depression among men after morning BLT (07:00-11:00) compared to the control condition [309], and also that evening BLT (16:00-20:00) was associated with increased daytime sleepiness in one of the two participating nursing homes [243].

Potential negative effects of BLT are important to consider. Van Hoof et al. [247] suggested that the light was uncomfortable for the participants and that they expressed discomfort through worsened behaviour. This is an important point that is largely overlooked in BLT research. Few studies have investigated which light levels people prefer in their environment [310, 311], and none have investigated this in relation to dementia. Here, it is also important to consider different preferences related to "focus lighting" in work environments and lighting in settings where people live. While short-wavelength light may be more efficient in terms of stimulating NIF-functions, light levels with a CCT that outperforms sunlight (5,700-7,700 K [103]), is perhaps not a viable solution in peoples everyday environment. We recommended in Paper 1 that studies should not use light levels of more than 6,500 K and 1,200 lux (measured vertically), particularly when delivered as ambient light in people's living environment. Although this recommendation was based on the existing literature, there is a clear need for studies that investigates preferences and light comfort in different indoor settings. More clinical studies should look into how light sensitivity is reduced with age and dementia, and identify the minimum light levels required to stimulate NIF responses in this population, as well as the upper limit in terms of negative effects and/or subjective preferences and comfort. When available, it is possible that we should harvest natural daylight (i.e., light emitted by the sun), as people seem to prefer natural light over electric light [312].

Beyond ensuring sufficient light exposure during the day, darkness at night is also an important aspect to consider, as a stable circadian rhythm depends on both daytime light exposure and nocturnal darkness [99]. Several of the more recent studies have employed light of low lux and CCT during the evening and night [106, 250, 251]. In the DEM.LIGHT trial, we reduced the light to 400 lux and 3,000 K at 15:00, and then further to 100 lux and 2,500 K at 18:00. However, we did not control the light outside the common room, and thus patients may have been exposed to light late in the evening and during the night. Although daytime light exposure reduce the sensitivity to nocturnal light exposure, this is an important weakness. More favourable results could have been achieved from securing low light levels and darkness during night, and future studies should endeavor to control the light environment also in patients' rooms.

5.1.3 Is the SDI a valid outcome measure of disrupted sleep in nursing home patients with dementia?

Few proxy-rater tools for assessing sleep in the nursing home are available. The SDI is a relatively short and easy-to-administer tool that has been validated for home-dwelling people with dementia, using in-living relatives as proxy-raters [203]. In Paper 2, we reported that the SDI adapted to the nursing home corresponded well to sleep measured by actigraphy in nursing home patients with dementia, using staff as proxy-raters. However, some important issues need to be considered.

Nursing homes are short-staffed at night and thus some sleep-related events may go unnoticed. In particular, wake time at night is often underestimated [264]. Still, the SDI performed quite well compared to actigraphy, in contrast to commonly used questionnaires assessing sleep using one or a few items [197]. In their study, Blytt et al. [197] found a specificity (correctly identified negative cases) of the sleep item of the Neuropsychiatric Inventory (Nursing Home Version) of 89%, and a sensitivity (correctly identified positive cases) of only 22%. Similar results were found for the sleep items of the Cornell Scale for Depression in Dementia. Thus, the SDI is more accurate in detecting sleep disturbances in nursing home patients with dementia, with a specificity of 78% and sensitivity of 70%, and may thus contribute to detection and

subsequent treatment of sleep problems in this population. Importantly, while the SDI may indicate if a patient has clinically significant sleep disruption, more deliberate approaches would be needed to identify the underlying cause of the sleep disturbances, such as obstructive sleep apnea, periodic limb movements, nocturia, or pain. Thus, the SDI may serve as a screening tool, but may not be used as a diagnostic tool. Further, we did not assess test-retest reliability or the responsiveness of the SDI over time to detect clinical change, which are weaknesses of Paper 2. Future studies should assess these aspects of the SDI.

Using the SDI to detect possible sleep disturbances

In Paper 2, we used the Youden's index to identify the best cut-off for defining disrupted sleep, where the cut-off that yields the highest Youden's index is regarded most "optimal" cut-off [294, 296]. The analyses revealed that a definition of sleep disturbances as a SDI total score of five or more yielded the highest Youden's index, and a sensitivity of 70%, a specificity of 78%, a positive predictive value of 73%, and a negative predictive value of 76%. Although clinically useful according to the AUC score of .78, these values are not great. The sensitivity of 70% means that the SDI will detect 70% of patients that have sleep problems (as defined by the actigraphy reference), and thus fail to detect almost a third of the cases. We could have chosen a lower cut-off, with a higher sensitivity and thus detecting more of those with disrupted sleep. However, this would also entail decreasing the specificity and producing more "false positives", i.e., categorizing patients who sleep well as having disrupted sleep.

An instrument with even higher sensitivity and specificity than found in Paper 2 would be ideal. This may not be possible without adding an element of systematic observation. Unless patients get out of bed or otherwise attract the attention of the night-time staff, patients may be awake or exhibit symptoms of sleep apnea, periodic limb movements, or other conditions, without the staff noticing. Because continuous observation is extremely labour-intensive and time-consuming, most approaches rely on intermediate observation, for example every 15 minutes or every hour [259, 313]. But, as nursing home patients with dementia often experience extremely fragmented

sleep, these approaches risk missing the occurrence of sleep and wakefulness in between observations. It may also disrupt the patients' sleep.

Future efforts to developing methods of detecting sleep disturbances that are feasible to use in nursing homes would greatly benefit the research field as well as clinical practice. Recent developments of a non-invasive radar-based sleep detector represent a promising solution [314]. In the meantime, the SDI may serve as a practically feasible tool with higher accuracy than many of the tools which are now commonly used in the nursing home context.

5.2 Discussion of the methods

5.2.1 Discussion of the methods used in Paper 1

Paper 1 was a systematic review providing an overview of studies assessing the effect of BLT in people with dementia. We used a systematic approach to the identification and selection of relevant studies to include in the review, and extracted predetermined data. To ensure transparency of the review, data were reported in line with the PRISMA Statement and the study protocol was preregistered in the PROSPERO database.

Originally, one of the aims of Paper 1 was to perform a systematic review with a meta-analysis, adding to the findings by Forbes et al. [226] and van Maanen et al. [227]. Meta-analyses combine data from multiple studies and provide a quantitative estimate of the combined effect [315]. Following the systematic identification and inclusion of relevant literature, however, it became apparent that a meta-analysis would require the exclusion of several of the identified studies. Overall study quality was low, with few RCTs, and many studies included relatively few participants. We aimed to provide a detailed overview of the field and thus to include as many studies as possible. Further, the studies were quite heterogenous, and they varied widely in terms of intervention characteristics, i.e., the timing and duration of treatment, illumination level, the spectral composition of the light, and the method of delivery (light box, ambient light), and also in terms of outcomes. Hence, pooling the data from heterogeneous studies

may not be appropriate [316]. In order to provide a broad overview of the field, we decided to pursue a narrative synthesis of the data.

Systematic reviews where a meta-analysis is not conducted has been referred to as "qualitative meta-analyses" [317]. Qualitative meta-analyses summarize the results from studies that have been identified using a systematic approach, but does not combine the data in a statistical analysis. Thus, conclusions about effects may not be established. Instead, we aimed to delve into the heterogeneity of the studies and mapped out the different approaches to delivering BLT, providing a comprehensive background for those searching to gain insight into the field. We also attempted to evaluate how differences across studies in terms of intervention strategies, population characteristics, or design could potentially have affected the results, in order to point out potential covariates, and also to provide some recommendations for future research.

Risk of bias

Systematic reviews entail a systematic search of the literature to minimize bias in the selection of studies [317]. The purpose of a systematic review is to provide a complete overview of the existing research on a topic, using a systematic approach to identify all available scientific evidence, and securing that the evidence accurately reflects the research that has been carried out [315]. In Paper 1, we used a predefined protocol-based search method, searched multiple relevant search engines, and selected studies for inclusion using predetermined criteria.

We did not, however, include grey literature, i.e., literature that is not published in peer-reviewed journals. Examples are conference abstracts, reports, and dissertations. Thus, we may have missed relevant research, and importantly, may have introduced publication bias. Publication bias arises when the publication of research depend on the results, where significant or positive results are more likely to be published than non-significant or negative results [318]. However, retrievable unpublished papers are not representative of unpublished literature in general [319].

To assess risk of bias in each of the included studies, we assessed study quality using a quality assessment instrument [288]. We chose to use a relatively simple scale because the review in itself aimed to address methodological issues in the included papers in great detail. However, more comprehensive quality scales such as the GRADE approach [320] are commonly used in systematic reviews, and could have increased the comparability across reviews in dementia research.

Study selection

As mentioned above, a systematic literature review summarize and analyse all the available research literature on a topic [315]. But what is considered "all the literature" in BLT research is not straightforward. Unlike previous systematic reviews [226, 227, 255, 303], we focused on studies using indoor electrical light interventions delivering bright light, thus excluding dawn-dusk simulation and outdoor light. Dawn-dusk simulation does not exceed standard light levels [321], as it entails a gradual increase of the light level from darkness to typically 200-300 lux, starting prior to wake-up. While Gasio et al. [321] found beneficial effects of this intervention, it deviates from what we defined as bright light, as it does not entail an increase in light exposure, but rather a change in the timing of exposure. Further, we did not include studies that had utilized outdoor daylight as an intervention [322, 323], obtained by taking the patients outside. This inevitably entail social interaction and physical activity. These activities may themselves have therapeutic effects [221], and may complicate the interpretation of results. Also, there is a potentially beneficial effect of exposure to the natural world [324]. While increased physical activity, social interaction, and outdoor environments, in addition to increased light exposure, could possibly represent an effective intervention in terms of mood, behaviour, sleep, and circadian rhythmicity in people with dementia, the goal of the systematic review was to synthesize studies that used indoor illumination alone. Paper 1 was therefore intended to be more relevant to researchers studying or planning to study the effect of indoor electrical lighting systems than previous reviews.

5.2.2 Discussion of the methods used in Paper 2 and 3

This section will discuss central methodological aspects pertaining to Paper 2 and 3: i) the placebo condition, ii) estimating light exposure, iii) challenges pertaining to actigraphy and to the SDI, iv) sleep as one of several outcomes, v) the analytic strategy of Paper 3, vi) sources of bias and internal validity, and vii) external validity.

The light characteristics of the placebo condition

In DEM.LIGHT, we used a placebo condition consisting of standard light values. Ideally, the control units should also have had new light fixtures installed, which could be programmed to deliver almost any light values. Unfortunately, this was not economically feasible. The best alternative was to replace the light sources of the existing light fixtures, with sources of identical light characteristics in all control units. As a result, the lux in the control units varied, as the number and placement of light fixtures and number and placement of windows varied. However, we secured that none of the control units used blue-enriched light sources of high CCT. The light levels in the control units were significantly lower than the light levels in the intervention units, as reported in Paper 3. Importantly, all control units had the lighting changed in the common room in their unit.

Estimating light exposure

In BLT studies using light boxes, participants sit in front of the light box for a restricted period of time, thus securing the target light exposure. When using ambient light, participants move freely in the BLT room/area, and may come and go as they please. Thus, individual light exposure is likely to vary across participants. In the DEM.LIGHT trial, we estimated individual exposure based on reports from the staff. As the staff had to approximate the average time spent in the living room each day for the last eight weeks for each patient, these estimates likely deviated somewhat from true exposure. Further, the participants may have sat with their face downwards or with their eyes closed, reducing the amount of light entering the eye. Future studies could benefit from improved accuracy of estimating light exposure by monitoring time spent in treatment areas, for example using wearable tracking devices. Accurately measuring light exposure was recently listed as one of the main goals of daylight

research in a report by Münch and colleagues [78]. Hopefully, future technological advances will result in accurate measures of light exposure that are also feasible to use in the nursing home context.

Another aspect of estimating light exposure pertain to the light metrics used in Paper 3. To increase comparability with other studies, we reported the illumination (lux) and CCT (K) of the intervention and placebo conditions. In addition, melanopic illuminance was reported, calculated using the toolbox developed by Lucas et la. [90]. It is a weakness of Paper 3 that we did not calculate light levels using the CIE toolbox [91], as this represents the most recent and updated standard. However, the CIE standard is based on the toolbox developed by Lucas et al., and produces an output that is marginally different from the Lucas et al. toolbox. Hence, there is little reason to believe that using the melanopic EDI, as opposed to the equicalent melanopic illuminance provided by Lucas et al., would significantly impact the results of Paper 3.

Challenges pertaining to actigraphy

In the DEM.LIGTH trial, actigraphy was used as an objective measure of sleep. Some specific challenges pertain to the use of this equipment.

Using actigraphy as a reference standard

The first issue related to actigraphy is the use of this measurement method as a reference standard in Paper 2.

To determine the accuracy of a test, the same people are subjected to the test as well as to a "gold standard" test (i.e., the reference standard), indicating the true presence of a disease or condition [325]. Then, test results are classified as either true positive, false positive, true negative, or false negative, compared to the reference standard. In the DEM.LIGHT trial, actigraphy was considered the most feasible option serving as an objective measurement of sleep and as the reference standard [283, 326]. The actigraphs are small and light, and are generally well tolerated, and thus actigraphy is widely used in sleep research involving people with dementia [283]. Actigraphy allows measuring sleep over a prolonged period of time and does not limit the patient

in his/her daily activities. However, actigraphy have some caveats that need to be considered.

Actigraphy may overestimate sleep [262, 263]. Research has shown that compared to PSG, the accuracy of actigraphy to detect sleep and wake declines with lower sleep efficiency, i.e., the accuracy is lower in populations with low sleep quality [262]. This is mostly due to a decline in specificity, i.e., the ability of the actigraphs to detect wake. Actigraphy is solely based on motor activity, and thus quiet wakefulness, when subjects are awake but not moving, may be interpreted as sleep [262]. This is particularly relevant for immobile nursing home patients. Sivertsen et al. [263] found that in older individuals, the specificity of actigraphy was only 36%, and that actigraphy overestimated sleep and underestimated sleep onset latency and total wake time compared to PSG. In a group of older women with insomnia, Taibi et al. [327] found a SE of 84% from actigraphy recordings, compared to only 67% when measured by PSG. A potentially low specificity of actigraphy might have caused measurement error, which would impact the convergence between the SDI and actigraphic parameters in Paper 2. The results of that study should be interpreted with these caveats in mind. Importantly, if total sleep time, which was used to define disrupted sleep (TST<6 h), was over-estimated, then the suggested cut-off on the SDI may be too high.

Using a fixed rest interval for actigraphy outcomes

To estimate sleep outcomes, *Actiware* requires a defined rest interval, either set automatically by the software, or defined by the user. Several protocols for defining the rest interval have been proposed [e.g., 197, 328]. These protocols rely heavily on the participants (or the nurses on duty) pressing the event button on the actigraphs at "lights out" in the evening and "lights on" in the morning, which results in marker set times in the actigraphy output. In the DEM.LIGHT trial, we encouraged the nursing home staff, through oral and written messages, to push the event marker to indicate bedtime and rise time. Unfortunately, the event markers were used in <50% of the intervals in the actograms.

Protocols for defining rest intervals often use activity and light exposure information to determine bedtime and wake-time when event markers are not available. We initially aimed to manually set the rest intervals for each individual night using a predetermined protocol. However, nursing home patients spend a significant amount of time in bed [197, 198], and determining a true bedtime and wake-time was thus challenging. The pattern of activity and light exposure was extremely irregular, complicating the definition of bedtime and wake-time. For these reasons, it is common to use a fixed rest interval in studies involving participants with dementia, and we decided to use a fixed rest interval from 22:00 to 06:00 in Paper 2 and Paper 3. This interval was based on previous studies including people with dementia [9, 18, 229, 243, 284, 329]. Although nursing home patients may spend more than 12 hours in bed [197, 198], bed time and wake time varies across nursing homes and across individuals. The interval from 22:00 to 06:00 was considered likely to capture the main sleep episode of the majority of patients, without including a significant amount of time spent out of bed.

One important drawback of using fixed rest intervals is that individual variations in sleep patterns [33] may be interpreted as poor sleep. Some patients might have a delayed circadian phase and prefer to go to bed later and get up later. For example, even though a person slept well from 24:00 to 08:00, the sleep efficiency would still be only 75% using a rest interval from 22:00 to 06:00. Further, if a participant slept from 22:30-06:00 at baseline and then shifted his or her sleep episode to 23:30-07:00 at follow-up, this would be interpreted as a deterioration of sleep in terms of TST and SE (as illustrated in Figure 7). Conversely, shifting the sleep episode to earlier hours would also be interpreted as a deterioration of sleep. However, such shifts in the sleep episode may not represent a deterioration of sleep in the perspective of the patient or the staff. A reliable way to determine each individual's bedtime and wake-time would therefore be ideal, however, this could not be achieved in the DEM.LIGHT trial.

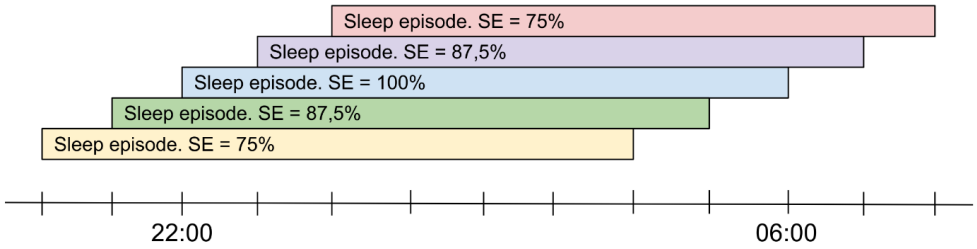

Figure 7: A demonstration of how the sleep efficiency declines if the timing of the sleep episode is shifted. SE= Sleep efficiency

Choosing an actigraphy-based cut-off to define sleep problems

In Paper 2, "disrupted sleep" was defined as a TST in the rest interval of below six hours, as measured by the actigraphs. This corresponds to a SE of 75% in the fixed rest interval. In otherwise healthy adults, disrupted sleep is often defined as having a sleep efficiency of below 85% [330, 331], and this cut-off was also used in a study including people with dementia by Blytt et al. [197]. The six hour cut-off used in Paper 2 was based on Yesavage et al. [332], and also on the original publication on the SDI by Tractenberg et al. [203]. However, different fixed rest intervals were used in the two publications, from 21:00-06:00 and 20:00-08:00, respectively. Thus, the cut-off from Yesavage et al. [332] correspond to a SE of 67% and the one from Tractenberg et al. [203] to 50%. Ju et al. [333] used a sleep efficiency of 75% as a cut-off in a study of people with Alzheimer's disease, although based on individually defined rest intervals. As elaborated in the background chapter, sleep often becomes more fragmented as we age, and dementia is associated with a further deterioration of sleep. Therefore, using a definition for sleep disturbances that is normally used in otherwise healthy adults (SE<85%) would perhaps be too inclusive, in terms of defining people as sleep disturbed while they actually slept quite well given the circumstances. Conversely, using a cut-off of a SE<67% or <50% seemed too lenient, in terms of defining people as not sleep disturbed and who actually only slept somewhat more than half of the time in bed. Using a cut-off corresponding to a SE<75% was all in all considered a golden middle ground.

Duration of actigraphy recording

In the DEM.LIGHT trial, patients wore the actigraphs for approximately seven days. There are some indications that actigraphs should ideally be used for 14 days, as this results in the highest stability coefficients [262, 334]. Due to night-to-night variability in sleep, sleep estimates based on only one or a few nights may not reflect the average sleep of a person, and measurements made a few days later may provide estimates that deviate greatly from the initial estimate (i.e., the sleep estimate has low stability, and thus reliability) [334]. By increasing the number of consecutive nights of measuring activity, the difference between the average sleep estimates calculated at two time points is reduced and the stability is increased. Although van Someren [334] recommended two weeks of recording, estimates based on seven days of recording had adequate reliability. Similarly, Rowe et al. [335] found that the aggregated means for TST, SE, SOL, and WASO were consistent across 3, 7, and 14 days of measurements. Using actigraphs for seven days is common in sleep research [262, 283], and was also the most practically feasible option in the DEM.LIGHT trial.

Challenges pertaining to the SDI

Daytime staff rating nocturnal behaviour

The SDI was completed by daytime staff. It is possible that the SDI completed by night-time staff would have reflected the sleep of the patients more accurately, as daytime staff did not directly observe the patients during the night.

The SDI was only one out of multiple scales the staff completed. We aimed to have one rater complete all questionnaires for the same patient to secure consistency across the proxy-rated scales. Further, the night shifts are generally poorly manned, where one nurse is often responsible for many patients [143], and where the night-time staff may not know the patients as well as the daytime staff. As argued in Paper 2, clinical decisions are often made by the nursing home physician in collaboration with daytime staff. Night-time staff convey information to the daytime staff orally and/or in written form in the patients' journals. Thus, daytime staff are normally well informed about how the night has passed and if there were any clinically relevant events during the night. However, these "distal" estimates may have introduced measurement error and

should inform he interpretation of the results. This is particularly relevant for Paper 2, as we compared the SDI completed by daytime staff with night-time actigraphy recordings. The fact that there was satisfactory correspondence between the SDI and actigraphy is uplifting as it suggests that the usual procedure for administering tests during the day is possible also with the SDI, given an adequate communication between the night and day shift.

