The effect of bright light on rest-activity rhythms and behavioural and psychological symptoms of dementia

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Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

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Abstract

Most people living with dementia have behavioural and psychological symptoms of dementia (BPSD), such as depression, anxiety, agitation, and disturbed sleep, that strongly affect well-being and care needs. The rest-activity rhythm (RAR), i.e., the diurnal pattern of activity, is often altered in individuals with dementia. Sleep and wakefulness may, for instance, occur at irregular intervals, characterised by restlessness and behavioural disturbances at night, and napping during the day. This disruption of the sleep-wake pattern is detrimental to functioning and well-being. It is also thought to reflect deterioration of the endogenous circadian rhythm. Pharmacotherapy is often used to treat BPSD, including sleep disturbances, but has limited efficacy and is associated with severe side effects.

Light influences the circadian rhythm, and can also have effects on alertness and mood. These are collectively referred to as non-image forming (NIF) effects of light. Bright light treatment (BLT) is a non-pharmacological intervention that has been found to improve affective symptoms, agitation, sleep disorders, and RARs in people with dementia in some studies, but results have been mixed.

The main aim of this thesis was to investigate the effect of BLT on RARs and BPSD in a 24-week cluster randomised controlled trial - the DEM.LIGHT trial (ClinicalTrials.gov identifier: NCT03357328). A secondary aim, and preparation for the trial, was to investigate the illumination in nursing home dementia units.

Paper 1 was a field study investigating nursing home illumination in 15 dementia units across seasons and gaze directions. Measured illuminances were compared to thresholds suggested by industry standards and research, and measurement units relevant to NIF effects of light were used. Paper 2 and 3 reported results from the DEM.LIGHT trial, conducted at 8 dementia units, with 69 participants. In the intervention group (4 units), ceiling mounted LED-panels provided ambient light of varying illuminance and correlated colour temperature throughout the day, with a peak of ~1000 lx and 6000 K (measured vertically at 1.2 m) between 10:00 and 15:00. In the control group (4 units), standard indoor light of ~150–300 lx, 3000 K

was used. Data were collected at baseline and at 8, 16, and 24 weeks. Paper 2 investigated the effect of the intervention on actigraphy-measured RARs, and paper 3 investigated the effect on proxy-rated BPSD measures: the Cornell Scale for Depression in Dementia (CSDD) and the Neuropsychiatric Inventory - Nursing Home Version (NPI-NH). Treatment effects were analysed using multilevel regression models, with dementia stage (score on the Functional Assessment Staging Tool, FAST) at baseline as a pre-determined covariate. In addition, baseline scores on the outcome measures were included as covariates in the models in paper 3.

In paper 1 we found that, regardless of season and gaze direction, nearly all measured illuminances in dementia units fell below the thresholds. In paper 2, we found that there was no effect of BLT on RAR outcomes in people with dementia when controlling for multiple testing. Without controlling for multiple testing, the acrophase (i.e., timing of the activity peak) was significantly less delayed (by one hour) in the intervention group compared to the control group, in week 16. Paper 3 found mixed results for the effect of BLT on BPSD. There was a significant reduction of scores on affective subscales in the intervention group in week 16, but not at other follow-ups, after controlling for multiple testing. There was a significant effect on the NPI-NH and CSDD total scores in week 16 before, but not after, controlling for multiple testing. There were no significant effects on other subscales.

In conclusion, the findings in paper 1 suggest that illumination in dementia units is inadequate compared to thresholds suggested for NIF effects of light. However, the results of the DEM.LIGHT trial, which increased the indoor illumination in dementia units, were mixed. Based on our results, we cannot make clear recommendations regarding the use of ambient BLT in dementia units. Several methodological challenges and sample characteristics may limit the generalisability of these results.

Sammendrag på norsk

De fleste som lever med demens har også atferdsmessige- og psykologiske symptomer ved demens (APSD) som for eksempel depresjon, angst, agitasjon, og søvnforstyrrelser. APSD påvirker livskvalitet og pleiebehov. Aktivitetsrytmen er ofte endret hos personer med demens. For eksempel kan søvn og våkenhet forekomme uregelmessig, med rastløshet og atferdsforstyrrelser på kvelds- og nattestid, og søvn på dagtid. Forstyrrelser i søvn og våkenhet har negative konsekvenser for daglig fungering, kognisjon, og affekt. I tillegg er det trolig at denne typen problemer gjenspeiler forstyrrelse av den endogene cirkadiane rytmen. APSD, inkludert søvnproblemer, behandles ofte medikamentelt, på tross av at slik behandling har begrenset effekt og kan medføre alvorlige bivirkninger.

Lys påvirker den cirkadiane rytmen, og kan i tillegg ha en innvirkning på våkenhet og humør. Disse omtales som ikke-visuelle effekter av lys. Lysterapi er en ikke-medikamentell behandling som ifølge noen tidligere studier kan ha en positiv effekt på affekt, agitasjon, søvnforstyrrelser og aktivitetsrytmer hos personer med demens, men resultatene fra ulike studier har ikke vært entydige.

Målet med denne avhandlingen var å undersøke effekten av lysterapi på APSD og aktivitetsrytmer, gjennom en klynge-randomisert placebo-kontrollert studie over 24 uker – DEM.LIGHT studien. Et sekundært mål, og et forarbeid til hovedstudien, var å undersøke lysforholdene ved demensenheter på sykehjem.

Artikkel 1 presenterte en undersøkelse av lys på 15 demensenheter i Bergen kommune, gjennomført ved to årstider og med lysmålinger i ulike retninger. Lysmålingene ble sammenlignet med grenseverdier basert på anbefalinger og tidligere forskning. Lysverdiene ble oppgitt i måleenheter som er relevante for ikke-visuelle effekter av lys. Artikkel 2 og 3 rapporterte resultater fra DEM.LIGHT-studien, gjennomført på 8 sykehjem med 69 deltagere. Intervensjonen besto av takmonterte LED-lys i fellesstuen på 4 demensenheter, som gav lys av ulik styrke og fargetemperatur gjennom dagen. Maksimalt nivå for intervensjonen var ~1000 lx og 6000 K, mellom kl. 10:00 og 15:00, målt vertikalt 1.2 m over gulvet. Kontrollgruppen

(4 demensenheter) hadde standard innendørsbelysning (~150–300 lx, 3000 K). Data ble innhentet ved baseline, og etter 8, 16 og 24 uker. Artikkel 2 undersøkte effekten av lysbehandlingen på aktivitetsrytmer registrert med aktigrafi, og artikkel 3 undersøkte effekten på proxy-vurderte APSD-mål (Cornell Scale for Depression in Dementia, CSDD og Neuropsychiatric Inventory – Nursing Home Version, NPI-NH). Effekten av behandlingen ble analysert ved bruk av blandede regresjonsmodeller (multilevel models), med demensstadium (Functional Assessment Staging Tool, FAST skåre) ved baseline som en a priori bestemt kovariat. I tillegg ble baseline-skårer på utfallsmålene inkludert som kovariater i analysene til artikkel 3.

I artikkel 1 fant vi at de fleste målingene av lyset på demensenhetene var under terskelverdiene, uavhengig av årstid og måleretning. I artikkel 2 fant vi ingen forbedring av aktivitetsrytmen etter BLT hos personer med demens når vi korrigerte for multippel testing. Uten slik korreksjon var akrofasen (tidspunktet for aktivitetrytmens makspunkt) signifikant mindre forsinket (med en time) i uke 16 i intervensjonsgruppen sammenlignet med kontrollgruppen. Artikkel 3 rapporterte blandede resultater for effekten av lysintervensjonen på APSD. Det var en signifikant effekt på underskalaer som måler affektive symptomer i uke 16, men ikke i uke 8 eller 24, etter korreksjon for multippel testing. Det var en signifikant effekt på CSDD og NPI-NH total-skårer i uke 16 før, men ikke etter, korreksjon for multippel testing. Det var ingen signifikant effekt på andre underskalaer.

Oppsummert peker funnene fra artikkel 1 mot at lyset på demensenheter er utilstrekkelig sett opp mot terskelverdier for ikke-visuelle effekter av lys. Likevel var resultatene fra DEM.LIGHT-studien, som økte belysningen på demensenheter, blandede. Basert på disse resultatene kan vi ikke anbefale takmontert lysterapi ved demensenheter. Det er imidlertid flere metodologiske utfordringer og karakteristikker ved utvalget som begrenser generaliserbarheten til disse funnene.

List of Publications

Kolberg E, Pallesen S, Hjetland GJ, Nordhus IH, Thun E, Flo-Groeneboom E. Insufficient melanopic equivalent daylight illuminance in nursing home dementia units across seasons and gaze directions. Lighting Research & Technology. 2021;54(2):163-77.

Kolberg E, Pallesen S, Hjetland GJ, Nordhus IH, Flo-Groeneboom E. The Effect of Bright Light Treatment on Rest-Activity Rhythms in People with Dementia: A 24-Week Cluster Randomized Controlled Trial. Clocks & Sleep. 2021;3(3):449-64.

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Abbreviations

AD	Alzheimer's disease
ANOVA	Analysis of variance
BLT	Bright light treatment
BPSD	Behavioural and psychological symptoms of dementia
CBT	Core body temperature
CCI	Charlson Comorbidity Index
CCT	Correlated colour temperature
CI	Confidence interval
CIE	International Commission on Illumination (Commission internationale de l'éclairage)
CS	Circadian stimulus
CSDD	Cornell Scale for Depression in Dementia
EEG	Electroencephalogram
FAST	Functional Assessment Staging Tool
FDR	False discovery rate
ipRGC	Intrinsically photosensitive retinal ganglion cell
IES	Illuminating Engineering Society
K	Kelvin
LED	Light-emitting diode

MCID	Minimum clinically important difference
MMSE	Mini-Mental State Examination
NIF	Non-image forming
NPI-NH	Neuropsychiatric Inventory-Nursing Home Version
RAR	Rest-activity rhythm
RCT	Randomised controlled trial
SCN	Suprachiasmatic nucleus
SD	Standard deviation
SDI	Sleep Disorder Inventory
SI	International System of Units
SPD	Spectral power distribution
Vλ	The spectral luminous efficiency function for photopic vision

Contents

1. Introduction

Dementia is becoming more prevalent as the average life expectancy increases [1, 2], and currently affects around 55 million people worldwide [3]. As there is no cure, emphasis is placed on ameliorating the considerable social, emotional, and economic impact of the disease [4]. In addition to the characteristic cognitive symptoms, the majority of those who have dementia experience behavioural and psychological symptoms of dementia (BPSD) that strongly impact psychological well-being, social relations, and care needs [5]. BPSD encompasses a wide range of symptoms, including depression, agitation, anxiety, aberrant motor activity, delusions, and disturbed sleep [6, 7]. Disruptions in sleep and wakefulness are reflected in the rest-activity rhythm (RAR). The RAR represents the diurnal pattern of activity, typically with inactivity at night during sleep and increased activity during the day. In people with dementia, this rhythm is often diminished, showing a fragmented and irregular pattern of rest and activity [8-10]. In addition to being a distressing symptom to both people with dementia and their caregivers, a disordered RAR is thought to reflect a deterioration of the endogenous circadian rhythm [11]. Currently, psychopharmacological drugs are often used to target BPSD, but they have limited efficacy and potentially severe side effects [12, 13]. There is, therefore, a demand for non-pharmacological alternatives. Bright light treatment (BLT) is one such alternative, which has shown promise in reducing a range of symptoms, including depression, agitation, and disturbed sleep, in people with dementia [14, 15].

The aim of this thesis was to investigate the effect of BLT on RARs and BPSD in nursing home patients with dementia. First, we investigated the light conditions in Bergen nursing home dementia units in terms of their potential to influence circadian rhythms and other non-image forming effects (paper 1). We then investigated the effect of BLT on RARs (paper 2) and BPSD (paper 3) in a cluster randomised placebo-controlled trial.

The following introduction will first provide a background on the biological effects of light and discuss how light can be described and measured. The subsequent section

will describe circadian rhythms and define RARs in this context. Then, the rationale for choosing the nursing home as a setting for research on BLT is presented, with an overview of current knowledge on nursing home illumination. The next section defines and describes dementia, including BPSD and circadian rhythms in dementia. Lastly, previous research on BLT for people with dementia is summarised, before the aims and hypotheses of the present thesis are presented.

The rationale for the DEM.LIGHT trial was based on the available literature at the time it was designed, in 2016. However, updated searches in relevant databases were made regularly while writing the thesis. The most recent database search was performed in the spring of 2022, in Medline, PsycINFO, CINAHL, Embase, and Web of Science, using various combinations of subject headings (MeSH) terms and phrases synonymous with “bright light treatment”, “dementia”, and “nursing home”.

1.1 Light and non-image forming effects

Light can be defined as electromagnetic radiation that can create a visual sensation [16]. However, in addition to enabling visual perception, light also elicits numerous other physiological and psychological responses. These non-image forming (NIF), or non-visual, effects of light have important consequences for health and well-being. Notably, NIF effects include the regulation of the sleep-wake cycle and other ~24-hour (circadian) rhythms of our physiology.

Daily cycles of light and darkness have been a constant throughout evolutionary history, and are mirrored in the biology of life on earth [17]. Internal rhythms with a period similar to that of the solar day are ubiquitous in nature, and termed “circadian” from the Latin for “about a day” [18]. Circadian rhythms are endogenously generated, and persist even in the absence of external time signals [18]. This ability to keep time internally allows organisms to anticipate and adapt to the cyclical changes in the environment, and enables precise temporal coordination of biological processes [19]. Human circadian rhythms have an intrinsic period that is on average ~24.2 hours [20, 21]. In order to be aligned with the 24-hour day, therefore, they need to be

synchronised ("entrained") by external signals, often called "zeitgebers". Although some non-photic stimuli, such as physical activity or other forms of arousal, may in some instances influence circadian rhythms [18, 22, 23], the light-dark cycle is the primary circadian zeitgeber [20, 24]. NIF effects also include acute responses, such as pupillary restriction, thermoregulation, melatonin-suppression, changes in brain activity, and increased alertness [16, 25, 26]. There is some evidence that light can influence mood and cognition, both indirectly through sleep and circadian rhythms, and acutely [27-30]. Circadian rhythms and other NIF effects are affected by various aspects of light, including the timing; duration; wavelength/spectral characteristics; and "intensity", i.e., irradiance (W/m2), photon density (photons/cm^2/s), or "brightness" (typically illuminance, lx) [31-33].

With the invention of electric lights, daily patterns of light exposure are no longer dependent on the day-night cycle. People typically spend a significant amount of time inside buildings [34], with reduced exposure to daylight and increased access to light at night. There is evidence that living in a constructed light environment, as opposed to an environment with no electric lights, can affect people's circadian rhythms and sleep [35, 36]. It has also been suggested that sub-optimal light exposure may have negative consequences for a wide range of health outcomes related to sleep and circadian rhythms, including diabetes, cardiovascular disorders, depression, cancer, and recovery from surgery [37-39]. In addition to enabling an altered timing of light exposure, electric light differs from daylight in terms of spectral composition (i.e., what wavelengths the light consists of) and illuminance. Daylight contains a wide range of wavelengths, and can reach illuminances up to ~100 000 lx [40]. Light from artificial sources, on the other hand, does not usually contain the whole spectrum of wavelengths, and indoor illuminances are most often below 500 lx [40, 41].

Research on light in the context of NIF effects has largely been conducted and reported using measurement methods developed for image-forming vision [42]. However, with increased knowledge about the physiology and impact of NIF effects, new measurement strategies have emerged [31, 43]. The following sections will outline how light can affect health and well-being, starting with photoreception as it

relates to NIF effects. A discussion of associated measurement approaches follows. Finally, various aspects of light are discussed in the context of eliciting NIF effects.

1.1.1 Photoreception

The retina of the human eye contains photoreceptors: cells that convert electromagnetic radiation in the visible spectrum (~380-780 nm) into electrical signals capable of affecting biological processes [44]. The output of these photoreceptors is determined by the irradiance (received power), as well as the wavelength, of light [45]. Different classes of photoreceptor cells contain distinct opsin photopigments, which absorb photons that trigger changes in the membrane potential of the cell. Characteristic patterns of wavelength sensitivity in the photopigments tune photoreceptors to particular regions of the visible spectrum, enabling functional specialisation [46]. This wavelength-dependent responsivity is referred to as spectral sensitivity. Rods and cones are the classic photoreceptors, well known for the roles they play in sight [47]. Rods are highly sensitive, enabling vision in low-light conditions (scotopic vision), whereas cone receptors are responsible for higher visual acuity, spatial resolution, and colour vision in conditions with more light (photopic vision). Cones can further be subdivided, based on their sensitivity to light of different wavelengths, into S-cones, M-cones, and L-cones, sensitive to "short", "medium" and "long" wavelengths, respectively [47]. Another type of photoreceptor was discovered more recently: the intrinsically photosensitive retinal ganglion cell (ipRGC) [48, 49]. IpRGCs directly and indirectly target a number of brain areas involved in NIF effects, such as sleep, circadian rhythms, mood regulation, and alertness [27, 50]. Notable examples include: the suprachiasmatic nucleus (SCN) responsible for circadian photoentrainment [27]; the ventro-lateral preoptic nucleus and the lateral hypothalamic area regulating sleep and wakefulness [51]; the olivary pretectal nucleus influencing the pupillary light reflex [52]; and the medial amygdala and lateral habenula, associated with mood regulation [27]. Distinct subtypes of ipRGCs innervate different brain targets, contributing to the diversity of NIF effects [52].

IpRGCs detect light directly due to the presence of the photopigment melanopsin, allowing NIF effects to occur even in the absence of visual photoreceptors [49, 53, 54]. The density of photopigment in the ipRGCs is much lower than in rods and cones, reducing photon capture, and thus photosensitivity [55]. The intrinsic light response of ipRGCs is slow, but once activated, the response is substantial and prolonged [47, 55]. Continuous exposure to bright light evokes a sustained response that faithfully encodes irradiance [56, 57]. Thus, the mechanics of the ipRGCs support long temporal integration, suitable for the purposes of NIF effects such as synchronizing circadian rhythms with the 24-hour day [55]. Melanopsin is maximally sensitive to short wavelengths, with peak light absorption (λ_{max}) at ~480 nm [58]. IpRGC-mediated NIF effects also show increased sensitivity to light at shorter wavelengths of ~460-490 nm [31, 43, 59-62]. For instance, a 2-hour exposure at night to monochromatic light at 460 nm was found to have a significantly greater impact on melatonin suppression, alertness, core body temperature (CBT), and heart rate than an equivalent exposure at 550 nm [62]. IpRGCs also receive input from rods and cones, but more research is still needed to determine what roles these play in eliciting ipRGC-mediated responses to light [31, 45, 63, 64].

1.1.2 The description of light and non-image forming effects

Illuminance and correlated colour temperature

In laboratory studies with monochromatic light, wavelength may be used to describe the light stimulus. However, most light sources are polychromatic, i.e., composed of multiple wavelengths. Photometry is an extension of radiometry that attempts to capture the impact of visible radiation (light) on the human eye, weighting measurements according to human photoreception [31, 65]. Most commonly, the weighting function used is the spectral luminous efficiency function for photopic vision, or Vλ [59]. The Vλ is used with the objective of creating light measures that correlate with human brightness perception for the light adapted eye, i.e., under photopic conditions [66]. The function reaches its maximum (λ max) at 555 nm [67]. Thus, photometric units based on the Vλ, such as the International System of Units (SI) base unit for luminous intensity (candela, cd), and the derived units luminous

flux (lumen, lm) and illuminance (lux, lx), quantify light in terms of visual function [66]. Many previous studies on NIF effects have measured light in terms of illuminance [31]. Defined as lumen/m^2, illuminance can be compared to the radiometric unit irradiance (W/m^2), with the distinction that lumen weights light emittance per time unit according to the Vλ [66]. In contrast, power (watt, W) is simply the rate of energy transfer with no weights assigned to different wavelengths. In addition, the correlated colour temperature (CCT) is often provided to characterise the appearance of light in everyday applications. It is defined as the temperature an ideal blackbody radiator would have if it emitted radiation with an appearance similar to the light being evaluated, expressed in kelvin (K) [68]. Lower CCT values (e.g., 2700 K) indicate a "warmer" (more orange-yellow) light, whereas higher values (e.g., 6500 K) reflect "cooler" (more blue-white) light [68]. Natural daylight usually falls within the range of ~5700-7700 K [69], although it depends on a number of factors such as atmospheric conditions, time of day and geographic location. Many common fluorescent lamps have a CCT of ~2700-3000 K [41].

Beyond vision

The Vλ mainly reflects the responses of the M-cones and L-cones [70], not the ipRGCs and NIF effects. In order to better estimate the biological impact of light, alternative approaches to light measurement have therefore emerged.

One such approach is to base metrics on the spectral sensitivities of the opsin-based photoreceptors, rather than on brightness perception. Quantities based on the spectral sensitivity of melanopsin have received particular interest [31, 59, 71]. Light exposures can be recorded as spectral power distributions, describing the irradiance as a function of wavelength. The ability of the light to stimulate each photoreceptor can then be estimated by accounting for the sensitivity of the photoreceptor to particular wavelengths [31, 72]. The term α-opic is used to denote a relation to the responses of a specific opsin-based photopigment, with α indicating one of five photoreceptors: S-cone-opic, M-cone-opic, L-cone-opic, rhodopic, and melanopic [70]. Thus, melanopic illuminance is based on the spectral sensitivity function for melanopsin [31, 58, 70]. It should be noted that, although NIF effects are mediated by

ipRGCs, the melanopsin action spectrum alone does not account for input from other photoreceptors to the ipRGCs. Furthermore, contributions from other photoreceptors to NIF effects can vary, depending on stimulus characteristics and the specific NIF effect in question [31, 73]. It is therefore unlikely that one single action spectrum or unit of measurement can account for all NIF effects across differing conditions [45, 59]. Consequently, the International standard CIE S 026:2018 "CIE System for Metrology of Optical Radiation for ipRGC-Influenced Responses to Light" recommends quantifying the input to each photoreceptor type that can contribute to ipRGC mediated responses [70]. In this way, light exposures can be reported and compared without making assumptions about the relative contributions of each photoreceptor. It is further recommended that researchers report the spectral power distribution, as it can be used to derive any current or future metrics that may be developed [31, 74]. For communication purposes, however, single units, such as lux or melanopic illuminance, offer a clear advantage in terms of parsimony and clarity.

There are also alternative approaches to light measurement that are not based on the action spectra of specific photoreceptors. Notably, the circadian stimulus (CS) metric is based on models of nocturnal melatonin suppression in response to light [43, 75]. A CS of ~0.1 (i.e., ~10 % nocturnal melatonin suppression after a 1 h exposure to light) is the threshold for circadian system activation, and response saturation occurs at a CS of ~0.7 (i.e., 70% suppression after 1 h) [76, 77]. While this measure more directly addresses the impact of light on a NIF effect, melatonin suppression is not necessarily an adequate indicator of other NIF effects, such as circadian phase shift (i.e., shifting the timing of the circadian rhythm) [78, 79].

Melanopic equivalent daylight (D65) illuminance

As daylight is the naturally occurring stimulus eliciting NIF effects, it represents a relevant benchmark for metrics relating to the biological impact of light. The CIE S 026:2018 uses standard midday daylight (standard illuminant D65, with a CCT of ~6500 K) as a reference illuminant to determine α-opic equivalent daylight (D65) quantities. Melanopic equivalent daylight (D65) illuminance (EDI) thus refers to the illuminance of D65 (daylight) radiation required to provide a melanopic irradiance

equal to that of the measured light [59]. The similar units melanopic lux [58] and melanopic equivalent lux [31] are predecessors to the melanopic EDI, but the CIE S 026:2018 proscribes their use in favour of the SI-compliant melanopic EDI [70].

Standards and recommendations for indoor illumination

Organisations such as the International Commission on Illumination (CIE) and the Illuminating Engineering Society (IES) have developed guidelines for indoor illumination, recently including specific recommendations for older people. However, these standards have been aimed at ensuring visual function [80, 81]. In recent years, the need to consider NIF effects has also been recognised by major international standards [70], independent certification organisations [75, 82], and in recommendations for practical applications [83] and research practices [74, 84]. In addition to suggesting the use of more biologically relevant metrics for light measurement, such as melanopic EDI, these also recommend that light be measured in a vertical orientation to approximate corneal illumination. For visual function, it is relevant to evaluate the illuminance of horizontal surfaces. However, horizontal measurements are likely to overestimate the amount of light reaching the vertically oriented cornea when the light source is overhead [85].

Stimulating NIF effects

Although the contributions of different photoreceptors to ipRGC mediated responses are still not fully known, mounting evidence suggests that melanopsin-based photoreception is largely responsible for known NIF effects [59, 71, 73]. In their 2019 position statement on non-visual effects of light, the CIE endorses the use of melanopic EDI to characterise light exposures for NIF effects [16]. The statement recommends the use of high melanopic EDI during the day and low melanopic EDI during the night to facilitate alertness, circadian entrainment and sleep in day-active people [16]. Empirical investigations have shown that melanopic EDI is superior to photopic illuminance for predicting melatonin suppression, circadian entrainment, and alerting responses, under a wide range of conditions [71].

Increasing the melanopic EDI, and thus the impact on NIF effects, can be accomplished by increasing the irradiance and/or the amount of short wavelengths. Dose-response models have been developed for the impact of illuminance on NIF effects such as circadian phase shift, melatonin suppression, and alertness assessed by subjective and electroencephalographic (EEG) measures [32, 86, 87]. These studies indicate a dose-dependent, non-linear relationship. Half the maximum effect on phase delay and alertness (found at ~9100 lx) was elicited by light of ~100 lx, which corresponds to regular room light [32, 87]. Furthermore, saturation of the response occurred at ~550 lx for phase-shifting responses and ~200 lx for melatonin suppression, also within the range of regular indoor lighting [87]. However, these studies were conducted at night, using exposures of long durations (> 6 hours), and under highly controlled conditions. The following discussion will highlight some of the complexity involved in predicting NIF effects.

Studies have indicated that polychromatic light with higher power in the short wavelength region of the spectrum (i.e., cooler or "blueish" light, CCT > 6000 K) has a larger impact on NIF effects than polychromatic light of lower (typically ~3000 K) CCT [88-90]. However, the evidence for blue-enrichment of polychromatic light is mixed [61, 90]. Particularly for very bright light exposures (thousands of lx) that are typically used in BLT, the difference between white and short-wavelength enriched light is not always found, indicating that both exposures might reach a saturation point for the response [91, 92]. It has been suggested that acute NIF effects, such as alertness and melatonin suppression, are more responsive to short-wavelength enriched polychromatic light than more long-term effects such as phase shifts, but more research is needed to clarify this issue [61, 90].

A number of other factors, such as the timing and duration of the light stimulus, and previous light exposure, will also determine the response [93]. The timing of the light stimulus relative to the endogenous circadian rhythm is crucial when the goal is to shift the circadian phase. Light administered before the minimum (nadir) of the CBT (i.e., subjective late night) can delay the circadian rhythm, whereas light after the CBT minimum (i.e., subjective early morning) can advance it [94]. Larger phase

shifts are attained when light is administered relatively near the CBT minimum (~2 h before or after) [94]. Exposures of 5-7 hours are often used to investigate circadian responses to light [86, 87, 94, 95], but durations as short as 12 minutes (~10 000 lx) have been found to impact the circadian phase [96]. Some responses, such as temperature, cortical EEG, pupil response, and cardiac output, may be registered within 5 minutes or less [97]. The effects of light on both circadian outcomes and acute alertness depend on the photic history of the preceding day or week [98-100]. When contrasted with complete darkness, timed light exposures of as little as 12 lx (for 3 cycles lasting 6.5 h) have been found to influence circadian entrainment [101]. In other words, the response to light is subject to adaptation and sensitisation, and the contrast between night and day may be at least as important as the absolute duration and illuminance needed to elicit a response under constant conditions [98-100]. This day-night contrast could be accomplished by lowering the night-time illumination, increasing daytime illumination, or both.

Findings about the optimal exposures required to suppress melatonin or phase shift at night are not necessarily applicable to other uses of BLT. It is possible that some effects of light (e.g., on heart rate, CBT, cortisol, melatonin and phase shift) depend on the time of day, while others (e.g., on fatigue and alertness) do not [102]. However, more research is needed to determine the light parameters necessary to elicit specific responses in daytime [103]. Finally, there are also individual differences in light sensitivity [104], with studies reporting large intraindividual variability in responses such as melatonin suppression and SCN activation after light exposure at night [105, 106]. While some of this variability may result from differences in daytime light exposure, a number of more immutable causes have been proposed, including genetic variants, ethnicity, sex, age, and chronotype [104]. Of particular relevance to this thesis, increased age is associated with changes to the eye such as reduced lens transmittance and pupil size. As a consequence, circadian photoreception appears to halve by the age of 45, and is 10 times lower at 95, when compared to that of a 10-year-old [107]. Thus, determining the light exposure needed to elicit a response will depend on a number of variables, including the specific NIF effect in question. The light exposures typically used in clinical applications are

discussed in section 1.5.2. An important NIF effect, and a likely mechanism for many of the proposed health benefits of BLT, is the entrainment of circadian rhythms.

1.2 Circadian rhythms

The most overtly visible result of circadian rhythmicity is the cycle of sleep-wake behaviour, but virtually every system in the body is under circadian regulation [108]. The following section describes the mechanisms and importance of the circadian "clockwork" and its regulation by light. Some central circadian rhythms are then discussed, highlighting the clinical relevance of circadian rhythms, as well as the complexity involved in assessing them. Particular emphasis is placed on RARs and their role in sleep and circadian rhythm research.

1.2.1 Keeping time

In mammals, the circadian system consists of a hierarchical network of oscillators, with a central pacemaker in the brain (the SCN) orchestrating subsidiary oscillators throughout the body [109, 110]. A molecular "clockwork" is present in nearly every cell, arising from autoregulatory cycles of clock gene activity. These clock genes are regulated by a network of transcriptional-translational feedback loops involving the protein products they encode, so that cycling levels of gene products feed back to affect their own transcription [109, 111, 112]. Delays inherent to these cycles ensure a period of about 24 hours, i.e., circadian rhythmicity [111]. Clock gene activity has tissue-specific effects on downstream physiological processes, and oscillators in different organs and tissues can sustain separate but interconnected rhythms [113]. The result is a system of interacting rhythms across every level of organisation, from cellular to behavioural, affecting a wide range of critical processes, including metabolic, cardiovascular, neurological, endocrine and immune functions [108].