However, it is possible that the correspondence between the SDI and actigraphy (Paper 2) would have been better if the former was completed by night-time staff, and future studies should address this issue. Importantly, errors stemming from the daytime staff rating sleep is 'non-differential', i.e., is not different for the intervention group and the control group [336].

Lack of temporal overlap between actigraphy and the SDI

Another limitation is the lack of a temporal overlap between the actigraphy recordings and the SDI, which is particularly relevant to Paper 2. The SDI asked about the last two weeks, while the actigraphy outcomes were summaries of at least five days of measurement (mean duration of measurement 7.7 days). The actigraphy recordings were made during the same week as the SDI was completed, hence, the SDI included time when the patients were not wearing an actigraph.

In relation to Paper 2, there is a possibility that the correspondence between the SDI and the actigraphy recordings would have been higher if there was complete temporal overlap between the two measurements.

Sleep as one of several outcomes in the DEM.LIGHT trial

The aim of the DEM.LIGHT trial was to assess the effect of BLT in nursing home patients with dementia. Due to the comprehensive effect of light on human functioning, including effects on circadian rhythmicity, alertness, and mood, the response to treatment can potentially be detected by many different oucomes. Thus, although sleep and circadian rhythmicity were the primary outcomes, important secondary outcomes were BPSD and functional status. Therefore, we used wide inclusion criteria, where participants had to have *either* disrupted sleep, clinically

significant BPSD, or significantly reduced function (ADL). Consequently, we included participants both with and without sleep disturbances. Ideally, we should have included enough patients to run subgroup analyses and thus be able to evaluate the effect in only those with sleep disturbances at baseline. We did, nevertheless, account for individual baseline values on the primary outcome including a random intercept in the mixed linear models.

Methodological issues relating to the analysis of data in Paper 3

In RCTs, known and unknown confounding factors are balanced between groups by using randomization [237]. The goal is to create a control group that is as similar as possible to the intervention group, so that differences in outcomes can be assigned to the intervention and not to baseline differences between the groups. Due to the nature of the BLT intervention in the DEM.LIGHT trial, namely an ambient light intervention in the common room of each nursing home unit, the patients living in the same unit had to belong to the same group. Thus, each unit represented one out of eight clusters that were randomized to either the intervention group or the control group. Cluster-randomized trials are subject to some specific challenges.

Sample size and power

The power-analysis showed that we needed 64 patients when including eight clusters. As we expected some drop-out, the aim was to recruit 80 participants from eight clusters. Because not all of the patients living in the included units could be included in the trial (were not eligible or declined to participate), we only achieved 69 participants at baseline. Further, participants died or moved (mostly to a somatic unit due to deterioration of physical health) during the study, and some were excluded from the analyses due to non-compliance. Thus, we might not have had sufficient power to detect effects. As the patient group had severe dementia and several medical comorbidities, a large improvement in sleep could not be expected. Ideally, the trial should have included more patients.

Beyond the total number of participants, the number of clusters was a weakness of the DEM.LIGHT trial. Although we accounted for cluster-effects when calculating the minimum number of participants needed, we did not calculate the optimal number of

clusters. In cluster-randomized longitudinal studies, data are clustered both within each individual (several measurements of one individual are likely to correlate) and within the cluster. Outcomes from subjects from the same cluster are likely to correlate more strongly than with the outcomes of subjects from other clusters [337]. In the DEM.LIGHT trial, routines or other characteristics of the different nursing home units may have deviated, representing cluster-specific influences on the patients in each unit. Importantly, statistical power increases with the number of clusters [338].

During the course of the trial, we changed the analytical strategy from analysis of variance (ANOVA), to linear mixed modelling. Linear mixed models use all available data, perform better when there are missing data, and adjust for correlation due to repeated measures [298, 299], and was therefore regarded superior to ANOVA. Unfortunately, in order to account for cluster-specific effects using linear mixed modelling, at least 10-15 clusters are needed [339]. Thus, the trial should ideally have included more clusters. Meanwhile, each cluster represented a significant economic cost related to the purchase and instalment of the LED units, and including more than the minimum number of required clusters was not possible.

Accounting for confounding variables

Confounding variables refer to other factors beyond the intervention that affect the outcome and distort the measured effect of the intervention [237]. Nursing home patients with dementia are characterized by several factors that are likely to affect the outcome, such as high age, multimorbidity, high use of medications, or eye disease. Hence, confounding variables were likely in the present study. In order to control for confounding variables, we agreed on potential covariates a priori. Variables were considered relevant based on the literature and we included them in the models if they improved model fit. For example, for the SDI, the average number of psychotropic drugs improved model fit and was thus included as a covariate. This implied that the model became better at predicting the observed outcomes when we controlled for psychotropic drugs, and that those with fewer psychotropic drugs had a larger improvement of sleep than those who received more drugs. This strategy was thus both theoretically and empirically founded [340].

Accounting for baseline differences

If the intervention group and the control group are very dissimilar regarding the primary outcome and confounding variables at baseline, the estimated treatment effect of an intervention may be biased [341]. Systematic baseline differences between the groups are minimized by randomization [342]. Some researchers test for significant differences between the groups at baseline, to evaluate if the randomization was "successful" [343]. However, using an alpha of .05, approximately one in twenty significance tests are bound to show a significant result [343]. Therefore, we did not test for baseline differences in Paper 3, but rather provided the baseline levels of relevant confounding variables (in addition to the primary outcomes) separately for the control group and the intervention group.

Sources of bias

In relation to Paper 2 and 3, some important threats to internal and external validity need to be considered. In the context of intervention studies, internal validity can be defined as the extent to which the differences between the intervention group and the control group can be correctly attributed to the intervention, while external validity refers to the generalizability of the results to other clinical contexts [237]. In the following, threats to internal validity, i.e., sources of bias, will be discussed, followed by a discussion of external validity.

Internal validity is threatened by systematic error. Systematic error, or bias, refers to systematic deviations of the results from the truth, caused by how the study was designed, conducted, or reported [237]. Relevant to Paper 3, bias can lead to an overestimation or underestimation of the true effect of an intervention. Bias may also have been operating in Paper 2, affecting the correspondence between the SDI and actigraphy.

Selection bias

Selection bias refers to systematic differences between the intervention group and the control group resulting from the way participants have been assigned to the groups [344]. In some cluster-randomized studies, individual participants are recruited after the clusters are randomized to either the treatment group or the control group. Then,

selection bias may be introduced because the researcher is aware which patients will end up in the intervention group or the control group, and may potentially recruit specific types of participants to the clusters [345]. In the DEM.LIGHT trial, randomization and recruitment of the participants of the included units happened simultaneously, as light installation needed to be planned and carried out in time before the study commenced. The patients already lived in the nursing home units that were randomized, i.e., we had no impact on which group (intervention or control) each patient ended up in. Participants were excluded from the trial only if they fulfilled the exclusion criteria (after discussion with the nursing home physician and nursing staff), or if the patient or the legal guardians declined participation.

Selection bias related to specific outcomes should be considered. For example, some patients refused to wear the actigraphs in one or several of the data collections. Those that did not want to wear the actigraph may have been more agitated, anxious, or confused than those agreeing to wearing them. Thus, the actigraphy outcomes should be considered with this in mind. The same issue applies to the MMSE, where several patient did not complete the instrument due to agitation or confusion, or because they did not want to.

Attrition bias

While randomization balance known and unknown confounding factors across the intervention and control group, attrition bias may arise if patients are lost to follow-up unequally between the groups [237, 346]. During the 24-week follow-up in the DEM.LIGHT trial, six patients were lost to follow-up in the intervention group (four passed away, two moved), while ten patients were lost to follow-up in the control group (nine passed away, one moved). The majority of those that moved, moved due to a deterioration of somatic health. Importantly, there is no reason to believe that the difference in attrition between the groups was related to the intervention, i.e., that the attrition was not random. The nurses did not report adverse events related to the intervention.

To avoid bias stemming from attrition, we used linear mixed modelling, which uses all available data and does not require that participants have completed all four data collections. In addition, whether or not a patient was lost to follow-up during the study was included as a covariate in the analyses.

Performance bias and information bias

Performance bias refers to systematic differences in how the intervention group and the control group are treated, other than the intervention [237]. For example, the people around a patient (clinicians, family members) may think that a treatment is working. This may create a more supportive and optimistic environment around the patient, which in turn could cause behavioural change [347]. Performance bias may significantly impact the effect estimates of a trial.

Information bias (or measurement bias) refers to bias arising from how data are collected or measured [344]. Information bias is relevant to discuss in relation to the SDI and other proxy-rated instruments, which may be subject to bias when the response of the proxy-rater is influenced by knowledge of the intervention received [348]. If blinding was not successful in the DEM.LIGHT trial, the proxy-raters in the intervention group may have reported more favourable outcomes than the raters in the control group.

To reduce performance bias and information bias, we created a placebo condition in the nursing home units in the control group by replacing the existing light sources. The participants and nursing home staff were blinded to which condition they had been assigned to. To prevent any effects of light in the control group, however, the placebo condition had standard light levels. To minimize the chance that nursing staff from different units could compare the light levels, the intervention and control units were at separate nursing homes. However, as lighting is inherently visible, it is challenging to blind participants completely to group allocation in BLT studies. The intervention light setup required that we installed new light fixtures and the light they emitted was much brighter than the lights in the rest of the unit, and thus the intervention may have been apparent to the staff. The patients did not seem very concerned about the new light

setup, but to the staff, the light might have constituted a constant reminder that they were participating in a clinical trial and consequently led to performance bias [347]. In contrast, many of the staff in the control units (those not involved in data collection) may not have been aware that they were participating in a trial. As a consequence, the staff in the intervention group and the control group may have behaved differently towards the patients and thus introducing performance bias.

At the end of the trial, we asked the staff to complete a short questionnaire asking about whether they believed they were in the intervention group or in the control group. Here, we asked all available staff, not limited to the outcome assessors. Five of the 19 staff members in the intervention group who returned the questionnaire believed that they were in the control group, while the remaining 14 respondents correctly thought that they were in the intervention group (not published). Similarly, two of the staff members, out of 12 respondents, in the control group thought that they were in the intervention group. Thus, most staff correctly guessed which group they were in when prompted, however, the blinding can be argued to have been somewhat successful as several wrongly guessed which group they were allocated to. Nevertheless, performance bias and information bias may not be ruled out and the results should be interpreted with this in mind.

External validity

External validity refers to the generalizability of the study results to other settings [237]. In the DEM.LIGHT trial, we recruited participants from nursing homes located in both urban and rural areas in and around the city of Bergen, and from nursing homes of different sizes. We only included dementia units, and thus the participants on average probably had more severe dementia than in other nursing home units. Thus, the results of Paper 2 and 3 may not be generalized to the general nursing home population. However, as approximately 80% of patients in Norwegian nursing homes have dementia, and approximately 47% have moderate and severe dementia [125, 139, 140], it can be argued that the findings may be generalized to a large part of the nursing home population in Norway. The generalizability to other countries depends on how comparable the nursing home populations are. Due to an extensive expansion

of the home-based services for older people in Norway, there has been a reduction in the proportion of people living in nursing homes since the 1990s [138]. As a consequence, more people live at home for a longer time, and those who are admitted to nursing homes are sicker than before. In 2011, 80% of nursing home residents in Norway had an extensive need for assistance in performing activities of daily living [138]. The circumstances are similar in countries such as Sweden, the Netherlands, and the United Kingdom [349], but generalizing to other countries should be done with caution. Overall, the findings in Paper 2 and 3 should be considered in light of the specific characteristics of the populations, such as high age, severe dementia, and multimorbidity. The suggested cut-off for identifying disrupted sleep using the SDI is based on this population, which may not translate to other populations. Further, the effect of BLT found in Paper 3, i.e., an improvement of the SDI and not actigraphy, should also be considered in light of the population. It is, for example, possible that more beneficial effects would be found including people with less severe dementia and a more intact nervous systems.

5.3 Ethical considerations

As the world's population ages, the challenges of dementia care will dramatically increase [152]. Thus, research on dementia care is of both public and academic importance. Informed consent represents one of the most important ethical challenges pertaining to clinical trials including people with dementia, as outlined in section 1.7.4 of the background chapter. As we elaborated in the methods section (section 3.1.12), the majority of patients did not have the capacity to consent to participate in the DEM.LIGHT trial. Thus, their legal guardians provided presumed consent, and the participants were informed about the study in an adapted manner. This means that we may have included people that would not themselves have agreed to participate. Considering this, it may be argued that people with severe dementia should never be included in clinical trials. Conversely, one can argue that the potential value of effective interventions for this population is of utmost importance.

Importantly, the burden on the patients can be argued to have been modest in the DEM.LIGHT trial. We used a non-invasive intervention and the majority of outcome measures involved the staff as proxy-raters rather than the patients. Three of the outcomes, however, involved the participants, namely the actigraphs, the cognitive testing (MMSE), and the pain assessmend (MOBID-2). These were only completed if the participant agreed to complete the assessment and were discontinued if the participant expressed any sign of not wanting to continue. Another important issue pertaining to the intervention is that everyone residing in the room where the intervention was installed are inevitably exposed to the intervention. In the DEM.LIGHT trial, we only installed BLT in the common room of each intervention unit, and patients had alternative spaces to socialize, and their private room had standard light. That said, the intervention entailed light levels far below outdoor light levels, and unwanted effects from the intervention were unlikely. Importantly, nursing home staff were asked to report any negative effects that were likely to be caused by the intervention.

5.3.1 Retinal safety

In healthy adults, light of 17,000 K and 2,500 lux has been determined to be safe in terms of retinal damage [101]. Sloane and colleagues [244] assessed the potential retinal adverse effects specifically in people with dementia. A retina specialist evaluated each participant before and after the study, and also evaluated the potential for retinal damage in those who had underwent cataract surgery (and thus lost the native yellow “blue blocking” lens). They found no eye changes following the intervention of six weeks of ambient light of 13,000 K and 400 lux, delivered from wake-up to 18:00. Although no eye examinations were conducted in relation to DEM.LIGHT, the intervention involved light levels well within safety limits.

6. Conclusion

Paper 1 showed that there are promising results regarding the effect of BLT on sleep, circadian rhythmicity, and also BPSD. However, large heterogeneity in terms of interventions, study designs, and population characteristics may explain the current inconsistency of results across studies. Studies also varied in terms of which sleep outcomes they measured and how they operationalized actigraphy outputs. Several potential moderating factors emerged as we reviewed the study designs and procedures.

Paper 2 showed a satisfactory internal consistency of the SDI and convergent validity between the SDI and actigraphy. The ROC analysis showed that the SDI was clinically useful, and based on calculations of the Youden's Index, we suggested a cut-off score on the SDI of five or more as defining disrupted sleep. These results should be interpreted keeping in mind that actigraphy have some important weaknesses, such as underestimating wake time. Also, proxy-rated tools may be vulnerable to bias. However, the SDI may represent a useful a screening tool to identify patients in the nursing home context with probable sleep problems.

Paper 3 showed that the SDI of the intervention group improved significantly from baseline to week 16 and baseline to week 24, compared to the control group, using an ambient BLT solution with a maximum of 1,000 lux and 6,000 K (10:00-15:00). However, these findings were not corroborated by actigraphy. Although these results are not conclusive about the effect of BLT on sleep in nursing home patients with dementia, it adds to the understanding of the potential value of BLT in this population.

In summary, the evidence for an effect of BLT on sleep in nursing home patients with dementia is equivocal. Importantly, clinical trials in the nursing home context face some important challenges in terms of measuring sleep in a multimorbid population with a range of potential confounding variables.

7. Implications and future perspectives

Based on the systematic review in Paper 1 and the results from the DEM.LIGHT trial reported in Paper 3, firm conclusions about the effect of BLT in nursing home patients with dementia cannot be drawn. However, some previous RCTs have found positive effects on sleep [19, 20, 252], and an improvement in proxy-rated sleep using an ambient BLT solution was reported in Paper 3. Importantly, the lack of a robust effect of BLT on sleep in dementia may be partly explained by methodological issues (e.g., intervention strategy and detecting changes in sleep) and characteristics of the population and setting (e.g., various neurodegenerative conditions, polypharmacy, and nursing home routines), and future studies should aim to address these issues.

As reported in Paper 2, the SDI may represent an improvement of the evaluation of sleep in the nursing home context. However, the SDI should be validated in a larger sample. Importantly, some patients suffering from disturbed sleep, for example sleep apnea, may go undetected using the SDI, and further improvements of sleep assessment in the nursing home are welcome. Similarly, BLT research involving people with dementia would greatly benefit from objective measurements of sleep that overcome the weaknesses of actigraphy.

Although Paper 3 showed an improvement in the SDI in the intervention group, these findings were not corroborated by actigraphy. Importantly, the participants recruited to the DEM.LIGHT trial had severe dementia. There is a possibility that BLT at this stage is less effective, as the patients may have severe neurodegeneration and eye pathology that prevent an effect of light on sleep. Future studies should assess the effect of BLT earlier in the course of the disease, e.g., among people with mild to moderate dementia.

The DEM.LIGHT trial demonstrated that it is possible to implement ambient BLT in nursing homes. A strength of the study was that we completed a pilot and adjusted the intervention strategy according to feedback from the staff. The BLT field would greatly benefit from more studies evaluating light preferences in the living environment, in order to strike a balance between sufficient light exposure to stimulate

NIF responses in people with dementia, while also providing a light setting that is comfortable for those who live there and are exposed to it. Light preference is understudied, and to my knowledge, no studies have evaluated light preference among nursing home patients and/or staff.

The low light levels reported in several studies measuring illumination in nursing homes indicate that optimizing indoor light levels in terms of non-visual effects is not prioritized in the health sector. In the future, the importance of daylight in sleep-wake regulation should be implemented more heavily in nursing homes. In addition to the potential of enhanced indoor electrical light/BLT, building nursing homes that allow for easy access to areas with ample daylight and facilitating light-orienting behaviour in patients might reduce the prevalence of sleep problems in this population. Particularly in high-latitude countries such as Norway, exposure to sufficient light during the day is challenging during winter. Then, BLT may offer a non-pharmacological intervention to improve or prohibit a deterioration of sleep among nursing home patients. However, more research is needed to identify the optimal treatment strategy.

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Appendices

Appendix 1: Paper 1

Appendix 2: Supplementary Table S1, Paper 1

Appendix 3: Paper 2

Appendix 4: Paper 3

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CLINICAL REVIEW

Light interventions and sleep, circadian, behavioral, and psychological disturbances in dementia: A systematic review of methods and outcomes

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Behavioral and psychological symptoms of dementia

SUMMARY

Dementia is a devastating disease with a global impact, and there is an urgent need for effective interventions to alleviate the accompanying disturbances in behavior, mood, sleep, and circadian rhythms. Bright light treatment (BLT) is a promising non-pharmacological intervention; however, studies have yielded conflicting results. This systematic review provides a comprehensive overview of the effect of BLT in dementia, with a specific focus on how study characteristics might have affected the available results. The included studies were small and comprised time-limited interventions and follow-ups. Light values, adherence to treatment, and time of year were not consistently reported. Varying designs, methods, and population characteristics such as age, gender, dementia diagnosis, circadian phase, and baseline symptoms may have moderated the outcomes and affected review results. The use of crossover designs and too high illumination as placebo lights might have nullified positive effects of BLT. Because some studies had negative outcomes after ambient BLT with high amounts of short wavelengths, more modest light levels should be further investigated. Employing rigorous designs and detailed reporting of intervention characteristics, i.e., the illumination, correlated color temperature, timing, and duration of light utilized, are of utmost importance to establish the optimal treatment approach in this population.

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Introduction

Approximately 50 million people worldwide are affected by dementia, and the number is estimated to exceed 150 million by 2050 [1]. Dementia is characterized by impaired cognition, and "behavioral and psychological symptoms of dementia" (BPSD), such as sleep problems, agitation, depression, and psychosis [2]. Approximately 90% develop one or more BPSD during the course of their disease [3,4] and over 70% experience disrupted sleep already in the early stages of dementia [5]. BPSD and sleep problems result in distress for the patient and family members [2] and are often the main causes of institutionalization [6,7]. Thus, effective interventions for BPSD and sleep problems are of great individual and societal importance.

People with dementia often show circadian dysregulation, with several sleep and wake periods occurring throughout the 24-h day [8,9]. Some patients exhibit a diurnal rhythm in BPSD, with increased agitation, confusion, and wandering in the afternoon and evening. This phenomenon is referred to as "sundowning" and is thought to reflect a breakdown of circadian rhythmicity [10–12]. Circadian dysregulation has further pervasive effects on neural and

Abbreviations: AD, Alzheimer's disease; BLT, Bright light treatment; BPSD, Behavioral and psychological symptoms of dementia; CCT, Correlated color temperature; CMAI, Cohen-Mansfield Agitation Inventory; K, Kelvin; MMSE, Mini-Mental State Examination; NIF, Non-image forming; RCT, Randomized controlled trial.

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neuroendocrine systems, including cognitive and emotional functioning [13].

Daylight, our most important "zeitgeber", entrains circadian rhythms, and directly affects wakefulness, mood, and cognition, phenomena referred to as non-image forming (NIF) functions [e.g., Ref. [14]]. The physiological response to light depends on duration and timing of exposure, the amount of light, in terms of illuminance (lux) and spectral composition, as well as on previous light exposure [15]. The NIF system is maximally sensitive to short wavelengths (~460 nm), corresponding to blue light [16,17]. Generally, by increasing the amount of short wavelengths emitted by light sources, i.e., increasing the correlated color temperature (CCT), lower illumination is sufficient to stimulate NIF responses. For example, 100 lux at the cornea with 4100 K was shown to cause a mean melatonin suppression of 10%, whereas 100 lux at the cornea with 8000 K caused a mean melatonin suppression of 32% [18].

With increasing age, the amount of light reaching the retina is reduced due to lens yellowing and pupil constriction [19,20]. While compensatory mechanisms may preserve light sensitivity to some degree [21], lens yellowing has been associated with self-reported sleep disturbances [22]. Alzheimer's disease (AD) is associated with pathological changes in the retina and the optic nerve. Importantly, these include the loss of intrinsically photosensitive melanopsin-containing retinal ganglion cells, which are largely responsible for NIF responses [23]. Other ocular changes associated with AD that may disrupt circadian regulation entail among others glaucoma, macular degeneration, pupillary dysfunction, and reduction in optical nerve fiber thickness [24]. Further, dementia care institutions generally appear to have low levels of illumination [25–27], and home-dwelling dementia sufferers are often exposed to lower light levels than healthy older adults [28]. In a study of seven nursing homes in the Netherlands, vertical illuminances in common rooms fell significantly below the 750 lux reference (based on an age-adjustment of standard EN 12464-1:2011 [27]) in at least 65% of the measurements [29]. In addition, the median color temperature was below the reference value of 5000 K set for daylight. Taken together, these factors imply that older people suffering from dementia are commonly exposed to insufficient light levels, in turn contributing to sleep problems and circadian disruption [25,28].

Increasing light exposure, in terms of illumination and/or CCT, i.e., bright light treatment (BLT), has therefore been suggested to be a promising non-pharmacological intervention for sleep disturbances and BPSD [30]. Typically, BLT has been delivered as high illumination white light using table-mounted "light boxes". Recent technological developments allow for manipulation of both the illumination levels and CCT, often delivered as ambient light in common rooms.

BLT has been shown to have positive effects on BPSD [31,32], sleep [32], and circadian rhythms [33] in dementia. However, a Cochrane meta-analysis from 2014 concluded that it was "premature to recommend the use of light therapy in practice" [34]. Other meta-analyses have reported more encouraging results, with moderate effect sizes in terms of behavioral disturbances and depression [35], but small effect sizes regarding sleep [34,36]. These meta-analyses only included randomized-controlled trials (RCTs), thus many studies were excluded. The mixed study results and mediocre effects in meta-analyses may partly be a consequence of differences in the design of interventions, such as the timing, duration, and spectral composition of light. Also, dementia diagnosis and severity varied across studies.

Against this backdrop, the present review aimed to synthesize results from BLT studies including people with dementia, focusing on identifying methodological characteristics that may have moderated the outcomes. Specifically, the aims of this review were to: 1) provide an overview of how light treatment has been administered (delivery method, timing, duration, illumination and CCT), 2) describe experimental study designs and outcome measures, 3) evaluate how study results might have been influenced by methodological factors.

Method

Systematic literature searches were conducted in relevant databases: CINAHL, Medline, PsychINFO, Embase, Web of Science, and Cochrane libraries. The systematic search was conducted in March 2019 covering MESH terms and free text phrases synonymous with "bright light treatment", "dementia", and "nursing home". A complete overview of the different MESH terms and free text is available as an online resource (Table S1). No time limit was set for the searches. We defined BLT as an enhanced indoor electrical light scheme aimed at impacting NIF responses including mood, behavior, sleep, and/or circadian rhythmicity. The interventions had to entail an increase in illumination (lux) and/or CCT compared to baseline or control conditions. BLT using outdoor daylight often involves physical and social activity, which have therapeutic effects [37]. Dawn-dusk simulation does not exceed standard light levels [38], and did not coincide with how BLT was defined in the present study. Hence, studies on such interventions were also excluded. The studies had to inform about lux or equivalent unit. Included studies had to implement BLT as an intervention using standard care group comparison, placebo group comparison, or a single group pre-post design. We only included studies with participants with dementia, based on medical records, diagnosed specifically for the study according to the Diagnostic and Statistical Manual for Mental Disorder (DSM) or the International Classification of Disorders (ICD) system, or by using a Mini-Mental State Examination (MMSE) cut-off. When both people with and without dementia were included, the study was included only if the results from the dementia participants were reported separately. Only quantitative study designs were included, excluding publications such as case studies, chronicles, guidelines, protocols, non-systematic reviews, legal documents, conference abstracts, and other grey literature, as well as non-English publications. We also excluded studies where BLT was combined with other treatments. Based on these criteria, the authors screened potential manuscripts at the abstract level (E.F. and G.H.) and subsequently applied the inclusion and exclusion criteria to selected full texts (G.H. and E.K., see Fig. 1). The reference lists of the full-text publications were searched for any relevant publications that were not identified in the systematic search.

All authors agreed on the information of interest, and one author (G.H.) extracted the content based on a standardized form. The following information was extracted: full reference, number of participants, participant characteristics, study design, type of intervention and control condition, time to follow-up, study setting, outcome measures, and results. To differentiate between types of interventions, BLT interventions using 1000 lux or more, without manipulating CCT, were categorized as "high illumination", as this threshold has been used as a definition of bright light in previous studies [39,40]. Interventions with a CCT of 5000 kelvin (K) or more were, for the purpose of this study and in line with [29], classified as "high CCT" interventions. In the case of a combination of high CCT and an illumination of 1000 lux or more, the study was classified as "high CCT".

The study quality was assessed using the Oxford Quality Scoring System [41], in terms of randomization, blinding procedure, and descriptions of withdrawals. Studies were graded from zero to five, where a higher score reflected a more rigorous study. The studies were evaluated by two authors (G.H. and E.K.), and any disagreements were discussed in a group meeting with a third author (E.F.) to reach consensus.

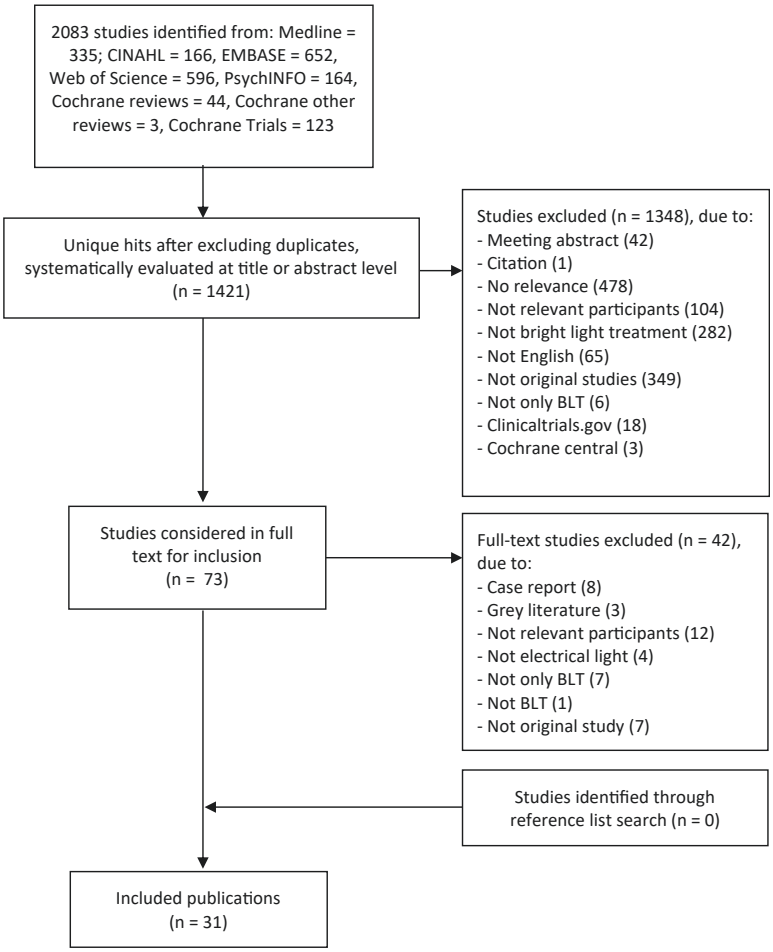

Fig. 1. PRISMA based flowchart of the systematic search and review process.

Results

The articles included in the review are presented in Table 1. A comprehensive overview of methodological characteristics of the included studies are available as a supplement (Table S2). The systematic search generated 1421 unique hits after duplicates were excluded (Fig. 1), 73 papers were identified for full-text evaluation, and of these 31 publications based on 24 studies met the inclusion criteria. Three publications by Fetveit et al. [42–44] reported from the same study, two publications by Ancoli-Israel et al. [33,45] reported from the same study, two publications by Onega et al. [46,47] reported from the same study, and Sloane et al. [48], Hickman et al. [49], and Barrick et al. [50] reported from the same study. Lovell et al. [51] reported on a sub-population from a second study by Ancoli-Israel et al. [52].

Population characteristics

The sample size ranged from 6 to 92. In all, 21 studies included institutionalized patients, and three studies included home-dwelling participants. Mean age ranged from 70.1 to 88.2 years. On average, the sample comprised 63% women. The mean MMSE score ranged from 0.6 to 22.1 (Table S2). Eight studies reported a specific symptom or diagnosis, e.g., depression, as an inclusion criterion [31,32,43,51,53–56]. Four studies excluded participants if they had sleep-wake disturbances [52,57], or depression [58,59].

Light therapy intervention

The interventions varied in terms of method of delivery, timing, duration, illumination, and CCT. A total of 16 studies provided BLT with high illumination (1000 lux or higher). Out of these studies, 14 employed light boxes [31,33,43,47,52,54–62] and one used ceiling-mounted white light [63]. Target light values of the light boxes ranged from 2500 to 10,000 lux at eye level from a distance of 0.3 m–1.0 m [31,43,45,47,51,52,54–62], as measured at eye level [33,52,55,61] or provided by the manufacturer. The ceiling-mounted light provided about 1100 lux measured at eye level [63]. Only one study reported if the measurement was done horizontally or vertically [63].

Table 1
An overview of the included studies.

Study ID [reference], country, quality grade	Participants	Intervention	Comparison	Outcomes
Ancoli-Israel et al. (2002) [52], USA, 3 Lovell et al. (1995) [51], USA, 1	$n = 77$, dementia by MMSE, mean 12.8 (8.8)	10 d, 2 h morning or evening, light box, 2500 lux. Control dim red.	RCT	[52] **Sleep**: Actigraph **Circadian rhythm**: Actigraph
	Subpopulation from [52]. $n = 6$, dementia defined by MMSE, range 0 −14		Pre-post.	[51] **BPSD**: Observed agitation
Ancoli-Israel et al. (2003a) [45], USA, 3 Ancoli-Israel et al. (2003b) [33], USA, 3	$n = 92$, dementia defined by MMSE, mean 5.7 (5.6)	10 d, 2 h morning or evening, light box, 2500 lux. Control dim light	RCT	[45] **BPSD**: Agitation
				[33] **Sleep**: Actigraph **Circadian rhythm**: Actigraph
Hickman et al. (2007) [49], USA, 1 Barrick et al. (2010) [50], USA, 1 Sloane et al. (2007) [48], USA, 1	$n = 66$, dementia diagnosis in medical record	3 wk, 4 or 13 h morning, evening or all day, ceiling-mounted light, approx. 2000−2500 lux, 6500 K.	Cluster-unit crossover	[49] **BPSD**: Depression
				[50] **BPSD**: Agitation
				[48] **Sleep**: Actigraph **Circadian rhythm**: Actigraph **Side effects**
Burns et al. (2009) [56], England, 3	$n = 48$, dementia diagnosis (WHO) confirmed by research team	2 wk, 2 h morning, light box, 10,000 lux.	RCT	**BPSD**: Agitation, behavioral disturbance, depression **Cognitive function** **Sleep**: Observation and actigraph **Circadian rhythm**: Actigraph
Fetveit et al. (2003) [43], Norway, 1 Fetveit and Bjorvatn (2004) [44], Norway, 1 Fetveit and Bjorvatn (2005) [42], Norway, 1	$n = 11$, dementia defined by MMSE and CDR, mean MMSE 11.7 (4.2) and mean CDR 2.5 (0.5)	2 wk, 2 h morning, light box, 6000 −8000 lux at 60−70 cm.	Pre-post.	[43] **Sleep**: Sleep chart, actigraph **Circadian rhythm**: Actigraph
				[44] **Sleep**: Actigraph **Circadian rhythm**: Actigraph
				[42] **Sleep**: Sleep chart, actigraph
Figueiro et al. (2014) [32], USA, 0	$n = 14$, dementia diagnosis (DSM-IV) confirmed by the resident physician	4 wk, all day, customized luminaires, ambient light, 300−400 lux, 9325 K.	Pre-post.	**BPSD**: Agitation, depression **Function/severity**: Activities of daily living **Sleep**: Questionnaire, actigraph. **Circadian rhythm**: Actigraph
Figueiro et al. 2015 [67], USA, 0	$n = 35$, dementia diagnosis (DSM-IV) confirmed by participants' physicians	4 wk, all day, customized luminaires, ambient light, 350−400 lux, 9325 K.	Pre-post.	**BPSD**: Depression **Sleep**: Actigraph **Circadian rhythm**: Actigraph
Graf et al. (2001) [59], Austria, 2	$n = 23$, dementia defined by MMSE score ≤ 23	10 d, 2 h evening, light box, 3000 lux. Control dim light.	RCT.	**Function/severity**: Cognitive function **Circadian rhythm**: Axillary temperature
Lyketsos et al. (1999) [57], USA, 2	$n = 15$, all met criteria for dementia (DSM-IV)	4 wk, 1 h morning, light box, 10,000 lux. Control blinking light.	RCT with cross-over,	**BPSD**: Behavioral disturbance, depression: **Sleep**: Observed hours of sleep
McCurry et al. (2011) [54], USA, 3	$n = 67$, dementia defined by diagnosis in medical record	2 mo, 1 h evening, light box, 2500 lux	RCT	**Sleep**: Questionnaire, actigraph

Mishima et al. (1994) [55], Japan, 0	$n = 14$, dementia diagnosed based on medical history, mental symptoms, or CT or MRI findings.	4 wk, 2 h morning, 3000–5000 lux	Pre-post.	**BPSD**: Observed behavior disorders **Sleep**: Sleep diary **Circadian rhythm**: Serum melatonin
Mishima et al. (1998) [61], Japan, 1	$n = 22$, dementia diagnoses based on MRI, CT, and DSM-IV.	2 wk, 2 h morning, light "box", 5000–8000 lux. Control dim light	RCT with crossover	**Sleep**: Actigraph
Münch et al. (2017) [66], Switzerland, 1	$n = 89$, dementia diagnosis (DSM-IV) in medical chart	8 wk, all day, dynamic ceiling-mounted light, 6500 K, 1000 lux. Control condition 2700 K, unknown lux.	Non-randomized parallel groups	**BPSD**: Agitation, observed emotions **Function/severity**: Activities of daily living **Other**: Quality of life **Sleep**: Actigraph **Circadian rhythm**: Actigraph, melatonin
Onega et al. (2016) [47] Onega et al. (2018) [46], USA, 3	$n = 60$, dementia diagnosis in medical chart, MMSE mean 7.22 (6.85)	8 wk, 30 min morning and evening, light box, 10,000 lux. Control dim light.	RCT.	**BPSD**: Depression, agitation
Satlin et al. (1992) [60], USA, 0	$n = 10$, all met DSM-III-R criteria for dementia	1 wk, 2 h evening, light box, 1500–2000 lux.	Pre-post.	**BPSD**: Daily ratings of agitation, use of restraints, and medication prescribed-as-needed. Sundowning score. **Sleep**: Actigraph and observation **Circadian rhythm**: Actigraph
Skjerve et al. (2004) [31], Norway, 1	$n = 10$, dementia according to ICD-10	4 wk, 45 min morning, light box, 5000–8000 lux.	Pre-post	**BPSD**: Behavioral disturbance, agitation **Sleep**: Questionnaire, actigraph **Circadian rhythm**: Actigraph
Sloane et al. (2015) [53], USA, 3	$n = 17$, dementia diagnosis in medical journal	6 wk, all day, customized luminaires, ambient light, 13,000 K, 400 lux. Control low CCT light.	RCT with crossover	**BPSD**: Depression **Function/severity**: Activities of daily living **Other**: Caregiver burden, quality of life, retinal adverse effects **Sleep**: Questionnaires, actigraph **Circadian rhythm**: Actigraph
Thorpe et al. (2000) [58], Canada, 0	$n = 16$, dementia diagnosis (DSM-IV) made by research team	5 d, 30 min morning, light box, 10,000 lux	Pre-post	**BPSD**: Agitation, observed behavior **Sleep**: Sleep charts
Van Hoof et al. (2009a) [64], the Netherlands, 1	$n = 26$, dementia diagnosis in medical record	3 wk, 10 h all day, ceiling-mounted, 1760–1810 lux, 6500 K. Control low CCT light.	Two groups, non-randomized	**BPSD**: Behavioral disturbance **Circadian rhythm**: Tympanic temperature
Van Hoof et al. (2009b) [65], the Netherlands, 1	$n = 22$, dementia diagnosis in medical record	4 d, 10 h all day, ceiling-mounted, 400–500 lux, vertically, 17,000 K (achieved mean sign lower, max light of 12,500 K). Control low CCT light.	RCT with cluster-unit crossover	**BPSD**: Behavioral disturbance **Circadian rhythm**: Tympanic temperature
Van Lieshout-van Dal (2019) [68], the Netherlands, 1	$n = 13$, dementia diagnosis (DSM-IV) in medical record	3 wk, 4 h all day, dynamic ambient light by floor lamps, around 1100 lux and around 6500 K	Pre-post (ABABAB-design)	**Sleep**: Activity sensor in bed
Van Someren et al. (1997) [63], the Netherlands, 1	$n = 29$, dementia diagnosed according to DSM-III-R	4 wk, all day, ceiling-mounted light, about 1100 lux.	Pre-post	**Circadian rhythm**: Actigraph
Wahnschaffe et al. (2017) [69], Germany, 1	$n = 12$, dementia diagnosis (ICD-10) in medical record	4 wk, 5 h all day, ceiling-mounted light, about 400 lux, 4440 K	Pre-post	**BPSD**: Agitation **Circadian rhythm**: Actigraph
Yamadera et al. (2000) [62], Japan, 0	$n = 27$, dementia diagnosis (DSM-IV and NINCDS-ADRDA) based on CT in medical record	4 wk, 2 h morning, light box, 3000 lux.	Pre-post	**Function/severity**: Dementia severity, cognitive function **Sleep**: Actigraph

Notes: CDR: Clinical Dementia Rating, DSM: Diagnostic and Statistical Manual of Mental Disorders, ICD: International Classification of Diseases, MMSE: Mini-Mental State Examination, NH: nursing home or equivalent institution, NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, RCT: randomized controlled trial, WHO: World Health Organization.

Eight studies provided BLT by high CCT light, either by ceiling-mounted light [48,64–66] or by a customized set-up of luminaires [32,53,67,68]. Two studies used lights providing 17,000 K and 6,500 K, but the on-site measurements revealed much lower CCT values of 7300–8300 K [65] and 4400 K [69], respectively, and with considerable spread. The remaining studies reported the CCT of the manufacturer; 6500 K–13,000 K [32,48,53,66–68]. Illumination ranged from ~300 lux to ~2500 lux measured at eye level [32,53,64–67] or at pre-determined locations [48,68]. Five studies reported if the measurements were done horizontally or vertically [32,48,64–66]. While the studies using very high CCT (9000–13,000 K) had modest illumination levels (300–400 lux) [32,53,65,67], three studies had both high CCT and high illumination (~1000–2500 lux and ~6500 K) [48,64,66]. A study by Wahnschaffe et al. achieved quite low light values [69], and with ~4400 K and 400 lux, the daytime illumination was comparable to the placebo condition in two other studies [48,53]. Notably, Wahnschaffe and colleagues measured their light vertically. Other included studies measured their light horizontally, which yielded higher illumination levels (see Table S2 for overview of light measuring methods).

Eight studies delivered BLT in the morning (between 07:00 and 12:00) [31,43,55–58,61,62], three studies in the evening (between 16:00 and 20:00) [54,59,60], and nine studies delivered BLT for the whole day (between 07:00 and 20:00) [32,53,63–69]. Three studies compared morning, evening, and all-day treatment [45,48,52], and one administered light both in the morning and evening [47].

Adherence to treatment was addressed in 22 of 24 studies (see Table S2). Adherence was assessed in different ways (distance to light source and time spent in relevant area) and only 13 studies reported the actual light received during treatment and/or time spent in BLT [32,45,48,52–54,61,63–67,69]. Hence, standardization concerning assessment and reporting of this in the future seems necessary.

Study designs and methods

Nine studies were RCTs comparing one or more active conditions to a control condition [45,47,52–54,56,57,59,61], of which three included a crossover [53,57,61] (Table 1). Two studies used a non-randomized crossover design [48,65], two had a non-randomized parallel group design [64,66], and 12 had a pre-post design [31,32,43,51,55,58,60,62,63,67–69]. Twelve studies had a placebo condition with lower illumination or lower CCT compared to the intervention [45,47,48,52,53,56,57,59,61,64–66]. Studies with a non-comparable control group were treated as pre-post designs in this review [55,67]. Nine studies attempted to blind staff and/or raters, four by concealing the study hypothesis [33,48,51,66] and five by using naïve outcome raters [47,54,56,57,59]. The study quality ranged from 0 to 3, with a median of 1 (M = 1.33, SD = 1.13) (Table 1).