The SCN is a set of nuclei in the ventral hypothalamus, often referred to as the master pacemaker, or master clock [110]. Multiple lines of evidence demonstrate the centrality of the SCN as a time keeper. Surgical removal or pathology of the SCN disrupts circadian rhythms, whereas grafts that replace removed or arrhythmic SCN

tissue can restore circadian rhythmicity [114, 115]. Similarly to peripheral oscillators, SCN cells can generate autonomous rhythms. However, the SCN as a whole displays additional organisational properties, such as local coupling between its constituent cellular oscillators, which make it an especially robust, persistent, and precise time keeper [110]. The SCN is located above the optic chiasm, where it receives direct photic input from the retina to synchronise its rhythm with the solar day. Temporal information is transmitted from the SCN via multiple pathways to other brain areas and peripheral tissues, modulating outputs such as autonomic activity, hormones, and behaviour, which in turn synchronise subsidiary oscillators [110, 114].

1.2.2 Circadian rhythms and health

Biological rhythms reach their peak at various times during a 24-hour day, and the relationships between them is a complex topic that is not yet fully explored [116]. The optimal performance of biological systems is not a static state but defined relative to external demands and other physiological processes. For example, cardiovascular and metabolic functions are optimised for energy expenditure, responsivity to stressors, and food intake during the active period, and for rest during the inactive period [117]. The immune system shows increased sensitivity and pro-inflammatory activity during the day, when the risk of infection or damage is higher [118], and wound healing appears to be more efficient if an injury is sustained during the active period [119]. During the inactive period, a number of processes involved with repair, restoration and resolution of inflammatory responses peak in activity [120]. Circadian rhythms also play an important role in regulating sleep (discussed in section 1.2.4 and 1.4.4), widely considered a critical determinant of health [121].

Disruption of circadian rhythms has been linked to numerous negative health outcomes, including cancer, cardiovascular disease, inflammatory disorders, metabolic disorders, mood disorders, psychosis, and other psychiatric conditions [122, 123]. Circadian disruption can refer to a disturbance of biological timing at or between any level of organisation, including misalignment between different rhythms or with external time [124, 125]. The disruption may be caused by external factors (e.g., irregular exposure to light, shift work, eating patterns, or jet lag), internal

factors (e.g., disease or damage to the SCN), or a combination [124, 125]. Sleep and circadian rhythm disruption is common in many neuropsychiatric diseases, including affective disorders and schizophrenia, and shared mechanisms between them may be potential treatment targets [126]. Circadian rhythms and sleep in dementia are further discussed in section 1.4.4.

1.2.3 Describing and assessing circadian rhythms

Some of the outputs influenced by the SCN are used to assess circadian rhythms in research and clinical practice. Most notably, this includes the melatonin, glucocorticoid, CBT, and activity rhythms. Temporal patterns in these outputs, frequently represented by sinusoidal waves, can be described by rhythmic parameters such as period (time to complete one cycle, typically 24 hours), phase (the timing of a specific point in the cycle, such as the peak), mesor (the rhythm adjusted mean), and amplitude (the magnitude of the difference between high and low values, or the distance from the mesor to the peak/trough) [127]. Methods for describing patterns in activity rhythms are further described in section 1.2.5.

Melatonin assessment has had a particularly central role in the study of light and circadian rhythms. Pineal melatonin is an important mediator of photic information from the SCN. Synthesised and released during the dark phase, it facilitates physiological adaptation to night-time, and functions as a time cue throughout the body. In dim light conditions, the rhythm of circulating melatonin is considered a reliable reflection of the endogenous rhythm of the SCN [128]. The time at which melatonin starts to rise, i.e., the “dim light melatonin onset” (DLMO) is by many considered the gold standard for assessing circadian rhythms [129, 130]. For healthy, young adults with conventional sleep timing, this typically occurs about 2-3 hours before habitual bedtime [131]. Meanwhile, exposure to light acutely suppresses melatonin secretion [132]. As a consequence, melatonin can be used as an indicator of circadian timing as well as acute response to light [128]. Melatonin increases sleep propensity, and affects the duration and timing of sleep [133, 134]. Exogenous melatonin can therefore be administered, alone or in combination with light, to treat sleep-wake disorders, or to adjust the timing of the circadian rhythm after disruptions,

such as travel across time zones or shift work [134, 135]. However, melatonin has numerous important effects on health beyond regulating sleep and alertness. Notable examples include antioxidant, anti-inflammatory, immunomodulatory and cytoprotective properties, with accumulating evidence indicating that melatonin may curtail multiple processes involved in dementia and neural damage [133, 136, 137]. The suppression or stimulation of melatonin secretion thus constitutes an important link between light exposure and health.

In contrast to melatonin, the diurnal glucocorticoid (cortisol in humans) rhythm typically peaks around the time of waking and reaches its nadir around bedtime, aiding adaptation to daytime demands through pervasive effects on the body and brain [138]. Cortisol is a primary product of the hypothalamic–pituitary–adrenal (HPA) axis, which plays an essential role in stress adaptation [139]. Dysregulation of the HPA axis and the cortisol response has been linked to negative mental and physical health outcomes, including anxiety and affective disorders; immune, cardiovascular and metabolic disorders; and cognitive decline [139, 140]. A strong diurnal pattern appears to be an important aspect of the regulatory function of the HPA axis and cortisol [139, 140].

The CBT rhythm falls during sleep at night, reaching its nadir around 2 hours before habitual wake time [18]. Although factors such as physical activity and food intake contribute to variations in CBT, it also follows a circadian rhythm. A reduction in CBT at night appears to increase sleep propensity and help maintain sleep [141, 142]. The CBT is used extensively in research on circadian rhythms, and is, as discussed in section 1.1.2, a common reference point for BLT timing [94, 143].

Measurements of circadian rhythms are, to varying degrees, influenced by non-circadian influences, such as light, food intake, movement, posture, caffeine, and medications [18, 129]. In order to assess the underlying rhythms, laboratory experiments may therefore ensure that all these variables are constant [18, 129]. While a controlled experimental setting provides the most accurate assessment of the underlying circadian rhythm, the labour, cost, and potential discomfort to participants

involved may be reasons to choose alternative approaches [129, 143]. Thus, the choice of measurement depends on the goal of the study. RARs can be measured using minimally invasive methods over long periods of time [144].

1.2.4 The rest-activity rhythm

The RAR, sometimes referred to as the circadian activity rhythm, describes a 24-hour rhythm of rest and activity that is influenced by the diurnal sleep-wake cycle. The sleep-wake cycle is regulated by both circadian and non-circadian influences [11, 18]. A notable non-circadian mechanism is the homeostatic sleep drive, which entails an increase or decrease in sleepiness following periods of wakefulness or sleep [145]. Sleep-wake rhythms in humans are also influenced by choice and opportunity. Social factors, such as work demands, entertainment, social interaction, or familial responsibilities, are important determinants of sleep timing [18]. Environmental factors, such as light, noise, or poor sleeping conditions, can impair the ability to sleep. A lack of synchrony between the circadian rhythm and the sleep-wake pattern is a common occurrence, for instance, as a result of shift work, travel across time zones, or simply choosing to stay up late on the weekend or get up early for work. The RAR is thus a result of both the endogenous circadian rhythm and other factors that influence sleep and activity [18].

Actigraphy is a frequently used measure of sleep and circadian rhythms in research involving people with dementia, where more invasive and/or demanding measures, such as polysomnography (i.e., comprehensive physiological recordings during sleep, utilising multiple sensors attached to the body), or repeated sampling of melatonin or cortisol, may be particularly unfeasible [146, 147]. The RAR is also relevant in its own right, and not just as a proxy for the endogenous circadian rhythm, since sleep-wake disturbance is a highly common and distressing symptom in dementia (discussed in section 1.4.4). RAR measures have been associated with important outcomes in older adults, such as depressive symptoms [148]; risk of dementia and cognitive impairment [149]; and mortality [150-152].

1.2.5 Measuring rest-activity rhythms

Wearable accelerometers, called actigraphs, can be used to record activity over multiple days [129, 144]. These are commonly used in the assessment of sleep disorders, particularly circadian rhythm sleep disorders, and in research on sleep and circadian rhythms [129, 144]. Actigraphy has been found to be well suited for identifying rhythms, and actigraphy-recorded RARs tend to correlate well with melatonin and CBT rhythms [144]. A number of parameters can be obtained from actigraphy recordings, and the choice of outcome depends on the research focus.

In sleep research, actigraphy outcomes such as total sleep time, wake after sleep onset (WASO), sleep onset latency (the time it takes to fall asleep), and sleep efficiency (ratio of sleep time to time in bed) are commonly used, with sleep and wakefulness estimated from movement [144, 153]. Studies that focus on circadian rhythms typically utilise measures that analyse rhythmic patterns in raw activity values, without making assumptions about sleep and wakefulness [144]. Common examples of RAR outcomes include the consistency of the activity profile over multiple days; the fragmentation, or variability, within each 24-hour cycle; the timing of the peak or minimum activity level; the relative difference between the high and low activity periods (or amplitude); and the degree to which a function with a 24-hour (i.e., circadian) period fits the data [10].

There is overlap between the outcomes associated with sleep and those that are used in research on circadian rhythms, as the two phenomena are inextricably linked. Studies will sometimes report both kinds of outcomes. Furthermore, the different outcomes may relate to the same underlying behaviour. For instance, frequent night-time awakenings will lead to a high WASO, as well as greater fragmentation of the RAR. However, some RAR variables also uniquely describe patterns of the activity rhythm (such as the stability over multiple days) that may capture important circadian phenomena [154].

There are various approaches to calculating RAR variables from activity counts. The most popular approach has been cosinor analysis [129], i.e., fitting a cosine curve to

the data. As activity profiles often deviate from the shape of a cosine curve, the traditional cosine model has been extended to better reflect the true shape of the RAR [155]. Additionally, nonparametric indicators can be used to describe RARs without having to make assumptions about the shape of the activity curve [156, 157]. These approaches are further described in section 3.3.1.

1.3 The nursing home setting

Governmental policies in Norway, as in many other countries, encourage "aging in place", i.e., continuing to live in one's own home as long as possible [158]. Higher levels of care, such as long term placement in a nursing home, are only offered if someone has a need for more extensive or specialised care that cannot be met at the lower levels [159]. In 2020, there were 31 981 people in long-term nursing home placement in Norway [160]. More than 80% of those admitted to a nursing home have dementia, and the majority of those also have at least one clinically significant BPSD, such as anxiety, depression, sleep problems, or agitation [161, 162]. One recent meta-analysis found that 20% of nursing home patients with dementia had a clinically significant sleep problem according to informant rated questionnaires, and 70% had sleep disturbance when assessed using actigraphy [163]. In addition, somatic illness and pain are common [161]. The most frequent comorbid somatic conditions among nursing home patients with dementia are cardiovascular diseases such as cerebrovascular disease (24.3%), coronary disease (23.3%), and congestive heart failure (19.1%), along with diabetes (14%) and cancer (13.7%) [161]. Despite this complexity and high level of care needs, nursing homes are often under-staffed, and researchers have found that employees frequently have to carry out care tasks that exceed their training and capacity [164]. Consequently, there is a demand for interventions that improve well-being for patients and relieve some of the burden for carers. Ensuring sufficient exposure to bright light may be one way to improve sleep, circadian rhythms, and affective symptoms, with minimal demands on staff [14, 15].

1.3.1 Light in the nursing home

Due to the degree of disability and care dependency, nursing home patients are unlikely to be spending time independently outdoors in natural daylight. Although staff may facilitate some outdoor activities, a high workload together with understaffing often imply that essential care tasks take priority. For a large part of the year, weather conditions also preclude outdoor activities in large parts of the northern hemisphere. Providing sufficient illumination indoors may therefore be necessary to ensure adequate stimulus for circadian entrainment and other NIF effects.

Although it is not the main focus of the present thesis, light also supports visual performance. Inadequate lighting in nursing homes has been linked to an increased risk of falls [165, 166], which are a common cause of severe, and sometimes fatal, injury [167]. Injuries sustained from falls, such as hip fractures, can adversely affect health and survival for nursing home patients and significantly impair functional independence [168]. The ability to safely navigate the environment facilitates independence and autonomy, and good visual function enables participation in social and leisure activities [169]. Furthermore, the ability to perform activities of daily living, such as dressing, personal hygiene, and eating, relies on visual performance. Adequate illumination and contrast during meals have been found to increase food and liquid intake [170]. Sufficient lighting also supports visual tasks performed by care takers and may lower the risk of medication errors [171, 172].

1.3.2 Research on nursing home illumination

Studies have found that older adults are often exposed to less bright light than younger individuals, especially if they are in a nursing home [166, 173, 174]. Previous research has found nursing home illumination to be insufficient both in terms of NIF effects and vision [41, 175, 176]. Shochat et al. found that the median daytime light exposure of institutionalised people with dementia was 54 lx, and that they only spent 10.5 minutes a day (median) in light over 1000 lx [176]. Similarly, Sinoo et al. found that a majority (65%) of vertical illuminances in nursing homes fell below 750 lx [41], and Konis found that for non-daylit spaces, the median vertical illuminance was 99 lx [177]. Measurements are naturally higher when facing a

window at close proximity [41, 177], but that does not represent most indoor spaces. Some of the studies also considered the spectral composition or CCT of nursing home lighting and concluded that the ability to stimulate NIF effects was low, with the exception of views facing a window at close proximity [41, 177]. Among the few studies performed on nursing home illumination, there is no consensus about the illuminance needed to support NIF effects. With very few exceptions (e.g., [177]), studies of lighting at nursing homes have reported results in the form of photopic illuminance, even when addressing NIF requirements [41, 175, 176].

For people with dementia, daily light exposure has been found to be positively associated with positive emotions, RAR amplitude (for men), and quality of life [178], and negatively associated with night-time awakenings [176]. Night-time activity among nursing home patients with dementia has been found to be higher on cloudy, short days than on clear or longer days [179]. One study found a positive association among nursing home patients between higher morning light exposure and more stable, less fragmented RARs with a higher relative amplitude [180]. In a 2022 review of nine studies, Guu et al. found evidence that low light exposure was associated with BPSD and RAR disruption among nursing home patients [181].

In the World Alzheimer Report 2020, the design of the built environment was recognised as a vital non-pharmacological intervention, with lighting being one such important design consideration [182].

1.4 Dementia

Dementia, or major neurocognitive disorder [183], is a syndrome, i.e., a group of symptoms, resulting from disease or injury that damages the brain [184]. It is characterised by a disturbance of multiple higher cortical functions, beyond what is expected with normal aging [184, 185]. Memory impairment is a common symptom, but numerous areas of cognition can be affected, including language, attention, spatial and psychomotor skills, comprehension, judgement, social cognition, and executive function [3, 184, 185]. As a result, dementia impairs the ability to manage everyday

activities and has significant psychological, social, professional, and economic impacts for the person with dementia, as well as their caregivers [3]. The emotional, physical and financial pressures of caring for someone with dementia can be a source of great stress and reduced health for many carers [3, 186]. The cost of dementia globally was estimated to be 1.3 trillion USD in 2019, of which the majority consisted of the cost of informal and social care [187]. Dementia is currently the seventh leading cause of death worldwide, as well as a major cause of disability [3]. In Norway, dementia affects ~6% of people who are 70–74 years old, and ~48% of those over 90 years old, in total about 100 000 people [1].

1.4.1 Etiology, symptoms and subtypes

As dementia can be the result of several conditions, causal mechanisms and presentations of the disease vary. Multiple factors contribute and may interact to cause disease, and more research is still needed to fully understand how to prevent, detect, and treat underlying pathology [188]. The most common dementia subtype is Alzheimer's disease (AD), responsible for about 60-70% of dementia cases worldwide [3]. In a Norwegian study of dementia in people over 70 years old, 57% of people with dementia had AD [1]. Vascular dementia constituted 10% of the dementia cases, 9% had mixed dementia, 4% had Lewy body dementia, and 2% had frontotemporal dementia. These evaluations were made based on clinical symptoms, and 17% of the participants were classified as having unspecified dementia due to insufficient information [1]. Similar prevalences were found in a large U.S study, although the prevalence of AD was slightly lower (43.5%) [189]. Other possible causes of dementia include traumatic brain injury, infections, and alcohol abuse [183]. The following discussion of etiology and clinical presentation only covers some of the most common subtypes, particularly AD.

AD usually has a gradual onset, developing slowly but steadily over several years [184]. Early symptoms typically include forgetfulness, and people may experience apathy or depression, as well as difficulties at work or in social settings [3, 190, 191]. Impaired sleep quality can also be an early sign of AD [192-194]. As the disease progresses, dependence increases as symptoms become more widespread and severe,

affecting multiple areas of functioning, including communication, orientation, judgement, motor control, behaviour, and eventually basic functions such as sitting and swallowing [3, 190, 191]. Brain changes associated with the disease may begin decades before symptoms manifest [195]. The defining neuropathological features of AD are accumulations of β-amyloid plaques and neurofibrillary tangles formed, respectively, from abnormally folded β-amyloid proteins and aggregated tau proteins [196]. The mechanistic links between these features, and their relationship with neuronal degeneration and AD, are still not fully understood [197]. Furthermore, multiple concurrent mechanisms, such as demyelination, neuroinflammation, metabolic dysfunction, and cerebrovascular changes, likely contribute to the development of clinical symptoms [198]. Most cases of AD are thought to be a result of interactions between environmental and genetic risk factors. The ε4 polymorphism of the APOE gene is the most prominent genetic risk factor for AD, but more than 20 genetic risk genes and loci have been reported [199]. These genes are linked to not just amyloid pathology, but to the immune system, synaptic function, and lipid metabolism, highlighting the diversity of pathways implicated in AD [199].

In vascular dementia, damage occurs as a result of diseases that interfere with blood supply to the brain [184, 190]. Multiple vascular pathologies may contribute to dementia, and the clinical presentation of the disease is highly variable, depending on the extent and location of the brain injuries [190, 200]. Vascular dementia most commonly occurs as part of a mixed pathology, but also occurs by itself in about 5-10% of individuals with dementia [190].

Dementia with Lewy bodies and Parkinson's disease can be jointly referred to as Lewy body dementias [201]. They are characterised by abnormal aggregation of the protein alpha-synuclein in cortical neurons, forming so-called Lewy bodies [202]. As in AD, neuropathology often begins years before the onset of symptoms [202, 203]. Common clinical features include deficits in attention, executive function, and subperceptual ability; fluctuating cognitive ability; visual hallucinations; REM sleep behaviour disorder; and parkinsonism [203]. In Parkinson's disease, motor functions are affected first, before dementia then develops in about 80% of cases [201, 204].

Older people with dementia often have mixed pathologies, such as more than one neurodegenerative disease and/or coexisting cerebrovascular disease [205-207]. One study of 1,079 deceased individuals with varying dementia status found that 94% had at least one neuropathology, and 78% of those had more than one [206]. Large individual variation was observed in neuropathologic comorbidity, with as many as 236 combinations of neuropathology found, each occurring in less than 6% of the sample [206]. Adding further complexity, many people with dementia related neuropathology do not exhibit symptoms of dementia in life [195, 208, 209], and having mixed pathologies increases the risk of developing dementia [205, 208]. Dementia is also frequently underdiagnosed [4, 161]. As a consequence, dementia research is likely to include individuals with multiple subtypes and underlying pathologies. Selecting samples or subgroups consisting only of people with specific subtypes of dementia may therefore not be feasible, particularly among older individuals with advanced dementia.

1.4.2 Treatment, prevention, and care

Pharmacological treatments, such as cholinesterase inhibitors and memantine, may offer some symptom reduction in some cases [210-212], but at present there is no cure for dementia [197]. Thus, much importance is placed on prevention, management and care. This is reflected in the vision of the World Health Organization global dementia action plan: “to improve the lives of people with dementia, their carers and families, while decreasing the impact of dementia on them as well as on communities and countries” [4]. The Norwegian dementia plan for 2025 calls for more research on causes, prevention and treatments, as well as interventions that may slow the progression or aid individuals living with the disease [12].

The heterogeneity of factors underlying dementia calls for individualised approaches, but it also motivates the search for broader prevention and treatment strategies. The role of frailty in moderating the relationship between dementia pathology and dementia status suggests a place for therapies targeting age-related processes and overall health [213]. A 2020 Lancet report suggested that about 40% of dementias are attributable to modifiable risk factors, such as hypertension, smoking, and diabetes

[214]. Strategies for dementia prevention and care may also target factors that help maintain cognitive reserve, i.e., the preservation of cognitive ability and everyday function despite brain pathology [215, 216]. Proposed modifiable influences on cognitive reserve include education, exercise, social contact, and treating depression [214-216]. In addition, interventions targeting sleep may reduce the risk of dementia by improving general health throughout the lifespan [217, 218].

1.4.3 Behavioural and psychological symptoms of dementia

The term BPSD encompasses a wide range of non-cognitive symptoms that may have distinct causes and treatment options [6, 219]. Twelve of the most commonly listed symptoms, as included in the Neuropsychiatric Inventory – Nursing home version (NPI-NH), are as follows: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, irritability, aberrant motor behaviour, disinhibition, sleep disturbances (which includes both sleep and circadian rhythm disturbances), and eating/appetite disturbances [7, 220-222]. Symptoms often co-occur, and several studies have identified symptom clusters, such as mood-related symptoms, agitation, and psychotic symptoms, using factor- and principal component analyses [6, 223-225]. Identifying and distinguishing between different BPSD can be challenging, as multiple symptoms are usually present simultaneously [222, 226]. In some cases, one symptom may constitute part of the clinical presentation of another (e.g., sleep disturbances in depression). Furthermore, people with dementia may have a reduced ability to express thoughts and emotions, making it difficult to separate symptoms and to accurately assess their cause [5, 226]. Assessment of BPSD by caregivers relies on perceptions of visible symptoms, which may correspond to varying degrees with the subjective experience of the person with dementia.

BPSD are exceedingly common [227, 228] and can be major sources of distress and reduced quality of life. BPSD are associated with excess morbidity, mortality, disability, faster cognitive decline, hospitalisation, and harmful pharmacological treatments [5, 226, 229]. For informal caregivers, the presence of BPSD is associated with reduced quality of life, worse mental and physical health, and reduced income, as well as deterioration of the relationship with the person who has dementia [5, 230,

231]. Managing BPSD such as anxiety, aggression, disinhibition and irritation can also be a source of distress for care staff [231, 232]. BPSD are thus an important aspect of dementia and a meaningful target for intervention [226]. Treating BPSD is one of the most complex and costly aspects of care for people with dementia, and these symptoms are a major cause of nursing home placement [5, 186]. As a result, BPSD are particularly prevalent in a nursing home context [228, 231].

1.4.4 Sleep and circadian rhythms in dementia

As elaborated in section 1.2.4, the RAR is closely associated with the sleep-wake cycle. Although the term RAR is not always used in relation to BPSD, RAR disruption in dementia typically manifests as sleep disturbances, altered sleep-wake timing, and night-time behavioural disturbances, which are considered BPSD with important consequences for the care needs and well-being of people with dementia [163, 226, 233-235]. It could therefore be argued that the behaviours reflected by a disrupted RAR are examples of BPSD. However, in this thesis, a distinction is made between RAR disruption and BPSD, due to the difference in measurement approaches and associated literature. RARs are usually described as measures of circadian rhythms in, among others, studies of BLT for people with dementia [236-239]. The roles of sleep and circadian rhythms are frequently discussed jointly, as reflected by the term "sleep and circadian rhythm disruption" (SCRD) [126].

Due to the conceptual overlap and reciprocal relationships between circadian rhythms, sleep, and RARs, the following discussion includes research on both sleep and circadian rhythms. Accumulating evidence suggests reciprocal relationships between circadian disruption, sleep and neurodegeneration [240].

Advancing age has been associated with reduced sleep, greater sleep-wake instability (i.e., more awakenings or transitions to lighter sleep), and altered circadian timing, as well as changes to sleep architecture, such as less "deep" (slow wave) sleep, less rapid eye movement (REM) sleep, and shorter and fewer sleep cycles [11, 241-244]. Sleep problems, such as insomnia, obstructive sleep apnea, and circadian rhythm sleep disorder, are also more common among older people, particularly in people

with comorbid medical conditions or dementia [244-246]. Nursing home patients with dementia often have a severely fragmented sleep-wake rhythm, falling asleep several times during the day and waking up at night. Many rarely spend a full hour awake or asleep at a time [8-10]. For people with dementia, sleep problems may aggravate many common issues, e.g., decrease the ability to perform daily tasks, increase pain sensation, impair memory and concentration, slow down response times, reduce enjoyment of social relationships, impair the ability to participate in activities, worsen BPSD, and increase the risk of falls due to daytime sleepiness or night-time wandering [247, 248]. Sleep problems and night-time behavioural disturbances are associated with distress in caregivers or nursing home staff, disruption of other patients at nursing homes, workplace impairment in informal caregivers, and an increased risk of institutionalisation [249-252]. Sleep disorders are a significant predictor of all-cause mortality in the general population, even after adjusting for age [253].

Disruption of sleep and circadian rhythms appears to exacerbate dementia pathology and cognitive decline. Multiple longitudinal studies have found that circadian disruption and sleep disorders predict greater cognitive decline and increase the risk of all-cause dementia several years later [10, 123, 149, 218, 254, 255]. Disturbed sleep may be considered a core component of AD [194], and has been associated with increased dementia pathology, including Aβ accumulation, tau pathology, inflammation, neuronal damage, hypoxia and cardiovascular disease [123, 194, 215, 256]. In mouse models of AD, there is strong evidence that sleep directly affects the accumulation of tau and Aβ [257]. A growing body of evidence suggests a bi-directional causal role of sleep disruption in dementia pathology in humans as well [194]. Conversely, better sleep consolidation (i.e., lower fragmentation) has been shown to attenuate the negative effect of the APOE ε4 allele on incident AD risk and neurofibrillary tangle pathology [258].

A systematic review of studies on RARs in people with dementia found that studies consistently reported less stable, more fragmented rhythms, with a worse fit to 24-hour models, and lower amplitude [10]. There was some evidence that RAR

disruption was associated with neurodegeneration biomarkers, and that lower amplitude and worse 24-hour fit predicted future cognitive impairment [10]. Circadian disruption in dementia has also been observed for multiple rhythms in addition to the RAR, including the CBT, hormonal rhythms (including melatonin and cortisol), clock gene expression, and SCN function [11, 259-261]. Due to the widespread influence of circadian rhythms (see section 1.2.2), circadian disruption may also impact dementia pathology in ways not directly linked to sleep, for instance through dysregulation of immune responses, including neuroinflammation [215, 262]. There is evidence that processes central to Aβ clearance falter without a circadian rhythm [263]. Even in the absence of dementia, circadian disruption can cause deficits reminiscent of those common in dementia. Inducing circadian desynchrony, for instance through misaligning sleep and feeding times or simulating jetlag, produces detrimental effects on hippocampal neurogenesis, inflammation, learning and memory in mice [240], and repeated exposure to jetlag in flight attendants has been linked to elevated cortisol, reduced temporal lobe volume, and deficits in spatial learning and memory [264].

The term "sundowning" is sometimes used to describe a perceived worsening of behaviour problems in the evening in people with dementia, possibly reflecting a circadian pattern in symptoms [248]. In one study of 85 nursing home patients, no evidence was found for classical sundowning, but agitation did nonetheless appear to have a diurnal rhythm, suggesting a possible circadian influence [265].

Causes of disrupted sleep and circadian rhythms in dementia

Circadian disruption and sleep problems in dementia have partly been attributed to the associated brain pathology, such as degeneration of the SCN, other hypothalamic regions, the brain stem, and basal forebrain [262]. For people with AD, levels of Aβ and phosphorylated tau have been found to correlate positively with sleep disruption [241]. Neurodegenerative disorders have also been shown to adversely affect the retina and ipRGCs [266]. However, the specific contributions of various brain pathologies to the changes in sleep and circadian rhythms are not fully understood. While SCN degeneration is frequently cited, it has also been argued that the SCN is

one of the most resilient structures in the brain, minimally affected by AD pathology and capable of maintaining its function even when structurally compromised [267]. Interventions such as BLT may, therefore, be capable of affecting the SCN even in people who have severe neurodegenerative conditions, such as AD [267]. However, empirical research is needed to investigate whether this is sufficient to elicit circadian entrainment and other NIF effects. Even if the SCN can maintain its function, impaired signalling to other brain areas and peripheral clocks may affect its ability to regulate sleep-wake behaviour and other rhythms [268].

Sleep and circadian rhythms in old age can also be impacted by a range of other factors. Major life changes, such as retirement, death of loved ones, moving to a nursing home, loss of independence, reduced ability to participate in activities, loneliness, or health concerns, may cause emotional distress, which is known to contribute to sleep problems [246]. Retirement may entail more opportunities for daytime napping. Various health conditions and medications can reduce daytime activity and increase sleep problems [248]. Aspects of the nursing home environment may contribute to circadian disruption and sleep problems, including noise and light interruptions at night, and spending extended periods of time in bed [248]. Low light exposure during the day likely contributes to further circadian disruption [176, 248].

Thus, sleep- and circadian rhythm disruptions are likely results of, as well as contributing factors to, dementia and associated symptoms, and represent potential targets for intervention [244].

1.4.5 Treating behavioural and psychological symptoms of dementia

The causes of BPSD, including sleep problems, are heterogenous. The risk of BPSD appears to increase with dementia severity [269], but this might depend on dementia subtype [270]. In addition, there is considerable individual variation, and symptoms tend to fluctuate, as well as change over the course of the disease [5, 228].

Environmental and psychosocial interventions are recommended as the first line of treatment for BPSD by international consensus panels and in Norwegian national guidelines [210, 219]. Effective management strategies for BPSD usually entail

careful assessment of individual triggers and needs, and interventions tailored to the person with dementia and their caregivers [5, 210, 271]. Individual and situational factors that may interact to influence BPSD include sensory over- or under stimulation, medication use, pain, hunger, discomfort, sleepiness, demands that exceed ability, gender, somatic disease, medical procedures, being restrained, visual and auditory impairment, disorientation, fear, sadness, stress, problems with communication, change or lack of routine, boredom and lack of activities, lack of autonomy or support, negative reactions from others, and depression or stress in caregivers [5, 210, 226, 272-275]. Thus, the identification and treatment of such symptoms, including evaluation of treatment response, can be complex and time consuming, and require training of caregivers [271, 275]. Time and resources are often limited in nursing homes, and providers may hesitate to use non-pharmacological strategies due to concerns about efficacy or lack of clear guidelines [5]. There may also be concerns about safety when dealing with aggressive and potentially harmful behaviour [276]. As a consequence, non-pharmacological strategies are often underutilised [271].