Outcomes

Behavioral and psychological symptoms of dementia

BPSD outcomes were reported in 17 studies [31,32,45,47,49,51,53,55–58,60,64–67,69]. Eight studies measured depression, where three studies found improvements [32,47,53], three studies found no change [56,57,67], and two studies found exacerbated depressive symptoms [49,65]. Season was reported and accounted for in all but one study of depression [57]. Twelve studies measured agitation, of which seven studies found reduced agitation after therapy [31,32,47,51,55,58,69], three reported no significant effects [56,60,66], and two had some negative results [45,50]. Six studies used scales assessing a range of dementia-related behaviors and psychological symptoms [31,56,57,64–66], where one study had positive results [31], three had no significant results [56,57,66], two had mixed results, including negative outcomes [64,65] (Table S2).

Nine of the studies investigating BPSD used high illumination light, where five had positive outcomes [31,47,51,55,58], three had no significant findings [56,57,60], and one had negative outcomes [45]. This latter study reported more observed agitation following evening BLT of 2500 lux delivered by light box [45]. One RCT using light boxes of 10,000 lux for eight weeks found improved depression and agitation, while two other RCTs reported no change using the same illumination but shorter intervention periods.

Seven studies used high CCT light [32,53,64–67], none of which were large RCTs, and with mixed results. A randomized crossover study [53] found decreased depression compared to baseline using 13,000 K light. However, there was no significant difference between the high CCT intervention and the low-CCT control (both 400 lux), indicating that the decrease in depression may reflect a placebo effect. Alternatively, the relatively high illumination of 400 lux at eye level in the placebo condition may have attenuated the depressive symptoms. That study also investigated carry-over effects and found no significant carry-over effect on depression after a four-week washout. Interestingly, three studies found negative effects of high CCT light [49,50,64,65]. Van Hoof et al. [65] found increased depressive and anxious behavior after a high CCT condition (aiming at 17,000 K, however achieving a maximum of 12,500 K, and 400–500 lux vertically at eye level) compared to a low CCT condition. The other study combined high CCT and illumination (6500 K and 1200 lux vertically at eye level) and reported increased apathetic behavior, but also decreased restlessness. One study found a negative impact of BLT in men only [49] and a negative impact in patients with mild to moderate dementia [50], suggesting that dementia severity and gender may be moderators. This study used 2500 lux and 6500 K, measured horizontally. Wahnschaffe et al. found reduced agitation at post-intervention compared to baseline using more moderate values of 400 lux and 4400 K (measured vertically at eye level) [69].

Thus, eight [31,32,47,51,53,55,58,69] out of 17 studies found positive effects of BLT on BPSD, and four studies reported negative effects. Three of these used high CCT ceiling-mounted light, from 6500 K combined with 1200 lux [49,50,64] to a maximum of 12,500 K combined with 400–500 lux [65]. One of nine studies using high illumination light boxes had negative outcomes [45]. Gender and dementia severity might moderate the effect of BLT on BPSD. Treatment periods of eight weeks or more might be more effective.

Functioning and dementia severity

Effects of BLT on functioning and cognition have not been extensively studied. Only three studies investigated cognitive function and dementia severity [56,59,62], and three investigated activities of daily living [32,53,66]. Using high illumination BLT, two studies found improved MMSE scores [59,62], while one study found no change in MMSE score in the intervention group compared to the controls [56]. All of the studies investigating activities of daily living delivered high CCT light [32,53,66], and none reported positive effects. One study [53] found a worsening in instrumental activities of daily living after high CCT light compared to low CCT light.

Sleep

Sleep was assessed with actigraphy in 15 studies (wrist-worn or bed installed); nine found improvements on some sleep outcomes [32,33,43,54,60–62,67,68], one reported both positive and negative outcomes [48], and five found no effect [31,52,53,56,66]. Nine of the 15 studies also measured sleep by questionnaires or observations [31,32,43,48,53,54,56,58,60]. These results were largely in concordance with actigraphy outcomes. One study measured sleep by observation only [55] (Table S2).

Nine studies used high illumination light [33,43,52,54–56,60–62]. Two of these reported positive effects compared to the control group on wakefulness at night [54] and duration of sleep bouts [33]. In contrast, Ancoli-Israel et al. [52] and Burns et al. [56] found no differences in sleep or activity levels between treatment and control groups using light boxes with 2500 lux and 10,000 lux, respectively. However, the treatment periods lasted for 10 and 14 days only. Interestingly, two of the controlled studies with significant effects included exclusively AD patients [33,54], while the non-significant studies included participants with different dementias [52,56]. One pre-post study found that sleep onset latency and sleep efficiency improved with BLT [43] and these effects remained significant at four and 12-week washout [44].

Six studies on sleep used high CCT light [32,48,53,66–68], of which two pre-post studies reported significant improvements in sleep duration and efficiency [32,67]. One study found positive effects compared to the control group on sleep duration and the number of sleep bouts [48]. One study reported increased time in bed and less wandering at night [68]. These improvements were not reflected in two of the studies with placebo conditions [53,66]. However, when stratifying participants by the light exposure data from the actigraphs, Münch et al. found that those with higher light exposure (above the median of 417 lux) had higher activity, less time in bed, later bed times, and sleep onset, compared to those with lower light exposure (below 417 lux), regardless of group allocation [66]. Sloane et al. investigated intervention carry-over effects and found a significant carry-over effect on proxy-rated sleep [53].

In summary, the majority of studies reported improvements in sleep parameters following BLT. The two RCTs with improvements in sleep included AD patients only [33,54]. The non-significant studies included all dementia diagnoses and had short treatment durations [52,56]. Two studies found that the BLT effects lasted beyond washout periods of up to 12 weeks [44,53].

Circadian rhythm

Twelve studies investigated circadian parameters from actigraphs [31–33,48,52,53,56,60,63,66,67,69]; nine reported significant effects [31–33,48,52,56,60,63,67], while three found no effects [53,66,69]. The majority of these outcomes reflect improved circadian rhythmicity, expressed as higher phasor magnitude [32,67], higher amplitude [60], reduced intradaily variability [60,63], increased interdaily stability [63], and a five-parameter model, encompassing a combination of rhythm indicators [33]. Two studies found effects on activity level [52,56] and three found effects on circadian phase [31,48,52], which is difficult to interpret clinically.

Six studies used high illumination light, and all reported some significant, but sometimes opposing, effects [31,33,52,56,60,63]. For example, Ancoli-Israel et al. found a within-group delay of the peak of the activity rhythm (acrophase) and an increase in the mean activity level (mesor) in the morning light treatment group [52]. In contrast, Skjerve et al. found an advance in acrophase [31] and Burns et al. found a reduction in activity level in the intervention compared to the placebo group [56].

Five studies investigated the effect of high CCT light on circadian rhythmicity, measured by actigraphy [32,48,53,66,67]; two combining high CCT and high illumination [48,66]. The two pre-post studies found improvements in phasor magnitude, a circadian rhythmicity variable reflecting the correspondence between light exposure and activity, after four weeks of BLT [32,67]. Improvements in circadian rhythmicity were not reflected in the studies with control groups [48,53,66]. However, one study found an advance in acrophase during morning BLT compared to the control condition [48].

Circadian parameters measured by other means than actigraphy have rarely been investigated. Two studies measured melatonin [55,66], and three studies measured body temperature under the arm [59] or in the ear [64,65]. Münch et al. found that participants with lower light exposure (<417 lux; $n = 5$) obtained an earlier melatonin onset than participants with higher exposure (>417 lux; $n = 4$) [66]. One study found a delay of the temperature minimum (nadir) after high illumination BLT in the evening [59], and one study found a within-group increase in individual temperature range after all-day high CCT light and a decrease after low CCT light [64].

The majority of studies on circadian rhythmicity found an effect of BLT on at least one outcome, combined with several non-significant outcomes (Table S2). Studies administering BLT in the morning found opposing results in terms of acrophase [31,48,52].

Discussion

The aim of this paper was to provide a comprehensive overview of studies investigating the effect of BLT in dementia, focusing on methodological characteristics. Overall, the results of the included studies are inconsistent. However, the studies varied widely in terms of intervention characteristics, designs, outcome measures, and population characteristics, which may have moderated the outcomes [31,32,47,51,53,55,58,69]. In addition, most of the studies had small sample sizes, with time-limited treatment durations of less than eight weeks, which also may have affected the results. Only five out of the 24 studies reported effect sizes [47,48,54,67,68]. As statistical significance is highly dependent on sample size, authors should in the future provide effect sizes in order to ease comparisons of results across studies. While the majority of studies found positive effects of BLT [31–33,43,47,48,52–55,58–64,67–69], a few of the included studies found negative effects of ambient high CCT light on BPSD [49,50,64,65], activities of daily living [53], and sleep [48]. While these studies had some methodological limitations, such as a short [53,64] or no [48,65] washout period before crossover, other possible reasons for the negative results should be considered. In one study, the CCT levels were very high, and the authors hypothesized that the light was perceived as unnatural and uncomfortable, and therefore led to negative behavioral outcomes [65]. Studies have shown that preference for different CCT levels depend on the type of activity or the task to be performed [70,71]. One study evaluated the preference of CCT levels ranging from 2000 K to 100,000 K and found a U-shaped curve, where the subjective preference and visual comfort was highest for a CCT ranging from 4400 to 6200 K, depending on the task (relaxing vs working) [71]. The maximum “acceptable range” spanned only up to 7600 K. Dementia patients may not have the capacity to express dissatisfaction with their light environment which may instead be expressed through disrupted behavior [72]. This impact might apply to all studies using high CCT ambient light.

The association between intervention characteristics and outcomes

Duration and timing

While three studies used high illumination light boxes and the same outcome measures [45,47,56], only the study with a long (eight-week) treatment period found improvements in BPSD as compared to treatment durations of ten [45] and 14 [56] days. It may be that changes in BPSD take longer than two weeks to manifest, and that longer treatment durations are warranted.

In terms of timing, no clear pattern emerges, corresponding with other reviews [34–36]. Three studies found more nocturnal sleep [48] and less nocturnal activity [43,55] with morning and all-day BLT, but so did one study using evening BLT [60]. Another study found increased agitation in response to evening BLT [45]. Two other studies also found similar effects of BLT irrespective of timing [33,50]. It might be that timing is less important than a general increase in light exposure, as this population is notoriously under-exposed to daylight [25,28,29,64].

Illumination and CCT

A moderator analysis in the meta-analysis by Chiu et al. showed that illumination levels of 2500 lux or higher produced stronger effects on depression than lower levels [35]. In the present review, only one of four studies using 2500 lux or higher had significant positive effects on depression [47], and one had negative outcomes [49]. Importantly, Chui et al. only included six of the studies covered in the present review [35]. Overall, it is challenging to delineate a relationship between illumination, CCT and outcomes based on the included studies. All high CCT studies used ambient light, and exposed the participants to all-day light, in contrast to the restricted duration of BLT by light boxes. Additionally, light levels were measured and reported differently across studies. The present results indicate that using light boxes delivering from 1500 to 10,000 lux for 30 min to two hours have negligible negative outcomes, but unclear effectiveness. Meanwhile, several studies reported that high CCT ambient light (from 6500 K and 1200 lux to 13,000 K and 400 lux) had a negative impact on some outcomes [48–50,53,64,65]. Indeed, Wulff and Foster suggested that there is a dose–response relationship between light exposure and health, where too little and too much light is aversive [73]. Thus, the effect of more moderate light levels should be explored. Positive effects of ambient light on depression and agitation were found using more moderate light levels of 400 vertically measured lux and 4400 K [69]. Those values exceed most indoor light levels [25,74], and may be sufficient in treating BPSD. However, higher light levels are probably more effective, considering the impaired light absorption associated with old age. Thus, when using ambient light, keeping the light below 6500 K and 1200 lux (measured vertically), but still as high as possible, could represent a viable solution. Keeping the CCT about 6000 K makes sense from an evolutionary perspective, because sunlight have a CCT of around 6000 K [75].

Adherence

In recent years, researchers have provided BLT by manipulating the ambient light setting. This has reduced the strain on caregivers to secure treatment compliance and may be more practically feasible than light boxes. One caveat however, is the challenge of measuring adherence to treatment. This was demonstrated in the study by Münch et al., who found no difference in daily light exposure between the intervention and the control group [66]. When they split the participants into a “high exposure” (above median of 417 lux) and “low exposure” group (below median), 40% of the original intervention group had low light exposure. Thus, lack of effects may be due to adherence issues.

Related to this, light at eye level was not consistently reported, and only five of 24 studies specified if light was measured vertically or horizontally [48,63–66]. Lux values vary substantially depending on the direction of measurement [64,65], and light should thus be measured vertically at eye level [64]. Another concern is the lack of standard light quantifiers. In addition to the contribution of rods and cones, NIF functions are heavily dependent on stimulation of melanopsin-expressing retinal ganglion cells. The sensitivity of these cells is not accounted for by lux, which is based on cone cell sensitivity [see e.g., Ref. [76]].

Choice of placebo/control condition

There is also no consensus on the most appropriate placebo condition, and choice of placebo might have nullified potential differences between intervention and control conditions. One study found no difference in sleep between the high CCT condition and the low CCT placebo condition [53]. Importantly, the placebo condition had an illumination of 400 lux and was delivered from wake-up until 18:00. Wahnschaffe et al. [69] found improved agitation using 400 lux, suggesting that placebo condition with such high illumination may improve symptoms. Meanwhile, Sloane et al. used a placebo condition of 500–600 lux, and found significant improvements in the intervention compared to the placebo [48].

Season

Although none of the studies accounting for day length found any association with depression scores [49,56,67], two studies found an effect on agitation [56,58]. Thorpe et al. reported lower agitation during the summer [58]. Meanwhile, Burns et al. reported that improvement in agitation was negatively associated with day length, in the intervention as compared to the control group [56]. Indeed, Burns et al. recommended that BLT should only be used during winter. Season was not consistently reported in the included studies, precluding analyses of the relationship between outcomes and season.

The association between study design and outcomes

Five studies had a crossover design; two had no washout before crossover [48,65], and three had only one to four weeks washout [53,57,61]. Considering the long-lasting effects of BLT reported by Fetveit and Bjorvatn [44] and the carry-over effects reported by Sloane et al. [53], carry-over effects might have attenuated differences between conditions in studies with cross-over designs. Positive results from pre-post studies (without control condition) may reflect well-known non-experimental confounders (e.g., time, regression towards the mean). In line with this, improvements in both intervention and placebo conditions were found in some studies [45,53,56]. To ensure adherence to treatment by light boxes, NH staff did in some cases interact with and motivate patients. Hence, it cannot be ruled out that this could have influenced outcomes beyond the effect of BLT. Lack of blinding may also have influenced the results in some studies, as some assessors were not blinded to group allocation. Unblinded studies may show biases related to placebo-by-proxy [77] and the Hawthorne effect [78,79].

Outcome measures

Choice of measurement tools might partially explain inconsistent results across studies. For example, Ancoli-Israel et al.

[45] and Barrick et al. [50] found no changes in agitation when using the proxy-rated Cohen-Mansfield Agitation Inventory (CMAI). Meanwhile, both studies found a worsening of agitation assessed by observation. The CMAI requires nurses to recall behavior over the past week and details may thus be lost. Temporal variations in behavior, such as sundowning, are not assessed by the CMAI.

Using self-report becomes increasingly challenging with advancing dementia. When using proxy-rated scales, raters may be influenced by factors such as information processing, educational level, and their relationship with the patient. The responses from self- and proxy raters often diverge, especially when the construct is latent [80]. NH staff and family members have different perspectives and may provide different answers. In addition, outcome measures may have low sensitivity to change and scales with different psychometric properties may yield different outcomes.

Sleep outcomes were defined differently across studies, and seemingly similar actigraphic outcomes were operationalized divergently. For example, sleep efficiency was sometimes calculated from individual bedtime and rise time [32,43,66,67], while other authors set fixed night intervals and calculated sleep efficiency based on these [53]. The use of different actigraphy equipment and software to compute outcome variables, as well as different durations of actigraph registration, may have influenced the results [81].

The association between population characteristics and outcomes

In their review, Mitolo et al. suggested that patients with mild to moderate AD might respond better to BLT than those with severe AD [82]. Barrick et al. found more agitation with BLT only among those with mild to moderate dementia, suggesting that individuals in the earlier stages of dementia are more sensitive to light exposure [50]. Onega et al. reported however, that BLT was equally effective on depression in all stages of dementia, and even more effective in severe dementia on some subscales [46]. Although the response to BLT might be moderated by dementia severity, the direction is not clear. It is also unclear whether type of dementia affects the response to BLT. For example, of two studies using the same protocol [33,52], only the one that exclusively included AD patients found improved sleep. Similarly, van Someren et al. reported that increased circadian rhythm amplitude was associated with AD [63]. Meanwhile, Mishima et al. found reduced night activity in patients with vascular dementia, not in AD patients [61].

Lastly, gender may affect BLT responses. Münch et al. found that higher light exposure was associated with a higher circadian rhythm amplitude in men only [66]. Hickman et al. reported higher depression scores in men during morning BLT compared to standard light [49]. Men may thus be more sensitive to changes in light.

The circadian response to light exposure depends on the circadian phase. Münch et al. found incommensurable melatonin profiles in patients with severe dementia [66]. Providing BLT at the same times to individuals with different rhythms will probably have diverging effects. For example, Skjerve et al. found that morning BLT advanced the acrophase of the activity rhythm only for patients that had an acrophase after 15:00 at baseline [31]. Studies investigating the circadian response to BLT should account for baseline rhythms.

Symptoms at baseline often had a wide range in the study populations and were sometimes subclinical. For example, Burns et al. found no effect on sleep [56]; however, the participants had a mean sleep duration within healthy parameters (8.3 h) at baseline. Although Van der Ploeg et al. recommended that target symptoms should be at clinical levels at baseline [83], this is not always possible in studies that measure a range of symptoms associated with dementia. Other patient characteristics that may have moderated study outcomes are medications, multi-morbidity, and pain. Such factors are difficult to control for, particularly with small study samples.

Conclusions

Overall, there are promising results regarding the effect of BLT on BPSD, sleep, and circadian rhythmicity. However, large heterogeneity in terms of interventions, study designs, and population characteristics occlude final conclusions. Outcomes are inconsistent and several potential moderating factors emerged as we took a closer look at study designs and procedures. Thus, the inconsistency of results should not be interpreted as a lack of effect of BLT in dementia, but can rather be ascribed to the heterogeneity of the studies.

To resolve the inconsistencies in this field, future BLT studies should use a randomized placebo-controlled design with a treatment period lasting for a minimum of two months. Cross-over designs should account for the potential long-lasting effects of BLT. Trials should have sufficient statistical power to allow for subgroup analyses regarding potential moderators such as dementia severity and diagnosis, gender, individual circadian phase, and level of baseline symptoms. Light levels should be measured vertically at eye level.

Because BLT has caused negative effects in some studies, the light delivered should stay within acceptable levels. The ability of light to produce NIF responses can be ensured by increasing both illumination and CCT over a prolonged period of time, without increasing the levels to uncomfortable levels. Ambient high CCT light of $\geq$6500 K combined with $\geq$1200 vertically measures lux, was associated with some negative outcomes. The effect of ambient light using lower CCT values should be investigated, i.e., 6000 K in combination with a maximum of 1200 lux. Bright light is relatively invasive in people's environment, and the physiological effect on the circadian system, alertness, and more cannot be disentangled from subjective experiences and preferences. Developing light solutions that are effective, as well as being comfortable and aesthetically pleasant, should be a priority.

Practice points

The majority of studies on bright light treatment in dementia have reported positive effects on sleep, circadian rhythm, and behavioral and psychological symptoms, however:

- Beneficial effects were found following BLT administered at different times, from early morning to early evening. Hence, the optimal timing of BLT is unclear, but is likely to depend on the circadian phase of the individual.
- Longer exposure duration, for months instead of days or weeks, is associated with better responses.
- Light with high amounts of short wavelengths might cause negative effects on mood and function.
- The use of crossover designs and too intense placebo lights in some studies might have nullified the positive effects of bright light treatment.

Future research

- Treatment periods should last for a minimum of two months.
- If a cross-over design is used, sufficient wash-out time between conditions is needed in order to eliminate confounding effects stemming from long lasting effects of BLT.
- When choosing placebo conditions, researchers should consider that even moderate light levels may affect sleep, circadian rhythms, mood and behavior.
- Light levels should be measured vertically at eye level, and both measurement procedures and results should be reported to allow for comparison across studies.
- Because some studies had negative outcomes after bright light treatment with high amounts of short wavelengths, the use of more modest light levels should be further investigated. Keeping the light below 6500 K and 1200 lux (measured vertically), but still as high as possible, could represent a viable solution.
- Trials should have sufficient statistical power to allow for subgroup analyses regarding potential moderators
- Studies investigating circadian rhythms should account for circadian phase at baseline.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2020.101310.