In most cases, BPSD are managed with pharmacotherapy, despite mixed or lacking evidence of efficacy [12, 13, 233, 277, 278]. The majority of nursing home patients with dementia are prescribed psychotropic medications, such as antidepressants, anxiolytics, antipsychotics, hypnotics, and sedatives, for the treatment of symptoms such as agitation, depression, and sleep problems [279, 280]. The use of these medications has been associated with an increased risk of adverse outcomes and side effects, including compounded cognitive decline, adverse cardiovascular effects, metabolic syndrome, behavioural disturbances, seizures, gastrointestinal reactions, drowsiness and sedation, confusion, and death [221, 277, 281]. The high use of antipsychotics among nursing home patients has been especially criticised, due to the known risks of severe adverse outcomes and death [273, 282, 283]. Despite some evidence of a modest short-term effect against psychotic symptoms and aggression, antipsychotic use has been discouraged in all but the most severe cases [284]. Adverse events and distressing side effects have also been associated with other medications used to treat BPSD, including antidepressants, benzodiazepines, mood

stabilisers, cholinesterase inhibitors, memantine, and hypnotics [5, 13, 233, 285]. Furthermore, people with dementia frequently take a number of prescription drugs for other diseases, leading to increased risk of unfavourable drug interactions and side effects [12, 286, 287]. The risk of falls is also higher for people who take multiple medications and/or psychotropic drugs [288-290]. A study of medication use in Norwegian nursing homes identified drug-related problems, such as use of unnecessary drugs, excess dosing, and a lack of monitoring of drug use, in about 83% of patients [291]. These problems were most frequently associated with psychotropic drugs and opioids [291]. Thus, there is a demand for interventions to manage BPSD without the side effects associated with pharmacological treatments.

1.5 Bright light treatment

1.5.1 Applications and rationale for bright light treatment

The therapeutic use of retinal light exposure is considered a first-line treatment for seasonal affective disorder, following more than 30 years of research [292, 293]. The use of light to regulate sleep-wake rhythms and treat sleep problems is also well-supported, in healthy individuals and in people with a range of psychiatric and medical conditions [143, 294-296]. Additionally, there is promising, albeit inconclusive, evidence that BLT may improve some clinical symptoms in a variety of other psychiatric conditions, including non-seasonal depression [297, 298], bipolar disorder [299], ADHD [300], borderline personality disorder [301], eating disorders [302], and dementia [303]. Although the mechanisms of action are largely unknown, a prominent hypothesis is that light targets circadian disruption and associated sleep disorders that are commonly observed in people with seasonal affective disorder and other conditions [292]. In addition, direct and acute effects of light on alertness, physiological arousal, task performance, and mood [27, 51, 304] may plausibly counteract some symptoms such as tiredness, listlessness, and impaired cognitive function. Neuroimaging studies have shown that light can modulate activity in widespread areas of the brain. These include, but are not restricted to, the thalamus and brainstem, which are important for the regulation of alertness and arousal; areas

associated with long-term memory and emotion, such as the amygdala and hippocampus; and cortical areas associated with working memory and attention [25, 305-307]. While some of the acute effects of light exposure, particularly during the night, may depend on SCN-mediated processes such as regulation of melatonin levels, non-SCN dependent pathways from the retina also influence mood and cognition [27, 304]. There is also some evidence that blocking blue light can negatively affect cognitive performance without impacting circadian measures [308]. Consequently, the effects of light on sleep, circadian rhythms, mood, and cognition may arise from multiple interacting processes.

1.5.2 Delivery of bright light treatment

"Light treatment", or "light therapy", has been used to describe a variety of approaches that involve altering the illuminance and/or spectral composition of light to achieve beneficial effects. The term can refer to increased exposure to natural daylight, but frequently entails the use of an electric lamp, or "light box". Commonly, these are table mounted devices that deliver 2500-10 000 lx of white (i.e., a broad range of wavelengths, sometimes enhanced in the short-wavelength portion of the spectrum) or blue (i.e., short-wavelength) light, when placed ~0.5-1 m from the person being treated [294, 309]. These require that the person being treated remain seated in front of the device for the duration of the light exposure, typically between 30 and 120 min [236, 294, 309]. If the person receiving treatment has dementia, someone will often need to stay with them to ensure exposure [310]. Some studies have investigated dawn and/or dusk simulation, usually with lower maximum intensities of around 300 lx [311, 312]. Other options include wearable light visors or light glasses, or changing the ambient illumination in a larger area, such as a whole room [313, 314]. With the advent of new technologies, manipulation of the ambient illumination can entail dynamic lighting schemes, in which the CCT and illuminance vary throughout the day [315]. These offer a substantial benefit over light boxes by enabling prolonged exposures for several people simultaneously. When used in treating people who have dementia, they obviate the need for staff facilitation, reducing strain on staff availability.

While the relationship between light characteristics and phase shifts or melatonin suppression at night is quite well understood, less is known about the optimal light parameters for circadian function, well-being and health more broadly [236, 294, 313]. The recommended duration of exposure depends on the illuminance. Common suggestions for white light are 30 minutes of 10 000 lx, 45-60 minutes of 5000 lx, and two hours of 2500 lx [316]. When light with more short wavelengths is used, it may be effective at a lower illuminance [317]. For people with dementia, increasing the light exposure throughout the day may be the most beneficial [318]. Although higher illuminance and/or CCT might produce stronger effects, they are also less similar to regular indoor lighting, and may be experienced as more unnatural or aversive [83], potentially increasing agitation [319]. Using longer exposure durations may promote adherence and comfort by requiring lower illuminance/CCT to produce an effect. Exposures of multiple (≥ 4) hours with neutral/white (CCT of 6000-6500 K) light of ~1000 lx have been used in studies with people who have dementia [15, 178]. However, there is great variation in the intervention strategies used in research with people who have dementia [146, 169, 236, 239, 303, 313].

1.5.3 Bright light treatment for people with dementia

For people with dementia, BLT has been found to reduce symptoms of depression [15, 320, 321] and agitation [320-323], attenuate cognitive and functional deterioration [15, 324], and improve sleep [318, 320, 324-326] and circadian rhythms [318, 320, 327]. However, the evidence recommending light treatment for people with dementia is equivocal, and a number of studies have reported non-significant effects on some or all of the above listed outcomes, with inconsistent combinations of significant and non-significant effects [146, 169, 236, 239, 303, 313].

Meta-analyses of research on light treatment for dementia have been inconclusive, and sometimes contradictory, despite overlap in the included studies. A 2014 Cochrane review by Forbes et al. analysed data from 11 randomised controlled trials (RCTs), and found no effect of light on cognitive function, sleep, or BPSD [313]. In a 2017 meta-analysis of 9 RCTs, Chiu et al. [303] found that light treatment had a moderate positive effect on behavioural disturbances and depression, and a small

effect on sleep time at night, in cognitively impaired people. Van Maanen et al. investigated the effect of BLT on various sleep disorders in a 2016 meta-analysis [294]. Out of the 53 included studies of varying design, 11 included people with dementia. Light treatment was found to be generally effective for sleep problems in people with dementia, although with a small effect size. Too few studies were found to conduct analysis for circadian outcomes in people with dementia, which is regretful, as the effect on circadian rhythm sleep disorders was among the largest effects in the overall analysis. A 2021 meta-analysis by Canazei et al. of 11 RCTs concluded that there was insufficient evidence to recommend light treatment for circadian rhythms and sleep, measured by actigraphy, in people with dementia [238]. In a 2022 meta-analysis of 18 RCTs on light treatment for sleep disturbances in dementia, Tan et al. [239] concluded that light treatment had negligible or non-significant effects on sleep outcomes. However, they noted that most studies were inconclusive due to small sample sizes.

Other reviewers have summarised the literature without conducting meta-analyses. They naturally include many of the same studies, and the conclusions of all reviewers reflect the heterogeneity of study results. Mitolo et al. [146] reviewed 32 articles about BLT for sleep, cognition, and/or BPSD in people with AD, concluding that the evidence was mixed, but with a trend towards positive effects. In 2020, we reviewed 31 publications from 24 studies on BLT for people with dementia [236]. Out of 17 studies on BPSD, 8 reported positive effects, and 4 reported an increase in agitation or depression. There was a positive effect on sleep measured by actigraphy in 10 out of 15 studies. A positive effect on at least one outcome was reported in 9 of the 12 studies on circadian outcomes from actigraphy measures, usually in combination with no effect on multiple additional outcomes. Based on a review of 36 articles, Cibeira et al. [237] concluded that there was a potential effect of BLT on BPSD but limited evidence for improvement of cognition, quality of life, or activities of daily living. A majority of included studies on sleep, agitation, and depression reported some positive results. A review by Goudriaan et al. [169] of 37 articles focused on the effect of environmental light for people with dementia, including both pre-existing and altered light conditions, but excluding devices such as light boxes. The most

promising effects were found for depressive symptoms and spatial orientation. There was only limited evidence for challenging behaviour or RAR disturbance. Most of the included studies (60%) only investigated existing light conditions, not interventions [169].

A few studies on BLT for people with dementia have been published more recently, and not included in earlier reviews. A 4-week randomised, non-blinded study (n = 39) by Cibeira et al. [328] found that, in people with moderate to severe dementia, 30 min of 10 000 lx in the morning had immediate positive effects on observed behavioural indicators of mood and stimulation level, increased blood oxygen saturation, and reduced the heart rate [328]. Cremascoli et al. [314] reported findings from a 4-week single-blind RCT (n = 13) for people with mild or moderate AD. The treatment group received blue-enriched light of 10 000 lx from light therapy glasses, for 20 min a day, timed according to each individual's circadian phase. There were no improvements of sleep time, sleep efficiency, depression, neuropsychiatric symptoms, or non-parametric RAR indicators. However, there were improvements in terms of subjective sleep quality, cognitive test score, an advance or delay in DLMO (depending on the timing of the light), and shorter times between DLMO and sleep [314]. Authors note that due to a small sample size, results may have been influenced by a few individuals who had very strong results. Liu et al. [329] provided ambient BLT (≥ 2500 lx at the cornea) for an hour every morning over 8 weeks in a single-blind controlled trial (n = 35). They found that the intervention significantly improved sleep efficiency and increased sleep time. Effectiveness peaked at the 4-week follow-up, and people with severe dementia had a larger effect than those with mild or moderate dementia [329]. A 2020 article by Figueiro et al. [76] reported results from a study (n = 47) that lasted 25 weeks, which is considerably longer than most trials. The light devices were tailored to the habits of each individual to provide a CS of 0.4 (~350-850 lx at eye level, CCT between 4000 and 7000 K). They found that the treatment improved subjective and objective measures of sleep, and subjective measures of depression and agitation. RAR outcomes were not improved.

Some of the inconsistencies in findings are likely due to significant variation in methodology and sample characteristics [146, 236, 303, 313, 314]. Aspects of the light treatment, such as illuminance and spectral composition/CCT, timing, and light source, vary across trials [146, 236, 303, 313]. The meta-analysis by Chiu et al. found light of more than 2500 lx to be more effective for depression than lower intensities [303]. Intensities between 2500 and 10 000 were also recommended by Cibeira et al. [237]. Our review found that durations of 8 weeks or more may be most effective [236]. However, these suggestions are tentative and based on few studies. Importantly, illuminance and spectral composition/CCT need to be considered in relation to each other and to treatment duration. Thus, comparisons considering only one of these aspects are not necessarily informative about the optimal light parameters. Differences in trial design (pre-post, RCT or crossover), outcome measures (e.g., rating scales, observations or actigraphy), setting (institutional or community dwelling), and the type and extent of blinding, likely contribute to the variation [236, 294, 303]. It has been suggested that the effects of BLT for people with dementia are more marked during winter [146, 330]. Further, there are some indications that responses to BLT may vary depending on individual factors, such as gender [178, 294, 331] or dementia subtype [332]. Dementia severity has been frequently suggested as a potentially important factor [324, 326, 333, 334], albeit with diverging findings regarding the direction of the impact. The 2014 Cochrane review [313], as well as other reviews [146, 169, 236], have identified dementia severity as a variable that researchers should take into account. Large variations in these and other sample characteristics, such as comorbidities, age, and the prevalence of visual impairments, BPSD and other clinical symptoms, constitute an obstacle to making comparisons across studies [146, 303, 313]. It has been frequently noted that most trials of BLT for people with dementia have been conducted with small samples [146, 236, 239, 313], compromising statistical power and making it difficult to compare subgroups. Inconsistent reporting of light parameters constitutes a further obstacle to comparison, and better descriptions of the light interventions have repeatedly been called for [74, 146, 169, 236, 294, 310]. Few trials of BLT for people with dementia have lasted for more than 8 weeks, and many were shorter than 4

weeks [146, 236, 313]. Evidence is also relatively scarce regarding BLT delivered in the form of ambient illumination [146, 169, 236, 313]. In a rare long-term RCT of ambient illumination for people with dementia (up to 3.5 years, 15 months on average), Riemersma-van der Lek and colleagues found that whole day (10:00-18:00) exposures of ±1000 lx at the cornea improved disruptions in cognition, mood, behaviour, functional abilities, and sleep [15]. It may be that longer trials, such as this one and the previously mentioned 2020 study by Figueiro et al. [76], are required to detect effects of BLT for people with dementia, but more trials of longer duration are needed before this can be determined.

In conclusion, more research is needed to determine the effect of BLT in people with dementia. It is frequently recommended that studies should be conducted with large sample sizes and long trial durations, using a randomised design with adequate control groups, and with improved and detailed reporting of light characteristics [146, 236, 303, 310, 313]. Ambient illumination is less researched than other ways of delivering BLT, but it represents an opportunity to study longer daily exposures and conduct longer trials without increased demands on staff [15, 146].

1.5.4 Safety of bright light treatment for people with dementia

BLT is generally considered a safe intervention, with low to no risk of severe side effects. The illuminances used for BLT are far below those of natural daylight, even in cloudy conditions, although artificial light is not identical to daylight. It has been noted that clinicians should be vigilant about incipient signs of hypomania or autonomic hyperarousal [335], as well as individuals with an eye condition [295]. Reported side effects include headache, eye irritation, blurry vision, and nausea, but these usually subside within few days [295, 335]. In people with dementia, it has been suggested that BLT, especially high CCT light, could lead to increased agitation or depression in some participants [319, 333, 336]. If light promotes alertness and increased activity levels during the day, this could plausibly entail an increase in behaviour that is considered disruptive in a nursing home context. However, reviewers have concluded that BLT does not carry a risk of significant adverse effects for people with dementia [146, 313]. In the study by Riemersma-van der Lek, which

used whole-day light exposures, no adverse effects were reported [15]. A review of 43 articles on light treatment concluded that it was safe for the eyes in physically healthy, unmedicated people [337]. In a study by Sloane et al. [338], no evidence of retinal light toxicity was found, even after 6 weeks of unusually high CCT (13 000 K) light. Regardless, potential exacerbation of symptoms or other negative reactions should be monitored.

1.6 Summary and rationale

The background and rationale for this thesis and the studies it describes can be summarised as follows:

1) Light can affect important aspects of human health and behaviour, such as circadian rhythms, alertness, and mood.
2) Studies have found insufficient illumination in nursing homes, although most studies have reported photopic illuminance.
3) Some studies have indicated that BLT can improve BPSD and RARs in people with dementia, but results have been mixed.
4) Trials of BLT for people with dementia have rarely lasted for more than 8 weeks, and only a few have investigated ambient illumination.

2. Aims and hypotheses

The primary aim of this thesis was to investigate whether ambient BLT in nursing homes can positively affect RARs and improve BPSD in people with dementia. The secondary aim was to investigate the current light conditions in nursing homes. Based on previous research, we hypothesised that 1) illumination in nursing homes would be insufficient according to recommendations; 2) ambient BLT would positively affect RAR outcomes; and 3) ambient BLT would improve BPSD outcomes.

2.1 Aim of paper 1

In paper 1, the aim was to investigate the illumination in nursing home dementia units, with an emphasis on its potential to stimulate NIF effects. We therefore wanted to measure light and calculate the melanopic EDI in all municipal nursing homes in Bergen, across two seasons, and in different gaze directions relative to windows. In addition, we aimed to assess the illuminance in the absence of daylight, i.e., the capacity of current indoor lights to compensate during winter months. We aimed to investigate the impact of season and gaze direction on melanopic EDI, and to compare measurements to thresholds based on industry recommendations and previous research.

2.2 Aim of paper 2

Paper 2 aimed to investigate the effects of ceiling mounted BLT on RARs in nursing home patients with dementia. A cluster randomised placebo-controlled trial, named "Therapy Light Rooms for Nursing Home Patients with Dementia – Designing Diurnal Conditions for Improved Sleep, Mood and Behavioural Problems" (DEM.LIGHT), was conducted over 24 weeks, and RARs were assessed using actigraphy. Circadian rhythms were one of the primary outcomes in the DEM.LIGHT trial. Our hypothesis was that ambient BLT would positively affect RAR outcomes calculated using a non-parametric approach (i.e., interdaily stability, intradaily

variability, L5, M10, and relative amplitude) and an anti-logistic cosine model (i.e., amplitude, mesor, pseudo-F statistic, acrophase, alpha, beta, and nadir).

2.3 Aim of paper 3

The aim of paper 3 was to investigate the effects of BLT on BPSD in nursing home patients with dementia. As part of the DEM.LIGHT trial, nursing home staff evaluated BPSD using validated proxy-rated instruments: the Neuropsychiatric Inventory Nursing Home Version (NPI-NH), and the Cornell Scale for Depression in Dementia (CSDD). BPSD comprised a secondary outcome in the DEM.LIGHT trial. Our hypothesis was that ambient BLT would improve BPSD.

3. Methods

This thesis is based on data from two scientific studies. Paper 1 reported results from a field study of illuminance in dementia units across seasons and gaze directions. Paper 2 and 3 reported results from a 24-week cluster randomised controlled trial (the DEM.LIGHT trial). I will first describe the methods and study procedures for paper 1, then the DEM.LIGHT trial design and outcome measures, followed by a description of the outcome measures and data analyses particular to paper 2 and 3.

3.1 Methods of paper 1

3.1.1 Participants and procedures

Bergen municipality provided permission to approach all municipal nursing homes about conducting light measurements. The nursing home managers were contacted and asked if they had a dedicated long-term dementia unit. All who answered affirmatively (n = 15) accepted the invitation to participate.

Light measurements were conducted in the common living room areas at three time points: during the daytime (between 10:00 and 14:00) in summer (August) and winter (February); and after astronomical darkness (after 18:00) in winter (to assess the artificial lights). Daytime measurements were conducted on cloudy days to ensure consistency across sites, and adjustable lights were turned to full capacity. Illuminance was measured with a spectrometer (GL Spectis 1.0 T Flicker spectrometer by GL optic), and spectral data were prepared using the corresponding software (GL Spectrosoft).

Vertical measurements were conducted at 1.2 m to approximate seated corneal illuminance. Measurements were taken in the centre of the living room, in four directions at 90-degree steps, including the wall with the most windows.

Horizontal measurements were included for comparison with standards and previous research, and to assess task area illuminance for visual function. These were conducted at 0.8 m (approximately table height) at three positions: 0.5 m from the

wall with the most windows, 0.5 m from the rear wall, and at a mid-point between these.

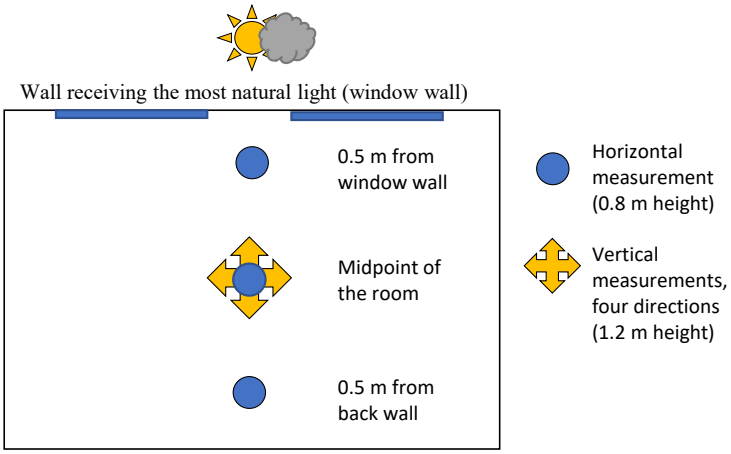

Figure 1: Measurement points in the dementia unit living rooms. As published in paper 1 [339].

3.1.2 Light assessment

The irradiance toolbox developed by Lucas et al. [31] was used to compute effective α-opic illuminances, including melanopic illuminance. To comply with the most recent guidelines for light measurement, melanopic EDI was later calculated by adjusting melanopic illuminance with a factor of 0.9058 [59, 70].

Three thresholds were selected for comparisons, based on previously published research and industry standards:

1) A melanopic EDI of 217 lx, recommended by the WELL certification system [82], and used in a previous field study of light at nursing homes [177].

2) A horizontal illuminance of 300 lx (photopic), corresponding to the lower end of the CIE [81] recommendation, and exceeding the IES [80] minimum recommendation for elderly people.

3) A vertically measured illuminance of 500 lx (photopic), which is sufficient to satisfy a CS of 0.3 in most cases, in accordance with the Underwriters Laboratory guidelines [41, 340].

3.1.3 Statistical analyses

All analyses were performed in R [341]. A multilevel regression model (also known as a linear mixed model) was fitted using the R package lme4 [342] to assess the effect of season and gaze direction on melanopic EDI (vertical measurement) at eye level. Random intercepts for nursing home units (n = 15) were added to account for repeated measurements at each unit. Restricted Maximum Likelihood (REML) estimation was used. Highly influential points were identified based on criteria of Cooks D above 1 and/or studentised residuals above 2 [343], resulting in the removal of two data points. Melanopic EDI was log-transformed due to a highly non-normal error-distribution. For the purposes of easing interpretation, it was also standardised to have a mean of 0 and a standard deviation of 1.

Illuminances were compared to standards and thresholds by tallying the number of nursing homes that met each illuminance threshold, across seasons and gaze directions.

3.1.4 Ethics

There were no data collected from patients or staff at the nursing homes, nor any interference with the nursing homes' or the patients' schedules. No information that could identify patients was recorded, and staff involvement was limited to providing researchers access to the unit upon arrival. Nursing home managers could decline to let their unit participate if the presence of researchers would constitute a disruption in the unit. Individual nursing homes were not identified in the published results, and there were no consequences for the participating units. In dialogue with the Norwegian Regional Committee for Medical and Health Research Ethics Western Norway, and the Privacy Officer (Personvernombud) at the University of Bergen, we concluded that the study was exempted from seeking ethical approval. This was based on the fact that no health data or private personal data were collected from any person (neither staff nor patients). In addition, the researchers' presence was deemed to have a marginal impact on the nursing home patients.

3.2 The DEM.LIGHT trial

3.2.1 Trial design

The DEM.LIGHT trial was a 24-week cluster randomised placebo-controlled trial. Eight nursing home units (clusters) were randomly assigned to either the intervention condition or the control condition, with four units in each condition. Data were collected at baseline, and subsequently after 8, 16, and 24 weeks. Sleep (reported in [344]) and circadian rhythms (including RARs) comprised the primary outcomes. BPSD were secondary outcomes. DEM.LIGHT was registered at ClinicalTrials.gov with the identifier NCT03357328.

3.2.2 Participants

The eight included nursing homes had a total of 78 patients who were invited to participate. Nursing homes and participants were recruited between September 2016 and August 2017. The study commenced in September 2017; thus, no participant had spent less than one month in the nursing home before baseline. Eligibility criteria for nursing homes were that they had a dementia unit, were currently not participating in other trials or care projects, and that light panels could be installed. Nursing homes were recruited with the help of the Municipal Agency for the Elderly and Nursing Homes, and the Department of Health and Care, City of Bergen. Principal investigator Elisabeth Flo-Groeneboom (EF) presented the trial to these departments, and to nursing home managers, on multiple occasions. A list of 14 eligible nursing homes were then provided by the municipality, and the managers of these were contacted by the candidate (EK) and PhD-fellow Gunnhild J. Hjetland (GJH) via email. When managers indicated an interest in participating, EK and GJH visited the nursing homes to inform the staff about the project, and to assess the feasibility of installing light fixtures in the living rooms. Enrolment ceased when eight nursing homes had agreed to participate. Four units declined to participate, and one unit was excluded by researchers due to having twice as many residents as other units.

After the recruitment of dementia units, patients were screened according to the inclusion criteria (Table 1). EK and GJH discussed these criteria with the resident

nursing home physicians, and continued to assess them upon meeting the participants and staff.

Table 1: Study inclusion and exclusion criteria. As published in paper 2 [345].

Participants were eligible if they:	Participants were not eligible 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 the capacity or, if not, a written proxy informed consent from a legally authorised 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 of less than 6 months, or other aspects that could interfere with participation - were psychotic or had a severe mental disorder

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

3.2.3 Intervention

Bright light treatment

The intervention was delivered using ceiling mounted LED panels, installed in the living rooms of the four dementia units assigned to the intervention group. The number and positions of LED units needed to meet the target illuminance were calculated by engineers from our light vendor, Glamox AS, accounting for windows and room size. The LED set-up delivered light of varying illuminance and CCT throughout the day with gradual (30 min) transitions (Figure 2). The peak of the intervention was between 10:00 and 15:00, consisting of 1000 lx, 6000 K, measured vertically at 1.2 m.

Figure 2: Illuminance (lx) and correlated colour temperature (kelvin, K) at different times of the day in the intervention group, with gradual transition periods of 30 min separating each phase. Between 21:00 and 07:00 the lights could also be turned off by staff if this was preferred. As published in paper 2 [345].

The duration, illuminance and CCT of the intervention were based on previous research, and on a pilot conducted in one dementia unit for 4 weeks, 3 months before commencement of the study. Feedback from nursing home staff during the pilot lead to a reduction in the duration of the period with peak illuminance (transitioning to the 400 lx, 3000 K condition earlier in the afternoon), as well as a reduction of the evening illuminance. Light panels (C95-R600x600 LED 4800 DALI 827-865 CCT LI MP) were installed before baseline data collection in all units. The panels were set to provide typical indoor lighting (100 lx and 3000 K) before the trial started. The light sequence was switched on in the intervention units after baseline data collection. The staff did not have opportunities to change the dynamic lighting scheme but could turn the light off at night.

Control condition

In the four units assigned to the control condition, the light sources of existing light fixtures were exchanged with similar replacements (CFL AURA UNIQUE-D/E LL 18W/830 G241-2 in three units and CFL AURA UNIQUE-L LL 18W/830 2G11 in one), providing typical indoor illuminance of ~150-300 lx and 3000 K (vertically), in the centre of the room, at 1.2 m.

Light measurement and quality assessment

Glamox engineers conducted light measurements during the installation process to ensure that the desired illuminance was achieved. In addition, EK and GJH measured the light at the start of the trial in control and intervention units (Table 2) using the GL Spectis 1.0 T Flicker spectrometer (GL Optic). Measurements were conducted in four directions (at 90-degree steps including the direction of the wall with the most windows), vertically, at 1.2 m, in the centre of the room. Averages were calculated for each unit. In addition to extracting photopic illuminances (in lx), the CIE S 026 toolbox [72] was used to calculate α-opic irradiances and melanopic EDI. All measurements were conducted on days with overcast weather in September, between 10:00 and 15:00.

One unit in the intervention group had an average photopic illuminance of 722 lx only, which was below the goal of 1000 lx. However, even this lowest value for the intervention group was well above the highest illuminance measured in the control group (368 lx).

Participants in the intervention group spent on average 3.6 (SD = 1.6) hours in the living room during the period of peak illuminance (10:00 to 15:00), and the control group spent on average 3.1 (SD = 1.4) hours in the living room in this time interval.

Table 2: Light measurements in 8 dementia units after installation of light fixtures. Abbreviated version of Supplementary Table S1 that was published online along with paper 2 [345].

	Control (4 units)	**Intervention (4 units)**
Photopic illuminance (lx)		
Mean (SD)	242 (101)	1039 (225)
Range	134 - 368	722 - 1242
Melanopic EDI (lx)		
Mean (SD)	124 (82)	779 (142)
Range	50 - 236	612 - 951

3.2.4 Outcome measures

This section provides an overview of the outcome measures of the DEM.LIGHT trial, on which paper 2 and 3 are based. A brief description of the primary outcome measures of the DEM.LIGHT trial are provided, along with a description of secondary outcome measures that were used in paper 2 and 3. Other secondary outcome measures from the DEM.LIGHT trial, which were not reported in paper 2 and 3, are listed at the end of this section. Selection and calculation of outcome measures, as well as statistical analyses specific to each paper, are described in greater detail under the methods subheadings for their respective papers.

Proxy-rated questionnaires were completed at all four time points by nursing home staff who knew the participants well. EK and GJH assisted proxy-raters in completing the questionnaires until they were familiar with the instruments, in order to ensure consistency of interpretation across sites. To further ensure consistency, we strived to ensure that the same staff member completed questionnaires at all time points. Medical journals were accessed by study researchers with clinical authorization (EK and GJH).

Primary outcome measures of the DEM.LIGHT trial

The primary outcome measures of the DEM.LIGHT trial were as follows: change in actigraphy recorded sleep and circadian rhythm (RAR), change in proxy-rated sleep, and change in circadian rhythm of the CBT.

Actigraphy was used for sleep outcomes, and for the RAR outcome measures described in section 3.3.1. Motor activity was recorded by wrist-worn actigraphs (The Actiwatch II by Philips Respironics). These are accelerometery devices that can be worn continuously for multiple days, allowing for uninterrupted activity monitoring in naturalistic conditions. As recommended for this population [346], actigraphs were placed on the dominant or most mobile wrist; epoch length was set to 1 minute, and the sensitivity was set to medium. Participants wore the device for seven days during the same week the proxy rated questionnaires were completed, or in the week preceding it. Staff could remove the actigraph if requested by the participant, or if they observed behaviour indicating that the device caused distress. A minimum of five days of continuous activity recording was required for inclusion in the analysis. Sleep outcomes extracted were as follows: sleep efficiency, total sleep time, sleep time in the wake interval (day), sleep time in the rest interval (night), and wake after sleep onset (WASO). For all sleep outcomes, a fixed interval for the rest period (22:00 to 06:00) was used due to insufficient information for determining the individual rest intervals. These preset intervals were then analysed by the Actiware software (version 6.0.9, Philips Respironics) to estimate the number of minutes spent sleeping and awake for each interval.