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Table S1: The search strategy of the systematic database search 12.mars 2019

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to March 11, 2019>
12. March 2019
1 dementia/ or alzheimer disease/ or frontotemporal lobar degeneration/ or lewy body disease/ (127103)
2 Delirium, Dementia, Amnestic, Cognitive Disorders/ (8918)
3 (dement* or alzheimer* or "Frontotemporal lobar degeneration" or "Lewy Body disease").tw. (196117)
4 1 or 2 or 3 (221121)
5 homes for the aged/ or exp nursing homes/ (42142)
6 Hospices/ (4858)
7 (nursing home* or "home* for the aged" or hospice*).tw. (39709)
8 5 or 6 or 7 (64296)
9 4 or 8 (277930)
10 phototherapy/ or color therapy/ or heliotherapy/ or intense pulsed light therapy/ (8483)
11 (Phototherap* or Photo Therap* or dawn-dusk or dawn dusk).ti,ab. (8235)
12 ((light* or illuminat*) adj2 (bright or therap* or treatment or box or visor* or exposure* or LED)).ti,ab. (19226)
13 10 or 11 or 12 (31221)
14 9 and 13 (335)
Ovid Embase <1974 to 2019 March 11>
12. March 2019
1 health care facility/ or hospice/ or nursing home/ (121516)
2 home for the aged/ (10518)
3 (nursing home* or "home* for the aged" or hospice*).tw. (52566)
4 1 or 2 or 3 (143100)
5 dementia/ or alzheimer disease/ or diffuse lewy body disease/ or frontotemporal dementia/ or "mixed depression and dementia"/ or exp senile dementia/ (268195)
6 (dement* or alzheimer* or "Frontotemporal lobar degeneration" or "Lewy Body disease").tw. (272239)
7 5 or 6 (323024)
8 4 or 7 (455269)
9 phototherapy/ or color therapy/ or intense pulsed light therapy/ (22235)
10 (Phototherap* or Photo Therap* or dawn-dusk or dawn dusk).ti,ab. (11289)
11 ((light* or illuminat*) adj2 (bright or therap* or treatment or box or visor* or exposure* or LED)).ti,ab. (22485)
12 9 or 10 or 11 (44953)
13 8 and 12 (652)
Ovid PsycINFO <1806 to March Week 1 2019>
12. March 2019
1 residential care institutions/ or nursing homes/ (17932)
2 hospice/ (3093)
3 (nursing home* or "home* for the aged" or hospice*).tw. (16824)
4 1 or 2 or 3 (27148)
5 dementia/ or dementia with lewy bodies/ or exp senile dementia/ or vascular dementia/ or alzheimer's disease/ or senile plaques/ (69929)
6 (dement* or alzheimer* or "Frontotemporal lobar degeneration" or "Lewy Body disease").tw. (96382)
7 5 or 6 (97149)
8 4 or 7 (119755)
9 phototherapy/ (911)
10 (Phototherap* or Photo Therap* or dawn-dusk or dawn dusk).ti,ab. (329)
11 ((light* or illuminat*) adj2 (bright or therap* or treatment or box or visor* or exposure* or LED)).ti,ab. (3923)
12 9 or 10 or 11 (4233)
13 8 and 12 (164)
Cochrane library (Wiley)
12. March 2019
#1 dement* or alzheimer* or "Frontotemporal lobar degeneration" or "Lewy Body disease":ti,ab,kw (Word variations have been searched) 21360

#2 MeSH descriptor: [Nursing Homes] explode all trees 1228
#3 nursing home* or "home* for the aged" or hospice*:ti,ab,kw (Word variations have been searched) 8991
#4 #1 or #2 or #3 26997
#5 "color therapy" or heliotherapy:ti,ab,kw (Word variations have been searched) 53
#6 Phototherap* or Photo Therap* or dawn-dusk or "dawn dusk":ti,ab,kw (Word variations have been searched) 2862
#7 (light* or illuminat*) near/2 (bright or therap* or treatment or box or visor* or exposure* or LED):ti,ab,kw (Word variations have been searched) 2770
#8 #5 or #6 or #7 4801
#9 #4 and #8 176

CINAHL (Ebsco) 1981 – now
12. March 2019

S1 (MH "Nursing Homes+") OR (MH "Nursing Home Patients") (32,103)
S2 (MH "Hospices") OR (MH "Hospice Patients") (3,335)
S3 TI ((nursing home* or "home* for the aged" or hospice*)) OR AB ((nursing home* or "home* for the aged" or hospice*)) (32,778)
S4 S1 OR S2 OR S3 (52,401)
S5 (MH "Dementia") OR (MH "Dementia, Senile+") OR (MH "Lewy Body Disease") OR (MH "Dementia, Multi-Infarct") (58,765)
S6 (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") (118)
S7 TI ((dement* or alzheimer* or "Frontotemporal lobar degeneration" or "Lewy Body disease")) OR AB ((dement* or alzheimer* or "Frontotemporal lobar degeneration" or "Lewy Body disease")) (61,437)
S8 S5 OR S6 OR S7 (75,726)
S9 S4 OR S8 (121,526)
S10 (MH "Phototherapy") (2,865)
S11 TI (Phototherap* OR "Photo Therap*" OR dawn-dusk OR "dawn dusk") OR AB (Phototherap* OR "Photo Therap*" OR dawn-dusk OR "dawn dusk") (1,340)
S12 TI ((light* or illuminat*) N2 (bright or therap* or treatment or box or visor* or exposure* or LED)) OR AB ((light* or illuminat*) N2 (bright or therap* or treatment or box or visor* or exposure* or LED)) (2,770)
S13 S10 OR S11 OR S12 (5,689)
S14 S9 AND S13 (166)

Web of Science (Thomson & Reuters), Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years
12.March 2019

8 596 - #7 AND #3
7 58,559 - #6 OR #5 OR #4
6 48,261 - TOPIC: ((light* or illuminat*) near/2 (bright or therap* or treatment or box or visor* or exposure* or LED))
5 11,225 - TOPIC: (Phototherap* or "Photo Therap*" or dawn-dusk or "dawn dusk")
4 108 - TOPIC: ("color therapy" or heliotherapy)
3 334,628 - #2 OR #1
2 45,583 - TOPIC: ("nursing home*" or "home* for the aged" or hospice*)
1 298,621 - TOPIC: (dement* or alzheimer* or "Frontotemporal lobar degeneration" or "Lewy Body disease")

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ORIGINAL RESEARCH
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An Actigraphy-Based Validation Study of the Sleep Disorder Inventory in the Nursing Home

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Background: Disrupted sleep is common among nursing home patients with dementia and is associated with increased agitation, depression, and cognitive impairment. Detecting and treating sleep problems in this population are therefore of great importance, albeit challenging. Systematic observation and objective recordings of sleep are time-consuming and resource intensive and self-report is often unreliable. Commonly used proxy-rated scales contain few sleep items, which affects the reliability of the raters' reports. The present study aimed to adapt the proxy-rated Sleep Disorder Inventory (SDI) to a nursing home context and validate it against actigraphy.

Methods: Cross-sectional study of 69 nursing home patients, 68% women, mean age 83.5 (SD 7.1). Sleep was assessed with the SDI, completed by nursing home staff, and with actigraphy (*Actiwatch II, Philips Respironics)*. The SDI evaluates the frequency, severity, and distress of seven sleep-related behaviors. Internal consistency of the SDI was evaluated by Cronbach's alpha. Spearman correlations were used to evaluate the convergent validity between actigraphy and the SDI. Test performance was assessed by calculating the sensitivity, specificity, and predictive values, and by ROC curve analyses. The Youden's Index was used to determine the most appropriate cut-off against objectively measured sleep disturbance defined as <6 h nocturnal total sleep time (TST) during 8 h nocturnal bed rest (corresponding to SE <75%).

Results: The SDI had high internal consistency and convergent validity. Three SDI summary scores correlated moderately and significantly with actigraphically measured TST and wake-after-sleep-onset. A cut-off score of five or more on the SDI summed product score (sum of the products of the frequency and severity of each item) yielded the best sensitivity, specificity, predictive values, and Youden's Index.

Conclusion: We suggest a clinical cut-off for the presence of disturbed sleep in institutionalized dementia patients to be a SDI summed product score of five or more. The results suggest that the SDI can be clinically useful for the identification of disrupted sleep when administered by daytime staff in a nursing home context.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT03357328.

Keywords: dementia, sleep, proxy-rating, actigraphy, nursing home

INTRODUCTION

Sleep problems and disturbed nocturnal behavior constitute important aspects of the behavioral and psychological symptoms of dementia (BPSD) (1). In nursing homes, night-time wandering, confusion, and related behaviors can increase the risk of patient injuries, e.g., falling (2), and may cause disturbances for other residents. Such behaviors are also distressing and resource demanding for the staff (3).

As part of normal aging, characteristic changes in sleep and circadian rhythmicity take place. These entail a reduction in sleep duration and the proportion of slow wave sleep, as well as sleep fragmentation and an increase in the frequency and duration of daytime naps (4). Commonly, the sleep phase is advanced, implying that older people tend to experience sleepiness earlier in the evening and wake up earlier in the morning than desired. Also, the prevalence of some primary sleep disorders, such as sleep-disordered breathing, increases with age (5).

Sleep and circadian alterations are more frequent in patients suffering from dementia than in normal aging, and studies have provided estimates of disturbed sleep from 24% (6, 7) to 70% in dementia populations (8, 9). Brain systems involved in sleep and wakefulness are often increasingly affected as neurodegeneration progresses (10). Moreover, the causes of disturbed sleep in dementia are multiple, and factors such as inactivity, medications, and reduced exposure to social interaction and reduced daylight exposure are all associated with disturbed sleep (11–13).

Disruption of sleep and circadian rhythmicity have been associated with increased agitation (14), depressive symptoms (15–17), and cognitive impairment (15, 18) in people with dementia. In addition, disturbed sleep has been identified as an important cause of caregiver distress (19, 20) and of institutionalization of patients suffering from dementia (21–23). Detecting and treating disturbed sleep is of crucial importance in relation to improving behavioral and mood related symptoms, enhancing well-being, and reducing caregiver distress.

Assessing disturbed sleep in people with dementia is challenging, as self-report may be unreliable and, in many cases, unfeasible. Most et al. (24) demonstrated that even in the early and middle stages of Alzheimer's disease (AD), patients had more objectively measured sleep problems compared to healthy age-matched controls, however, the former group self-reported fewer sleep problems. Hence, clinicians and researchers often rely on proxy-rater instruments, where nurses or relatives answer on behalf of the patient. Unfortunately, research suggests that nursing home staff often provide unreliable and inaccurate reports of their patients' sleep when not using adequate instruments (25–27). For example, using the sleep items of the Cornell Scale of Depression in Dementia (CSDD) and the Neuropsychiatric Inventory (NPI) in a nursing home population, Blytt et al. (25) found that staff reported significantly fewer sleep problems than measured by actigraphy. Their study suggested that disturbed sleep may go largely undetected in the nursing home population when measured by staff rated instruments with only one or a few items. Meanwhile, using the comprehensive 21-items Circadian Sleep Inventory for Normal and Pathological States (CSINAPS), completed by nursing home nurses, Hoekert et al. (27) found only small-to-medium associations between actigraphy parameters and scale items and subscales. However, systematic observation of sleep behavior often requires that staff frequently or continuously observe each patient across several days (28, 29). Such time consuming and resource intensive assessments are not necessarily feasible in a nursing home context. Further, objective measures of sleep such as actigraphy are rarely used in clinical contexts due to the cost of the equipment and the time and skill needed to interpret the output. Thus, identifying a relatively short questionnaire that more accurately detect sleep problems in dementia populations has the potential of providing caregiving staff with a clinically important and more feasible tool.

To the authors' knowledge, the Sleep Disorder Inventory (SDI) (30) is the only short-form scale that exclusively focuses on evaluating sleep in dementia populations. Tractenberg and colleagues (30) have demonstrated appropriate convergent validity (i.e., significant correlations with actigraphy) in a group of home-dwelling participants suffering from AD. To date, the SDI has not been validated for use in the nursing home context, despite the need for clinically relevant and easy-to administer sleep assessment tools in these settings.

Accordingly, the aim of the current study was to evaluate the SDI in the nursing home context after adapting item wording accordingly. Specifically, we aimed to: (i) assess the adapted SDI's internal consistency, (ii) investigate the convergent validity of the adapted SDI against actigraphy, (iii) and suggest a clinical cut-off for disturbed sleep in nursing home patients with dementia.

MATERIALS AND METHODS

Sample and Setting

This study used baseline data from a 6-months cluster-randomized placebo-controlled trial, evaluating the effectiveness of bright light treatment in people with dementia (the DEM.LIGHT trial, ClinicalTrials.gov Identifier: NCT03357328).

TABLE 1 | List of sample inclusion and exclusion criteria.

Participants were eligible if they:	Patients were not included in the study if they:
- were ≥60 years and in long-term care (>4 weeks) - had dementia in accordance with DSM-5 - had either sleep/circadian rhythm disturbances, BPSD as identified by NPI-NH, or severely reduced ADL function - provided written informed consent if the participant had capacity or, if not, a written proxy informed consent from a legally authorized representative	- were blind or may otherwise not benefit from light - took part in another trial - had a condition contra-indicated to the intervention - had an advanced, severe medical disease/disorder and/or expected survival less of than 6 months or other aspects that could interfere with participation - were psychotic or had a severe mental disorder

ADL, Activities of Daily Living; BPSD, Behavioral and Psychological Symptoms of Dementia; DSM-5=Diagnostic and Statistical Manual of Mental Disorders-5; FAST, Functional Assessment Staging; NPI-NH, Neuropsychiatric Inventory-Nursing Home Version.

The trial was conducted in Norway from September 2017 to April 2018. We invited the Department of Health and Care, City of Bergen, Norway, to participate in the study with eight eligible nursing home dementia units (e.g., nursing homes that were not involved in other trials or quality of care projects and that had an architecture that allowed for ceiling light installment). See **Table 1** for inclusion and exclusion criteria.

Measurements

Researchers involved in the DEM.LIGHT trial supervised nurses in the use of assessment tools. Only staff that knew the patients well, i.e., the regular nursing staff, working directly with the patients, completed the questionnaires. Daytime personnel completed the questionnaires used in the present study, as part of a larger data collection. The daytime nurses usually convey information about patients to the attending physician and are normally well-informed about nocturnal behavior of the patients. In the present study, the questionnaires were administered either the same week as the patients wore an actigraph or the following week. The questionnaires were completed once. Sociodemographic characteristics, medication status, and diagnoses were collected from medical records.

The Mini-Mental State Examination (MMSE) (31) was used to evaluate cognitive impairment at baseline. The total score ranges from 0 to 30; zero to ten points corresponds to severe dementia, 11–20 to moderate, 21–25 to mild dementia, 26–29 to questionable dementia, and 30 to no dementia (32). The MMSE was administered the same week as the patients wore the actigraph.

Sleep disturbance symptoms were assessed with the SDI, which evaluates nocturnal behavior for the last 2 weeks (30). The SDI is derived from the sleep item and its follow-up-questions of the Neuropsychiatric Inventory (NPI) (33). The NPI evaluates the frequency, severity, and caregiver distress of several behavioral and psychological disturbances which commonly occur in dementia, including disturbed sleep. The questions pertain to the previous 4 weeks. Each item (e.g., agitation/aggression, anxiety, sleep) has a description to aid determining whether and to what extent a disturbance occurs. For the sleep item the description includes: "Does the patient have difficulty sleeping? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?" Endorsement of any of these behaviors elicits seven follow-up questions. The NPI sleep item score is based on a single frequency and severity rating for all the sleep disruption-related behaviors. The SDI was developed by assigning a frequency (0–4), severity (0–3), and caregiver distress (0–5) score to each of the follow-up questions of the NPI sleep item (30).

The SDI was developed to be rated by the live-in caregivers of home-dwelling seniors suffering from dementia. For the DEM.LIGHT trial, the SDI was translated to Norwegian and adapted to the nursing home context. Item 4 ("awakening you during the night") was changed into ("awakening at night"), in order to take into account that patients may be awake at night without engaging in any of the behaviors covered by other items (e.g., wandering, getting out of bed). The translation process adhered to standard guidelines to reach a cultural equivalence of instruments (34). As some of the wording in the SDI was identical to the NPI, which had already been translated to Norwegian (35), we used the existing translations when possible. The SDI contains eight items (see **Supplementary Material**), where the eighth item asks about any additional information not captured by items 1–7. Only items 1–7 were included in the total score.

In the original paper, Tractenberg et al. (30) calculated the total SDI score as the average frequency multiplied by the average severity. This total score has been used by other authors adopting the scale (36, 37). When using this calculation, the total score may however vary greatly depending on the distribution of frequency and severity scores across items. For example, having three frequently occurring symptoms (frequency = 4) of mild severity (severity = 1) produces a higher total score (=0.74, calculations provided in the **Supplementary Material**) than having one frequently (frequency = 4) occurring symptom of marked severity (severity = 3; = 0.25). Other authors have therefore calculated the total score as the sum of the products of the frequency and severity of each of the single items of the scale (38, 39). This way of calculating the total score provides the same total score for both of the scenarios outlined above (both = 12). In the present study, both approaches to total score calculation were investigated, where the former is referred to as the "*SDI average total score*" and the latter is referred to as the "*SDI summed product score.*" We also calculated summed frequency as a general indicator of "overall disturbance" (referred to as the "*SDI summed frequency score*"). Higher values on all of these composite scores represent "worse sleep disturbance," although as noted above, these summaries are not linearly comparable. In line with the original paper (30), mean frequency, severity, and caregiver distress were also calculated.

The single sleep item from the nursing home version of the NPI (NPI-NH) (35, 40) was investigated in relation to the SDI. The NPI-NH asks about the previous 4 weeks. The NPI-NH sleep item comes with a description similar to the NPI, followed by six follow-up questions (including "other nighttime

behaviors"). Previous studies have suggested a cut-off product score of frequency (1–4) multiplied by severity (1–3) of ≥4 to define the presence of sleep disturbance on this single item from the NPI-NH (25, 41). In contrast to the SDI, the NPI-NH follow-up questions do not ask about excessive daytime sleep (SDI item 7) or if the patient wake up during the night without engaging in any specific behaviors (SDI item 4).

Sleep was objectively measured using the *Actiwatch II (Philips Respironics)*. Actigraphs are wrist-worn devices that can measure activity across several days, and even weeks (42). The actigraphs were placed on the dominant wrist, in accordance with previous studies in this population (8, 25). Each 1-min epoch was scored as either sleep or wake by the *Actiware 6.0.9 (Philips Respironics)* software, based on activity from the two epochs immediately preceding and following the relevant epoch. The threshold for wakefulness was set to medium. Activity data were collected for 7 days and patients had to complete at least five nights of recordings to be included in the analyses. We initially planned to score the actigraphic recordings manually, in line with a premediated scoring protocol (25). However, it was challenging to determine the start and end of the rest intervals. The event buttons were not consistently pressed by the nursing home staff. Additionally, many dementia patients have severely fragmented sleep, thus, there were rarely clear indications of bedtime and rise time in the actograms, normally indicated by a marked and sustained decrease/increase in activity and/or light levels (25, 43). These challenges are common in this population, and researchers have typically solved these issues by setting a fixed rest interval [e.g., (8, 14, 44–53)]. A range of rest intervals have been used earlier and a fixed rest interval from 22:00 to 06:00 was chosen for the present study, as it represents a sensible intermediate of these. It was expected that the majority of patients would be in bed by 22:00 and that the aforementioned interval would overlap with the main sleep episode of most of the participants. When using a fixed rest interval, some commonly reported actigraphy outcomes become invalid, such as sleep onset latency and early morning awakenings. Thus, the following actigraphy outputs were extracted from the rest interval: Sleep efficiency (SE, the percentage of time spent asleep in the rest interval), total sleep time (TST), and wake-after-sleep-onset (WASO, the time spent awake after sleep onset). While TST is a quantitative measure of sleep, SE and WASO reflect mainly sleep quality, although the latter parameters do not necessarily correspond with subjectively reported sleep quality (54). The scores used for SE, TST, and WASO were calculated as the mean value for all nights of recorded actigraphy. These outputs are largely linear in a fixed rest interval. In addition, the 24 h fragmentation index was extracted, as an indication of the overall disturbance of the sleep-wake rhythm across the day and night.

Having a SE of below 85% is often used as a cut-off for identifying disrupted sleep in otherwise healthy populations (55, 56). This corresponds to a TST of 6 h and 48 min in the fixed rest interval, which is close to the 7 h that is considered normal in healthy populations (57). Dementia patients frequently sleep during the day and some stay in bed for 12–13 h per day (25), and it was therefore considered too strict to use a cut-off of 6 h and 48 min TST in the present study. Thus, in agreement with Yesavage et al. (52), we used TST as the indicator of overall sleep disturbance and TST values <6.0 h were characterized as "disturbed" sleep, while those sleeping 6 h or more were characterized as having "not disturbed" sleep. This cutoff corresponds to a SE of 75% in the fixed rest interval (22:00–06:00), a cutoff that has previously been used in dementia populations (58).

Statistical Analyses

Statistical analyses were performed in *SPSS for Windows, version 25.0*. All data were analyzed for normality and non-normal data were analyzed using non-parametric tests. Confidence intervals (CIs) for medians were calculated using the Ratio Statistic in SPSS. Due to the lack of distributional assumptions, the 95% CIs for the Ratio Statistic represent approximations.

Missing Data and Imputation

There were some missing data on the SDI at baseline. Little's MCAR test was not significant ($p = 0.151$), meaning that data were missing completely at random (59). Imputations were thus made by Expectation Maximization (EM) when questionnaires were missing <20% of items (31 items from 11 patients, 2.2% of all items). Three questionnaires were missing ≥20% and data from these were excluded altogether from the analyses.