Telemetric core temperature monitoring, using ingestible capsules, was also included as a primary outcome [347]. The capsules collect data on temperature continuously while passing through the body. Data can be extracted via a handheld Bluetooth device before the capsule is discharged. However, data from this measurement were not used, as insufficient and low-quality data were available for circadian analysis due to technical issues and practical challenges.

The Sleep Disorder Inventory (SDI) [348] is a proxy-rated assessment of disordered sleep. It is an extension of the NPI-NH and was scored by summarising the severity x frequency product scores for 7 symptoms (range 0 – 84) [344, 348]. The SDI has demonstrated good convergent validity with actigraphy in people with dementia [348].

Secondary outcome measures and covariates of the DEM.LIGHT trial

The Cornell Scale for Depression in Dementia (CSDD) [349] describes 19 observable symptoms of depression to be rated as absent (0), mild/intermittent (1) or severe (2), yielding a total score with range 0 to 38. The CSDD and its Norwegian translation have demonstrated acceptable psychometric characteristics [349, 350].

The Neuropsychiatric Inventory - Nursing Home Version (NPI-NH) [351] was used to evaluate the frequency and severity of BPSD in 12 behavioural domains in the preceding week: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, sleep and night-time behaviour, and appetite and eating. The frequency (range 0 – 4) and severity (range 0 – 3) ratings are multiplied to provide a composite total score (range 0 – 144). The Norwegian version of the NPI-NH has demonstrated good psychometric properties [352].

The Functional Assessment Staging Tool (FAST) [191] is a scale that describes the progression of AD in seven stages from 1 (normal adult) to 7 (severe AD). Other forms of dementia do not necessarily follow the same progression; however, we used it to characterise the degree of impairment at baseline. At higher scores, the ability to perform activities of daily living is increasingly impaired. The scale has adequate validity and reliability [353].

The Charlson Comorbidity Index (CCI) is a weighted assessment of comorbid conditions, with scores reflecting both the number and seriousness of comorbidities. Composite scores are positively associated with 1-year mortality rates [354].

The Mini-Mental State Examination (MMSE) [355] is a screening tool used to assess cognitive function. It has good reliability and validity when used to evaluate cognitive impairment and change over time in patients with dementia [355, 356]. Total scores range from 0 to 30, with higher scores indicative of better cognitive function.

Medical journals were accessed to extract information about the participants' age, gender, weight, height, marital status, blood pressure, heart rate, diagnoses (including somatic, psychological and dementia diagnoses) and medication use.

Time spent in the living room was assessed at each follow-up (week 8, 16, and 24). Staff were asked to estimate how much time the participant had spent in the living room daily during the preceding 8 weeks. For the intervention group, this approximates the daily exposure to BLT. In addition, time in the living room may indirectly reflect other potential confounders, such as being confined to the bed, or a lack of social participation. The questionnaire given to staff was divided into time slots based on the light sequence, and data for the 10:00-15:00 period (corresponding to the period of peak illuminance) was reported.

In addition to the outcomes used in paper 2 and 3, the DEM.LIGHT trial collected data using proxy rated measures of activities of daily living (PSMS [357]), quality of life (QUALID [358]), agitation (CMAI), resource utilisation (RUD-FOCA [359]), as well as a pain assessment (MOBID-2 [360]), which were not used in the papers presented in this thesis.

3.2.5 Sample size

The aim was to recruit 80 participants, allowing for a 20% drop out. This number was based on a power analysis performed with the assumption that effect sizes would be moderate (Cohen's d = .50) using ANOVA analysis. The power analysis (two-tailed alpha level of .05 and power set to .80) indicated that 64 participants and 8 clusters were necessary to detect differences between active and control conditions [361, 362].

3.2.6 Group allocation and randomisation

Units were randomly assigned to the control or intervention condition by EK and EF using random group assignment in SPSS [363]. All participants in the same unit were thus assigned to the same condition.

3.2.7 Blinding

The aim was to conceal condition allocation from the participants and the staff, making the DEM.LIGHT trial single-blinded. The included units were not in the same nursing home, and direct comparison between light conditions was therefore avoided. In order to mimic the procedure of changing the lights, EK and GJH installed new light sources in the control units. Staff were told that we were changing the lights, but not informed about how the intervention would look. The fact that similar light sources were used in the control units also ensured similar lighting across the control units. Due to the degree of memory loss experienced by the participants, blinding of participants was not considered an issue. Meanwhile, a complete blinding of the staff was difficult to achieve due to the visual nature of the intervention.

3.2.8 Statistical analyses

All statistical analyses and generation of figures were performed in R [341], while early stages of data management and missing data imputation were done using SPSS [363]. Missing item scores were imputed using expectation maximisation in SPSS if the participant was missing less than 20% of the items on a given scale. Scores were excluded from analysis at the given time point if more than 20% of the scale items were missing, or if a participant had spent less than 30 minutes on average per day in the living room since the previous data collection. Multilevel regression models were used to assess the effect of the intervention in both paper 2 and 3, with random intercepts for participants to account for repeated measurements. This analysis approach tolerates missing data for some time points, allowing us to retain data from other time points. Models were fitted using restricted maximum likelihood (REML) estimation, and an unstructured variance-covariance matrix, using the lme4 package [342]. FAST scores were added as a covariate to all models to control for dementia

severity, following recommendations by previous reviews to determine and account for this potential confounder [313, 324, 326, 333, 334]. Benjamini-Hochberg [364] false discovery rate (FDR) correction was applied for all outcomes, adjusting the significance level to account for the increased risk of a type 1 error when conducting multiple tests. Results were reported both with and without this correction [365].

3.2.9 Ethics

The DEM.LIGHT trial was conducted in accordance with the Declaration of Helsinki [366], and the protocol was approved by the Norwegian Regional Committee for Medical and Health Research Ethics, health region South East (project no. 2016/2246). Prior to inclusion in the trial, each participant's capacity for consent was discussed with the nursing home physician at the respective nursing home. Legal guardians of all participants were contacted by EK and GJH and informed about the trial, first by phone and subsequently in a letter along with the consent form. The information provided covered topics such as the purpose, methods, potential risks and benefits of the trial, and the option to withdraw consent at any time. In compliance with the Helsinki declaration [366], guardians were asked to provide presumed consent, i.e., to respond in the way they thought the participant would have responded if able to do so. In addition, some participants were deemed potentially able to comprehend aspects of the trial. These individuals were provided information, and opportunities to opt out, in a personally adapted manner. During the trial, researchers and staff were sensitive to verbal and non-verbal expressions of dissent by participants, which could be interpreted as withdrawal of consent in relation to specific procedures throughout the trial. Nursing home patients were free to move away from the intervention area if they wished. Prior to data collection, approval to gather data was granted by Bergen municipality and by each research site. The collected data were stored and processed using the Secure Access to Research Data and E-infrastructure (SAFE) secure server solution offered by the University of Bergen. The data on the server can only be accessed by the designated research team through a secure desktop with 2-factor authentication.

3.3 Methods of paper 2

Paper 2 was based on data from the DEM.LIGHT trial, described in section 3.2.

3.3.1 Outcome measures

The main outcome in paper 2 was RARs. All RAR outcomes were derived from actigraphy data. Non-parametric indicators were obtained using the NparACT package [367] in R, and parameters for the extended cosine model were calculated using the RAR package [368] in R.

There are a variety of methods available for characterising RARs. Non-parametric approaches and cosine-based models are common examples, used in a number of previous publications [10, 369]. Previous research has found that the standard cosine-model often shows poor fit with the true shape of the RAR [155, 369, 370]. We therefore chose to compute RAR indicators using a non-parametric approach [157], as well as an extended cosine model [155].

Non-parametric indicators describe the RAR without inherent assumptions about the shape of the activity rhythm [156, 157]. Previous publications have utilised these to investigate RARs in people with dementia [156, 371-375] and to assess the effect of BLT for these individuals [178, 327]. They have been found to have good sensitivity for detecting changes in RARs of people with dementia after BLT [370]. The variables are defined as follows [156, 157, 367, 370].

Interdaily stability (IS) captures the stability of the activity profile from day to day, on a scale from 0 (no similarity between days) to 1 (perfect similarity between days):

$IS = \frac{n \sum_{h=1}^{p} (\bar{X}_h - \bar{X})^2}{p \sum_{i=1}^{n} (X_i - \bar{X})^2}$ where n = the total number of data, p = the number of data per day, $\overline{x}$ = the overall mean of all data, $\overline{x}_h$ = the hourly means and x_i = the individual data points. A high IS indicates that 24-hour profiles from different days resemble each other, i.e., that the RAR is regular. This regularity is sometimes interpreted as a strong coupling between the RAR and external zeitgebers [156, 367].

Intradaily variability (IV) quantifies the fragmentation of activity levels over the 24-hour period. A rhythm with a perfectly sinusoid shape would have an IV of near zero, while an IV of about 2 would characterise Gaussian noise [370]. It is the ratio of hourly variability to overall variability:

$\mathrm{IV} = \frac{n\sum_{i=2}^{n}(X_i - X_{i-1})^2}{(n-1)\sum_{i=1}^{n}(X_i - \bar{X})^2}$. A high IV reflects more transitions between activity levels within a day, for instance as a result of waking up during the rest period or sleeping during the active period.

L5 and M10 represent average activity levels in the least active 5-hour period, and the most active 10-hour period, respectively. Typically, L5 captures night-time activity, and M10 reflects daytime activity levels, but the measure does not take the time of day into account.

Relative amplitude (RA) represents the ratio of the difference in activity levels during the periods defined by M10 (most active) and L5 (least active) to the total activity level. $\mathrm{RA} = \frac{(M10 - L5)}{(M10 + L5)}$. A high RA thus indicates that there is a defined difference in activity between the rest period and the activity period.

The anti-logistic extended cosine model [155, 265] builds on the traditional cosine models but has additional parameters that allow for a more flexible fit to activity rhythms [265]. This is particularly useful when analysing rhythms that do not conform to sinusoidal patterns, and the approach has been used in research with older people and people with dementia [149, 376, 377]. The variables we computed are defined as follows [155, 265].

Amplitude is the difference between the peak (maximum) and nadir (minimum), i.e., the magnitude, of the activity rhythm.

Midline-estimating statistic of rhythm (MESOR) is roughly analogous to the MESOR of the standard cosine model, representing the estimated middle of the data (minimum + amplitude/2). Larger values reflect higher overall activity levels.

The pseudo-F statistic is a measure of the goodness of fit of the data to the periodic function. A high F-statistic can be interpreted as a more robust activity pattern, which can be modelled by a function that has a 24-hour period. It has therefore sometimes been referred to as a measure of "overall circadian rhythmicity" [150].

Acrophase is the time at which the fitted function reaches its peak.

Alpha reflects the relative widths of the troughs (lows) and peaks (highs) of the activity curves, with larger values indicating that the troughs are relatively wide, and the peaks narrow.

Beta provides information about the steepness of the curve. A steeper curve, with sharper transitions between activity and rest, have a larger beta value. Larger values result in curves that have more square shapes. Along with the alpha parameter, the addition of the beta parameter allows the curve to have a more square wave pattern than the traditional cosine model, more closely resembling the shape of observed activity rhythms [155].

Nadir reflects the time of the minimum value of the curve.

3.3.2 Statistical analyses

After exclusion and attrition of participants, analyses in paper 2 were performed with 61 nursing home patients at baseline. The impact of the intervention on RARs was investigated using multilevel regression models, as described in section 3.2.8. In order to improve the normality of the residual distribution, a log transformation was applied to the amplitude, mesor, pseudo-F statistic, and beta values. One extreme outlier had to be removed from the beta model in order to fit the model. In addition to FAST scores, we also tested the following potential covariates: age, composite score on the CCI, gender, number of psychotropic medications, and whether the participant was prescribed hypnotic or sedative medications. As adding these covariates did not substantially improve the models, or change the interpretation of the results, they were not included in the final models.

The impact of BLT on RAR timing might differ for participants who are phase advanced and phase delayed. As we did not have reliable CBT-based estimates of circadian timing for the participants, we split the sample according to acrophase. The average acrophase in a sample of healthy older adults (i.e., 12:59), as reported by Gehrman et al. [378], was chosen as a reference point for this split. As only two participants deviated negatively from this reference point, subgroup analysis was not performed. These observations, and subsequent observations from the same participant (in total 4 observations from 2 participants), were instead excluded from analysis.

Spearman correlation coefficients were calculated for the relationships between parametric and non-parametric indicators at baseline.

3.4 Methods of paper 3

Paper 3 was based on data from the DEM.LIGHT trial, described in section 3.2.

3.4.1 Outcome measures

The main outcome measures in paper 3 were the CSDD and the NPI-NH. In addition to total scores, subscale scores were calculated as described below. In a secondary analysis, the SDI and the actigraphy derived sleep outcome WASO (i.e., minutes of wakefulness between the onset of sleep and the last awakening during the rest interval) were used for calculating baseline correlations with the scores on the NPI-NH and CSDD. WASO was chosen to represent actigraphy measured sleep because it is less impacted by the use of fixed rest intervals than some of the other sleep outcomes.

Scores were calculated for the CSDD subscales “Mood-related signs” (consisting of anxiety, sadness, lack of reactivity to pleasant events, and irritability), “Behavioural disturbance” (agitation, psychomotor retardation, multiple physical complaints, and loss of interest), and “Cyclic functions” (mood worse in the morning, difficulty falling asleep, multiple nocturnal awakenings, and early-morning awakening). Data from two additional subscales were excluded from analysis. The subscale “Physical

signs” (loss of appetite, weight loss, and loss of energy) was omitted because many participants had severe somatic illnesses that could cause the symptoms it represents. “Ideational disturbance” (suicidal ideation, low self-esteem, pessimism and mood-congruent delusions) was omitted because most participants were incapable of expressing such symptoms verbally.

Scores were calculated for the following NPI-NH subsyndromes, based on a previous factor analysis [6]: "Affective symptoms" (depression and anxiety, range 0 – 24), "Psychosis" (delusions and hallucination, range 0 – 24), and “Agitation" (agitation, aggression, disinhibition and irritability, range 0 – 24).

3.4.2 Statistical analyses

After exclusion and attrition of participants, 69 nursing home patients were included for analysis in paper 3 at baseline. Multilevel regression models were used to assess the impact of the intervention, as described in section 3.2.8. A square root transformation, with an added constant of 0.001, was applied to the NPI-NH total and subsyndrome scores due to violations of residual distributional assumptions. Estimated marginal means were extracted for all outcomes, which for the NPI-NH scores entailed back-transforming the scores.

In addition to FAST scores, baseline scores on the dependent variables were included as covariates in their respective models [379]. The following variables were tested as potential covariates, but were not added, as they did not impact the interpretation of the results: time in the living room (i.e., exposure time in the intervention group), age, having an AD diagnosis vs. a different dementia diagnosis, being prescribed sedatives or hypnotics, the number of psychotropic medications prescribed for regular use, melanopic EDI, eye disease, and CCI score.

Spearman correlation coefficients were calculated for the relationships between the various outcomes at baseline.

4. Summary of results

4.1 Paper 1

Season and gaze direction had a significant ($p < 0.05$) effect on melanopic EDI, measured vertically at eye level (1.2 m) in the centre of the living room. Median melanopic EDI for inward-facing measurements was 112 lx in summer and 57 lx in winter. Only the summer measurement was significantly different from the measurement taken after astronomical darkness (median 45 lx). Facing a window had a significant effect on melanopic EDI, compared to facing inward, in summer (median = 186 lx) but not in winter (median = 98 lx).

Regardless of gaze direction and season, most measurements fell below even the lowest predetermined thresholds based on previous research and recommendations. None of the inward-facing measurements reached any of the thresholds in winter, and only two reached the lowest threshold (217 lx, melanopic EDI) in summer. Six of the window-facing measurements reached this lowest threshold in summer, and one in winter. Only window-facing measurements (one in winter, two in summer) achieved a photopic illuminance of 500 lx. No higher thresholds were included, as only one measurement reached a photopic illuminance of 750 lx.

The median melanopic EDI after dark (i.e., using only electrical lights) was 45 lx. None of the measurements reached any of the thresholds after astronomical darkness.

The median horizontal (task area) photopic illuminances were below 300 lx for all measurement occasions, except for the measurements near windows during the day, which exceeded 300 lx in daytime in both seasons.

4.2 Paper 2

Actigraphy recordings from 61 participants were analysed. There was a group difference in change on the acrophase between baseline and week 16, which was significant (B = -1.02, 95% CI = -2.00, -0.05) before correcting for multiple testing.

Between baseline and week 16, the mean acrophase of the control group shifted to about one hour later compared to the intervention group. This difference was, however, non-significant when FDR correction for multiple testing was applied. The control group acrophase was delayed by about 30 minutes from baseline compared to the intervention group in week 8 and 24, but these did not reach statistical significance. There were no significant group differences in change on any other RAR measure, or at any other time point.

Out of 35 Spearman correlation coefficients calculated between parametric and non-parametric indicators, 25 were significant. Two of the correlations had coefficients with an absolute value above 0.80 (very strong correlation): between the pseudo-F statistic and RA ($rs = 0.82$), and between the pseudo-F statistic and IS ($rs = 0.81$). Five had coefficients with an absolute value between 0.60 and 0.79 (strong correlation): amplitude and IS ($rs = 0.66$), amplitude and RA ($rs = 0.60$), mesor and M10 ($rs = 0.67$), nadir and RA ($rs = 0.62$), and nadir and L5 ($rs = 0.66$).

4.3 Paper 3

Data from 69 participants were analysed for paper 3. Using a cut-off of 8 on the CSDD total [350], 55% of the sample could be classified as depressed at baseline. This number was distributed unequally between the groups, with 14 participants in the control group and 24 in the intervention group fulfilling this criterion.

The CSDD and NPI-NH total scores of the intervention group were reduced more than the scores of the control group from baseline to week 16. This difference was significant without, but not with, correction for multiple testing. After correcting for multiple testing, the only significant ($p < 0.05$) group differences in change from baseline were on the CSDD subscale Mood related signs, and on the NPI-NH subsyndrome Affective symptoms, in week 16. There were no significant group differences on other subscales.

In week 16, the estimated marginal means in the intervention group were reduced by 3.2 points more than the control group on the CSDD total, 9.3 points more on the

NPI-NH total, 1.8 points more on the CSDD Mood-related signs, and 2.6 points more on the NPI-NH Affective symptoms.

A number of significant correlations were found between scores on the scales at baseline. The Spearman correlation coefficient (rs) for the NPI-NH and CSDD total scores was 0.63, indicating a strong correlation. CSDD Mood-related signs and NPI-NH Affective symptoms correlated strongly (rs = 0.70), while the NPI-NH Agitation and CSDD Behavioural disturbance only correlated weakly (rs = 0.28). The only scores that correlated with WASO were the CSDD Cyclic functions (rs = 0.29) and the NPI-NH total (rs = 0.25). The SDI total correlated with the CSDD total (rs = 0.28), CSDD Cyclic functions (rs = 0.62), NPI-NH total (rs = 0.49), and NPI-NH Agitation (rs = 0.33).

5. Discussion

5.1 Dicussion of results

The main objective of this thesis was to investigate whether ambient BLT can have a positive effect on RARs and BPSD in nursing home patients with dementia. These were the main aims in paper 2 and 3, respectively. A secondary objective, and preparatory work for the trial described in paper 2 and 3, was to investigate the illumination in nursing home dementia units in terms of its potential to influence NIF effects. This was the main aim of paper 1, which assessed light conditions in dementia units across seasons and gaze directions. The measured illuminances were compared to thresholds set by previous research and recommendations with a focus on NIF effects. We found that nursing home illuminances were low compared to even conservative thresholds, suggesting a potential for improvement by interventions targeting this aspect of the nursing home environment. Following this, we conducted a 24-week cluster randomised controlled trial to investigate the effects of ambient BLT in nursing home dementia units. In paper 2 we reported that this intervention did not lead to significant improvement of RARs. The acrophase was shifted one hour later in the control group compared to the intervention group after 16 weeks, but not after 8 or 24 weeks. This group difference was significant before, but not after, FDR correction for multiple testing. The clinical significance of a one-hour difference in acrophase is not clear. Overall, we therefore concluded that these results did not support our hypothesis that BLT would have a positive impact on RAR outcomes. In paper 3, we reported that the effects of BLT on proxy-rated BPSD were mixed. There was a larger improvement on the CSDD and NPI-NH total scores in the intervention group than in the control group in week 16 (January and February, i.e., winter in Norway), but this group difference was only significant without correcting for multiple testing. However, the group difference in week 16 remained significant after FDR correction for subscales measuring affective symptoms. There was no significant improvement on any other subscales of the NPI-NH or CSDD.

In conclusion, we found that nursing home illuminance was insufficient, but we found no support for our hypothesis that BLT would have a beneficial effect on RARs, and only partial support for our hypothesis that BLT would improve BPSD.

5.1.1 Is the lighting insufficient in nursing home dementia units, and what does this mean?

In paper 1, we did not assess circadian rhythms, BPSD, or other outcomes, and thus we cannot conclude whether the light conditions in dementia units negatively impacted patients. However, measured illuminances were insufficient in comparison with thresholds based on previous research and industry recommendations. Accordingly, illuminances fell short of the levels assumed to be necessary for adequate stimulation of NIF effects, which may impact circadian rhythms, sleep, alertness, and mood [16, 25, 26, 59, 93]. These are important determinants of health and well-being [122, 123], and perhaps particularly relevant for people with dementia, who frequently experience disturbed sleep and circadian rhythms, fluctuating daytime alertness, and mood disorders [5, 10, 163, 380]. There is observational and experimental evidence linking nursing home illumination to BPSD, sleep and RARs [15, 76, 176, 178-180], although more experimental research is needed to establish causality. Many of the light measurements also fell short of standards relating to visual function, which may reduce the ability to perform visual tasks, increase the risk of falls, and impair mobility and functional independence [165, 167]. These findings are in line with previous studies of light in nursing homes, which found that illumination was likely insufficient for NIF effects as well as visual function [41, 176, 177, 340, 381].

The selected thresholds related to NIF effects are, however, provisional, as there is at present no consensus about the illuminance required to ensure sufficient stimulation of NIF effects for people with dementia. Determining such a threshold can be complex, as the required illuminance depends on factors such as the timing and duration of the light exposure, individual differences affecting sensitivity and exposure, and the contrast in illuminance between day and night [32, 100]. Standards for nursing homes may need to account for reduced photoreception as a result of

ageing and neurodegeneration [107]. Some studies on light conditions in nursing homes [41, 340], and most studies on BLT [236, 239, 313], set their threshold or target illuminances higher than we did in paper 1. However, higher thresholds were not included, as very few measurements exceeded the thresholds we used.

A recent report provided general recommendations for indoor light, based on expert scientific consensus [84]. The recommended minimum melanopic EDI in daytime for supporting NIF effects was 250 lx, measured vertically at 1.2 m. This is slightly higher than the melanopic EDI threshold of 217 lx used in paper 1, and not aimed specifically at older individuals. The chosen melanopic EDI threshold in paper 1 is, therefore, likely a conservative one, and in winter all but one measurement still fell short of this.

As discussed further in section 5.2.2 and 5.2.3, the light measurements do not represent the light exposure patterns of individual nursing home patients, nor the full range of potential illuminances in the living rooms on days with different weather and cloud conditions. However, living rooms are usually spaces where the majority of patients spend most of their day. Furthermore, outside light conditions may be relevant mainly for measurements close to, and facing, a window. Konis [177] showed that, even on clear days in California, facing away from a window reduced the median vertical illuminance from 750 lx (facing the window) to 117 lx, even at a 1 m distance. As demonstrated in paper 1, illuminance in the middle of the room is typically low even when facing a window, in both seasons. In winter, the day-night difference in illuminance was non-significant, suggesting that not much natural daylight reached the middle of the room. Thus, ensuring that the indoor electrical lights are capable of producing sufficient illumination is necessary, particularly in locations (such as Norway) where sunlight is limited during winter (the sun rises around 09:45 and sets around 15:45 in Bergen in December). Measurements taken after astronomical darkness showed that the electrical lights could not provide sufficient illumination. These findings demonstrate a large potential for improvement in this aspect of the nursing home environment, but experimental trials are needed to demonstrate the effects of implementing such improvements.

5.1.2 Did the intervention improve behavioural and psychological symptoms of dementia, and rest-activity rhythms?

Estimated effects of BLT on the CSDD total, NPI-NH total, and acrophase were significant without correction for multiple testing, but only subscales measuring affective symptoms remained significant with this correction. Furthermore, these effects were seen in week 16 only. The absence of robust and lasting effects across outcomes in paper 2 and 3 may indicate that the intervention had no, or only a limited, impact on RARs and BPSD in the current sample. However, it could also be a result of methodological issues, further discussed in section 5.2. Importantly, an insufficient sample size entails low statistical power, i.e., likelihood of detecting an effect if there truly is one [382]. Correcting for multiple testing, while reducing the risk of falsely rejecting the null-hypothesis (type 1 error), also increases the risk of falsely concluding that there was no effect (type 2 error). The choice of whether to give more weight to the corrected or uncorrected result is largely a matter of judgement, and it is recommended to report both [365]. Thus, the fact that results are non-significant after correction weakens confidence in the results, but should also be viewed in light of the sample size. We have emphasised the effects on affective subscales, which remained significant after FDR correction, but also included a discussion of the total scores. The clinical relevance of the observed changes should also be considered.

The one-hour group difference in acrophase shift may be an indication that the light had a stabilising effect on the timing of the circadian rhythm during the darkest months of the year. However, the clinical relevance of this is not clear, particularly in the context that none of the other RAR measures, such as the fragmentation, amplitude, or stability, were changed. The change in NPI-NH total scores exceeds the minimum clinically important difference (MCID) suggested for the NPI by Howard et al. based on expert opinion and the distribution of scores [383]. They proposed a change of 8 points from baseline as the MCID. In the DEM.LIGHT trial, the estimated marginal mean on the NPI-NH in the intervention group was reduced by 9.3 points between baseline and week 16. The estimated marginal mean of the control group did not change. An MCID was not found for the CSDD [384]. The number of

participants who could be categorised as depressed, i.e., had a total score > 8 on the CSDD [53], were reduced from 24 to 11 in the intervention group in week 16. However, there was also a reduction in the control group, from 14 to 8. The fact that there was a larger potential for improvement in the intervention group may have influenced the results. No comparable clinical cut-off could be found for RAR measures. Studies on RAR outcomes typically consider change relative to baseline, or to another group, rather than absolute values [10, 148, 150, 152, 370]. While changes such as lower fragmentation, more stability, higher amplitudes, and better fit to a 24-hour rhythm are considered desirable [10, 148, 150, 370], more research is needed to determine the associations of specific values on these outcomes with health and well-being.

It may be that BLT is only effective for certain types of symptoms, or that the effect can be better detected by certain types of measures. Across paper 2 and 3, the only significant finding after FDR correction was the effect on affective subscales from both the NPI-NH and CSDD. This finding is in line with the fact that BLT is a frequently recommended treatment for affective disorders [385-388]. It is also in line with a number of studies that have found significant improvements in mood following BLT for people with dementia, e.g., [15, 76, 328]. There were no improvements on the NPI-NH subscales “Psychosis” or “Agitation”. Psychotic symptoms are not among the symptoms usually targeted with BLT [146, 236, 239, 303]. Furthermore, the occurrence of psychotic symptoms in the sample was very low; thus, a larger sample would likely be needed to detect changes in such symptoms. The absence of a significant effect on agitation differs from a number of previous trials of BLT for people with dementia, e.g., [320-323], but has also been reported previously [178, 389]. The absence of a significant effect on CSDD Cyclic functions is noteworthy, as it reflects items relating to diurnal variations and sleep (mood worse in the morning, difficulty falling asleep, multiple nocturnal awakenings, and early-morning awakening) that could plausibly be linked to circadian function and sleep-wake disruption. However, the subscale only assesses a limited range of sleep problems and cyclic phenomena.

Improvement of affective symptoms, without any effect on RAR measures in the same trial, has been reported previously [76]. It may be that light impacts mood through mechanisms other than circadian rhythms [27, 304, 308]. It is also possible that RAR measures do not reflect the true impact of BLT on circadian rhythms (further discussed in section 5.2.4). However, it is important to note that many studies have reported findings that diverge from the present results, and that emphasizing the particular pattern of results in one trial, such as the DEM.LIGHT trial, is premature. Overall, the literature includes studies reporting significant effects on RARs [318, 320, 327, 389], and studies that found no effect on affective symptoms [314, 330, 331, 336]. Shochat et al. found a positive association between higher daily bright light exposure and later acrophase [176], which is not in line with our results.

Diverging findings on various outcome measures between trials, and within the same trial, is common in research on BLT for people with dementia [146, 169, 236, 239, 303, 313], and may be linked to the heterogeneity of the samples. We were not able to control for all these sources of heterogeneity. We chose to add dementia severity as a covariate to all analyses, as this was among the most frequently mentioned confounders in previous literature, and a variable we could obtain data on for all participants. We used FAST over MMSE scores, as there were more missing scores for the MMSE. Adding all potential covariates was not feasible, as the list included a large number of variables, which were in many cases uncertain (e.g., dementia subtype), rare (e.g., eye disease), or complex (e.g., medications used and comorbidities). A number of individual differences not measured in the DEM.LIGHT trial, including genetic variation and chronotype, also affect people's sensitivity to light [104].

5.1.3 What was the effect of treatment duration and timing?

The DEM.LIGHT trial was longer than most previous studies on BLT for people with dementia, which have rarely lasted for more than 8 weeks [146, 236, 313]. A few studies of longer duration have found that all-day ambient illumination improved measures of BPSD (e.g., [15, 76]), and one of these reported that effects appeared to be cumulative over time [76]. However, trials of 8 weeks or less have sometimes also

resulted in significant improvements [320, 321, 323, 327, 329]. It is possible that the significant effect on affective symptoms was observed in week 16 because more than 8 weeks of treatment were needed to elicit a response. However, it is not clear, then, why the effect did not remain in week 24.

The follow-up in week 16 occurred during winter (January and February), while the 24-week follow-up was in spring (April). A larger effect of BLT on agitation and sleep during winter has been reported previously [330]. Variations in natural daylight may have impacted the results. December and January are the darkest months of the year in Bergen, where the trial was conducted. The occurrence of seasonal affective disorder appears to peak during this time [390], and greater levels of circadian disruption among people with dementia have been reported during winter [174].

However, the group difference in change from baseline to week 16 on affective subscales was largely comprised of a relative reduction of these scores in the intervention group, which then returned to baseline levels in week 24. In comparison, control group scores on affective subscales remained relatively stable in week 16. This is not consistent with the hypothesis that BLT prevented a temporary increase in affective symptoms during winter.