Internal Consistency

Internal consistency of the adapted SDI was evaluated using Cronbach's alpha (60), estimated as item-total correlations. A Cronbach's alpha of 0.7 and above is normally considered acceptable (61). The internal consistency analyses were computed separately for the frequency and severity ratings.

Convergent Validity

The strength of the relationships between the three different SDI total scores, the single NPI sleep item (frequency × severity), and actigraphic parameters were explored using Spearman correlations. As TST and SE are perfect linear functions of each other in a fixed rest interval, only TST, WASO, and fragmentation index were included in this analysis.

Test Accuracy

Receiver operating characteristic (ROC) curves were calculated for the actigraphy-based cut-off ("disturbed sleep" defined as a TST of <6 h) against the SDI outcomes, in order to investigate the diagnostic performance of each of the SDI composite scores (*SDI average total score, SDI summed product score*, and *SDI summed frequency*). We defined "disturbed sleep" as an average actigraphy TST value of <6 h; this dichotomous variable was the outcome in the ROC curve analysis (30, 52). The "area under the curve" (AUC) score reflects the discriminatory ability of the test (62) or SDI summary, in this case, for the outcome (disturbed sleep as defined by TST). A high AUC score implies that the rate of true positives is high and that the rate of false positives is low. An AUC score below 0.75 is not considered clinically useful (62).

Sensitivity, specificity, predictive values, and the rate of true positives, false positives, true negatives, and false negatives were calculated for the SDI summaries, to investigate which outcome and which cut-off was the most clinically useful. Sensitivity refers

to the proportion with the condition that get a positive test result (true positives), while specificity refers to those who do not suffer from the condition and that get a negative test result (true negatives) (63). The positive predictive value refers to the proportion of positive results that are true positives, while the negative predictive value refers to the proportion of negative results that are true negatives.

Youden's Index

The Youden's index (sensitivity + specificity-1) is a common summary measure for the ROC curve and is used to determine the most appropriate cut-off value for a scale (64–66). This index incorporates sensitivity and specificity and the cut-off that yields the highest Youden's index value is regarded as the "optimal" threshold value. The Youden's Index was calculated for the *SDI summed product score* and the *SDI summed frequency score*.

Ethical Approval and Consent to Participate

Through conversations with the physician at each nursing home, patients who were most likely able to provide informed consent were identified. The researchers endeavored to inform all participants about the study in an adapted way, and continuously evaluated the capacity to provide consent. Most patients were not able to provide consent. In these cases, the patient's legal guardian was contacted directly. After being approached by a phone call, they received a letter by postal mail containing all relevant information about the aims, proceedings, and ethical approval of the trial, after which they gave a presumed informed consent on behalf of the patient. In giving a presumed consent, the patient's guardian was instructed to consider what the patient would have wished for in this situation, not what they themselves believed was most pertinent. Across the study period, the researchers were sensitive to any expressions of discomfort or protests from the participants; and considered this as withdrawal of consent. The study was approved by the Regional Ethics Committee (REC South East 2016/2246).

RESULTS

A total of 69 participants were enrolled, of whom 68% were women, mean age was 83.5 (SD 7.1), and mean MMSE was 6.4 (SD 6.7). Descriptive statistics and diagnoses are provided in **Table 2**. **Figure 1** shows the full inclusion and exclusion of study participants leaving 62 with actigraphy recordings over at least 5 days and 65 with completed SDIs. A total of 59 patients had both completed SDI and had sufficient actigraphy recordings.

TABLE 2 | Descriptive statistics for the 69 patients.

Age (mean, SD)	83.5 (7.1)
Female (%)	68.0%
Mini mental state examination sum score, mean (SD) ($n = 56$)	6.4 (6.7), median 4.0
Dementia diagnoses, *n* (%)	
Alzheimer's disease (AD)	38 (55.1)
Mixed AD and vascular dementia	0
Lewy body dementia	1 (1.4)
Other dementia	2 (2.9)
Vascular dementia	4 (5.8)
Frontotemporal dementia	0
Parkinson's dementia	0
Unknown dementia	21 (30.4)
No diagnosis¤	3 (4.4)
Neuropsychiatric inventory (NPI) ($n = 69$)	
NPI total score, median (25th−75th percentile)	21.0 (6.0–42.0)
Sleep item score, median (25th−75th percentile)	0.0 (0.0–4.0)
Sleep item score ≥ 4, *n* (%)	18 (26.1)
Sleep item score 0, *n* (%)	38 (55.1)
Total number of medications (mean, SD)	6.7 (2.8)
Number of psychotropic medications* (mean, SD)	2.9 (1.3)
Number of sedatives and hypnotics§, *n* (%)	
0	60 (87.0)
1	8 (11.6)
2	1 (1.4)

**All medications with an ATC code starting with N.*

§*All medications with an ATC code starting with N05C.*

¤*These patients were still included as their scores on the Mini Mental State Examination and the Functional Assessment Staging suggest moderate and severe dementia. In addition, clinically trained researchers concluded that they with high probability suffered from dementia according to the DSM-5 criteria.*

Sleep Assessed With SDI

The SDI scores were not normally distributed, with the majority of patients obtaining low scores. Therefore, the median was used to summarize the group, instead of the mean (**Table 3**). In all, 19 patients (32%) had a total score of 0. The median of the *SDI average total score* was 0.06 and the median of the *SDI summed product score* and *the SDI summed frequency score* was 3.00. Mean frequency was 0.43, mean intensity was 0.14, and mean staff distress was 0.29. All SDI-based scores had a wide range, reflecting heterogeneity in the sample.

The most frequent behavior was waking up at night, happening at least once a week (i.e., endorsed by the staff) for 46% of the patients (**Table 4**). Getting up during the night was endorsed for 34% of the patients and 31% engaged in wandering or inappropriate activities during the night. The three items reflecting these behaviors were also the most distressing to the nursing personnel. One third of the patients were reported to sleep excessively during the day at least once a week, but this behavior caused less distress among staff.

Sleep Assessed With Actigraphy

The actigraph results were based on recordings including a mean of 7.6 (SD 1.4, range 5–14) nights. The median sleep length (TST) within the rest interval (i.e., at night) was 6 h 19 min (95% CI 5 h 23 min−6 h 41 min) and the median SE was 79% (95% CI 69–84) (**Table 5**). The time spent awake after sleep onset (WASO) was normally distributed and had a mean of 1 h 9 min (95% CI 57 min−1 h 20 min). The 24 h fragmentation index had a mean of 93.2 (95% CI 88.0–98.3). All actigraphy outcomes had a wide range, reflecting heterogeneity in the population.

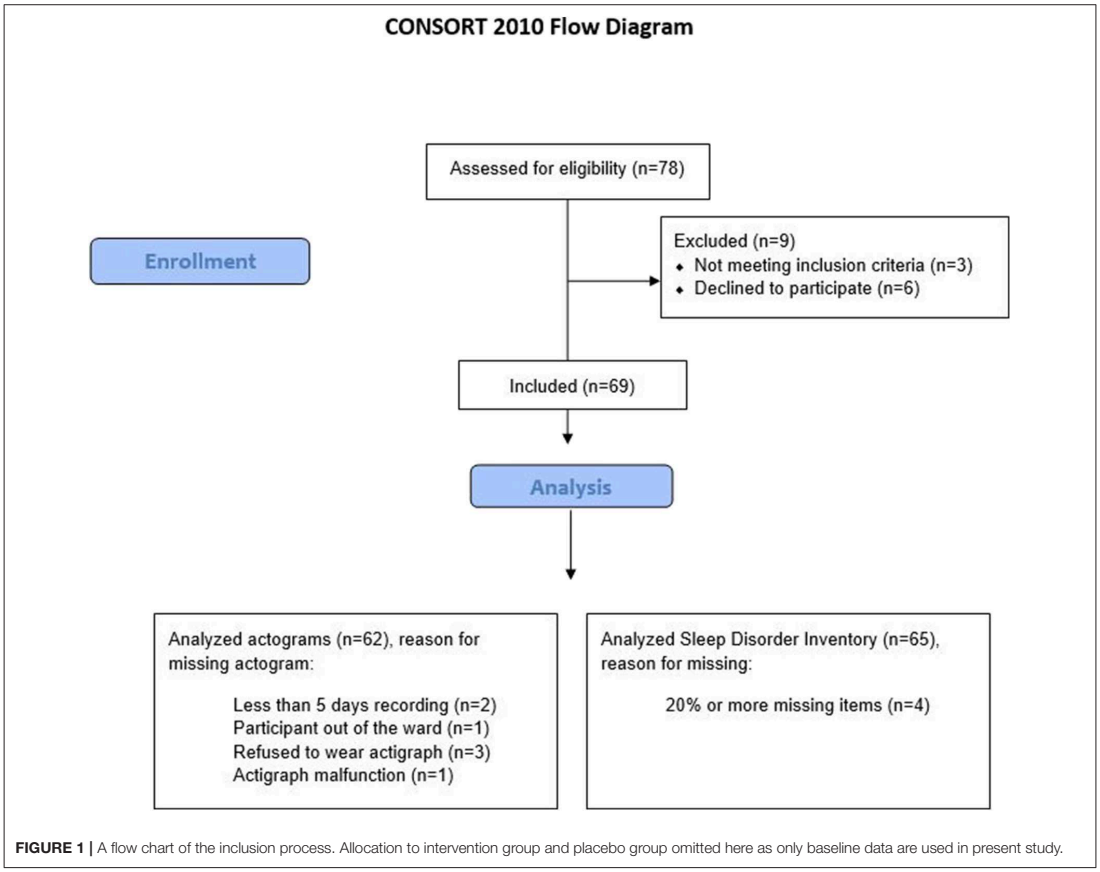

FIGURE 1 | A flow chart of the inclusion process. Allocation to intervention group and placebo group omitted here as only baseline data are used in present study.

TABLE 3 | Median values for the SDI outcomes for the 59 patients that had both SDI and actigraphy data, all of which had non-normal distributions.

SDI outcome (possible min-max score)	Median	25th percentile	75th percentile	Min-max	95% CI of median*
SDI average total (0–12)	0.06	0.00	1.84	0.00–6.12	0.04–0.57
SDI summed product (0–84)	3.00	0.00	18.00	0–60	2.00–9.00
SDI summed frequency (0–28)	3.00	0.00	11.00	0–22	2.00–7.00
SDI mean frequency (0–4)	0.43	0.00	1.57	0–3	0.29–1.00
SDI mean severity (0–3)	0.14	0.00	0.86	0–2	0.14–0.57
SDI mean distress (0–5)	0.29	0.00	1.43	0–4	0.00–0.86

SDI, Sleep Disorder Inventory.
**CI for medians were calculated with the Ratio Statistic in SPSS, which provide varying coverage, but always more than 95%.*

Internal Consistency of the SDI

Cronbach's alpha for the adapted SDI was 0.82 for the frequency ratings and 0.87 for the severity ratings. The item-total correlations varied across items and were below 0.3 for the frequency of item 7 (excessive sleep during the day;0.22), the severity of item 6 (wake up too early;0.23) and the severity of item 7 (excessive sleep during the day;0.25). Removing these items caused only negligible increases of alpha. Daytime sleep propensity became more severe with increasing AD severity (67), hence the daytime sleep item (item 7) provided relevant clinical information; thus even if item-total correlations are lowest for these items/ratings, they are a clinically-essential component of the instrument and its scores.

TABLE 4 | The endorsement of each SDI item (frequency ≥2), percentage rated as being moderately to markedly severe (severity ≥2), and percentage rated as moderately to extremely distressing (staff distress ≥3), in accordance with Tractenberg et al. (30).

Symptom	% Endorsement	% Moderate/ marked severity	% Moderate/ extreme distress
Difficulty falling asleep	25.43	16.95	13.56
Getting up during the night	33.90	27.12	25.42
Wandering, pacing or getting involved in inappropriate activities at night	30.51	23.73	25.42
Awakening at night	45.76	30.51	23.73
Awakening at night, dressing, and planning to go out, thinking that it is morning and time to start the day	11.86	8.48	6.78
Awakening too early in the morning (earlier than is his/her habit)	8.48	3.39	1.70
Sleeping excessively during the day	33.90	13.56	3.39

SDI, Sleep Disorder Inventory.
Frequency ratings: 0 = not present; 1 = less than once per week; 2 = 1–2 times per week; 3 = several times per week but less than every day; 4 = once or more per day (every night). Severity ratings: 0 = not present; 1 = mild; 2 = moderate; 3 = marked. Staff distress ratings: 0 = not at all; 1 = minimally; 2 = mildly; 3 = moderately; 4 = severely; 5 = very severely/extremely (30).

TABLE 5 | Actigraphy variables for the 59 participants with complete SDI and actigraphic recordings based on a mean of 7.6 days.

	Mean (SD)	Range	95 % CI§
TST night	379.10 (290.86–423.00)*	123.00–463.40	323.57–401.00
SE	79.00(60.60–88.13)*	25.63–96.54	68.59–83.54
WASO	68.47 (43.72)	3.00–212.71	57.08–79.87
24 h fragmentation index	93.15 (19.58)	61.03–141.63	88.04–98.25

SE, sleep efficiency; TST, total sleep time; WASO, wake after sleep onset.
**Non-normal data presented as medians with the 25th and 75th percentile in parentheses.*
§CI for medians were calculated with the Ratio Statistic in SPSS, which provide varying coverage, but always more than 95%.

Convergent Validity: SDI Compared to Actigraphy and NPI-NH

Table 6 shows the Spearman correlation coefficients between different SDI variables and the actigraphy parameters. For TST at night, all SDI outcomes had a significant and moderate correlation (minimum −0.40 and maximum −0.44). As expected, greater SDI scores were associated with lower TST (resulting in a negative correlation), higher WASO, and higher scores on the single NPI-NH sleep item (positive correlations). The SDI summaries did not correlate significantly with the 24 h fragmentation index.

Test Accuracy

As noted, we defined "disturbed sleep" to be actigraphy-derived TST of <6 h for the ROC curve analysis (1 = TST at night <6 h, 0 = TST at night ≥6 h). Twenty-seven patients had a TST below 6 h, and 32 patients had a TST of 6 h or more. We evaluated how the three SDI summaries performed against this standard (**Table 7**). The AUC scores were above 0.75 for all three SDI summaries, indicating that all are clinically useful. The scores were almost equivalent, however, the *SDI summed product score* and the *SDI summed frequency score* both had slightly higher AUC scores than the *SDI average total score,* with AUC scores of 0.78, 0.78, and 0.77, respectively.

TABLE 6 | The correlation coefficients (Spearman's rho) for the SDI outcomes against actigraphy outcomes and the NPI-NH sleep item.

SDI outcome	TST night (actigraphy)	WASO (actigraphy)	24 h fragmentation index (actigraphy)	NPI-NH sleep item
SDI average total	−0.431*	0.389*	0.216	0.746*
SDI summed product	−0.432*	0.402*	0.216	0.751*
SDI summed frequency	−0.436*	0.395*	0.213	0.754*
Mean frequency	−0.436*	0.395*	0.213	0.754*
Mean severity	−0.403*	0.369*	0.195	0.749*
Mean distress	−0.408*	0.372*	0.160	0.755*

NPI-NH, Neuropsychiatric Inventory—nursing home version; SDI, Sleep Disorder Inventory; TST, total sleep time; WASO, wake after sleep onset.
**Correlations were significant at the 0.01 level (2-tailed).*

TABLE 7 | The ROC output for the SDI summaries against the 6 h actigraphy TST cut-off.

				95% CI	
SDI outcome	Area	Std. error	Asymptotic sig	Lower bound	Upper bound
Total *SDI average total*	0.771	0.064	0.000	0.646	0.895
Total *SDI summed product*	0.777	0.063	0.000	0.653	0.900
Total *SDI summed frequency*	0.780	0.062	0.000	0.659	0.901

CI, confidence interval; ROC, Receiver operating characteristic; SDI, Sleep Disorder Inventory; TST, Total sleep time.

The sensitivity, specificity, predictive values, and ratios of true positives, false positives, true negatives, and false negatives were calculated for each level of the *SDI summed product score* (range 1–84) (**Table 8**) and the *SDI summed frequency score* (range 1–28) (**Table 9**). For both the *SDI summed product score* and the *SDI summed frequency score*, Youden's index peaked at cut-off scores of 5–6 and the results are presented for values 1–10. The sensitivity, specificity, and Youden's Index of the *SDI average total score* (not shown) were all worse than the two best AUC performing summaries.

Comparing the *SDI summed product score* and the *SDI summed frequency score*, the former achieved the highest Youden's index (0.485 compared to 0.480). These values were obtained for both a cut-off of ≥5 and a cut-off ≥6, for both the *SDI summed product score* and *the SDI summed frequency score.* For the *SDI summed product score*, these cut-offs had a sensitivity

TABLE 8 | The sensitivity, specificity, positive and negative predictive values, and the rate of true positives, false positives, true negatives, false negatives, and the Youden's Index for each value of the *SDI summed product score* (sum of frequency × severity).

SDI summed product score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV(%)	TP	FP	TN	FN	Youden's Index
≥1	85	47	58	79	23	17	15	4	0.321
≥2	85	47	61	81	23	15	17	4	0.321
≥3	78	63	64	77	21	12	20	6	0.403
≥4	74	72	69	77	20	9	23	7	0.460
≥5	70	78	73	76	19	7	25	8	0.485
≥6	70	78	73	76	19	7	25	8	0.485
≥7	63	81	74	72	17	6	26	10	0.443
≥8	63	81	74	72	17	6	26	10	0.443
≥9	63	81	74	72	17	6	26	10	0.443
≥10	59	84	76	71	16	5	27	11	0.437

Total n = 59. FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; SDI, Sleep Disorder Inventory; TN, true negative; TP, true positive.

TABLE 9 | The sensitivity, specificity, positive, and negative predictive values, and the rate of true positives, false positives, true negatives, false negatives, and the Youden's Index for each value of the *SDI summed frequency score*.

SDI summed frequency score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	TP	FP	TN	FN	Youden's Index
≥1	85	47	58	78	23	17	15	4	0.321
≥2	85	53	61	81	23	15	17	4	0.383
≥3	78	63	64	77	21	12	20	6	0.403
≥4	70	75	70	75	19	8	24	8	0.454
≥5	67	81	75	74	18	6	26	9	0.480
≥6	67	81	75	74	18	6	26	9	0.480
≥7	63	84	77	73	17	5	27	10	0.474
≥8	59	84	76	71	16	5	27	11	0.477
≥9	56	84	75	69	15	5	27	12	0.400
≥10	48	88	77	67	13	4	28	14	0.357

Total n = 59. FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; SDI, Sleep Disorder Inventory; TN, true negative; TP, true positive.

of 70%, a specificity of 78%, a positive predictive value (PPV) of 73% and a negative predictive value (NPV) of 76%. For the *SDI summed frequency score*, these cut-offs yielded a sensitivity of 67%, a specificity of 81%, a PPV of 75%, and a NPV of 74%.

DISCUSSION

The aim of the present study was to validate the SDI in a nursing home context and to determine a clinically useful cut-off score on the SDI to identify sleep disturbance in this population. The analyses showed that the SDI had high internal consistency and convergent validity.

Even though two items had low item-total correlation, they were not excluded because they minimally affected the overall internal consistency and thus may provide important clinical information. Three different ways of summarizing the SDI correlated significantly with the actigraphy outcomes TST at night and WASO, with medium-strength associations. Considering frequency, severity, and staff distress separately, frequency had the strongest association to these actigraphy sleep variables. The SDI summaries did not correlate with 24 h sleep fragmentation. Although the SDI contains one item pertaining to daytime sleep, the total score did not seem to reflect the fragmentation of the sleep-wake rhythm across the day and night. The ROC curve analyses indicated that the *SDI average total score*, the *SDI summed product score*, and the *SDI total frequency score* led to correct predictions of disrupted sleep (yes and no) about 78% of the time (95% CI about 65–90%), which is considered to be "clinically useful" (62). The *SDI summed product score*, using a cut-off for disturbed sleep of five or more or six or more had the highest Youden's Index values. Both cut-offs yielded a sensitivity of 70%, a specificity of 78%, a positive predictive value (PPV) of 73% and a negative predictive value (NPV) of 76% for predicting disturbance defined as <6 h in TST defined by actigraphy. The *SDI summed frequency score* had the highest AUC score, however, obtained a slightly lower maximum Youden's index. The maximum Youden's index on this summary was also obtained by both a cut-off of five or more and six or more, yielding a sensitivity of 67%, a specificity of 81%, a PPV of 75%, and a NPV of 74%. Because it is important to be as sensitive to disrupted sleep as possible, we believe that the SDI summary providing the highest sensitivity should be used (i.e., the *SDI summed product score*), and also that the lower cut-off (≥5) should be used. Thus, we suggest a clinical cut-off

for the presence of disturbed sleep in institutionalized dementia patients to be a *SDI summed product score* of five or more. Even though the SDI was developed for home-dwelling seniors and their caregivers (30), the present study demonstrates that the SDI can be clinically useful for the identification of sleep disturbance when administered by daytime staff in a nursing home context.