5.2 Methodological considerations

5.2.1 Delivery of the intervention

Previous studies on BLT for people with dementia have often used light boxes [236, 237, 313]. There are a number of benefits to this approach over ours, such as lower initial cost, more opportunity for individualisation, and greater precision in terms of the illuminance, spectral composition, and exposure duration. However, ceiling mounted dynamic lights also offer substantial advantages. Perhaps most importantly, it does not require care personnel to set up and monitor the treatment. While individually administered BLT with light boxes may be feasible for short term trials, or for treatment of a few individuals, it is less likely to be implemented as a long-term strategy in dementia units, where staff availability is a common challenge. For

research purposes, ambient illumination is less noticeable than a light box, and may therefore to a larger extent allow blinding. Ceiling mounted light solutions also allow people to move freely, enable longer durations of exposure, and can be programmed to provide varying illuminance and CCT throughout the day. Alternatives such as wearable visors may provide the option to tailor the light exposure while also allowing the user to move around, but the comfort level and feasibility in people with severe dementia, who may remove such devices, needs to be established.

Natural daylight provides light at much higher illuminances than electric lights, without the levels of discomfort electrical sources might produce at the same illuminances, and at no cost. People may also have a preference for light from natural sources [391]. Konis et al. found significant reductions of CSDD scores among nursing home patients after 2-hour morning exposures to natural daylight for 12 weeks [392]. However, paper 1 demonstrated that current architectural designs do not allow enough daylight into the common rooms. Spending time outdoors every day, especially for extended periods of time, is likely not a feasible option in most dementia units, especially during winter. Thus, in order to rely on natural daylight, deliberate choices need to be made both in the construction of nursing homes, and in the placement of seating.

Regardless of delivery method, determining the optimal light treatment parameters for people with dementia remains an important research goal. It may be that higher illuminances and/or CCT are needed to induce the benefits of increased daily illumination for individuals with dementia. However, similar illuminance to the DEM.LIGHT trial (1000 lx) was used by van der Lek et al. [15], who found significant effects of all-day ambient illumination in a long term (median 15 months) study. Figueiro et al. [76] used lower illuminances (350-850 lx, with a target CS of 0.4) in their long-lasting (25 week) study of all-day ambient illumination, in which they found significant effects. Some effects of light also depend on the timing of the exposure relative to the individuals' circadian rhythm (as described in section 1.1.2). It is therefore possible that a more individualised approach is beneficial. Cremascoli et al. used DLMO to tailor their intervention to each individual [314]. It is noteworthy

in the present context that they reported an effect on DLMO timing, and on the relationship between DLMO and sleep, but not on non-parametric RAR outcomes or neuropsychiatric symptoms [314]. In other words, they saw an effect on the melatonin rhythm that was not accompanied by effects on the outcomes described in the present thesis. However, the trial lasted only about 4 weeks, and the results were preliminary.

A more individualised approach could also entail providing BLT to only those who have substantial levels of BPSD and/or sleep and circadian rhythm disturbances at baseline. Although investigating the unit-wide effect of BLT in a heterogenous sample, as we did, has high relevance to real-world settings, it may require a larger sample size to detect significant results. Individualising ambient BLT in nursing homes may be challenging, as patients often spend their time in common areas with other patients.

Combining daytime BLT with other interventions, such as walking [393], melatonin [15], or increased daytime activity along with reduced night-time disruption [394], could potentially be useful strategies for improving RARs and BPSD. In the DEM.LIGHT trial, reducing light at night was not part of the intervention. However, we know that it can have a powerful influence on circadian rhythms, especially if it occurs near the body temperature nadir [94]. Regardless of the intervention used, addressing individual needs and triggers will remain essential in clinical practice.

5.2.2 Light measurement

Consistency and precision in measuring and reporting light exposures is an important step towards ensuring replicability and enabling synthesis of research on light, and a necessary precondition for providing practical recommendations [74, 395]. We therefore strived to conduct and report light measurements in accordance with recent recommendations. However, both in the field study reported in paper 1, and in the DEM.LIGHT trial, light was measured in a limited number of positions, and in specific conditions. Multiple sources of variability are therefore unaccounted for. Vertical illuminances were measured on cloudy days, in the centre of the room, in

four directions, and at 1.2 m above the floor. Illuminance will naturally be higher closer to a window, especially in the presence of direct sunlight [177]. Conversely, the illuminances reported are likely overestimated for days with denser cloud coverage, and for placements farther from windows. Measurements for paper 1 were also taken with ceiling lights turned on, with no dimming, which is not necessarily representative of everyday use. The measurements thus reflect estimates of average illuminance at the approximate eye level of a seated person, on days with fairly typical cloud coverage. Individual light exposures will depend on a large number of additional factors, such as the amount of time spent napping, personal preferences for brightly lit or dimmer areas, retinal health, and time spent outside of the nursing home.

The choice of measurement unit for light in the context of NIF effects is a source of some debate. Proponents of the CS argue that this metric better accounts for the actual sensitivity of the human circadian system, and that no model based on the response of a single photopigment (melanopsin) can adequately represent the potential of a light exposure to stimulate NIF effects [43, 77]. We nonetheless decided to follow the official CIE recommendation, and the research suggesting that melanopic EDI is a good predictor of NIF effects [71], although recognising that this is a topic of ongoing research.

5.2.3 Achieved light exposure in the intervention group

The target corneal illuminance during the peak of the intervention period (10:00 to 15:00) was 1000 lx (in terms of photopic illuminance) at 1.2 m. Measurements in the centre of the room reached this target, with the exception of one unit, which only achieved a mean of 722 lx. However, even this lowest value for the intervention group was well above the highest illuminance measured in the control group (368 lx). It was also well above the average inward facing illuminances in dementia units as reported in paper 1 (192 lx in summer and 125 lx in winter). With a mean of 1039 lx, the illuminance of the intervention condition was also higher than illuminances reported by previous studies of light in nursing homes [41, 175, 176].

None of the participants included for analysis in paper 2 and 3 spent less than 30 minutes a day on average in the intervention area during the peak exposure period, according to the estimates of proxy-raters. Participants in the intervention group spent on average 3.6 hours in the intervention area. However, this estimate is based on retrospective reports. Estimating the individual light exposure of each participant more precisely may be important for the interpretation of results. For instance, Munch et al. [178] found no significant effects of an 8-week dynamic lighting intervention in people with severe dementia. However, when splitting the sample based on the median daily light exposure (417 lx, measured by actigraphs), there were group differences on measures of quality of life, sleep timing, RAR amplitude (in men), and emotions. The intervention used was quite similar to that used in the DEM.LIGHT trial, with peak illuminance of 1000 lux, 6500 K between 11:00 and 16:00. It is possible that other factors, such as individual preferences for spending time in more brightly lit areas, can contribute more to individual differences in light exposure than the intervention.

Individual light exposures can be measured using ambulatory photosensors worn by participants, for instance on the wrist, as a clip pinned to clothing, on spectacles, or on a lanyard around the neck [173, 396, 397]. The actigraphs we used also have light sensors. However, our experience with using actigraphs in the DEM.LIGHT trial demonstrates a challenge with using a wrist worn device for light measurement. As many participants became preoccupied with the actigraph, we opted to cover it under the sleeve of their shirt or sweater as much as possible. This would naturally obscure light measurements. Additionally, the illuminance measured at the wrist would deviate from the illuminance at the cornea in most positions. Using devices worn on glasses or headbands could better approximate corneal illuminance, but would carry the same risk of removal by participants, and increase the cost of the trial. Furthermore, ensuring proper wear of an additional device would add to the work load of the nursing home staff.

5.2.4 Assessing the effect of bright light treatment in the nursing home

Multiple outcomes

A variety of outcomes have been reported in trials of BLT in the nursing home, including actigraphy measures of sleep and RARs, proxy-rated measures of sleep and BPSD, and, less commonly, observations of mood and agitation [146, 169, 236, 239, 303, 313]. The DEM.LIGHT trial also included multiple outcomes, due to the heterogeneity of findings reported previously, and the potential for multiple beneficial effects of BLT.

Furthermore, utilising multiple measures may provide insights about the relationship between different outcomes. It could be, for instance, that light affects BPSD indirectly through improvement of circadian rhythms and sleep. Although we did not obtain results that allowed us to investigate this hypothesis, we can make some observations regarding the differing results on various outcomes. The difference in results for affective symptoms and RARs may indicate independence between the outcomes, but it could also be a result of measurement methodology. In another paper from the DEM.LIGHT trial that is not part of the current thesis, we reported that the intervention had an impact on proxy-rated, but not actigraphy-measured, sleep [344]. Similarly, RARs were measured with actigraphy, whereas BPSD were proxy-rated. This may indicate that the proxy-rated measures were more sensitive to the effects of the intervention, or that they introduced a common source of bias, such as proxy-raters being able to guess the condition.

Correlations between different outcome measures at baseline were included as secondary analyses in paper 2 and 3. In both papers, many outcomes correlated significantly. However, the actigraphy sleep measure (WASO) only correlated weakly with the NPI-HN total and the CSDD Cyclic functions, whereas the proxy-rated sleep measure (SDI total) correlated moderately and strongly, respectively, with these same outcomes. In addition, the SDI total correlated (weakly) with the CSDD total and NPI-NH Agitation. Proxy-rated outcomes were thus more similar to each other than to the actigraphy outcomes.

The use of multiple outcome measures raises the risk of spurious results. Conducting multiple significance tests increases the probability of a type 1 error, i.e., falsely rejecting the null-hypothesis. The effects of treatment were estimated with and without [365] FDR correction, which adjusts the significance level according to the expected proportion of false positives [364]. However, this correction was done for each paper separately, not for all outcomes included in the whole trial. With a relatively low sample size, using more conservative significance corrections would likely have eliminated any significant findings, increasing the risk of falsely accepting the null hypothesis (type 2 error). While the former often is viewed as a larger concern in research, it is not unproblematic to falsely conclude that a low risk and potentially helpful treatment is ineffective.

Assessing behavioural and psychological symptoms of dementia

BPSD refers to a wide range of symptoms that can be both hard to distinguish, and to assess accurately. Many of the participants in the DEM.LIGHT trial were not able to communicate verbally. As a consequence, we had to rely on staff who knew the participants well to observe their symptoms. Both the NPI-NH and the CSDD are proxy-rated instruments. Thus, interpretations of behaviours (e.g., pacing or verbalisations as expressions of anxiety, irritability, increased activity, or something else), depend on assumptions made by the proxy-rater. Some trials that have found an effect of BLT on agitation have utilised instruments aimed specifically at detecting agitation, such as CMAI, with scores based on observation of a larger number of specific behaviours [320-322]. The categorization of behaviour also depends on the instrument used. “Irritability” is, for instance, part of the Mood-related signs subscale on the CSDD, but included in the Agitation subscale on the NPI-NH. Two CSDD subscales were omitted from subscale analysis due to inherent challenges with judging the items they contained. Multiple proxy-raters expressed difficulties with judging the presence and source of these symptoms. “Physical signs” was left out due to the high occurrence of somatic illness and problems with motor-functions, and “Ideational disturbance” was left out because participants were largely unable to verbally communicate such ideas. The subscale “Behavioural disturbance” was analysed, but also contains items (psychomotor retardation, physical complaints, and

loss of interest) that may be subject to confounding from somatic illness and/or an inability to verbally communicate interest and participate in activities.

Assessing rest-activity rhythms and circadian rhythms

Actigraphy is the most common method for assessing circadian rhythms in studies of BLT for people with dementia [236-239]. It offers a non-invasive and labour-effective way to monitor rhythms over extended periods of time. However, the RAR is only partly influenced by the endogenous circadian rhythm of the SCN. This may be particularly true for people with dementia, for whom the relationship between different circadian rhythms is often altered [398, 399]. The terms circadian rhythms and RARs are therefore not used interchangeably in the present thesis. Actigraphy simply measures physical movement, and RAR measures aim to describe aspects of the activity pattern over time. Thus, factors such as nursing home routines, physical disability, and illness that limits mobility, may mask the influence of the endogenous circadian rhythm. Including measures such as melatonin secretion or CBT may have provided a better approximation of endogenous circadian rhythms, and allowed us to investigate the relationships between various rhythms. While we did attempt to use a telemetric core temperature measure, we were unable to collect sufficient data, due to participants having trouble swallowing capsules, as well as technical issues with the equipment. However, RARs are not only of interest as a proxy for circadian rhythms, but have been directly linked to important outcomes such as morbidity, depressive symptoms, and cognitive decline, also in people with dementia [151, 154, 378, 400, 401]. As discussed in the introduction, there is overlap between traditional sleep outcomes and RAR outcomes. Furthermore, sleep problems and night-time behavioural disturbances are also examples of BPSD. The activity patterns described by the RAR could therefore be interpreted from a variety of perspectives, and it is challenging to draw clear distinctions between sleep, BPSD, and RARs. This, however, does not in itself limit the utility of RARs as an outcome measure.

5.2.5 Randomisation and control

Paper 2 and 3 investigated a causal relationship between BLT and clinical outcomes. A placebo treated control group was therefore used, with the aim of ruling out

alternative explanations for any observed changes, increasing the internal validity of the results. Potential confounders should ideally be distributed equally between the groups, so that any observed group difference can plausibly be attributed to the treatment. Cluster randomisation involves particular susceptibility to certain sources of bias [402-404]. With clustering, accidental factors that affect the outcomes tend to pertain to multiple participants at the same time, who all belong to the same condition [403]. Hence, even with randomisation, there is a remaining chance of systematic differences. The following subsections will address the adequacy of the control condition as a comparison group.

Balancing the groups

Randomising the allocation of participants is done to prevent selection bias, i.e., systematic baseline differences which may impact estimations of treatment effect. A concern particular to cluster randomised trials is that bias can be introduced if participants are selected after their cluster has been assigned to a condition, preventing allocation concealment [405, 406]. Knowing which condition a participant would be allocated to could, for instance, lead researchers to preferentially include participants likely to achieve the desired outcomes in the intervention condition. Improper allocation concealment has accordingly been shown to produce inflated estimates of treatment effect [407]. In the DEM.LIGHT trial, random number generation was used to assign units to conditions, and all participants at the unit were included as long as they met the inclusion criteria. While selective application of inclusion criteria, or differential sensitivity to objections from participants, were still possible, only three participants were excluded before the trial based on the criteria. There were no apparent differences between the groups in terms of participants refusing actigraphs or testing. As recommended [407], tables of descriptive statistics at baseline were included in paper 2 and 3, allowing readers to compare important clinical and demographic characteristics between the groups. Baseline differences in scores on outcome scales were noted and reported in paper 3. Most notably, 14 participants in the control group and 24 in the intervention group scored 8 or above on the CSDD at baseline, and could thus be classified as clinically depressed [350]. We included baseline scores on the dependent variables as covariates in the analyses

of BPSD outcomes, but this does not rule out the possibility that the intervention group had more room for improvement and/or was more affected by regression toward the mean due to higher baseline scores on the outcome measures. Statistical testing for group differences at baseline is generally discouraged [407, 408], but was conducted for outcomes in paper 3 when requested during peer review.

Unbalanced groups can also arise if participants or data are lost at unequal rates in the two groups, referred to as "attrition bias" [404]. This can occur if there are group differences in important characteristics, such as severe illness. With cluster randomisation, there is a possibility that nursing home units differ in their capacity to care for severely ill people, or have differing intake criteria. Attrition bias can also arise as a result of response to treatments. In the case of BLT, there is no reason to suspect that the treatment could cause adverse reactions leading to death or severe illness. Conversely, there is no evidence to suggest that BLT prevents such adverse events. In the DEM.LIGHT trial, a total of six participants were lost in the intervention group, and ten in the control group, which does not amount to large group differences in attrition. There is, however, a possibility that other factors, such as staff availability for questionnaire completion, affected clusters differently at one or more time points. The use of multilevel regression ensures that remaining data from other time points are still used, somewhat reducing the bias this entails compared to analysis methods that exclude entire cases if there is missing data (case-wise deletion) [409].

Blinding

Knowledge of group allocation can influence the expectations, behaviours and perceptions of participants, researchers, and carers in ways that bias treatment estimates [410]. As a result, efforts are made to keep those involved in the trial unaware of which participants were assigned to each group, i.e. "blinded" [411]. The degree of blinding varies, with double- or triple-blinded trials sometimes concealing allocation from participants, staff, researchers, outcome assessors, and sometimes even those analysing or reporting data [412]. In practice, however, double blinding is not always feasible [410, 411]. The DEM.LIGHT trial was single-blinded, meaning

that the researchers conducting the trial were aware of condition assignment. Detection of condition assignment by the participants themselves was not considered a risk, due to the degree of cognitive impairment and memory loss. However, outcome assessors and other staff may have guessed their group allocation. This knowledge may affect interactions with patients, or other aspects of their environment, leading to an effect known as “performance bias” [404, 411]. Carers could, for instance, perceive and respond to patients more positively if they expect and notice positive changes which they attribute to the treatment. A related risk is the possibility of outcome assessment being influenced by knowledge of group allocation, sometimes referred to as “detection bias” (also called “observer bias” or “ascertainment bias”) [404, 413]. This is particularly relevant to subjective measurements, such as the proxy-rated measures reported in paper 3 [410]. If proxy-raters were expecting improvements of BPSD, they may have been more likely to notice, and thus report, such improvements when asked to recall symptoms.

Visible interventions, such as BLT, present a challenge in terms of concealment. The control condition in the DEM.LIGHT trial involved exchanging the light sources in existing light fixtures, whereas the intervention entailed construction work and noticeably altered light. As control units and intervention units were never in the same nursing home, it can be argued that staff could not compare the two conditions. Furthermore, we did not inform the staff of which aspects of the light we would be altering, or what outcomes were most likely to improve. Thus, outcome assessors and other staff in the control group were not necessarily expecting a large change. However, the units in the intervention group clearly received a more noticeable and convincing treatment. Installing similar light fixtures in control group units was not economically possible.

A survey was administered after the end of the trial (not published due to very inconsistent response rates between units), asking outcome assessors and other staff which condition they believed their unit was assigned to. The number of people who responded was unequally balanced between units and conditions, and may not be representative of the opinions of all staff. Regardless, the responses give some insight

into the perceptions of staff members. In the intervention group, 19 people responded, and 14 correctly ascertained that they belonged to the intervention group. In the control group, 2 out of 12 respondents guessed that they were in the intervention group. Most respondents thus correctly identified which group they belonged to when asked directly at the end of the trial.

5.2.6 Sample and generalisability

The sample of nursing homes in paper 1 consisted of all municipal nursing homes in Bergen with a long-term dementia unit. Thus, the reported findings are representative of a broad range of buildings in a variety of locations, and may plausibly generalise beyond the municipality, and specific type of care facility (i.e., dementia units).

The nursing home dementia units included in the DEM.LIGHT trial were located throughout Bergen municipality, in both central and more rural areas. We strived to ensure that the units all had a comparable number of patients (~8-10 individuals), and only one unit had to be excluded on this basis. The inclusion criteria did not contain items that would set the sites apart from the typical dementia unit, and factors such as orientation and construction year of the buildings varied between the units. However, we necessarily only included nursing home units that expressed an interest in participating. Hence, it may be that the included units had higher staff availability or a particular interest in the intervention.

A strength of the DEM.LIGHT trial is that it was conducted in a clinical setting, which provided ecological validity and clinical relevance. Although applying more stringent inclusion criteria and controlling extraneous factors could improve internal validity, a naturalistic approach means that the results, if valid, are more likely to be applicable in routine clinical practice [414]. However, certain characteristics of the sample and study setting should be considered before generalising to a broader context. The participants were on average 85 years old, and had severe dementia. The median MMSE score was 4, which corresponds to severe cognitive impairment [356], and the majority (91%) has a FAST score of 6 or 7, with 7 indicating a degree of functional impairment characteristic of the most severe stage of AD. The fact that the

research was conducted in specialised dementia units also entails a higher likelihood that participants had challenging symptoms or severe dementia. A slight majority (55%) had AD, but many also had other, unknown or mixed dementia types. In other words, the sample was both heterogenous and characterised by severe illness and a high degree of dependency. Although there are mixed results regarding the impact of these variables, they may limit comparisons with trials that include younger or healthier participants, or people with a specific dementia subtype. In Norway, around 80% of nursing home patients have dementia [162], but the findings may not necessarily generalise to care settings where dementia is not as prevalent. In addition to severe dementia, participants were frequently diagnosed with comorbidities, which may limit both the ability to elicit a beneficial response to treatment, and to detect change.

The trial was conducted in Norway, mainly during winter months. It is possible that standard pre-intervention light conditions, as described in paper 1, are different in places with more sunlight. The intervention used in the DEM.LIGHT trial might therefore not constitute as much of a change in other geographical locations and/or in buildings with large window surfaces.

Participants used on average 2.85 different psychotropic medications at baseline, with about half the sample using antidepressants and/or antipsychotics. About a third of the sample used benzodiazepines, and over 10% used hypnotics or sedatives. Both intended effects (such as reduction of depression, anxiety and agitation) and unintended effects (such as daytime sedation) may have interfered with the response to BLT, and with our ability to accurately assess symptoms and measure change. For ethical reasons, treatment was allowed to continue as usual, although we asked that no unnecessary changes were made to medications during the trial.

5.2.7 Clustering and sample size

In the initial DEM.LIGHT protocol, the plan was to use ANOVA analysis. The number of clusters and participants needed was calculated based on this assumption. However, due to the amount of missing data, we opted instead to use multilevel

models. By adding a random effect for individuals, these models account for the correlation between scores from the same participant at different data collection points. Ignoring repeated measurements or other types of clustering of the data could lead to an underestimation of the standard error estimates if the outcome depends on the clustering [415]. Ideally, we would also control for the clustering comprised of dementia units, by adding another random effect (level) for units. However, we did not have a sufficient number of clusters to do so. Recommendations for the necessary number of clusters vary, but between 10 and 30 is often cited as a minimum [415].

The sample size was insufficient for subgroup analyses (or interaction effects) by important variables such as dementia diagnosis, dementia severity, psychotropic drug use, and more. The aim was to include 80 participants to allow for drop-outs, but the number of participants at baseline was 69. Furthermore, some actigraphy recordings were not used, due to non-compliance or technical failure. The number of complete actigraphy recordings at baseline was 61. Due to attrition (mainly due to deaths, as well as some relocations to other units) and missing or excluded data, the numbers were lower at later data collections. At the last follow-up (week 24), data from 51 and 46 participants were included in the analyses for paper 2 and 3, respectively. While this is still higher than many previous trials of BLT for people with dementia, it may not have been sufficient to achieve statistically significant results. Moderate effect sizes may not have been a realistic expectation on which to base sample size calculations. Larger samples may be necessary to detect smaller effect sizes, or effects that only occur in a subset of participants. Recruiting more clusters was unfortunately not feasible due to the cost of the LED units used for the intervention.

5.3 Ethics

The data collection procedures for paper 1 did not impose any burden on staff nor patients, and no patient data were collected. However, as we did enter spaces that constitute people's residences and work places, we called staff at each nursing home to ask permission to conduct measurements. In advance, permission was also

provided by Bergen municipality to approach all municipal nursing homes about conducting light measurements at their facilities.

The remainder of this section concerns the DEM.LIGHT trial, described in paper 2 and 3. The study was conducted in line with the Declaration of Helsinki, and approved by the Regional Committee for Medical and Health Research Ethics, Health Region South East (project no. 2016/2246). Vulnerable groups, such as people with dementia, require specific protections to prevent harm, and to enable self-determination, privacy, and dignity. A few key aspects of ethical research will therefore be discussed in the context of research with people who have dementia.

5.3.1 Consent and representation

Acquiring the informed consent of participants is a an ethical and legal obligation in clinical research [366]. In order to do so, researchers must inform potential participants about all relevant aspects of the study, including the purpose, methods, potential benefits and risks, as well as the option to withdraw consent at any time. Valid consent should be given voluntarily, unaffected by coercion, by someone with decision-making capacity [416]. The cognitive impairment experienced by people with dementia will, to varying degrees, affect their ability to comprehend, carefully consider, and communicate choices about their own health and intentions. At the same time, including people with dementia as participants in clinical research is key to improving treatment and care. Despite the recognition that research with healthy adults may not generalise to people with dementia, this group is often excluded from research due to challenges such as polypharmacy, multimorbidity, impaired cognition, and behavioural symptoms. To enable inclusion of people with reduced decision-making capacity, presumed consent can be provided by a legally authorised representative on behalf of the participant [366]. The participants themselves should also be given information tailored to their abilities, and given the opportunity to dissent. The capacity to consent may vary across time, context and different aspects of a trial; thus, researchers must be sensitive to the current state of a potential participant [417].

In the DEM.LIGHT trial, legal guardians gave presumed consent on behalf of the participants. Some participants were also given information in an adapted manner, based on conferring with the nursing home physician and meeting with the participant, and as such could decline to participate. Researchers and staff were attentive to verbal and non-verbal expressions of dissent by all participants. This could at times be challenging, as many of the participants could be upset or agitated for reasons unrelated to the procedures, or unable to express discomfort or dissent in ways that researchers could interpret. For this reason, it was important that staff who knew the participant well were also informed about the importance of allowing the participant to withdraw if they judged this to be their intent. Most measures were assessed by proxy-raters, but some participants objected to actigraphs, temperature capsules, and cognitive testing with the MMSE, at certain points. Some actigraphs were removed due to apparent discomfort or preoccupation with the device. The option to withdraw also pertained to leaving the intervention area, although participants were generally not aware that the lights were altered. Procedures for acquiring consent, and for storing data, are described in section 3.2.9.

5.3.2 Risk of harm

The safety of BLT is outlined in section 1.5.4. We were heedful of signs that the light was causing distress or negative effects. Nursing home staff were asked to report any negative effects that they thought might be a result of the intervention, and contraindications for light treatment were considered in conference with resident physicians at the nursing homes. No adverse effects were reported, and no worsening of symptoms as a result of the intervention was detected during data analysis. With the exception of 1-3 days in which the living rooms were unavailable due to installation of the light panels, the intervention did not interfere with daily routines. Staff were encouraged to continue care as usual, including necessary pharmacological treatment.

The experiences of nursing home staff should also be considered, as the treatment and trial procedures affected them as well. Programming of the lights was done in cooperation with staff to ensure that the light conditions were not aversive. Data

collection procedures, particularly proxy-rated questionnaires, required an investment of time from the staff assisting us. However, identifying treatments that improve BPSD and rest-activity rhythms in nursing homes could also benefit staff, as it has the potential to ease the burden on caregivers.

5.4 Clinical implications and future directions

The results from paper 2 and 3 do not provide a basis for recommending all-day ambient BLT as a way to improve RARs or BPSD in people with dementia. There was a reduction of affective symptoms after 16 weeks, which remained after correcting for multiple testing, but this effect was transient. It was also accompanied by multiple non-significant results on other BPSD and RAR outcomes, and at other time points. More research is therefore needed to confirm the effect on affective symptoms. However, it is premature to dismiss the hypothesis that BLT is an effective non-pharmacological treatment for people with dementia. Results from paper 1 showed that the illuminance in dementia unit living rooms was inadequate according to recommendations for NIF effects. Daily light exposure among nursing home patients has been linked with sleep, mood, and RARs [176, 178-180], but more experimental studies are needed to establish a causal relationship. Trials with larger samples and/or more stringent inclusion and exclusion criteria are needed to determine if the effect of BLT depends on factors such as dementia severity, comorbidities, or dementia subtype. It is also relevant to investigate the impact of BLT at earlier stages of dementia, or even before symptom onset, as disrupted circadian rhythms and sleep can impact dementia symptoms years later [10, 123, 149, 218, 254, 255].

Laboratory studies and clinical trials investigating the timing, illuminance, duration, and delivery method necessary to elicit NIF effects in elderly people with dementia are needed, and should inform future clinical trials. More knowledge about the extent to which neurodegeneration impairs the ability to elicit NIF responses is needed. Adherence to recent guidelines for measuring and reporting light exposures for NIF effects will benefit the field by allowing relevant comparisons across trials. Using

individualised light measurement devices may provide insights about the light parameters needed to elicit effects. Future studies may also investigate whether inclusion of additional components, such as reducing night-time illumination, or adding stimulating daytime activities, increases the effectiveness of BLT. The impact of ambient BLT on staff should be investigated.

Developing and testing methods for assessing circadian rhythms, sleep, RARs, and BPSD in people with dementia is necessary in order to conduct research on interventions targeting these outcomes. Importantly, establishing which measures are most related to the well-being of people with dementia, and sufficiently sensitive to change, is a prerequisite for conducting relevant and useful research. It could be, for instance, that objective or observational measures, which depend to a lesser extent on recall and subjective judgement, are more suitable for assessing behavioural changes in this population. Although challenging to implement, ensuring sufficient blinding of outcome assessment is recommended to reduce the risk of bias [236, 303, 313].

Results from paper 1 indicate that there is a large potential for improving the illumination in nursing homes. Although findings from clinical trials investigating BLT in people with dementia have been mixed [236, 237, 313], maintaining a day-night contrast in melanopic EDI is recommended to support health and well-being, based on decades of research [84]. Thus, designing nursing home environments to maximise light exposure during the day and reduce light at night is likely to benefit patients and staff. The DEM.LIGHT trial demonstrated that implementing a dynamic lighting scheme in dementia units was possible, and well tolerated at ~1000 lx, 6500 K. Building design and strategic placement of seating relative to windows can also have an impact on light exposure, and spending time outdoors is encouraged when possible. As increasing daytime light exposure is a low-risk intervention, it is generally recommended for both visual function and NIF effects.

5.5 Concluding remarks

This thesis has presented results from a 24-week cluster randomised controlled trial and from a field study investigating light conditions in dementia units. Results from the field study showed that illumination in nursing home dementia units was insufficient according to recommendations for NIF effects. Results from the trial showed that proxy-rated affective symptoms were reduced after 16 weeks of BLT. However, there were no significant effects on other BPSD, at other time points, or on RAR outcomes, after controlling for multiple testing. Several methodological challenges, such as an insufficient sample size, and a study population with complex health conditions, may have limited our ability to detect an effect of the intervention. Although no clinical recommendations can be made on the basis of the current results, the theoretical foundation for BLT, as well as a number of previous trials, still suggest that this is a topic worthy of further research.