The present finding of the clinical utility of a proxy-rated sleep tool stands in contrast to the findings by Blytt et al. (25), where the sleep items of the CSDD and the sleep item from the NPI-NH underreported sleep problems when compared to actigraphy parameters. Other than using different subjective sleep outcomes, the discrepancy between the present results and the results from Blytt et al. (25) may in part be explained by differences in the choice of actigraphy-based cut-offs for defining disturbed sleep. In the present study, disturbed sleep was defined as sleeping <6 h between 22:00 and 06:00, corresponding to a SE of 75% or less. More conservatively, Blytt et al. (25) defined disturbed sleep as having <85% SE, in each participants' individual rest interval (based on light, activity, and event marker information in the actogram, indicating bedtime and wake time), which is a common cut-off for defining disturbed sleep (55, 56), albeit in normal populations.

In the original paper by Tractenberg et al. (30), they defined a rest interval from 20:00 to 08:00. To avoid the inclusion of time spent out of bed, we instead used a rest interval from 22:00 to 06:00, reflecting a more realistic interval in this specific population. The use of a common night-time interval for all participants in our sample reflects a period when patients are expected to be in bed. Using a wider rest interval might have increased the variability of SDI ratings across wards or nurse raters, as problematic night-time behavior in one ward could, for example, be classified as afternoon or evening restlessness in a ward with later bed time. Conversely, a narrow rest interval may have excluded time when many patients were in bed and asleep, as nursing home patients spend substantial time in bed (25).

In the original study, Tractenberg et al. (30) found a higher prevalence of symptoms than in the present study. However, in their study, participants were recruited based on sleep complaints, while disrupted sleep was only one of several optional inclusion criteria in the present study. Also, bed-sharing caregivers [as in (30)] are likely to be more sensitive to nocturnal behavior than nursing home staff, as staff generally do not attend to the patients at night unless they get up or call for assistance. Further, sleep difficulties or nocturnal behavior might not be reported consistently in the patient records and may not always be conveyed to the day shift staff. This might explain the low clinical cut-off suggested in the present study: A sum frequency of five is low, given that the maximum score is 84. This suggests that even this slight subjective impression of sleep disturbance among patients on the nursing home staff, may reflect a significant disruption of sleep. However, we did observe that the distributions of SDI summary scores were skewed toward the low-scoring end of the continuum, and 44% of the sample would be qualified as "sleep disturbed" using the cut-off of 5, as compared with 46% characterized as "sleep disturbed" using the clinical and objective TST cut-off of <6 h.

The present study suggests that the SDI, rated by daytime staff, may be used to detect sleep problems in institutionalized dementia patients. The cut-off score identified can be used as a means of identifying patients for inclusion in clinical trials of sleep interventions. To treat disturbed sleep, it is necessary to identify the underlying cause. In line with this, the SDI can serve as a screening tool to identify patients who struggle with sleep problems, and form the basis for a more deliberate mapping of sleep problems. For example, sleep disturbance caused by nocturia requires a different treatment than sleep disordered breathing. Hoeckert et al. (27) used the CSINAPS scale, that specifically asked about snoring, breathing problems and unusual movements. These items were rarely endorsed despite high prevalence of sleep disordered breathing and periodic leg movements in dementia patients (68), reflecting the need to more deliberately evaluate these symptoms. Importantly, the use of objective measurements presents a challenge as many patients struggle with tolerating the equipment (69). Thus, deliberate and continuous observation of patients that struggle with sleep, for example patients identified by the SDI, is probably necessary in order to identify the specific underlying problems. However, the routine use of validated sleep scales may encourage the awareness among staff of how clinically relevant sleep problems in these patients are, increasing staff sensitivity to the importance of detecting signs of poor sleep as a significant component in understanding the patient's overall behavioral problems.

Strengths and Limitations

The majority of the included participants provided good quality actigraphy data for a minimum of 5 nights (mean 7.6 nights). The patients who agreed to wear the actigraph generally wore it continuously until it was collected by the researchers. Because the presence of disturbed sleep was not a required criterion for inclusion, the participants exhibited a wide range in scores on the sleep parameters. The present study demonstrated the utility of the SDI in a heterogeneous sample that is representative of institutionalized patients suffering from dementia.

One important limitation is the choice of an actigraphy-based outcome as the reference against which the SDI was validated. Wrist actigraphy has been shown to be a reliable method of assessing sleep in different clinical populations, compared to the "gold standard" of polysomnography and observation (70), including nursing home patients with severe dementia (69). However, studies have demonstrated that actigraphy has low specificity (poor wake detection) (71) and that it overestimates sleep in people with very disturbed sleep (8, 72). Thus, actigraphy has acknowledged weaknesses in terms of detecting wakefulness, hence the correlations between SDI summaries and actigraphic data found in the present investigation might represent overestimates. Another limitation is the suboptimal use of the event marker and consequently the use of a fixed rest interval. Future studies should secure a robust indication of bedtime and rise time to obtain more accurate reports of each participants' sleep.

Further, even though the ROC curve analysis revealed a clinically useful cut-off for the SDI summaries, the AUC scores of 0.77 (*SDI average total*) and 0.78 (*SDI summed product,*

SDI summed frequency) still correspond to a relatively low discriminatory power (62). The confidence intervals for the AUC scores were quite wide and ranged from about 0.65, corresponding to no clinical value, to 0.90, corresponding to high clinical value (62). This indicates somewhat uncertainty about value of the SDI summaries. We thus suggest that the findings should be replicated in a larger sample.

The correlation between the SDI summed product score and actigraphically-measured TST was 0.43, corresponding to a moderate correlation (73), but also shows that there is significantly residual variance in TST not captured by the SDI. In fact, the amount of shared variability was <20% ($0.43 \times 0.43 = 0.185$) and over 80% of the variability in SDI scores was not explained by the TST value. As the actigraphy-based TST was a summary across a minimum of 5 days (mean 7.7), and the SDI is a summary across 2 weeks, there was not an exact temporal overlap between the two measures. The SDI covered the last 14 days and was completed in the same week that the actigraph was worn by the participants. Hence, the temporal overlap between the two measures was incomplete, and thus the SDI includes behavior not captured by the actigraph. Importantly, there is however a well-documented discrepancy between subjective and objective measures of sleep (74, 75), and this discrepancy is probably a strong contributor to the residual variance in actigraphically measured TST in the present study, in addition to the lack of temporal correspondence. Further, there is a lot more complexity to "disrupted sleep" than what is captured by actigraphically assessed TST alone, which is, at its core, a reflection of immobility. However, both outcomes (actigraphy-measured TST and the SDI summary) were used as approximations of general sleep disturbance, where both can serve as indicators that a more deliberate evaluation of sleep is warranted.

The completion of the SDI was part of a larger data collection project and all questionnaires were completed by nurses during the day. Few nurses are at work during the night and our data collection corresponds with clinical assessments in nursing homes, which are normally performed during the day in collaboration with the nursing home physician. The night time staff are obliged to write reports and to note in the medical record if clinically relevant events have taken place during night shifts. It is also common that staff share information orally during handover. Thus, daytime staff should be informed about any nocturnal events. It would however be preferable to obtain both night and daytime staff reports on the SDI. Nevertheless, the fact that we did achieve an AUC score of 0.78 and significant correlations between the SDI and actigraphy demonstrates that daytime staff have significant information about patients' behavior outside their own shift. It also suggests that the usual procedure of administering tests during the day is feasible also with the SDI, provided adequate communication between the night and day shift.

While the *SDI summed product score* and the *SDI summed frequency score* both led to the same cut-off value (≥5) for identifying disrupted sleep, the sample size of the present study was relatively small and confirmatory studies in larger samples are warranted. We did not interrogate the specific diagnoses or prescriptions of sedatives of the participants included in the trial, and there may be important differences among those with AD, dementia with Lewy bodies, and vascular dementia. Future studies should address these issues.

CONCLUSION

Overall, the results of the present study showed that the scores on the proxy-rated Sleep Disorder Inventory correspond well to objectively measured sleep disruption (defined as a TST<6 h, corresponding to a SE<75%) in institutionalized dementia patients, using a clinical cut-off of a summed product score of five or more. The present results should be interpreted with caution bearing in mind that actigraphy was used as the reference outcome measure of sleep. Even though the SDI seems to identify patients with disturbed sleep successfully, some patients suffering from disturbed sleep may still go undetected. The recommended cut-off score (≥5) is low, suggesting that only a slight clinical impression of disrupted sleep may reflect significant sleep disruption. Nursing home staff should be vigilant to document any signs of sleep problems among patients at all times. The SDI appears to be useful as a screening tool to identify patients with probable sleep problems. However, determining the cause of the disrupted sleep normally would require a more deliberate approach, such as continuous observation and/or polysomnografic/polygraphic recordings.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on reasonable request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Ethics Committee (REC South East 2016/2246). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GH, EK, SP, EF, ET, IN, and RT were involved in the acquisition or analysis of the data. All authors were involved in the interpretation, drafting, revision of the work, approved the manuscript for submission, agreed to be accountable for the work, and contributed in the conception or design of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00173/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Doctoral Theses at The Faculty of Psychology, University of Bergen

1980	Allen, Hugh M., Dr. philos.	Parent-offspring interactions in willow grouse (Lagopus L. Lagopus).
1981	Myhrer, Trond, Dr. philos.	Behavioral Studies after selective disruption of hippocampal inputs in albino rats.
1982	Svebak, Sven, Dr. philos.	The significance of motivation for task-induced tonic physiological changes.
1983	Myhre, Grete, Dr. philos.	The Biopsychology of behavior in captive Willow ptarmigan.
	Eide, Rolf, Dr. philos.	PSYCHOSOCIAL FACTORS AND INDICES OF HEALTH RISKS. The relationship of psychosocial conditions to subjective complaints, arterial blood pressure, serum cholesterol, serum triglycerides and urinary catecholamines in middle aged populations in Western Norway.
	Værnes, Ragnar J., Dr. philos.	Neuropsychological effects of diving.
1984	Kolstad, Arnulf, Dr. philos.	Til diskusjonen om sammenhengen mellom sosiale forhold og psykiske strukturer. En epidemiologisk undersøkelse blant barn og unge.
	Løberg, Tor, Dr. philos.	Neuropsychological assessment in alcohol dependence.
1985	Hellesnes, Tore, Dr. philos.	Læring og problemløsning. En studie av den perseptuelle analysens betydning for verbal læring.
	Håland, Wenche, Dr. philos.	Psykoterapi: relasjon, utviklingsprosess og effekt.
1986	Hagtvet, Knut A., Dr. philos.	The construct of test anxiety: Conceptual and methodological issues.
	Jellestad, Finn K., Dr. philos.	Effects of neuron specific amygdala lesions on fear-motivated behavior in rats.
1987	Aarø, Leif E., Dr. philos.	Health behaviour and sosioeconomic Status. A survey among the adult population in Norway.
	Underlid, Kjell, Dr. philos.	Arbeidsløyse i psykososialt perspektiv.
	Laberg, Jon C., Dr. philos.	Expectancy and classical conditioning in alcoholics' craving.
	Vollmer, Fred, Dr. philos.	Essays on explanation in psychology.
	Ellertsen, Bjørn, Dr. philos.	Migraine and tension headache: Psychophysiology, personality and therapy.
1988	Kaufmann, Astrid, Dr. philos.	Antisosial atferd hos ungdom. En studie av psykologiske determinanter.

	Mykletun, Reidar J., Dr. philos.	Teacher stress: personality, work-load and health.
	Havik, Odd E., Dr. philos.	After the myocardial infarction: A medical and psychological study with special emphasis on perceived illness.
1989	Bråten, Stein, Dr. philos.	Menneskedyaden. En teoretisk tese om sinnets dialogiske natur med informasjons- og utviklingspsykologiske implikasjoner sammenholdt med utvalgte spedbarnsstudier.
	Wold, Bente, Dr. psychol.	Lifestyles and physical activity. A theoretical and empirical analysis of socialization among children and adolescents.
1990	Flaten, Magne A., Dr. psychol.	The role of habituation and learning in reflex modification.
1991	Alsaker, Françoise D., Dr. philos.	Global negative self-evaluations in early adolescence.
	Kraft, Pål, Dr. philos.	AIDS prevention in Norway. Empirical studies on diffusion of knowledge, public opinion, and sexual behaviour.
	Endresen, Inger M., Dr. philos.	Psychoimmuniological stress markers in working life.
	Faleide, Asbjørn O., Dr. philos.	Asthma and allergy in childhood. Psychosocial and psychotherapeutic problems.
1992	Dalen, Knut, Dr. philos.	Hemispheric asymmetry and the Dual-Task Paradigm: An experimental approach.
	Bø, Inge B., Dr. philos.	Ungdoms sosiale økologi. En undersøkelse av 14-16 åringers sosiale nettverk.
	Nivison, Mary E., Dr. philos.	The relationship between noise as an experimental and environmental stressor, physiological changes and psychological factors.
	Torgersen, Anne M., Dr. philos.	Genetic and environmental influence on temperamental behaviour. A longitudinal study of twins from infancy to adolescence.
1993	Larsen, Svein, Dr. philos.	Cultural background and problem drinking.
	Nordhus, Inger Hilde, Dr. philos.	Family caregiving. A community psychological study with special emphasis on clinical interventions.
	Thuen, Frode, Dr. psychol.	Accident-related behaviour among children and young adolescents: Prediction and prevention.
	Solheim, Ragnar, Dr. philos.	Spesifikke lærevansker. Diskrepanskriteriet anvendt i seleksjonsmetodikk.
	Johnsen, Bjørn Helge, Dr. psychol.	Brain assymetry and facial emotional expressions: Conditioning experiments.
1994	Tønnessen, Finn E., Dr. philos.	The etiology of Dyslexia.
	Kvale, Gerd, Dr. psychol.	Psychological factors in anticipatory nausea and vomiting in cancer chemotherapy.

	Asbjørnsen, Arve E., Dr. psychol.	Structural and dynamic factors in dichotic listening: An interactional model.
	Bru, Edvin, Dr. philos.	The role of psychological factors in neck, shoulder and low back pain among female hospitale staff.
	Braathen, Eli T., Dr. psychol.	Prediction of exellence and discontinuation in different types of sport: The significance of motivation and EMG.
	Johannessen, Birte F., Dr. philos.	Det flytende kjønnet. Om lederskap, politikk og identitet.
1995	Sam, David L., Dr. psychol.	Acculturation of young immigrants in Norway: A psychological and socio-cultural adaptation.
	Bjaalid, Inger-Kristin, Dr. philos.	Component processes in word recognition.
	Martinsen, Øyvind, Dr. philos.	Cognitive style and insight.
	Nordby, Helge, Dr. philos.	Processing of auditory deviant events: Mismatch negativity of event-related brain potentials.
	Raaheim, Arild, Dr. philos.	Health perception and health behaviour, theoretical considerations, empirical studies, and practical implications.
	Seltzer, Wencke J., Dr. philos.	Studies of Psychocultural Approach to Families in Therapy.
	Brun, Wibecke, Dr. philos.	Subjective conceptions of uncertainty and risk.
	Aas, Henrik N., Dr. psychol.	Alcohol expectancies and socialization: Adolescents learning to drink.
	Bjørkly, Stål, Dr. psychol.	Diagnosis and prediction of intra-institutional aggressive behaviour in psychotic patients
1996	Anderssen, Norman, Dr. psychol.	Physical activity of young people in a health perspective: Stability, change and social influences.
	Sandal, Gro Mjeldheim, Dr. psychol.	Coping in extreme environments: The role of personality.
	Strumse, Einar, Dr. philos.	The psychology of aesthetics: explaining visual preferences for agrarian landscapes in Western Norway.
	Hestad, Knut, Dr. philos.	Neuropsychological deficits in HIV-1 infection.
	Lugoe, L.Wycliffe, Dr. philos.	Prediction of Tanzanian students' HIV risk and preventive behaviours
	Sandvik, B. Gunnhild, Dr. philos.	Fra distriktsjordmor til institusjonsjordmor. Fremveksten av en profesjon og en profesjonsutdanning
	Lie, Gro Therese, Dr. psychol.	The disease that dares not speak its name: Studies on factors of importance for coping with HIV/AIDS in Northern Tanzania
	Øygard, Lisbet, Dr. philos.	Health behaviors among young adults. A psychological and sociological approach
	Stormark, Kjell Morten, Dr. psychol.	Emotional modulation of selective attention: Experimental and clinical evidence.

	Einarsen, Ståle, Dr. psychol.	Bullying and harassment at work: epidemiological and psychosocial aspects.
1997	Knivsberg, Ann-Mari, Dr. philos.	Behavioural abnormalities and childhood psychopathology: Urinary peptide patterns as a potential tool in diagnosis and remediation.
	Eide, Arne H., Dr. philos.	Adolescent drug use in Zimbabwe. Cultural orientation in a global-local perspective and use of psychoactive substances among secondary school students.
	Sørensen, Marit, Dr. philos.	The psychology of initiating and maintaining exercise and diet behaviour.
	Skjæveland, Oddvar, Dr. psychol.	Relationships between spatial-physical neighborhood attributes and social relations among neighbors.
	Zewdie, Teka, Dr. philos.	Mother-child relational patterns in Ethiopia. Issues of developmental theories and intervention programs.
	Wilhelmsen, Britt Unni, Dr. philos.	Development and evaluation of two educational programmes designed to prevent alcohol use among adolescents.
	Manger, Terje, Dr. philos.	Gender differences in mathematical achievement among Norwegian elementary school students.
1998 **V**	Lindstrøm, Torill Christine, Dr. philos.	«Good Grief»: Adapting to Bereavement.
	Skogstad, Anders, Dr. philos.	Effects of leadership behaviour on job satisfaction, health and efficiency.
	Haldorsen, Ellen M. Håland, Dr. psychol.	Return to work in low back pain patients.
	Besemer, Susan P., Dr. philos.	Creative Product Analysis: The Search for a Valid Model for Understanding Creativity in Products.
H	Winje, Dagfinn, Dr. psychol.	Psychological adjustment after severe trauma. A longitudinal study of adults' and children's posttraumatic reactions and coping after the bus accident in Måbødalen, Norway 1988.
	Vosburg, Suzanne K., Dr. philos.	The effects of mood on creative problem solving.
	Eriksen, Hege R., Dr. philos.	Stress and coping: Does it really matter for subjective health complaints?
	Jakobsen, Reidar, Dr. psychol.	Empiriske studier av kunnskap og holdninger om hiv/aids og den normative seksuelle utvikling i ungdomsårene.
1999 **V**	Mikkelsen, Aslaug, Dr. philos.	Effects of learning opportunities and learning climate on occupational health.
	Samdal, Oddrun, Dr. philos.	The school environment as a risk or resource for students' health-related behaviours and subjective well-being.
	Friestad, Christine, Dr. philos.	Social psychological approaches to smoking.
	Ekeland, Tor-Johan, Dr. philos.	Meining som medisin. Ein analyse av placebofenomenet og implikasjoner for terapi og terapeutiske teoriar.

H	Saban, Sara, Dr. psychol.	Brain Asymmetry and Attention: Classical Conditioning Experiments.
	Carlsten, Carl Thomas, Dr. philos.	God lesing – God læring. En aksjonsrettet studie av undervisning i fagtekstlesing.
	Dundas, Ingrid, Dr. psychol.	Functional and dysfunctional closeness. Family interaction and children's adjustment.
	Engen, Liv, Dr. philos.	Kartlegging av leseferdighet på småskoletrinnet og vurdering av faktorer som kan være av betydning for optimal leseutvikling.
2000 V	Hovland, Ole Johan, Dr. philos.	Transforming a self-preserving "alarm" reaction into a self-defeating emotional response: Toward an integrative approach to anxiety as a human phenomenon.
	Lillejord, Sølvi, Dr. philos.	Handlingsrasjonalitet og spesialundervisning. En analyse av aktørperspektiver.
	Sandell, Ove, Dr. philos.	Den varme kunnskapen.
	Oftedal, Marit Petersen, Dr. philos.	Diagnostisering av ordavkodingsvansker: En prosessanalytisk tilnærmingsmåte.
H	Sandbak, Tone, Dr. psychol.	Alcohol consumption and preference in the rat: The significance of individual differences and relationships to stress pathology
	Eid, Jarle, Dr. psychol.	Early predictors of PTSD symptom reporting; The significance of contextual and individual factors.
2001 V	Skinstad, Anne Helene, Dr. philos.	Substance dependence and borderline personality disorders.
	Binder, Per-Einar, Dr. psychol.	Individet og den meningsbærende andre. En teoretisk undersøkelse av de mellommenneskelige forutsetningene for psykisk liv og utvikling med utgangspunkt i Donald Winnicotts teori.
	Roald, Ingvild K., Dr. philos.	Building of concepts. A study of Physics concepts of Norwegian deaf students.
H	Fekadu, Zelalem W., Dr. philos.	Predicting contraceptive use and intention among a sample of adolescent girls. An application of the theory of planned behaviour in Ethiopian context.
	Melesse, Fantu, Dr. philos.	The more intelligent and sensitive child (MISC) mediational intervention in an Ethiopian context: An evaluation study.
	Råheim, Målfrid, Dr. philos.	Kvinners kroppserfaring og livssammenheng. En fenomenologisk – hermeneutisk studie av friske kvinner og kvinner med kroniske muskelsmerter.
	Engelsen, Birthe Kari, Dr. psychol.	Measurement of the eating problem construct.
	Lau, Bjørn, Dr. philos.	Weight and eating concerns in adolescence.
2002 V	Ihlebæk, Camilla, Dr. philos.	Epidemiological studies of subjective health complaints.

	Rosén, Gunnar O. R., Dr. philos.	The phantom limb experience. Models for understanding and treatment of pain with hypnosis.
	Høines, Marit Johnsen, Dr. philos.	Fleksible språkrom. Matematikklæring som tekstutvikling.
	Anthun, Roald Andor, Dr. philos.	School psychology service quality. Consumer appraisal, quality dimensions, and collaborative improvement potential
	Pallesen, Ståle, Dr. psychol.	Insomnia in the elderly. Epidemiology, psychological characteristics and treatment.
	Midthassel, Unni Vere, Dr. philos.	Teacher involvement in school development activity. A study of teachers in Norwegian compulsory schools
	Kallestad, Jan Helge, Dr. philos.	Teachers, schools and implementation of the Olweus Bullying Prevention Program.
H	Ofte, Sonja Helgesen, Dr. psychol.	Right-left discrimination in adults and children.
	Netland, Marit, Dr. psychol.	Exposure to political violence. The need to estimate our estimations.
	Diseth, Åge, Dr. psychol.	Approaches to learning: Validity and prediction of academic performance.
	Bjuland, Raymond, Dr. philos.	Problem solving in geometry. Reasoning processes of student teachers working in small groups: A dialogical approach.
2003 **V**	Arefjord, Kjersti, Dr. psychol.	After the myocardial infarction – the wives' view. Short- and long-term adjustment in wives of myocardial infarction patients.
	Ingjaldsson, Jón Þorvaldur, Dr. psychol.	Unconscious Processes and Vagal Activity in Alcohol Dependency.
	Holden, Børge, Dr. philos.	Følger av atferdsanalytiske forklaringer for atferdsanalysens tilnærming til utforming av behandling.
	Holsen, Ingrid, Dr. philos.	Depressed mood from adolescence to 'emerging adulthood'. Course and longitudinal influences of body image and parent-adolescent relationship.
	Hammar, Åsa Karin, Dr. psychol.	Major depression and cognitive dysfunction- An experimental study of the cognitive effort hypothesis.
	Sprugevica, Ieva, Dr. philos.	The impact of enabling skills on early reading acquisition.
	Gabrielsen, Egil, Dr. philos.	LESE FOR LIVET. Lesekompetansen i den norske voksenbefolkningen sett i lys av visjonen om en enhetsskole.
H	Hansen, Anita Lill, Dr. psychol.	The influence of heart rate variability in the regulation of attentional and memory processes.
	Dyregrov, Kari, Dr. philos.	The loss of child by suicide, SIDS, and accidents: Consequences, needs and provisions of help.
2004 **V**	Torsheim, Torbjørn, Dr. psychol.	Student role strain and subjective health complaints: Individual, contextual, and longitudinal perspectives.

	Haugland, Bente Storm Mowatt Dr. psychol.	Parental alcohol abuse. Family functioning and child adjustment.
	Milde, Anne Marita, Dr. psychol.	Ulcerative colitis and the role of stress. Animal studies of psychobiological factors in relationship to experimentally induced colitis.
	Stornes, Tor, Dr. philos.	Socio-moral behaviour in sport. An investigation of perceptions of sportspersonship in handball related to important factors of socio-moral influence.
	Mæhle, Magne, Dr. philos.	Re-inventing the child in family therapy: An investigation of the relevance and applicability of theory and research in child development for family therapy involving children.
	Kobbeltvedt, Therese, Dr. psychol.	Risk and feelings: A field approach.
2004 H	Thomsen, Tormod, Dr. psychol.	Localization of attention in the brain.
	Løberg, Else-Marie, Dr. psychol.	Functional laterality and attention modulation in schizophrenia: Effects of clinical variables.
	Kyrkjebø, Jane Mikkelsen, Dr. philos.	Learning to improve: Integrating continuous quality improvement learning into nursing education.
	Laumann, Karin, Dr. psychol.	Restorative and stress-reducing effects of natural environments: Experiencal, behavioural and cardiovascular indices.
	Holgersen, Helge, PhD	Mellom oss - Essay i relasjonell psykoanalyse.
2005 V	Hetland, Hilde, Dr. psychol.	Leading to the extraordinary? Antecedents and outcomes of transformational leadership.
	Iversen, Anette Christine, Dr. philos.	Social differences in health behaviour: the motivational role of perceived control and coping.
2005 H	Mathisen, Gro Ellen, PhD	Climates for creativity and innovation: Definitions, measurement, predictors and consequences.
	Sævi, Tone, Dr. philos.	Seeing disability pedagogically – The lived experience of disability in the pedagogical encounter.
	Wiium, Nora, PhD	Intrapersonal factors, family and school norms: combined and interactive influence on adolescent smoking behaviour.
	Kanagaratnam, Pushpa, PhD	Subjective and objective correlates of Posttraumatic Stress in immigrants/refugees exposed to political violence.
	Larsen, Torill M. B. , PhD	Evaluating principals` and teachers` implementation of Second Step. A case study of four Norwegian primary schools.
	Bancila, Delia, PhD	Psychosocial stress and distress among Romanian adolescents and adults.
2006 V	Hillestad, Torgeir Martin, Dr. philos.	Normalitet og avvik. Forutsetninger for et objektivt psykopatologisk avviksbegrep. En psykologisk, sosial, erkjennelsesteoretisk og teorihistorisk framstilling.

	Nordanger, Dag Øystein, Dr. psychol.	Psychosocial discourses and responses to political violence in post-war Tigray, Ethiopia.
	Rimol, Lars Morten, PhD	Behavioral and fMRI studies of auditory laterality and speech sound processing.
	Krumsvik, Rune Johan, Dr. philos.	ICT in the school. ICT-initiated school development in lower secondary school.
	Norman, Elisabeth, Dr. psychol.	Gut feelings and unconscious thought: An exploration of fringe consiousness in implicit cognition.
	Israel, K Pravin, Dr. psychol.	Parent involvement in the mental health care of children and adolescents. Emperical studies from clinical care setting.
	Glasø, Lars, PhD	Affects and emotional regulation in leader-subordinate relationships.
	Knutsen, Ketil, Dr. philos.	HISTORIER UNGDOM LEVER – En studie av hvordan ungdommer bruker historie for å gjøre livet meningsfullt.
	Matthiesen, Stig Berge, PhD	Bullying at work. Antecedents and outcomes.
2006 H	Gramstad, Arne, PhD	Neuropsychological assessment of cognitive and emotional functioning in patients with epilepsy.
	Bendixen, Mons, PhD	Antisocial behaviour in early adolescence: Methodological and substantive issues.
	Mrumbi, Khalifa Maulid, PhD	Parental illness and loss to HIV/AIDS as experienced by AIDS orphans aged between 12-17 years from Temeke District, Dar es Salaam, Tanzania: A study of the children's psychosocial health and coping responses.
	Hetland, Jørn, Dr. psychol.	The nature of subjective health complaints in adolescence: Dimensionality, stability, and psychosocial predictors
	Kakoko, Deodatus Conatus Vitalis, PhD	Voluntary HIV counselling and testing service uptake among primary school teachers in Mwanza, Tanzania: assessment of socio-demographic, psychosocial and socio-cognitive aspects
	Mykletun, Arnstein, Dr. psychol.	Mortality and work-related disability as long-term consequences of anxiety and depression: Historical cohort designs based on the HUNT-2 study
	Sivertsen, Børge, PhD	Insomnia in older adults. Consequences, assessment and treatment.
2007 V	Singhammer, John, Dr. philos.	Social conditions from before birth to early adulthood – the influence on health and health behaviour
	Janvin, Carmen Ani Cristea, PhD	Cognitive impairment in patients with Parkinson's disease: profiles and implications for prognosis
	Braarud, Hanne Cecilie, Dr.psychol.	Infant regulation of distress: A longitudinal study of transactions between mothers and infants
	Tveito, Torill Helene, PhD	Sick Leave and Subjective Health Complaints

	Magnussen, Liv Heide, PhD	Returning disability pensioners with back pain to work
	Thuen, Elin Marie, Dr.philos.	Learning environment, students' coping styles and emotional and behavioural problems. A study of Norwegian secondary school students.
	Solberg, Ole Asbjørn, PhD	Peacekeeping warriors – A longitudinal study of Norwegian peacekeepers in Kosovo
2007 H	Søreide, Gunn Elisabeth, Dr.philos.	Narrative construction of teacher identity
	Svensen, Erling, PhD	WORK & HEALTH. Cognitive Activation Theory of Stress applied in an organisational setting.
	Øverland, Simon Nygaard, PhD	Mental health and impairment in disability benefits. Studies applying linkages between health surveys and administrative registries.
	Eichele, Tom, PhD	Electrophysiological and Hemodynamic Correlates of Expectancy in Target Processing
	Børhaug, Kjetil, Dr.philos.	Oppseding til demokrati. Ein studie av politisk oppseding i norsk skule.
	Eikeland, Thorleif, Dr.philos.	Om å vokse opp på barnehjem og på sykehus. En undersøkelse av barnehjemsbarns opplevelser på barnehjem sammenholdt med sanatoriebarns beskrivelse av langvarige sykehusopphold – og et forsøk på forklaring.
	Wadel, Carl Cato, Dr.philos.	Medarbeidersamhandling og medarbeiderledelse i en lagbasert organisasjon
	Vinje, Hege Forbech, PhD	Thriving despite adversity: Job engagement and self-care among community nurses
	Noort, Maurits van den, PhD	Working memory capacity and foreign language acquisition
2008 V	Breivik, Kyrre, Dr.psychol.	The Adjustment of Children and Adolescents in Different Post-Divorce Family Structures. A Norwegian Study of Risks and Mechanisms.
	Johnsen, Grethe E., PhD	Memory impairment in patients with posttraumatic stress disorder
	Sætrevik, Bjørn, PhD	Cognitive Control in Auditory Processing
	Carvalhosa, Susana Fonseca, PhD	Prevention of bullying in schools: an ecological model
2008 H	Brønnick, Kolbjørn Selvåg	Attentional dysfunction in dementia associated with Parkinson's disease.
	Posserud, Maj-Britt Rocio	Epidemiology of autism spectrum disorders
	Haug, Ellen	Multilevel correlates of physical activity in the school setting
	Skjerve, Arvid	Assessing mild dementia – a study of brief cognitive tests.

	Kjønniksen, Lise	The association between adolescent experiences in physical activity and leisure time physical activity in adulthood: a ten year longitudinal study
	Gundersen, Hilde	The effects of alcohol and expectancy on brain function
	Omvik, Siri	Insomnia – a night and day problem
2009 V	Molde, Helge	Pathological gambling: prevalence, mechanisms and treatment outcome.
	Foss, Else	Den omsorgsfulle væremåte. En studie av voksnes væremåte i forhold til barn i barnehagen.
	Westrheim, Kariane	Education in a Political Context: A study of Konwledge Processes and Learning Sites in the PKK.
	Wehling, Eike	Cognitive and olfactory changes in aging
	Wangberg, Silje C.	Internet based interventions to support health behaviours: The role of self-efficacy.
	Nielsen, Morten B.	Methodological issues in research on workplace bullying. Operationalisations, measurements and samples.
	Sandu, Anca Larisa	MRI measures of brain volume and cortical complexity in clinical groups and during development.
	Guribye, Eugene	Refugees and mental health interventions
	Sørensen, Lin	Emotional problems in inattentive children – effects on cognitive control functions.
	Tjomsland, Hege E.	Health promotion with teachers. Evaluation of the Norwegian Network of Health Promoting Schools: Quantitative and qualitative analyses of predisposing, reinforcing and enabling conditions related to teacher participation and program sustainability.
	Helleve, Ingrid	Productive interactions in ICT supported communities of learners
2009 H	Skorpen, Aina Øye, Christine	Dagliglivet i en psykiatrisk institusjon: En analyse av miljøterapeutiske praksiser
	Andreassen, Cecilie Schou	WORKAHOLISM – Antecedents and Outcomes
	Stang, Ingun	Being in the same boat: An empowerment intervention in breast cancer self-help groups
	Sequeira, Sarah Dorothee Dos Santos	The effects of background noise on asymmetrical speech perception
	Kleiven, Jo, dr.philos.	The Lillehammer scales: Measuring common motives for vacation and leisure behavior
	Jónsdóttir, Guðrún	Dubito ergo sum? Ni jenter møter naturfaglig kunnskap.
	Hove, Oddbjørn	Mental health disorders in adults with intellectual disabilities - Methods of assessment and prevalence of mental health disorders and problem behaviour
	Wageningen, Heidi Karin van	The role of glutamate on brain function

	Bjørkvik, Jofrid	God nok? Selvaktelse og interpersonlig fungering hos pasienter innen psykisk helsevern: Forholdet til diagnoser, symptomer og behandlingsutbytte
	Andersson, Martin	A study of attention control in children and elderly using a forced-attention dichotic listening paradigm
	Almås, Aslaug Grov	Teachers in the Digital Network Society: Visions and Realities. A study of teachers' experiences with the use of ICT in teaching and learning.
	Ulvik, Marit	Lærerutdanning som danning? Tre stemmer i diskusjonen
2010 V	Skår, Randi	Læringsprosesser i sykepleieres profesjonsutøvelse. En studie av sykepleieres læringserfaringer.
	Roald, Knut	Kvalitetsvurdering som organisasjonslæring mellom skole og skoleeigar
	Lunde, Linn-Heidi	Chronic pain in older adults. Consequences, assessment and treatment.
	Danielsen, Anne Grete	Perceived psychosocial support, students' self-reported academic initiative and perceived life satisfaction
	Hysing, Mari	Mental health in children with chronic illness
	Olsen, Olav Kjellevold	Are good leaders moral leaders? The relationship between effective military operational leadership and morals
	Riese, Hanne	Friendship and learning. Entrepreneurship education through mini-enterprises.
	Holthe, Asle	Evaluating the implementation of the Norwegian guidelines for healthy school meals: A case study involving three secondary schools
H	Hauge, Lars Johan	Environmental antecedents of workplace bullying: A multi-design approach
	Bjørkelo, Brita	Whistleblowing at work: Antecedents and consequences
	Reme, Silje Endresen	Common Complaints – Common Cure? Psychiatric comorbidity and predictors of treatment outcome in low back pain and irritable bowel syndrome
	Helland, Wenche Andersen	Communication difficulties in children identified with psychiatric problems
	Beneventi, Harald	Neuronal correlates of working memory in dyslexia
	Thygesen, Elin	Subjective health and coping in care-dependent old persons living at home
	Aanes, Mette Marthinussen	Poor social relationships as a threat to belongingness needs. Interpersonal stress and subjective health complaints: Mediating and moderating factors.
	Anker, Morten Gustav	Client directed outcome informed couple therapy

	Bull, Torill	Combining employment and child care: The subjective well-being of single women in Scandinavia and in Southern Europe
	Viig, Nina Grieg	Tilrettelegging for læreres deltakelse i helsefremmende arbeid. En kvalitativ og kvantitativ analyse av sammenhengen mellom organisatoriske forhold og læreres deltakelse i utvikling og implementering av Europeisk Nettverk av Helsefremmende Skoler i Norge
	Wolff, Katharina	To know or not to know? Attitudes towards receiving genetic information among patients and the general public.
	Ogden, Terje, dr.philos.	Familiebasert behandling av alvorlige atferdsproblemer blant barn og ungdom. Evaluering og implementering av evidensbaserte behandlingsprogrammer i Norge.
	Solberg, Mona Elin	Self-reported bullying and victimisation at school: Prevalence, overlap and psychosocial adjustment.
2011 V	Bye, Hege Høivik	Self-presentation in job interviews. Individual and cultural differences in applicant self-presentation during job interviews and hiring managers' evaluation
	Notelaers, Guy	Workplace bullying. A risk control perspective.
	Moltu, Christian	Being a therapist in difficult therapeutic impasses. A hermeneutic phenomenological analysis of skilled psychotherapists' experiences, needs, and strategies in difficult therapies ending well.
	Myrseth, Helga	Pathological Gambling - Treatment and Personality Factors
	Schanche, Elisabeth	From self-criticism to self-compassion. An empirical investigation of hypothesized change prosesses in the Affect Phobia Treatment Model of short-term dynamic psychotherapy for patients with Cluster C personality disorders.
	Våpenstad, Eystein Victor, dr.philos.	Det tempererte nærvær. En teoretisk undersøkelse av psykoterapautens subjektivitet i psykoanalyse og psykoanalytisk psykoterapi.
	Haukebø, Kristin	Cognitive, behavioral and neural correlates of dental and intra-oral injection phobia. Results from one treatment and one fMRI study of randomized, controlled design.
	Harris, Anette	Adaptation and health in extreme and isolated environments. From 78°N to 75°S.
	Bjørknes, Ragnhild	Parent Management Training-Oregon Model: intervention effects on maternal practice and child behavior in ethnic minority families
	Mamen, Asgeir	Aspects of using physical training in patients with substance dependence and additional mental distress
	Espevik, Roar	Expert teams: Do shared mental models of team members make a difference
	Haara, Frode Olav	Unveiling teachers' reasons for choosing practical activities in mathematics teaching

2011 H	Hauge, Hans Abraham	How can employee empowerment be made conducive to both employee health and organisation performance? An empirical investigation of a tailor-made approach to organisation learning in a municipal public service organisation.
	Melkevik, Ole Rogstad	Screen-based sedentary behaviours: pastimes for the poor, inactive and overweight? A cross-national survey of children and adolescents in 39 countries.
	Vøllestad, Jon	Mindfulness-based treatment for anxiety disorders. A quantitative review of the evidence, results from a randomized controlled trial, and a qualitative exploration of patient experiences.
	Tolo, Astrid	Hvordan blir lærerkompetanse konstruert? En kvalitativ studie av PPU-studenters kunnskapsutvikling.
	Saus, Evelyn-Rose	Training effectiveness: Situation awareness training in simulators
	Nordgreen, Tine	Internet-based self-help for social anxiety disorder and panic disorder. Factors associated with effect and use of self-help.
	Munkvold, Linda Helen	Oppositional Defiant Disorder: Informant discrepancies, gender differences, co-occuring mental health problems and neurocognitive function.
	Christiansen, Øivin	Når barn plasseres utenfor hjemmet: beslutninger, forløp og relasjoner. Under barnevernets (ved)tak.
	Brunborg, Geir Scott	Conditionability and Reinforcement Sensitivity in Gambling Behaviour
	Hystad, Sigurd William	Measuring Psychological Resiliency: Validation of an Adapted Norwegian Hardiness Scale
2012 V	Roness, Dag	Hvorfor bli lærer? Motivasjon for utdanning og utøving.
	Fjermestad, Krister Westlye	The therapeutic alliance in cognitive behavioural therapy for youth anxiety disorders
	Jenssen, Eirik Sørnes	Tilpasset opplæring i norsk skole: politikeres, skoleledereres og læreres handlingsvalg
	Saksvik-Lehouillier, Ingvild	Shift work tolerance and adaptation to shift work among offshore workers and nurses
	Johansen, Venke Frederike	Når det intime blir offentlig. Om kvinners åpenhet om brystkreft og om markedsføring av brystkreftsaken.
	Herheim, Rune	Pupils collaborating in pairs at a computer in mathematics learning: investigating verbal communication patterns and qualities
	Vie, Tina Løkke	Cognitive appraisal, emotions and subjective health complaints among victims of workplace bullying: A stress-theoretical approach
	Jones, Lise Øen	Effects of reading skills, spelling skills and accompanying efficacy beliefs on participation in education. A study in Norwegian prisons.

2012 H	Danielsen, Yngvild Sørebø	Childhood obesity – characteristics and treatment. Psychological perspectives.
	Horverak, Jøri Gytre	Sense or sensibility in hiring processes. Interviewee and interviewer characteristics as antecedents of immigrant applicants' employment probabilities. An experimental approach.
	Jøsendal, Ola	Development and evaluation of BE smokeFREE, a school-based smoking prevention program
	Osnes, Berge	Temporal and Posterior Frontal Involvement in Auditory Speech Perception
	Drageset, Sigrunn	Psychological distress, coping and social support in the diagnostic and preoperative phase of breast cancer
	Aasland, Merethe Schanke	Destructive leadership: Conceptualization, measurement, prevalence and outcomes
	Bakibinga, Pauline	The experience of job engagement and self-care among Ugandan nurses and midwives
	Skogen, Jens Christoffer	Foetal and early origins of old age health. Linkage between birth records and the old age cohort of the Hordaland Health Study (HUSK)
	Leversen, Ingrid	Adolescents' leisure activity participation and their life satisfaction: The role of demographic characteristics and psychological processes
	Hanss, Daniel	Explaining sustainable consumption: Findings from cross-sectional and intervention approaches
	Rød, Per Arne	Barn i klem mellom foreldrekonflikter og samfunnsmessig beskyttelse
2013 V	Mentzoni, Rune Aune	Structural Characteristics in Gambling
	Knudsen, Ann Kristin	Long-term sickness absence and disability pension award as consequences of common mental disorders. Epidemiological studies using a population-based health survey and official ill health benefit registries.
	Strand, Mari	Emotional information processing in recurrent MDD
	Veseth, Marius	Recovery in bipolar disorder. A reflexive-collaborative exploration of the lived experiences of healing and growth when battling a severe mental illness
	Mæland, Silje	Sick leave for patients with severe subjective health complaints. Challenges in general practice.
	Mjaaland, Thera	At the frontiers of change? Women and girls' pursuit of education in north-western Tigray, Ethiopia
	Odéen, Magnus	Coping at work. The role of knowledge and coping expectancies in health and sick leave.
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