6. References

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Insufficient melanopic equivalent daylight illuminance in nursing home dementia units across seasons and gaze directions

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Adequate illumination plays an important part in providing a healthy environment for nursing home patients with dementia. With increasing awareness of non-visual responses to light, new approaches to quantifying illuminance have emerged. In the present study, we assessed the illuminance in nursing home dementia units in terms of melanopic equivalent daylight illuminance, a metric which aims to quantify the non-visual physiological effects of light by weighing irradiance according to non-visual photoreception. It is among the most comprehensive studies of light conditions conducted in dementia units in terms of melanopic equivalent daylight illuminance to date, and the first to elucidate seasonal differences in melanopic illumination. Light conditions were assessed in all 15 nursing homes with dedicated long-term dementia units in Bergen municipality (60.39°N), Norway, during summer and winter. Results indicated that seasonal differences and gaze direction had some impact on melanopic equivalent daylight illuminance, but most measurements still fell below even conservative recommendations across seasons. The findings indicate a need for additional light sources that can compensate for limited natural daylight in dementia units. The ubiquity of insufficient melanopic equivalent daylight illuminance in dementia units suggests a role for lighting interventions in future research seeking to improve entrainment, sleep and mental health of dementia unit residents.

1. Introduction

Exposure to light has important regulatory functions, affecting numerous aspects of human health and behavior, such as sleep–wake behavior, cognitive performance and

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mood.[1] Illumination is therefore an important aspect of the indoor environment, particularly for people who spend most or all of their day indoors, such as patients in dementia units. Many of the non-visual effects elicited by light are linked to circadian rhythms; behavioral and physiological cycles of approximately 24 hours that help us anticipate and adapt to the changing demands of our environment. In mammals, circadian rhythms are adjusted ('entrained') daily by external stimuli, especially daylight.[2,3]

The retina contains a specialized type of non-visual cell, the intrinsically photoreceptive retinal ganglion cell (ipRGC) that projects directly to the hypothalamic suprachiasmatic nuclei, the master clock,[4] as well as other targets, eliciting circadian entrainment as well as acute effects on mood and alertness[1,5,6] in response to retinal illuminance. The ipRGCs receive input from rods and cones, but also have the ability to detect light independently via the light sensitive photopigment melanopsin.[7–9] Collectively, the effects of light that are independent of the visual perception of our environment (image formation) are referred to as non-visual, or non-image forming, responses.[1,10]

Maximal non-visual responses, such as melatonin suppression, increase in core body temperature and alertness, are elicited by short wavelength light (about 460–490 nm).[11–15] Other factors such as the timing, illuminance and duration of the light stimulus will also determine the response.[16] In addition, the response partly depends on light exposure history of the individual.[2] Research suggests that an adequate day–night light contrast is necessary to establish a well-adjusted circadian rhythm (i.e., ensuring sleep at night and wakefulness during daytime). Low illuminance during the day may result in sensitization to the disruptive effects of light at night, whereas high levels of daytime illuminance may protect against this.[2,17,18]

Ageing leads to changes in eye physiology, such as reduced lens transmission and decreased pupil size. By the age of 45 years, circadian photoreception is half that of a 10-year old, and at 95 years it is 10 times lower.[19] Paradoxically, studies have found that older individuals, particularly nursing home patients, are exposed to far less bright light than younger people.[20,21] For nursing home patients, poor lighting has been associated with an increased risk of falls,[20,22] which is a common cause of severe and sometimes fatal injury.[23] Furthermore, circadian disruption is implicated in a wide range of health outcomes, including mental disorders and sleep problems.[24–26] Sleep problems are common among nursing home residents[27] and people suffering from dementia,[28] and have been linked to increased morbidity and mortality, cognitive decline[29] and additional symptoms such as agitation, hallucinations, depressed mood and disturbed appetite.[30,31] Studies have found that exposure to bright light can improve sleep and entrainment of circadian rhythms,[32] as well as ameliorate aggressive behavior and depression[33–35] in people with dementia, suggesting that dementia patients are exposed to inadequate levels of illuminance.

Standards for indoor illumination are often intended to ensure visual function and comfort, and vary in terms of the task to be performed and the population. They also typically refer to horizontally measured illuminance on surfaces, whereas the eye is most frequently vertically oriented, and thus receives less direct illumination from overhead light sources.[36] Furthermore, lighting standards are normally expressed as photopic illuminance (irradiance weighted according to perceived brightness for a standard human observer, with a peak in sensitivity at 555 nm) and do not account for the fact that non-visual responses to light are most sensitive to shorter wavelengths (~480 nm).[15] Although determining the most suitable approach to

measuring the non-visual impact of light is a subject of ongoing debate and research, illuminance quantified according to its impact on melanopsin has been shown to be a better predictor than photopic illuminance of non-visual responses such as melatonin suppression[37] and alertness.[38] This quantification has been adopted by the International Commission on Illumination (CIE) in the form of the SI-compliant metric 'melanopic equivalent daylight (D65) illuminance' (melanopic equivalent daylight illuminance, EDI), based on previous work by Lucas *et al.*[39] and Enezi *et al.*[40] A reanalysis of 19 laboratory studies[41] showed that melatonin suppression, circadian resetting and alerting responses could be accurately predicted by melanopic EDI, supporting its utility as a basis for guidelines. Notably, other metrics have been proposed, such as Circadian Stimulus (CS), which is based on nocturnal melatonin suppression in response to light.[15,42]

Although the importance of non-visual responses is increasingly acknowledged by international authorities on illumination, research has still not reached consensus with regards to developing standards/recommendations to account for these responses.[43–45] Standards, such as those provided by the CIE and the Illuminating Engineering Society of North America (IES) provide recommendations regarding lighting for older people in terms of photopic illuminance of a horizontal surface, reflecting requirements for visual performance.[45,46] For these purposes, 200–1000 lx are considered adequate.[45,46] The WELL Building Institute recommends 240 equivalent melanopic lx (EML, equivalent to about 217 melanopic EDI).[10,43] A previous version of this recommendation was also used as a threshold in a 2018 field study of melanopic illuminance in nursing homes.[47] In addition, the Underwriters Laboratory (UL)[42] gives recommendations in terms of CS. While not directly comparable to the EML, the suggested CS of 0.3 is achieved with an EML of 240 for a variety of common light sources, including daylight.[42] The UL guideline states that 500 lx (photopic) should be sufficient to achieve this CS in 90% of commercially available light sources.

Most previous studies on nursing home illumination have reported threshold values in terms of photopic illumination,[20,24,48,49] ranging from 750 to 2000 lx. Consequently, we will relate current results to the melanopic EDI threshold of 217 lx (240 EML)[10] and to two photopic illumination thresholds; 300 lx reflecting the lower end of the CIE recommendation for older people, and 500 lx as it is estimated to satisfy a CS of 0.3 in the majority of cases.[42]

Among the few existing studies evaluating nursing home illuminance in terms of non-visual requirements,[24,48] most have still reported results in the form of photopic illuminance. One exception is a recent study by Konis,[47] which found that daylit spaces in dementia care facilities offered substantial benefits in terms of higher equivalent melanopic illuminance, with gaze direction and proximity to windows making a significant difference. These findings were measured on clear mornings in Southern California, representing conditions that are not comparable to typical environments further away from the equator, for instance in Northern Europe. Furthermore, seating arrangements and activities are not necessarily situated in ways that prioritize light exposure.

Consequently, we wanted to investigate melanopic EDI in Norwegian dementia units as it is likely to be experienced by a resident on a typical day and at a representative position relative to windows. We also wanted to evaluate seasonal variations, and the capacity of installed electric light independently to produce illuminance above recommended thresholds. Specifically, we aimed to: (i) assess the contribution of seasonal variation (measurement occasion) and physical orientation (window/non-window) to the illuminance in

nursing homes; (ii) assess the amount of illumination provided by electric light sources in the absence of natural light, and thus the capacity of the current electric lights to compensate during the darkest winter months; and (iii) compare measured illuminance with recommended thresholds for indoor lighting.

2. Method

2.1 Setting

Managers at all public nursing homes in Bergen municipality were asked whether they had a dedicated dementia unit for long-term care. All those who answered affirmatively ($n = 15$) also agreed to allow us to measure illuminance at their facilities, and the units in question were consequently included in the present study. As most nursing homes in Norway are public, and typically situated in both old and new institutional buildings, the 15 units arguably yielded a representative sample. In the eight cases where the nursing home had multiple dementia units, one was selected using random assignment in SPSS.[50] The assessments were restricted to the living room. Although the measured illuminance may not be equal to that of the patients' bedrooms, bathrooms and hallways, we selected the living room as it is the space most frequently occupied by the patients during daylight hours. Furthermore, bedroom illumination may be subject to high variation due to placement of private furnishings such as lamps and curtains, as well as patient preferences.

2.2 Procedure

Illuminance was measured using the GL Spectis 1.0 T Flicker spectrometer by GL optic. The spectrometer has a spectral range of 340–780 nm, and a frequency range of 0.1 Hz–12.5 kHz. The software used for the corresponding spectral analysis was GL Spectrosoft. Effective illuminances for each of the photopigments, including melanopic illuminance, were calculated according to the α-opic illuminance model using the irradiance toolbox developed by Lucas *et al.*[39] Melanopic illuminances were converted to melanopic EDI using a factor of 0.9058. Although a spectral correction function based on the age of the observer has been proposed,[43] we opted to report results without this correction, as the age range of patients in dementia units varies considerably.

Measurements were conducted on three occasions: daytime winter, daytime summer and after astronomical darkness. Daytime illuminance was recorded in February 2017 and in August 2018, between 10:00 and 14:00 to stay well within the limits of daylight in winter, and to capture the times at which most patients would be awake and present in the living room according to nursing home schedules. In addition, measurements of indoor illuminance were recorded during winter, after astronomical darkness, i.e. after 18:00 hours at local coordinates 60.393° N 5.3242° E. Daytime measurements were carried out on cloudy days (defined as sky visibly covered by clouds, as confirmed by the weather service) to ensure consistency between the measurements across nursing homes. If dimmers were used, the light was turned to full capacity in order to assess the potential of the electric lights for providing adequate illumination. Although vertical measurements are the focus of the present study, horizontal measurements were also conducted in order to allow for comparisons with previous research and standards which have been reported for this measurement angle. For each nursing home, and on each occasion, measures were taken at seven different positions, amounting to a total of 315 data points.

Figure 1 shows the seven points of measurement at each occasion (three horizontal and four vertical measurements). The horizontal (task area) measurements

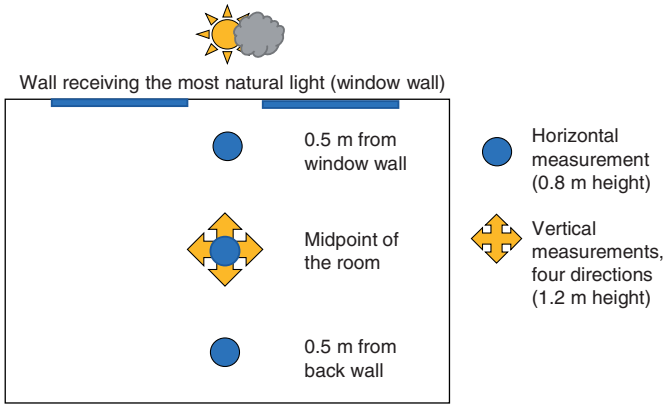

Figure 1. Measurement points in the dementia unit living rooms

were taken 0.5 m from the place receiving the most natural light (i.e. the wall with the most windows), 0.5 m from the rear wall and at the midpoint between these. Measurements from the middle and back of the room were averaged to generate one composite non-window assessment, in order to approximate average light exposure in most orientations that were not directly window facing.

Vertical (corneal) illuminances were measured at the midpoint of the room (equidistant to all corners), in four measurement directions: facing the window, as well as three other directions at 90° steps relative to the window facing measure. The three non-window facing directions were averaged to create one inward facing variable. The height of the vertical measurement was chosen to approximate corneal illuminance of a seated resident (1.2 m above the floor), and horizontal measurements were taken at the typical height of reading or other visual tasks (0.8 m above the floor).

2.3 Data analysis

Statistical analyses were conducted using the statistical software R,[51] with vertically measured melanopic EDI as the dependent variable.

To assess the impact of season and gaze direction on vertical (corneal) illuminance, a multilevel regression model was fitted using lme4,[52] with random intercepts for each nursing home ($N = 15$) to account for repeated measures at the same locations. The final model was fitted using restricted maximum likelihood (REML) estimation. Two highly influential points were identified and removed based on a criteria of Cooks D above 1 and/or studentized residuals above 2.[53] Due to a highly non-normal error distribution, the dependent variable (melanopic EDI) was log-transformed. It was also standardized to have a mean of 0 and a standard deviation of 1, for the ease of interpretation.

3. Results

3.1 Descriptive statistics

We succeeded in collecting all data as planned in all nursing homes in Bergen municipality on all occasions, implying no missing data. Descriptive statistics for vertical (corneal) and horizontal (task surface) measurements are presented in Table 1.

Vertical (corneal) melanopic EDI in the middle of the room facing inward ranged

Table 1. Illuminance in 15 dementia unit living rooms, by measurement angle, occasion, and orientation relative to windows

Orientation	Median vertical illuminance, lx, (range)				Median horizontal illuminance, lx, (range)			
	Dark	Summer	Winter	Total	Dark	Summer	Winter	Total
Non-window[a]								
Melanopic EDI	45 (23–108)	112 (30–276)	57 (23–104)	57 (23–276)	77 (22–185)	138 (56–868)	84 (28–202)	94 (22–868)
Illuminance (photopic)	128 (58–235)	192 (92–435)	125 (63–185)	140 (58–435)	209 (58–408)	267 (156–969)	187 (64–307)	215 (58–969)
Window[b]								
Melanopic EDI	38 (13–100)	186 (36–863)	98 (23–405)	78 (13–863)	62 (16–199)	1376 (67–4945)	405 (38–3153)	199 (16–4945)
Illuminance (photopic)	102 (37–221)	296 (92–978)	176 (49–507)	184 (37–978)	158 (48–410)	1390 (140–5312)	398 (77–3413)	319 (48–5312)

[a]For vertical measurements: average of three inward-facing directions, middle of the room at 1.2 m above the floor.
For horizontal measurements: average of two measurements at 0.8 m above the floor, in the middle and in the back of the room.
[b]For vertical measurements: in the middle of the room, facing the wall serving as the main source of natural light.
For horizontal measurements: 0.5 m from the wall serving as the main source of natural light.

from 23 to 108 (median = 45) after astronomical darkness, 30–276 in summer (median = 112), and 23–104 (median = 57) in winter. The mean correlated color temperature of the composite vertical measurements (all directions) was 3212 K in winter, 3761 K in summer, and 2737 K after astronomical darkness. Figure 2 shows example spectrometer outputs from the data collection, illustrating the differences in light composition between natural daylight and indoor measurements. They show irradiances at each wavelength (y-axis on different scales to enable visibility of the indoor measurement).

3.2 Multilevel regression – seasonal variation and gaze direction

Table 2 shows the results of the multilevel regression.

The reference categories in the multilevel regression model were 'dark' (night time, electric illuminance only) for occasion, and 'inward' (not facing a window) for gaze direction. For the inward facing measurements, melanopic EDI during daytime in summer (median = 112) was significantly higher than the dark (median = 45) condition ($B = 1.03$, CI = 0.51–1.55). Melanopic EDI during daytime in winter (median = 57) was not significantly higher than the dark (median = 45) condition ($B = 0.18$, CI = −0.34 to 0.69). Thus, for inward facing measurements, the day–night difference was only significant during summer. The season × gaze direction interaction was significant for measurements taken during summer, at which point the median melanopic EDI was 74 lx higher for window facing (median = 186) compared to non-window facing (median = 112) measurements ($B = 0.85$, CI = 0.11–1.59). The corresponding difference of 41 lx in winter was non-significant. Figure 3 shows a box plot of melanopic illuminance at different occasions and gaze directions.

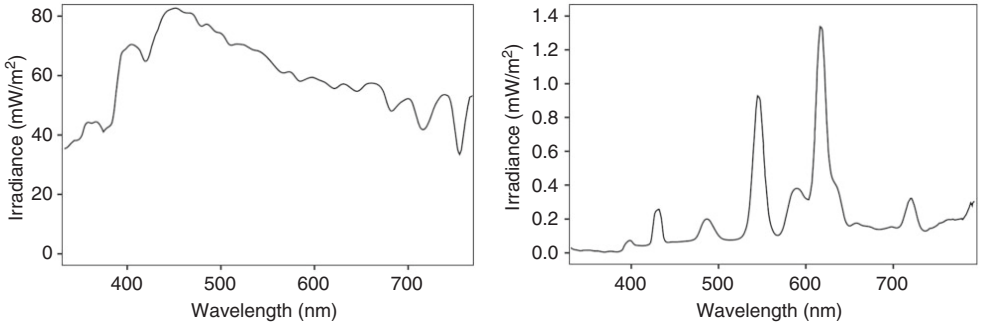

Figure 2. Typical spectral power distributions for (left) outside during winter on a cloudy day (4997 lx, 6908) and (right) inside dementia unit living room (25 lx, 2745 K), both in February. This shows irradiance (mW/m^2) at different wavelengths (nm). Shorter wavelengths (~480 nm) are more effective at eliciting non-visual responses

Table 2. Multilevel regression model testing the effect of occasion (season) and gaze direction on illuminance at eye level

	Melanopic EDI, lx[a]		
Predictors	Estimates	CI	*P*
(Intercept)[b]	−0.54	−0.93 to −0.14	**0.010**
Summer	1.03	0.51–1.55	**<0.001**
Winter	0.18	−0.34 to 0.69	0.510
Window	−0.19	−0.71 to 0.33	0.483
Season – gaze direction interaction			
Summer – facing window	0.85	0.11–1.59	**0.027**
Winter – facing window	0.62	−0.12 to 1.36	0.106
ICC		0.15	
Marginal R^2/Conditional R^2		0.404/0.496	
Observations		88	

[a]Log transformed, and scaled to have a mean of 0 and a standard deviation of 1.
[b]Reference categories are 'dark' for occasion, and 'inward' for gaze direction.
ICC: intraclass correlation coefficient, indicating the similarity between measurements at the same nursing home (on a scale from 0 to 1). Marginal R^2/Conditional R^2 = proportion of variability (on a scale from 0 to 1) explained by the fixed effects (marginal) and the fixed + random effects (conditional).[54]

The intraclass correlation coefficient (ICC) is interpreted as the proportion of the variance that can be attributed to group-level variance, on a scale ranging from 0 (no similarity between scores from the same nursing home) to 1 (all variance accounted for by differences between nursing homes).[55] The ICC of .15 indicates that only 15% of the unexplained variance was due to differences between nursing homes.

3.3 Comparisons with thresholds and standards

The number of nursing homes whose illuminance reached three predetermined values based on recommendations/standards is presented in Table 3.

Of the inward-facing measurements, only 2 out of 15 nursing homes exceeded 217 melanopic EDI during summer, and none during winter. Of the window-facing

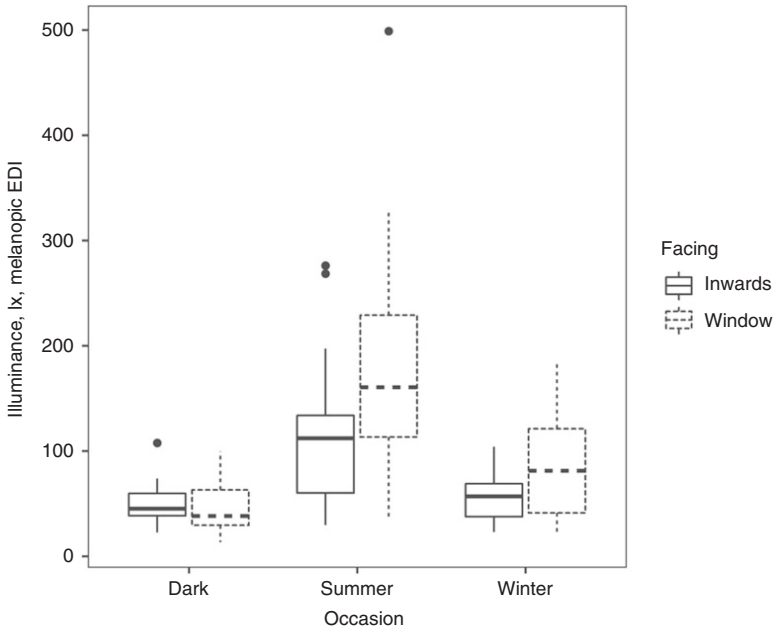

Figure 3. Influence of gaze direction and occasion on illuminance (in melanopic EDI)

Table 3. Number of nursing homes, out of 15, achieving specified illuminance levels measured vertically.[a]

Occasion	Facing	217 lx (melanopic EDI)[b]	300 lx (photopic)[c]	500 lx (photopic)[d]
Dark	Inwards	0	0	0
	Window	0	0	0
Summer	Inwards	2	2	0
	Window	6	7	2
Winter	Inwards	0	0	0
	Window	1	1	1

[a]Values based on previous research, recommendations, or industry standards.
[b]Sufficient for maximum points according to the WELL certification system (≥240 EML).[10] Close to the threshold used by Konis,[47] (250 EML, or 226 lx in melanopic EDI).
[c]Lower end of the CIE[46] recommendation, and slightly above the IES[45] minimum recommendation (200 lx) for elderly individuals. Both thresholds refer to horizontally measured photopic illuminances.
[d]Sufficient to ensure a CS of 0.3 for 90% of commercially available light sources.[42] Previous studies on illumination at nursing homes,[49,56] and most studies on bright light therapy[57] set their threshold at this point or higher (up to 10.000 lx).

measurements, six reached 217 melanopic EDI in summer, and one in winter. Only window-facing measurements reached the photopic illuminance threshold of 500 lx; two of these in summer and one in winter. Higher thresholds were not included in the table, as only one measurement (during summer, facing the window) reached 750 lx.

After astronomical darkness, none of the measures reached even the lowest thresholds, suggesting that none of the installed electrical lights could independently provide illumination above these thresholds without the presence of natural light from windows.

Across all occasions, the median horizontal (task area) photopic illuminances in the middle and back of the room were below 300 lx. However, in the window zone it exceeded this in daytime both during summer and winter (see Table 1).

4 Discussion

Melanopic illuminance at eye level in nursing home dementia units was partly dependent on seasonal variations and gaze direction, although differences were small. The electrical lights were not capable of independently providing sufficient melanopic illumination in the absence of natural light, and the absence of day–night differences in winter suggests that very little natural light reaches the inside environment even during the day. Almost all measurements, regardless of direction and measurement occasion, were below even conservative industrial standards and thresholds recommended for eliciting non-visual responses to light, also during summer.

Measurements during winter were lower than corresponding summer measurements, and facing the window in the center of the room increased melanopic illuminance significantly only during summer. The absence of a significant day–night contrast in melanopic illuminance during winter suggests that the amount of natural light available in central room positions during winter is negligible, highlighting the need for electric lights capable of independently producing sufficient melanopic illuminance. Current electric lights only produced a median of 45 melanopic EDI, or 128 lx (photopic) when turned to their maximum capacity in the absence of daylight (after astronomical darkness), which is about 172 melanopic EDI below the recommendation of the WELL Building Standard,[10] or 172 and 72 lx (photopic) below the minimum horizontal illuminances recommended by CIE[46] and IES[45] respectively. The lack of day–night contrast observed in melanopic EDI during winter is suggestive of an absence of a reliable time signal for circadian entrainment.

4.1 Comparisons to standards and predetermined thresholds

Only two inward-facing measurements reached 217 melanopic EDI (Table 3), none of these during winter. None of the measurements conducted after astronomical darkness reached any of the recommended thresholds. Even the highest median vertical illuminance achieved (186 melanopic EDI or 296 lx), directly facing the window during summer, barely exceeds the lowest recommended thresholds.[10,45,46] Thus, even when windows are present, the amount of light that actually reaches the inside environment for a resident seated in the middle of the room on an overcast day is too low. This was consistent across all locations, with only about 15% of the unexplained variation attributable to random differences between nursing homes (e.g. room size, the number of windows, location and orientation of the building, choice of indoor light fixtures, etc.). Based on our findings, it is therefore reasonable to conclude that nursing home patients do not receive light cues sufficient for entrainment of circadian rhythms regardless of gaze direction, especially in winter.

Of the horizontal measurements, window adjacent measurements during summer and winter were the only two conditions in which median light levels exceeded the minimum recommendation of 300 lx for horizontal photopic illuminance.[46] It is therefore likely that the illuminance available to perform visual tasks is also too low if seated in the

back or the middle of the room, and at times when daylight is limited.

Higher illuminance than what is reported here will naturally occur on days of more direct sunlight, or if sitting very close to a window looking out. For most nursing home patients, however, especially in the Northern hemisphere during winter, it is likely that the vast majority are exposed to even lower levels of corneal illuminance, for instance due to sitting far back in the room, short day lengths (mid-winter), daytime napping, eye placement lower than 1.2 m or gazing in a downward direction. During the darkest period of the year (December/January), the period of daylight lasts only for about 6 hours (09:45–15:45) at the local coordinates (60.393°N 5.3242°E). Furthermore, we utilized conservative thresholds, not accounting for eye disease, degenerative conditions affecting neural signaling, or very advanced age, which may impact illuminance requirements. In any standard that is not adjusted for age, the illuminance will probably have to be at least doubled for elderly individuals to account for age related loss of retinal sensitivity[19] and reduced responsivity to short wavelength light.[58]

It should be noted that the thresholds used for comparison in the present study are merely of suggestive nature. While there are a number of studies suggesting that high illuminances and shorter wavelength light are more effective at stimulating non-visual responses,[59] there is no consensus concerning the amount or composition of light that is an appropriate minimum for nursing homes. The efficacy of light in stimulating non-visual responses depends on multiple factors, including timing and duration of the light stimulus,[16] as well as previous light exposure history and individual differences.[17] Setting appropriate standards for nursing homes will require knowledge about the effects of absolute and relative illuminance, timing and light composition, in terms of both acute and delayed responses. The levels of adjustment needed for ageing individuals and patients suffering from dementia in terms of non-visual responses also need to be empirically validated, in light of ample evidence that photoreception becomes significantly reduced as we age.[19]

Adapting a consistent standard for measuring and reporting light is a necessary step in this process, as previous studies on ambient light conditions and research on light therapy seldom report how light was measured (e.g. vertical or horizontal), and have mostly resorted to reporting photopic illuminance.[39] In the present study, we opted for melanopic EDI as a way to account for the wavelength sensitivity of the non-visual responses; however, effective illuminances for other photopigments are reported in supplementary materials (Table S1).

The clinical impacts of insufficient illumination in nursing homes are potentially many and severe. The low light levels described in this paper may impair the ability to perform visual tasks, reduce mobility and increase the risk of falls and injuries.[22,23] Conversely, improved lighting conditions may produce improvements in terms of circadian entrainment, sleep, mood and behavioral symptoms.[34,60,61]

4.2 Strengths, limitations and suggestions for future research

A strength of the present study is that time of day, weather and placement of measurements were standardized across all nursing homes. Measurements were repeated to investigate the effects of seasonal variation. Furthermore, we considered both the photopic and the melanopic aspects of light, as well as various standards, when assessing the adequacy of the indoor illuminance. We measured illuminance at every nursing home with a long-term dementia unit in Bergen municipality, thus ensuring a broad sample

across building years, placements and structural variation.

We did not, however, assess the illuminance under different weather conditions, such as direct sunlight. The generalization of the findings to geographical locations with far more sunlight is thus uncertain. Neither did we investigate light at night in the patients' bedrooms, as it is likely subject to a large amount of individual variation in preferences and habits. However, based on previous research we know that low exposure to illumination during the day can have a sensitizing effect on responses to illumination at night,[2,17,18] possibly causing circadian disruption. Furthermore, worn dosimeters allow for more personalized estimates of the illuminance experienced by wearers over time[62] and would be a useful supplement to the present findings about the living environment. Due to the cost as well as potential demands on staff involved in ensuring proper wear and minimizing discomfort, we did not utilize dosimetry in the current study. Important visual aspects of light, such as glare and flicker, were not evaluated in the present study, but should also be considered when designing the nursing home light environment.[45] Increases of illuminance that cause more glare may result in a significant reduction of visual acuity and comfort, particularly for people who have glaucomas.[63] More research is needed to appraise the implications of the light conditions on multiple health factors and well-being among residents at nursing home dementia units. Specifically, future research on light conditions in nursing homes should aim to link the light conditions to circadian rhythm parameters of the resident. The present study suggests there is little natural variation in light levels between nursing homes, seasons or physical orientation/gaze direction. This calls for experimental designs with light fixtures capable of providing a wider range of illuminances. Furthermore, investigations of the ways in which ageing and associated conditions may affect non-visual responses to light would enable us to better estimate the thresholds necessary to ensure circadian entrainment, mental health and well-being.

5. Conclusion

Despite the lack of a definite standard for melanopic illumination, the present study shows that illuminances in dementia unit living rooms are below even the most conservative recommended thresholds, with respect to both visual and non-visual requirements. There was no significant difference between day and night-time measurements in the contribution from natural daylight to indoor illuminance in winter, even when directly facing a window. It is therefore concluded that, overall, there is a need for improved indoor lighting in nursing home dementia units, especially during winter. Given the ubiquity of insufficient illumination, optimization of illumination in the nursing home setting has the potential to better entrain the circadian rhythm and improve sleep and mental health of residents.

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The Effect of Bright Light Treatment on Rest–Activity Rhythms in People with Dementia: A 24-Week Cluster Randomized Controlled Trial

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Abstract: Bright light treatment is an effective way to influence circadian rhythms in healthy adults, but previous research with dementia patients has yielded mixed results. The present study presents a primary outcome of the DEM.LIGHT trial, a 24-week randomized controlled trial conducted at nursing homes in Bergen, Norway, investigating the effects of a bright light intervention. The intervention consisted of ceiling-mounted LED panels providing varying illuminance and correlated color temperature throughout the day, with a peak of 1000 lx, 6000 K between 10 a.m. and 3 p.m. Activity was recorded using actigraphs at baseline and after 8, 16, and 24 weeks. Non-parametric indicators and extended cosine models were used to investigate rest–activity rhythms, and outcomes were analyzed with multi-level regression models. Sixty-one patients with severe dementia (median MMSE = 4) were included. After 16 weeks, the acrophase was advanced from baseline in the intervention group compared to the control group (B = −1.02, 95%; CI = −2.00, −0.05). There was no significant difference between the groups on any other rest–activity measures. When comparing parametric and non-parametric indicators of rest–activity rhythms, 25 out of 35 comparisons were significantly correlated. The present results indicate that ambient bright light treatment did not improve rest–activity rhythms for people with dementia.

Keywords: dementia; nursing homes; bright light therapy; rest–activity rhythms; actigraphy; circadian rhythms; clinical trial

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1. Introduction

Dysregulation of circadian rhythms, including the rest–activity rhythm (RAR), is common in people with dementia. The RAR describes a diurnal pattern in activity, typically in terms of cycles of nighttime sleep and daytime activity [1]. In people with dementia, however, the day–night difference in activity is often severely diminished, and the RAR pattern over time is typically characterized by a high degree of irregularity and fragmentation [2]. This coincides with disordered sleep and behaviors such as nocturnal restlessness and daytime inactivity that can impact the care needs and daytime functioning of people with dementia [3]. Furthermore, loss of stability and periodicity in sleep–wake behavior are thought to reflect a deterioration of the endogenous time-keeping mechanisms responsible for circadian rhythmicity [4].

Circadian rhythms (CR) are 24 h oscillations present in physiological processes, including hormone secretion, immune function, body temperature, metabolism, and sleep–wake

behavior. CR are coordinated and synchronized by the "master clock" of the body, the suprachiasmatic nucleus (SCN) of the hypothalamus [5], which is entrained by the solar day, allowing various systems to respond in a predictive and coordinated manner to the varying environmental demands and inputs. Although circadian rhythms are frequently studied for their role in sleep, they also play an essential role in synchronizing internal physiology, behavior, and responses to external demands [6,7]. Misalignment of circadian rhythms has been linked to a number of processes that may increase the risk of negative health outcomes, including cardiovascular disease, diabetes, obesity, cancer, and psychiatric conditions including mood disorders and psychosis [6,7].

Multiple lines of evidence indicate a disruption of circadian rhythms in old age and especially in dementia [4,6]. Age-related changes, such as decreased circadian rhythm amplitude (day–night difference), loss of rhythmicity, poor entrainment to the solar day, and internal desynchronization, have been observed for physiological processes, including hormone regulation, core body temperature, and RAR [8].

A disrupted RAR has been linked to behavioral and psychological symptoms of dementia (BPSD) [9], and agitation in dementia patients appears to have a circadian component [10]. Longitudinal studies have found that circadian disruption, including RAR irregularities, may even precede cognitive decline, leading some to hypothesize that disrupted circadian rhythms play a role in accelerating aging and dementia [2,6].

Deterioration of circadian rhythms in old age and dementia has been partially attributed to neural degeneration [11] and partially to lowered exposure to environmental time cues [4]. The most important stimulus to the circadian pacemaker is light, particularly light of short wavelength and high intensity [12,13]. With advancing age, changes to eye physiology impair circadian phototransduction [14]. In addition, lifestyle changes or situational and contextual changes may further reduce daylight availability. For example, people with dementia are often exposed to low levels of environmental illumination, especially those living in nursing homes [15–18]. Providing a robust environmental time cue through bright light therapy (BLT) is a well-established treatment for disruption of the circadian rhythms in otherwise healthy adults [19,20], but the efficacy of BLT for people with dementia is not yet established. Previous research on BLT in people with dementia has found positive effect on outcomes such as BPSD, cognition, sleep, and circadian rhythms (e.g., [21–26]), although studies do not consistently report improvements for all outcomes. BLT is typically administered using light boxes that provide increased illuminance, high correlated color temperature (CCT, i.e., more blue or white in appearance), or both. However, providing BLT using a ceiling-mounted light source eliminates the need to stay with the patient to ensure adherence and allows for longer daily exposures. There is some indication that use of ambient BLT, in particular, may improve circadian rhythmicity for people with dementia [22,27,28], but results have so far been mixed [24,29–31]. One reason for diverging results is large variations in methodology, including light parameters (illuminance and CCT or spectral power distribution), exposure time, delivery method, sample size and sample characteristics, trial duration, trial design, and outcome measures [32–34].

In the present study, we present a primary outcome from the DEM.LIGHT trial; a 24-week cluster randomized controlled trial to assess the effect of ceiling-mounted BLT for nursing home patients with dementia. Our hypothesis was that the RAR would improve in the group receiving BLT compared to the control group.

2. Materials and Methods

The DEM.LIGHT trial (full trial name: "Treatment Light Rooms for Nursing Home Patients with Dementia–Designing Diurnal Conditions for Improved Sleep, Mood, and Behavioral Problems", ClinicalTrials.gov Identifier: NCT03357328) is a cluster randomized placebo-controlled trial that was conducted in Bergen, Norway, between September 2017 and April 2018. Data was collected at baseline and at 8, 16, and 24 weeks.

2.1. Participants

Eligible nursing homes were identified with the assistance of Bergen municipality. Any nursing home was eligible if it had a dedicated dementia unit, the architecture allowed for installation of light panels, and the unit was not currently participating in other projects. Fourteen nursing home dementia unit leaders were invited, of which eight agreed to allow their unit participate in the trial. Four units declined to participate, and one unit signaled interest after the desired number of units was achieved. One unit was excluded due to having twice as many residents as other units. A total of 78 residents lived in the included units and were screened for inclusion (see Table 1 for eligibility criteria) by clinical psychologists (EK and GJH) in collaboration with the nursing home physician.

Table 1. Study inclusion and exclusion criteria.

Participants Were Eligible If They:	Patients Were Not Eligible 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 of less 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; NPI–NH = Neuropsychiatric Inventory–Nursing Home Version.

2.2. Sample Size and Power Calculation

The power analysis indicated that a minimum of 64 participants and 8 clusters were needed in order to detect differences between conditions [35,36] using ANOVA analysis. Alpha level was set to 0.05 (two-tailed), and the power, to 0.80, expecting moderate effect sizes (Cohen's d = 0.50). Allowing for a 20% dropout, the aim was to recruit 80 participants.

2.3. Delivery of the Intervention

Four units (intervention group) had ceiling-mounted LED panels (Glamox, 1 × C95 48 CCT 6500 MP 47 W/4702 lm, Glamox, Keila, Estonia) installed in the living rooms. The panels were programmed to mimic daily variations in the natural light cycle, delivering light at varying illuminances and CCT throughout the day (see Figure 1). Peak illuminance (1000 lx at eye level) was delivered between 10 a.m. and 3 p.m. each day. The CCT during this period was set to be around 6000, which is within the interquartile range for natural daylight across various atmospheric conditions, i.e., 5712–7757 K [37]. In the control group (four units), lights bulbs were changed (CFL AURA UNIQUE-D/E LL 18W/830 G241-2 in three units and CFL AURA UNIQUE-L LL 18W/830 2G11 in one) but still delivered standard indoor illumination (~150–300 lx, 3000 at eye level in the center of the room).

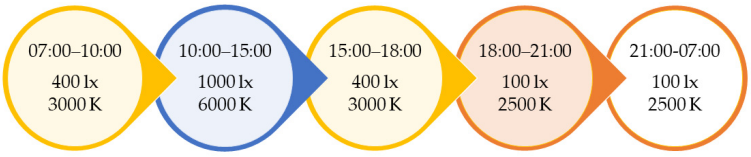

Figure 1. Illuminance (lx) and correlated color temperature (kelvin, K) at different times of the day in the intervention group, with gradual transition periods of 30 min separating each phase. Between 21:00 and 07:00 the lights could also be turned off by staff if this was preferred.

2.4. Group Allocation and Blinding

The eight nursing home units were randomized to the intervention (four units) or control condition (four units) by EK and EF using random group assignment in IBM SPSS Statistics. All participants in a unit were assigned to the same condition. Light bulbs were changed in the control units by researchers in order to conceal condition assignment and to ensure similar light across control group units. Employees at the nursing homes were informed that the aim was to investigate the effect of different kinds of light but were not told which aspects of the light we would be studying. Blinding of residents was not considered an issue due to the degree of cognitive decline experienced by those in the target population.

2.5. Measurements

2.5.1. Rest–Activity Rhythms

Movement patterns were assessed using wrist-worn accelerometry devices (Actiwatch II, Philips Respironics Inc., Murrysville, PA, USA) known as actigraphs, which allow for continuous recordings of motor activity under naturalistic conditions. Actigraphy has been validated for the detection of RAR, including for people with dementia [1]. The actigraphs were worn continuously for seven days at each data collection point. As recommended by Camargos et al. [38], actigraphs were placed on the wrist of the dominant arm, epoch length was set to one minute, and the wakefulness threshold was set to medium. Actigraphy data were exported from Actiware (version 6.0.9, Philips Respironics Inc., Murrysville, PA, USA).

Previous research has utilized a variety of methods for characterizing RAR, with non-parametric approaches and cosine-based models being popular [2,39]. As the standard cosine model often shows poor fit with the true shape of the RAR [39–41], RAR indicators were computed using a non-parametric approach [42], as well as an extended cosine model [41].

Non-parametric indicators are used to describe the RAR patterns without making assumptions about the shape of the rhythm [42,43]. They have previously been used to describe RAR disturbances in dementia patients [9,43–47], and to evaluate the effect of BLT in such patients [22,24], with good sensitivity [40]. Non-parametric RAR indicators (inter-daily stability, intra-daily variability, least active 5 h, most active 10 h, and the relative amplitude) were calculated from raw actigraphy data using the NparACT package in R [48].

Inter-daily stability (IS) quantifies the consistency of the activity profile from day to day, defined as the ratio of the variability within a 24 h period to the total variability.

$\mathrm{IS} = \frac{n\sum_{h=1}^{p}\left(\overline{X}_h-\overline{X}\right)^2}{p\sum_{i=1}^{n}\left(X_i-\overline{X}\right)^2}$ with n = the total number of data, p = the number of data per day, $\overline{X}$ = the overall mean of all data, $\overline{X}_h$ = the hourly means, and X_i = the individual data points. The resulting value has a range of 0 (Gaussian noise, no similarity between days) to 1 (perfect stability and similarity between days). A high IS, therefore, indicates that different levels of activity occur at similar times across days.

Intra-daily variability (IV) measures the degree of fragmentation within 24 h periods, defined as the ratio of hour-to-hour variability to the overall variability.

$\mathrm{IV} = \frac{n\sum_{i=2}^{n}\left(X_i-X_{i-1}\right)^2}{(n-1)\sum_{i=1}^{n}\left(X_i-\overline{X}\right)^2}$. A perfect sine wave has an IV of near zero, while Gaussian noise has a value of about 2 (or sometimes higher). A larger IV indicates a higher number or magnitude of transitions between activity and inactivity, typically reflecting frequent daytime naps or nighttime awakenings.

L5 and M10 reflect the average activity levels during the least active consecutive 5 h and the most active consecutive 10 h, typically occurring during the night and day, respectively.

Relative amplitude (RA) is the ratio of the difference in activity level during the most active 10 h (M10) and the least active 5-h period (L5) to the total activity in these two periods.

RA $= \frac{(M10-L5)}{(M10+L5)}$. A high RA thus indicates a robust rhythm with relatively higher activity in the active period and rest during the inactive period.

In addition, we estimated RAR using the anti-logistic extended cosine model [10,41], which builds on the traditional cosine models. The additional parameters allow for a more flexible fit to activity rhythms that do not conform to sinusoidal patterns [10]. This approach has, therefore, been utilized in research with older people and dementia patients (e.g., [49–51]). Extended cosine parameters were calculated using the RAR package [52] in R.

Amplitude represents the difference in activity between the peak (maximum) and nadir (minimum), in other words the magnitude of the rhythm.

Midline-estimating statistic of rhythm (MESOR) captures the mean level of activity (i.e., minimum + amplitude/2), with higher levels indicating more overall activity.

The pseudo-F statistic measures the goodness of fit to the periodic function. Higher values indicate more regular activity patterns that can be modeled by a function with a 24 h period, indicating a robust daily activity rhythm.

Acrophase is the time of peak activity level. Later or earlier times may reflect a delayed or advanced circadian phase, respectively.

Alpha describes the relative width of the trough and peak of the rhythm. Larger values indicate relatively more activity during the rest period than the active period, resulting in wider troughs and narrower peaks.

Beta represents the steepness of the rise and fall of the curve. Larger values indicate steeper curves, i.e., sharper transitions between rest and activity, resulting in a curve with a "squarer" shape.

Nadir is the time at which the activity curve reaches its minimum value.

2.5.2. Light Measurements

The number of light panels needed to provide the required intervention illuminance was calculated by Glamox engineers for each unit before installation. In addition, light was measured after the start of the trial by researchers using the GL Spectis 1.0 T Flicker spectrometer (GL Optic, Puszczykowo, Poland). As recommended by Spitschan et al. [53], the spectral distribution of the light was measured from an observer point of view (vertically at 1.2 m height, to approximate corneal illuminance for a seated patient), and α-opic irradiances were calculated with the CIE S 026 toolbox [54], in addition to photopic illuminance (lx). Data on melanopic equivalent daylight (D65) illuminances (EDI) were also extracted from the toolbox. All measurements were conducted on an overcast day in September between 10 a.m. and 3 p.m., in four directions (facing the wall with the most windows, and at 90-degree steps relative to it).

2.5.3. Other Measurements

To approximate light exposure, staff estimated how much time, on average, the patient had spent in the living room each day between 10 a.m. and 3 p.m. (i.e., the period of peak illuminance and CCT in the intervention condition) since the last data collection point. Patients' medical journals were accessed by authors with clinical authorization in order to extract information about diagnoses and medications. The Charlson Comorbidity Index (CCI) assesses the number of comorbid conditions, weighted by the seriousness of the disease, and its scores are positively associated with 1-year mortality rates [55]. The Mini-Mental State Examination (MMSE) is a test of cognitive functions [56], with good reliability and validity in the assessment of cognitive impairment and change over time in patients with dementia [56,57]. It is scored on a scale ranging from 0 to 30, with higher scores indicating better cognitive function. The Functional Assessment Staging Test (FAST) [58] describes the progression of Alzheimer's disease in seven stages from

1 (normal adult) to 7 (severe Alzheimer's disease). It has demonstrated adequate validity and reliability [59]. Higher stages indicate reduced ability to perform activities of daily living. Such deterioration is not necessarily seen in all forms of dementia, so we only used the scale as a means of characterizing the degree of impairment at baseline.

2.6. Data Management and Statistical Analyses

Data analyses were performed in R. Multi-level regression models were fitted using the lme4 library [60] with restricted maximum likelihood estimation, random intercept for each patient, and an unstructured variance–covariance matrix. Amplitude, MESOR, pseudo-f statistic, and beta were transformed using a natural log function (ln) to improve normality of the residual distribution. For the beta model, one extreme outlier had to be removed for the model to be estimated. Significance levels are reported with and without Benjamini–Hochberg false discovery rate correction [61] in order to account for increased risk of a type 1 error when performing multiple tests. Associations between RAR outcomes at baseline were investigated using Spearman correlations.

Scores on the functional assessment staging test (FAST) at baseline were added to control for dementia severity, following the recommendations of Forbes et al. [34]. The following covariates were also tested: age, composite score on the CCI, gender, number of psychotropic medications, and whether the patient was on hypnotic/sedative medications. As they did not change the interpretation of the outcomes, they were not included in the final model.

Patients in either group who had spent less than 30 min on average per day in the living room during the main period of the intervention (10 a.m. to 3.p.m.) were excluded from the analyses.

Acrophase is reported in terms of decimal hours (minutes expressed as the percentage of a full hour). As the effect of light on the timing of RAR might differ for phase advanced and phase-delayed patients, the sample was split according to their deviance from the average acrophase of healthy adults (i.e., 12:59) as reported in a previous study [62]. However, only two patients had a negative deviance from the reference point of 12.59, and sub-group analysis was, therefore, not performed. Rather, these observations, as well as the subsequent observation from the same patient, were removed, amounting to a total of 4 observations (from 2 patients) removed.

2.7. Ethical Considerations

Informed consent was provided by legal guardians on behalf of the patients. Patients who were potentially able to understand, as identified by the nursing home physician, were informed in a personally adapted manner and given the option to consent or decline to participate. Any verbal and non-verbal expressions of distress or unwillingness to participate in data collection procedures expressed by the patients were regarded as withdrawal of consent. Patients could freely withdraw to other areas if they were uncomfortable with the light installed in the living rooms.

3. Results

3.1. Sample Descriptive Statistics

Eight dementia units at separate nursing homes, with 78 residents in total, were included at baseline. See Figure 2 for a diagram of the participant flow. Three patients were excluded because they did not meet the inclusion criteria (listed in Table 1), and six declined to participate. After allocation, eight more patients were excluded due to absent baseline measurements (details in Figure 2), amounting to 61 with complete actigraphy recordings available for analysis at baseline.

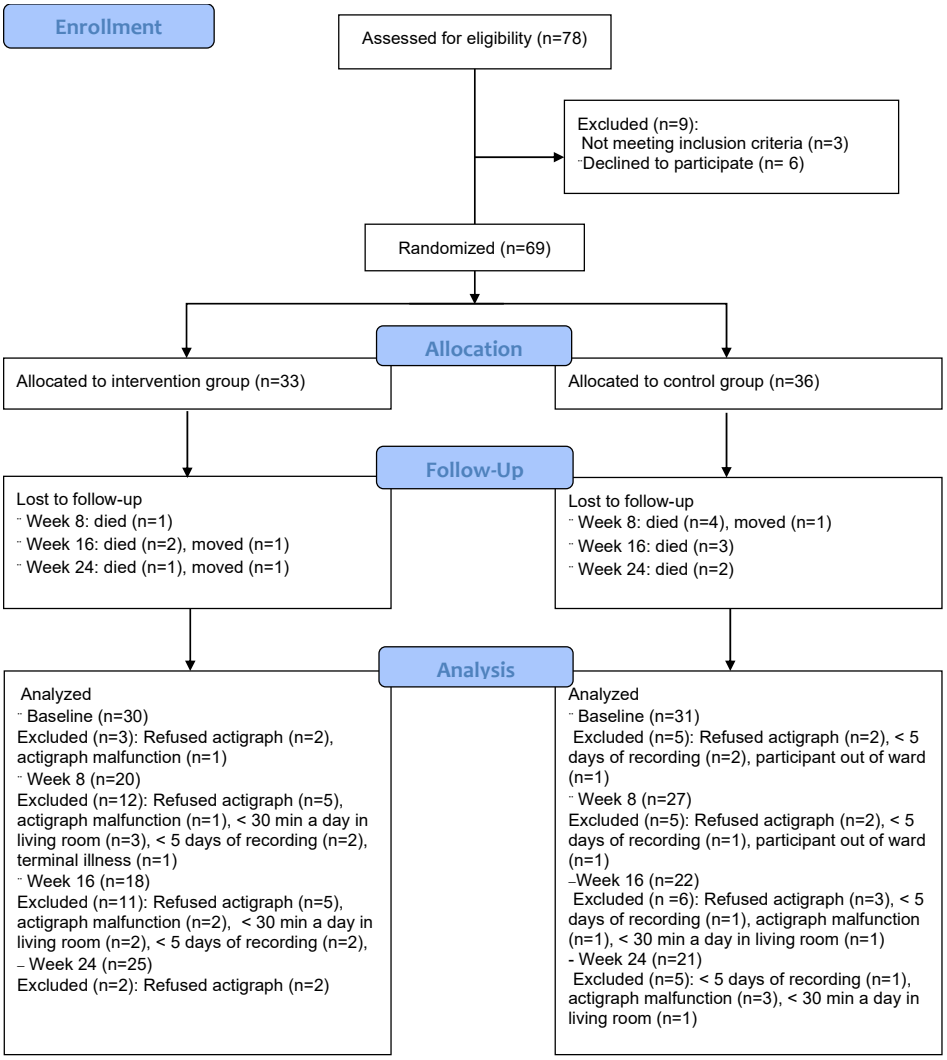

Figure 2. Flow diagram showing participant inclusion, allocation, and attrition through each stage of the trial until analysis.

At baseline, 71% of the included patients were women, and the median age was 84 (Table 2). A total of 75% had an MMSE score below 10, indicating severe cognitive impairment [57], and 75% had a FAST score of 6, indicating functional impairment corresponding to moderate Alzheimer's dementia [58]. All but three patients had a formal dementia diagnosis. Undiagnosed patients were included, as they all had MMSE scores below 26 following assessments by clinicians. In all, 54% of the patients had an Alzheimer's diagnosis, while the second largest group (31%) was "unknown dementia". Two patients were diagnosed with Parkinson's disease.

Table 2. Baseline descriptive statistics.

	Control (N = 31)	Intervention (N = 30)	Total (N = 61)
Female	20 (64.5%)	23 (76.7%)	43 (70.5%)
Age—*M* (*Q*1, *Q*3)	82.0 (78.5, 87.5)	86.0 (83.0, 88.8)	84.0 (79.0, 88.0)
FAST			
4	0 (0.0%)	2 (6.7%)	2 (3.3%)
5	1 (3.3%)	1 (3.3%)	2 (3.3%)
6	21 (70.0%)	24 (80.0%)	45 (75.0%)
7	8 (26.7%)	3 (10.0%)	11 (18.3%)
CCI—*M* (*Q*1, *Q*3)	1.0 (1.0, 2.0)	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)
MMSE—*M* (*Q*1, *Q*3)	4.0 (2.0, 9.0)	4.0 (1.0, 11.0)	4.0 (1.0, 10.0)
Psychotropic med. *—*M* (*Q*1, *Q*3)	3.0 (2.0, 3.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
No. using hypnotics/sedatives †	10 (32.3%)	12 (40.0%)	22 (36.1%)
No. with eye disease	6 (19.4%)	4 (13.3%)	10 (16.4%)
Dementia diagnoses			
Alzheimer's	17 (55%)	16 (53%)	33 (54%)
Vascular	1 (3%)	2 (7%)	3 (5%)
Lewy body	1 (3%)	0 (0%)	1 (2%)
Other	1 (3%)	1 (3%)	2 (3%)
Unknown	9 (29%)	10 (33%)	19 (31%)

* Average number of ATC N-code drugs. † N05C drug in ATC system. M = median, Q1 = 25th percentile, Q3 = 75th percentile, FAST = Functional Assessment Staging Test, CCI = Charlson Comorbidity Index, MMSE = Mini-Mental State Exam.

3.2. Adherence

Estimated time spent in the living room during the main intervention period (10 a.m. to 3 p.m.) was on average 3.1 h (SD = 1.4) in the control group and 3.6 h (SD = 1.6) in the intervention group.

3.3. Light Measurements

Supplementary Table S1 shows mean illuminance, α-opic irradiance, and melanopic EDI for the two conditions. Figure 3 shows typical examples of α-opic weighted spectra for nursing home units in the control group and intervention group. Spectral distributions are available in supplementary Table S2. Mean illuminance in the intervention group units was 1039 lx in terms of photopic illuminance (SD = 225, range = 722–1242). In the control condition, it was 242 lx (SD = 101, range = 134–368). One nursing home had an average illuminance measurement (722 lx) below the goal of 1000 lx. However, the highest illuminance in the control condition was 368 lx; thus, even the lowest value achieved in the intervention condition was almost double the highest value in the control group.

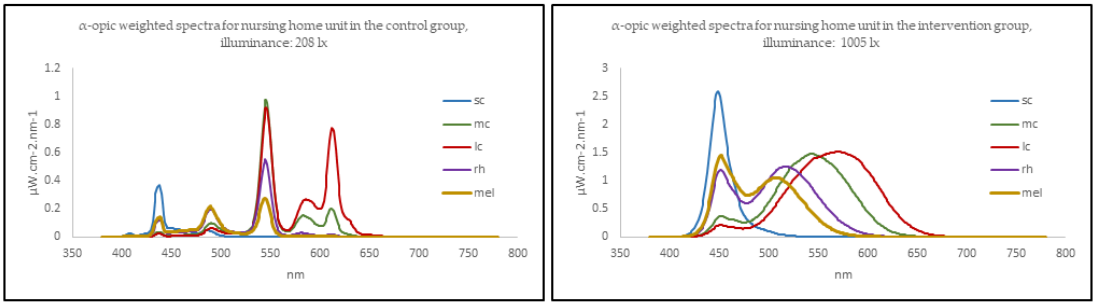

Figure 3. Typical α-opic weighted spectra for nursing home units in the control group (**left**) and the intervention group (**right**). Measured at 1.2 m height, in the center of the room, facing the back wall. Created using the CIE S 026 toolbox [54].

3.4. Rest–Activity Rhythms

Scores on all outcome measures by week of study and treatment group are shown in Supplementary Table S3.

Correlations between Circadian Rhythm Outcomes at Baseline

Spearman correlations between non-parametric indicators and indicators from the extended cosine model at baseline are shown in Table 3. A total of 25 of the 35 correlations were significant. There were two very strong (i.e., absolute value above 0.80) correlations: between the pseudo-F statistic and RA (r_s = 0.82) and between the pseudo-F statistic and IS (r_s = 0.81). Five correlations were strong (i.e., absolute value 0.80–0.79): amplitude and IS (r_s = 0.66), amplitude and RA (r_s = 0.60), MESOR and M10 (r_s = 0.67), nadir and RA (r_s = 0.62), and nadir and L5 (r_s = 0.66).

Table 3. Spearman correlation coefficients between non-parametric and parametric RAR indicators at baseline.

	IS	IV	RA	M10	L5
Amplitude	0.66 ****	−0.52 ****	0.6 ****	0.46 ****	−0.29 *
MESOR	0.11	−0.21	−0.19	0.67 ****	0.54 *
Alpha	0.06 *	−0.26	0.15 *	−0.02	−0.11 ****
Beta	−0.18 *	0.26 ****	−0.10	0.00 *	0.02
F-statistic	0.81 ****	−0.58 ****	0.82 ****	0.48 ****	−0.49 ****
Acrophase	0.14 *	−0.23 *	−0.03	0.09 ****	0.09
Nadir	−0.41 ****	0.32 ****	−0.62 ****	0.18	0.66 ****

**** $p < 0.0001$, * $p < 0.05$. IS = inter-daily stability, IV = intra-daily variability, RA = relative amplitude, M10 = activity during the 10 most active hours, L5 = activity during the 5 least active hours. Estimated treatment effect.

Table 4 provides an overview of the estimated treatment effects (week-by-condition interactions) for all outcomes. Standardized coefficients, displaying all interaction coefficients on a standardized scale, are shown in Figures 4 and 5. There was a significant difference between the groups in acrophase shift from baseline to week 16 (B = −1.02, 95% CI = −2.00, −0.05). In other words, the mean of the control group was delayed by about one hour from baseline to week 16 compared to the intervention group. In weeks 8 and 24, the control group was delayed by 0.51 and 0.59 h, respectively (i.e., about 30 min) from baseline compared to the intervention group, but this was not sufficient to reach statistical significance (Table 4). With correction for repeated measurements (Benjamini–Hochberg correction), none of the interactions reached statistical significance. There was no significant week-by-condition interaction on any other RAR measure or at any other time point.

Table 4. Results of mixed models, showing the week-by-group interactions.

	Week 8 × Intervention B (95 % CI)	Week 16 × Intervention B (95 % CI)	Week 24 × Intervention B (95 % CI)	N	N (id)	R^2 (Fixed)	R^2 (Total)	ICC
Non-Parametric Indicators								
IS	−0.01(−0.12–0.10)	−0.02(−0.15–0.10)	0.02(−0.10–0.13)	187	64	0.04	0.57	0.55
IV	−0.07(−0.22–0.09)	−0.02(−0.19–0.15)	−0.08(−0.23–0.07)	187	64	0.01	0.77	0.77
RA	−0.07(−0.19–0.05)	−0.05(−0.18–0.08)	−0.04(−0.16–0.09)	187	64	0.04	0.61	0.59
M10	11.3(−20.62–43.22)	−9.34(−44.51–25.83)	11.68(−20.04–43.40)	187	64	0.13	0.75	0.71
L5	8.47(−3.70–20.64)	−1.26(−14.65–12.13)	2.85(−9.25–14.94)	187	64	0.03	0.67	0.66
Extended Cosine Model								
Amplitude (ln)	−0.82(−1.81–0.17)	−0.41(−1.52–0.70)	−0.26(−1.28–0.75)	166	61	0.02	0.32	0.31
MESOR (ln)	−0.01(−0.44–0.43)	−0.21(−0.70–0.28)	−0.19(−0.64–0.25)	166	61	0.05	0.45	0.42
Acrophase *	−0.51(−1.39–0.37)	−1.02(−2.00–−0.05) †	−0.59(−1.49–0.30)	163	61	0.10	0.63	0.59
Nadir *	0.41(−0.02–0.84)	0.01(−0.47–0.50)	−0.06(−0.50–0.38)	166	60	0.04	0.52	0.49
Alpha	−0.12(−0.38–0.14)	−0.14(−0.44–0.16)	−0.19(−0.46–0.08)	166	61	0.05	0.51	0.48
Beta (ln)	0.29(−0.65–1.24)	0.48(−0.57–1.53)	0.57(−0.40–1.54)	165	61	0.03	0.08	0.05
F-statistic (ln)	−0.4(−0.82–0.03)	−0.01(−0.49–0.47)	−0.06(−0.50–0.38)	166	61	0.05	0.78	0.77

Controlling for score on the Functional Assessment Staging Test (FAST). B = regression coefficient, N = number of observations, N(id) = number of participants, R2 (fixed) = marginal R2 (i.e., the proportion of variance explained by the fixed effects alone), R2 (total) = conditional R2 (i.e., the proportion of variance explained by fixed and random factors), ICC = intraclass correlation coefficient, IS = inter-daily stability, IV = intra-daily variability, RA = relative amplitude, M10 = activity during the 10 most active hours, L5 = activity during the 5 least active hours, ln = natural logarithm. * In decimal hours. † $p = 0.04$ without correction for false discovery rate.

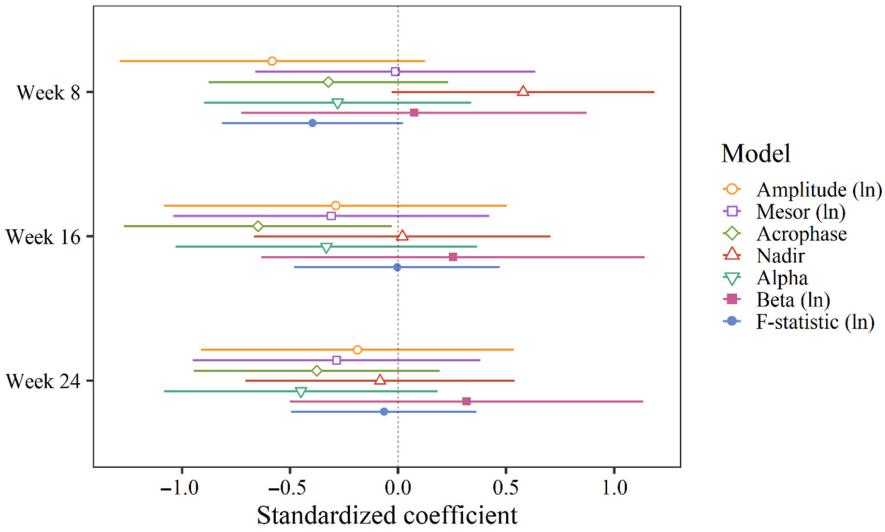

Figure 4. Standardized coefficients for week-by-condition interactions (i.e., change from baseline in the intervention group relative to the control group) for the extended cosine model.

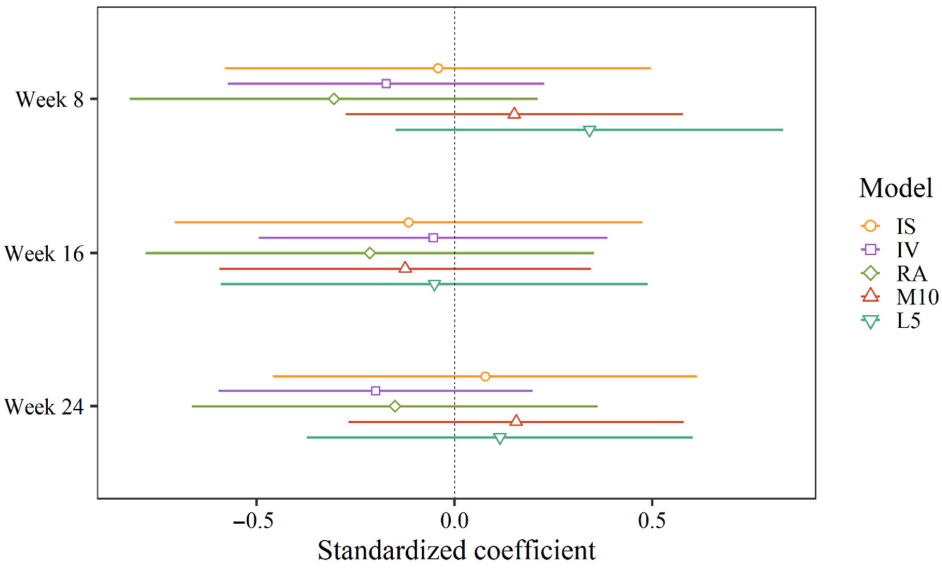

Figure 5. Standardized coefficients for week-by-condition interactions (i.e., change from baseline in the intervention group relative to the control group) for non-parametric indicators.

4. Discussion

The present results do not support the hypothesis of the study, namely that RAR would improve in the intervention group relative to the control group. However, the results do suggest that ceiling-mounted dynamic bright light treatment at nursing home dementia units influenced timing of the activity acrophase after 16 weeks. The group-by-

time interaction was, however, not significant for any other time points, RAR outcomes, or after correction for multiple testing.

Although a slight advance of the acrophase in week 16 was observed in the intervention group, the delay in the control group makes up most of the group difference in change from baseline. At the 8- and 24-week follow-ups, the control group was 30 min delayed from baseline compared to the intervention group, but this difference did not reach statistical significance. As week 16 coincided with the months of January/February, it may be hypothesized that the intervention helped prevent phase delay during the darkest months of the year but made less of a difference in April (spring) when more natural light may be more available. An absence of significant group differences at week 8 follow-up in November, which also took place during winter, could indicate that the effect of BLT takes a while to emerge and thus to be detected by significance testing [63].

The efficacy of light in terms of entraining human circadian rhythms, including RAR, has been well documented [19,64], but clinical research with dementia patients has been inconclusive. In line with the present findings, advancement or stabilization of activity acrophase together with non-significant results on other circadian rhythm outcomes have been reported after BLT [31,65,66]. However, a delay of activity acrophase following morning BLT has sometimes been reported [50]. The magnitude and direction of phase shift in response to light depends on the endogenous circadian phase of the recipient [67]. One explanation for the diverging results across studies might, therefore, be variations in the timing of light administration relative to individual circadian time. Studies on BLT in dementia typically do not assess CR by core body temperature or melatonin sampling at baseline, and self-reports or observation are rarely feasible, making it difficult to adequately time the BLT. While an advance of the circadian rhythm with increasing age has frequently been reported [8], studies have suggested a possible association between a delayed acrophase and dementia [51,62,68]. The mean acrophase in the current sample was at 3.35 p.m. (SD = 1.66). Previous studies have found the mean acrophase of older adults without dementia to be around 1 p.m. [62,68], implying that the acrophase in the present sample was somewhat delayed. The sleep schedules of patients were not altered in order to deliver BLT; thus, patients would likely receive the intervention after their natural wake times. Unfortunately, there were not an adequate number of patients with an advanced acrophase to estimate their response to the treatment.

The clinical relevance of affecting acrophase timing is not yet clear. The endogenous circadian rhythm cannot be directly inferred from the rest–activity cycle, as RARs are also subject to environmental influences. Additionally, the relationship between various CR may be altered in old age and dementia [69–71], and the endogenous CR might not overlap with the RAR. However, both advanced and delayed acrophase have been linked to mortality [62,72,73], depressive symptoms [74], and cognitive decline [75]. For some individuals, stabilizing or shifting the RAR so that sleep and wakefulness occur at more conventional times might increase opportunities for social participation, ease care-giving, and allow sleep to take place at night when it is less likely to be interrupted. Although also a measure of RAR timing, the nadir did not differ significantly between groups. It may be that the nadir varies less than acrophase due to consistent bedtimes at nursing homes and few opportunities for movement during the night, especially for patients with limited mobility.

Addressing RAR dysfunction in dementia also involves aspects of the RAR beyond acrophase timing, including dampened amplitude, high fragmentation, and the absence of a 24 h rhythm [2]. The present results deviate from a number of previous studies on BLT in dementia that reported improvements on circadian outcomes such as IS [22], IV [22,76], RA [76], the F-statistic [26,50], phasor magnitude (i.e., entrainment to the light-dark cycle, [27,28]), and increased MESOR [50]. However, these studies also report null findings for a number of additional rhythm indicators measured in the same trials. There are also researchers who report no effect of light on any circadian outcome [24,29,30]. In addition to variability in the intensity, composition, timing, delivery method, and duration

of the BLT, differences in sample characteristics may partly explain conflicting findings. For instance, old age and advanced neuropathology may entail attenuated responsivity to the effects of BLT [8,14,77]. In the present study, we tested a variety of covariates, including age, comorbidities, gender, and medications, as well as exclusion based on eye disease or use of sedative medications, but did not have sufficient power to perform sub-group analyses. Performing post hoc analyses on patients with circadian disruption at baseline only, or with specific dementia sub-types, was also precluded due to insufficient group sizes. The moderate sample size, along with the large number of possible confounders, represent notable weaknesses of the current study. Although the heterogeneity of our sample entails possible confounding influences, it represents a realistic reflection of a typical nursing home population.

The ultimate goal of providing non-pharmacological treatments at nursing homes is to improve the well-being of the residents. Utilizing outcome measures that accurately reflect the challenges and improvements that are most relevant to the well-being of the residents is, therefore, crucial. We have previously reported that traditional sleep parameters, as measured by actigraphs, were not improved by the current trial [78]. However, previous publications based on data from the current trial found a positive effect of BLT in terms of proxy-rated sleep [78] and depressive symptoms [79]. While reporting biases may play a role regarding the discrepancies between objective and subjective findings, it cannot be ruled out that actigraphy is not optimal for detecting treatment response in individuals who are largely sedentary and whose daily activity rhythms are influenced by nursing home routines.

In the present study, we investigated numerous common indicators of RAR, but the optimal way to capture RAR is a topic of continuing research [2,39]. The two approaches used in the present study yielded correlated, but not equivalent, estimates of RAR (Table 3). Future research is needed to determine which RAR measure has the highest clinical relevance and sensitivity to change. Although actigraphy is commonly used due to the convenience of unobtrusive multi-day measurements, measures based on melatonin and cortisol sampling or core body temperature rhythms may provide a better insight into circadian function. Furthermore, synchrony between various circadian rhythms may constitute an important aspect of circadian function in dementia [69,80]. The use of actigraphy alone is a limitation of the current study, and future studies using multiple measures of circadian rhythms may elucidate the complex interplay between them.

Future research should determine if BLT in combination with other interventions such as melatonin, daytime activity, and nighttime light restriction is more effective than BLT alone [21,81,82]. The current sample was characterized by severe dementia and a high number of comorbidities and medications. While this is representative of the nursing home dementia population, these factors may also interact with or mask the effect of BLT. As circadian disturbance is evident before the onset of cognitive impairment [51,83], targeting at-risk individuals at an earlier stage may also yield different results and should thus be prioritized in future research.

5. Conclusions

The results suggest that there was no significant improvement of RAR after 8, 16, or 24 weeks of dynamic ceiling-mounted BLT in nursing home dementia units. However, the control group experienced a significantly larger delay of the acrophase in week 16. More research with larger sample sizes and with subjects with less severe dementia is needed in order to establish the efficacy of BLT on CR disruption in dementia patients.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/clockssleep3030032/s1, Table S1: "Light measurements in 8 dementia units after installation of light fixtures"; Table S2: "Spectral power distributions for participating dementia units"; and Table S3: "Rest activity rhythm measures by week of study for each treatment group".

Author Contributions: Conceptualization, E.F.-G., S.P. and I.H.N.; formal analysis, E.K.; investigation, E.K. and G.J.H.; data curation, E.K. and G.J.H.; writing—original draft preparation, E.K.; writing—review and editing, E.F.-G., S.P., I.H.N., G.J.H. and E.K.; visualization, E.K.; supervision, E.F.-G., S.P. and I.H.N.; project administration, E.F.-G., G.J.H., E.K., S.P. and I.H.N.; funding acquisition, E.F.-G., I.H.N. and S.P. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Regional Committee for Medical and Health Research Ethics, Health Region South East (project no. 2016/2246 6 March 2017).

Informed Consent Statement: Informed consent was obtained from legal guardians on behalf of all subjects involved in the study, and when possible, from the patients themselves.

Data Availability Statement: The data presented in this study are available from the corresponding author on reasonable request. The data are not publicly available due to the risk of compromising the privacy of participating individuals.

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RESEARCH ARTICLE Open Access

The effects of bright light treatment on affective symptoms in people with dementia: a 24-week cluster randomized controlled trial

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Abstract

Background: The majority of people with dementia have behavioral and psychological symptoms of dementia (BPSD), including depression, anxiety and agitation. These may be elicited or aggravated by disrupted circadian rhythms. Bright light treatment (BLT) is a promising non-pharmacological approach to the management of BPSD, but previous research has yielded mixed results.

Methods: Eight nursing home dementia units (1 unit = 1 cluster) with 78 patients were invited to participate in a cluster randomized controlled trial from September 2017 to April 2018 investigating the effects of BLT on sleep and circadian rhythms (primary outcome) and BPSD (secondary outcome). Ceiling mounted LED-panels were installed in the intervention group (four units), providing light at 1000 lx and 6000 K (vertically at 1.2 m) between 10 a.m. and 3 p.m., with lower values in the mornings and evenings. Standard indoor light was used in the control group (four units). BPSD were assessed with The Cornell Scale for Depression in Dementia (CSDD) and the Neuropsychiatric Inventory Nursing Home Version (NPI-NH). Data collection took place at baseline and after 8, 16 and 24 weeks. Multilevel regression models with and without false discovery rate correction were used for the analysis, with baseline values and dementia stage entered as covariates.

Results: Sixty-nine patients were included in the study at baseline. Compared to the control group, the intervention group had a larger reduction on the composite scores of both the CSDD (95% CI = − 6.0 – − 0.3) and the NPI-NH (95% CI = − 2.2 – − 0.1), as well as on the NPI-NH Affect sub-syndrome, and the CSDD Mood related signs sub-scale at follow-up after 16 weeks. With FDR correction, the group difference was significant on the CSDD Mood related signs sub-scale (95% CI = − 2.7 – − 0.8) and the NPI-NH Affect sub-syndrome (95% CI = − 1.6 – − 0.2). No differences were found between conditions at weeks 8 or 24.

Conclusion: Compared to the control condition, affective symptoms were reduced after 16 weeks in the group receiving BLT, suggesting BLT may be beneficial for nursing home patients with dementia.

Trial registration: ClinicalTrials.gov Identifier: NCT03357328. Retrospectively registered on November 29, 2017.

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Keywords: Dementia, Nursing homes, Bright light therapy, Depression, Affective symptoms, Behavioral and psychological symptoms of dementia, Clinical trial

Background

Behavioral and psychological symptoms of dementia (BPSD), including depression, anxiety, agitation and sleep problems have significant impact on the quality of life and care requirements of nursing home patients. The treatment of these symptoms can be challenging and complex [1, 2]. Pharmacotherapy is widely used in the management of depression and other BPSD, despite mixed evidence regarding efficacy and a high risk of adverse outcomes, including mortality [3–6]. Environmental and behavioral interventions are recommended as a first-line of treatment, but are often underutilized as they are challenging to implement, require time, staff resources and training, and may have limited efficacy in acute situations [7]. Research suggests that bright light treatment (BLT) represents a feasible non-pharmacological intervention, with studies reporting improvements in agitation, depression and sleep for people with dementia [8–10].

There are multiple mechanisms that may explain how light affects BPSD. Light plays a key role in regulating circadian rhythms [11, 12], which entail 24-h cycles in the activity of most bodily processes, including sleep-wake behavior, hormone secretion, metabolism and immune functions [13, 14], which are essential to health and well-being. Circadian rhythms are orchestrated by the suprachiasmatic nucleus of the hypothalamus [15], and entrained mainly by retinal illuminance [12]. Light of short wavelengths (i.e., high correlated color temperatures, CCT) and/or high illuminance (light intensity) is the most effective at eliciting non-visual responses such as circadian entrainment [16, 17].

Disruption of circadian rhythms has been implicated as a contributing factor to a range of health problems [18], mood disorders [19], sleep disturbances [20], and even neuropsychiatric disorders such as dementia [21]. It is well-established that sleep is related to mood and mental health [22]. Disturbed circadian rhythms and sleep may thus represent an important pathway through which light affects mood.

Light may also have acute and direct effects on mood, alertness, and cognitive function though pathways from the retina (e.g., to hypothalamic and limbic regions) that do not depend on the suprachiasmatic nucleus [11, 23, 24]. BLT is recommended as the treatment of choice for seasonal affective disorder [25, 26], and multiple studies have found evidence that BLT may improve depression in non-seasonal affective disorders [27–29], also in older adults [29, 30].

Providing BLT to people with dementia by using light boxes can be challenging, as they require patients to remain in front of the light source for the duration of the treatment. Using ceiling-mounted light technology allows for delivery of BLT without interfering with the daily routine at nursing homes, as all patients can receive BLT simultaneously, without staff facilitation.

In one of the few studies to date on ambient BLT in dementia units, Riemersma-van der Lek et al. [31] found that ceiling mounted whole-day light treatment (±1000 lx) significantly ameliorated depressive symptoms (measured by the Cornell Scale for Depression in Dementia, CSDD) in a double-blind trial ($n = 189$). Depression scores were reduced by 1.47 points, or 19%, after 3.5 years (1.76 points at a 1.5-year follow-up), in the group receiving BLT alone ($n = 49$) [31]. Using a pre-post design ($n = 14$ nursing home patients), Figueiro et al. found that 300–400 lx of high-CCT all-day ambient light improved depression, agitation, and sleep after 4 weeks [10]. Other studies on ambient BLT for dementia patients have, however, reported conflicting or mixed results, possibly due to significant methodological differences [32, 33].

Systematic reviews of research on BLT in dementia have called for more high-quality research and detailed reporting of procedures in order to determine the appropriate intensity, frequency, method of delivery, duration, and timing of light treatment on outcomes [34–37]. In addition, the dementia population is heterogenous, and the efficacy of BLT may depend on the severity of the disease [38, 39]. Few studies investigating the effect of BLT on depression have lasted for more than 4 weeks [29, 35, 40]. We aimed to take these concerns into account by controlling for dementia severity, reporting detailed information about light parameters measured at eye level, and conducting a trial of long duration with data collection at multiple points, in order to ascertain the time needed to achieve any beneficial effect.

The present results are secondary outcomes from the 24-week cluster randomized controlled DEM.LIGHT trial. In the present study, the main aim was to assess whether BPSD, as measured by the Neuropsychiatric Inventory Nursing Home Version (NPI-NH) and the Cornell Scale for Depression in Dementia (CSDD), were reduced from baseline to follow up at weeks 8, 16 and 24 in the group receiving BLT compared to the control group. In order to gain better understanding of the results, the correlations between the outcome scales at baseline were also investigated. Our hypothesis was that

BPSD would be reduced in the group receiving BLT compared to the control group at follow-ups.

Methods

Trial design

The DEM.LIGHT trial ("*Treatment Light Rooms for Nursing Home Patients with Dementia– Designing Diurnal conditions for Improved Sleep, Mood and Behavioral Problems*", ClinicalTrials.gov Identifier: NCT03357328) was a cluster randomized placebo-controlled trial conducted from September 2017 to April 2018 in Bergen, Norway. Data was collected at four time points; at baseline, week 8, week 16 and week 24. The data collected included proxy-rated questionnaires about BPSD, sleep, activities of daily living, quality of life, and resource utilization; a pain assessment; cognitive assessment; information from medical journals; and assessment of sleep and circadian rhythms. Sleep outcomes have been reported previously [41]. The study adheres to the CONSORT guidelines [42].

Participants

All nursing homes with a dedicated dementia unit in Bergen municipality, Norway were eligible unless they were participating in other projects or had architectural features prohibiting installation of the light panels. Out of 14 invited nursing home unit leaders, 8 agreed to partake in the trial, and we thus invited a total of 78 residents to participate. The units that were not included either declined to participate (four units), were excluded due to having twice as many residents as other units (one unit), or signalled interest only after the desired number of units was achieved (one unit). All residents at the participating units were screened for inclusion (see Table 1 for eligibility criteria) by clinical psychologists (EK and GJH), in collaboration with the nursing home physician. Inclusion criteria were that the patients had to be at least 60 years old; be in long term (i.e., > 4 weeks) care; have dementia according to the DSM-5 criteria; have sleep/circadian rhythm disturbance, BPSD, or reduced activities of daily living (ADL); and that consent was given for participation by the patient or a proxy. Patients were excluded if they were blind; unable to benefit from BLT; were already taking part in another trial; had a condition contra-indicated to the intervention; had an advanced, severe medical disease and/or expected survival of less than 6 months, or other aspects that could interfere with participation; and if they were psychotic or had a severe mental disorder. Legal guardians provided consent on behalf of the patients after receiving information verbally and in writing. Patients who were potentially able to understand were informed in a personally adapted manner, and given the option to not consent. Verbal and non-verbal expressions of unwillingness to participate by the patients were regarded as withdrawal of consent during the whole data collection. Patients were also allowed freely to withdraw to other areas if they were uncomfortable with the light. Recruitment of nursing home units and patients took place between September 2016 and August 2017, ensuring that participants had spent at least 1 month in the nursing home unit before baseline measurements. Resident physicians and nursing home staff were encouraged to provide care as usual, including necessary psychopharmacological treatment.

Group allocation and blinding

Eight nursing homes were randomized (one cluster per nursing home) by EK and EF to either the intervention group (four clusters) or the control group (four clusters), using random group assignment in SPSS [43]. All participants in each nursing home unit were thus assigned to the same group. Employees in the nursing home units were only told that the researchers were investigating the effect of different kinds of light, not specifically which aspects of the light they would be studying. Blinding of residents was not considered an issue due to the degree of memory loss experienced by those in the target population.

Delivery of the intervention

Ceiling mounted LED light panels (Glamox, 1 x C95 48 CCT 6500 K MP 47 W/4702 lm) were installed in the living rooms of the four nursing home units in the

Table 1 Study inclusion and exclusion criteria

Participants were eligible if they:	Patients were not eligible 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 of less 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, *NPI-NH* Neuropsychiatric Inventory-Nursing Home Version

intervention group. The number of light panels needed to provide the required illuminance was calculated for each site by Glamox engineers, taking room size and number of windows into account. The lights were programmed to deliver light at varying illuminances and CCT throughout the day with gradual transition periods, mimicking daily variations in the natural light cycle (see Fig. 1). Peak illuminance and color temperature was delivered between 10 a.m. and 3 p.m. each day, and consisted of approximately 1000 lx and 6000 K (vertically) at the cornea (falling within the interquartile range of observed CCT values for natural daylight across atmospheric conditions, i.e. 5712–7757 K [44]). In the nursing home units assigned to the control group, lights were also changed, but the new light bulbs (CFL AURA UNIQUE-D/E LL 18 W/830 G241–2 in three units and CFL AURA UNIQUE-L LL 18 W/830 2G11 in one) delivered standard indoor illumination (~ 3000 K, 150–300 lx at eye level in the center of the room). In addition to measurements taken by engineers during the installation, illuminance was measured after the start of the trial in all eight units, using the GL Spectis 1.0 T Flicker spectrometer (GL Optic). Measurements were taken vertically at 1.2 m above the floor, to approximate corneal illuminance for a seated patient. Melanopic equivalent daylight (D65) illuminance (EDI) was calculated according to recommendations by the International Commission on Illumination (CIE) [45], using the CIE S 026 toolbox [46]. The daily schedules of the patients were not altered to encourage exposure. Rather, the time spent in the intervention area was meant to reflect the regular habits of the patients.

Outcomes

The aim of this study was to investigate the effect of BLT on BPSD. In addition to the BPSD-measures described below, demographic information and health data were extracted from patients' medical journals by authors with clinical authorization. Additionally, the Mini-Mental State Examination (MMSE) was administered by clinical psychologists (EK and GJH). The MMSE is a validated brief clinician-administered test of cognitive functions, such as orientation, reading, writing, and memory, scored on a scale with a composite score ranging from 0 to 30 where a lower score indicates more impaired cognition [47, 48]. The Charlson Comorbidity Index (CCI) was completed by the researchers based on the patients' medical journal. The CCI is a tool for classifying comorbid conditions, with weights assigned according to the number and seriousness of diseases. A higher score is associated with increased 1-year mortality rates [49]. The Functional Assessment Staging Test (FAST) describes seven stages in the progression of Alzheimer's disease, with good validity and reliability [50, 51]. It focuses on the ability to perform activities of daily living, delineating the progressive loss of functioning through seven stages (from 1 = normal adult to 7 = severe Alzheimer's).

Symptoms of BPSD were evaluated at baseline and after 8, 16 and 24 weeks, using proxy-rater scales validated for people with dementia. See Table 2 for an overview of items contained in the scales and sub-scales used. Proxy-raters were nursing home staff that knew the patients well. Questionnaires were completed with guidance from researchers to ensure consistency of completion across different nursing home units.

The Cornell Scale for Depression in Dementia (CSDD) [52] consists of 19 items, each reflecting the presence of an observable symptom in the preceding week. The items are rated as absent (0), mild/intermittent [1] or severe [2], resulting in a composite score ranging from 0 to 38. Individual items are clustered in groups of five sub-scales under the headings "Mood-related signs" (consisting of anxiety, sadness, lack of reactivity to pleasant events, and irritability), "Behavioral disturbance" (consisting of agitation, psychomotor retardation, multiple physical complaints, and loss of interest), "Cyclic functions" (mood worse in the morning, difficulty falling asleep, multiple nocturnal awakenings, and early-morning awakening), "Physical signs" (loss of appetite, weight loss, and loss of energy), and "Ideational disturbance" (suicidal ideation, low self-esteem, pessimism and mood-congruent delusions). Sub-scale scores (range 0–8) were calculated for the first three of these sub-scales. Physical signs were excluded based on the high occurrence of severe somatic illness in the sample, making it difficult to identify physical signs as depressive

Fig. 1 Phases of the light sequence in the intervention group. Illuminance (lux) and correlated color temperature (kelvin, K) at different times of the day in the intervention group, with gradual transition periods of 30 min separating each phase. Between 21:00 and 07:00 o'clock the lights could also be turned off by staff if this was preferred

Table 2 Overview of outcome scales and sub-syndromes included in analyses

CSDD total	Mood-related signs, behavioral disturbance, cyclic functions (see descriptions below), physical signs (loss of appetite, weight loss, and loss of energy), and ideational disturbance (suicidal ideation, low self-esteem, pessimism, and mood-congruent delusions).
CSDD Mood-related signs	Anxiety, sadness, lack of reactivity to pleasant events, and irritability.
CSDD Behavioral disturbance	Agitation, psychomotor retardation, multiple physical complaints, and loss of interest.
CSDD Cyclic functions	Diurnal variation (mood worse in the morning), difficulty falling asleep, multiple nocturnal awakenings, and early-morning awakening.
NPI-NH total	Delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, sleep and night-time behavior, and appetite and eating.
NPI-NH Agitation	Agitation/aggression, disinhibition and irritability.
NPI-NH Affective symptoms	Depression and anxiety.
NPI-NH Psychosis	Delusions and hallucination.

CSDD The Cornell Scale for Depression in Dementia, *NPI-NH* The Neuropsychiatric Inventory Nursing Home Version

symptoms. Ideational disturbance was excluded because few of the participants were capable of verbally expressing such ideas. The CSDD has shown high interrater reliability, internal consistency and sensitivity [52], and the Norwegian translation has demonstrated satisfactory psychometric properties [53].

The Neuropsychiatric Inventory Nursing Home Version (NPI-NH) assesses 12 common psychological and behavioral symptoms in dementia: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, sleep and night-time behavior, and appetite and eating [54]. Each symptom is scored according to frequency (range 0–4) and severity (range 0–3) of the symptoms in the preceding week. The product of the scores of each item (frequency x severity, range 0–12) are added up to a total score (range 0–144). We also report scores on the sub-syndromes "Affective symptoms" (depression and anxiety, range: 0–24), "Psychosis" (delusions and hallucination, range: 0–24), and "Agitation" (consisting of items on agitation/aggression, disinhibition and irritability, range: 0–24), which are based on stable co-occurrence of symptoms in factor analyses [55]. The Norwegian version of the NPI-NH has good reliability and validity [56].

Estimated light exposure time was assessed by asking staff to estimate how many hours the patient on average had spent in the living room between 10 a.m. and 3 p.m. (i.e., the period of peak illuminance and CCT in the intervention condition) since the last data collection.

Other measurements used in baseline correlations. The Sleep Disorder Inventory (SDI) is an extension of the NPI-NH, and was scored by summarizing the severity x frequency ratings for seven symptoms (range 0–84) [41, 57]. The SDI has been shown to correspond well with actigraphy-measured sleep in people with dementia [57]. Wake After Sleep Onset (WASO) was assessed using actigraphs (*Actiwatch II, Philips Respironics)* worn on the dominant wrist [58] for 1 week, during the same week as the questionnaire completion took place or in the week preceding it. Medium sensitivity, and an epoch length of 1 min. Were used. Due to absent cues for accurately determining rest intervals, fixed intervals were set for the rest period (10 p.m. to 6 a.m.), and these intervals were then automatically analysed by the Actiware software *(version 6.0.9, Philips Respironics)* to yield the number of minutes spent awake or asleep in each interval. WASO was defined as the number of minutes spent awake between the onset of the first sleep period and the final awakening in the rest interval. WASO was chosen because it is less impacted than sleep onset latency and early morning awakening when using fixed rest intervals.

Sample size and power calculation

The necessary sample size was estimated with an expectation of moderate effect sizes (Cohen's d = .50) using ANOVA analysis. With a .05 alpha level (two-tailed), and the power set to .80, the power-analysis indicated that a minimum of 64 participants and 8 clusters were needed in order to detect differences between active and control conditions [59, 60]. The aim was to recruit 80 participants, allowing for a 20% dropout.

Data management and statistical analyses

Statistical analyses were conducted using R [61]. For all outcomes, multilevel regression models were fitted with lme4 [62] using restricted maximum likelihood estimation, and with a random intercept for each patient. As the residuals for models using untransformed NPI-NH total and sub-syndrome scores violated distributional assumptions, a square root transformation (with an added

constant of 0.001) were applied to all NPI-NH scores. After transformation of NPI-NH scores, all models satisfied assumptions of multilevel linear regression modelling. Estimated marginal means with confidence intervals were calculated for all outcomes. The NPI-NH scores were calculated from transformed variables, and then back-transformed for estimated marginal means. All models were fitted with and without a Benjamini-Hochberg [63] false discovery rate (FDR) correction, which adjusts the significance level to account for an increased probability of a type 1 error when multiple tests are conducted. Both corrected and uncorrected results are reported [64]. Associations between variables at baseline were investigated using Spearman correlations.

The FAST score was added as a predetermined covariate to all analyses in order to control for dementia severity, following recommendations by previous authors [34]. Baseline levels of the dependent variable were also added as a covariate to all models [65]. In addition, the following covariates were tested after the completion of the main analysis to investigate their impact on the results: time spent in the living room (i.e., exposure time in the intervention group), having an Alzheimer's diagnosis, age, the number of psychotropic medications prescribed for regular use, melanopic EDI, prescription of sedatives or hypnotics, being diagnosed with an eye disease, and scores on the Charlson Comorbidity Index. The sample size was not sufficient to perform sub-group analyses on categorization based upon the aforementioned or other variables, such as dementia sub-type.

Patients missing 20% or more of a single outcome scale at any time point were excluded from analysis at that particular time point. If less than 20% was missing, data points were imputed using expectation maximization in SPSS [43]. Patients in either group who had spent less than 30 min on average per day in the living room since the previous data collection were excluded from analysis.

Results

Sixty-nine patients from eight dementia units at separate nursing homes were included, out of 78 potential participants. Reasons for exclusion were failure to meet eligibility criteria ($n = 3$) and declining to participate ($n = 6$). Figure 2 shows a flow diagram detailing the number of patients included at each stage of the trial, as well as reasons for those excluded. In all, 38 of the included patients (55%) had an Alzheimer's diagnosis, 21 (30.5%) had an unknown dementia type, and 7 (10%) had other dementia diagnoses. Three patients did not have a registered dementia diagnosis but were included based on an MMSE score below 26 and assessment by clinicians. Two of the included patients were diagnosed with Parkinson's disease. Baseline descriptive statistics are reported in Table 3. The median age of the participants at baseline was 85 years, 47 patients (68%) were female, and the median MMSE score was 4, corresponding to severe cognitive impairment [48]. The estimated time per day that each group spent in the living room between 10 a.m. and 3 p.m. is shown in Fig. 3. The types of psychotropic medications prescribed for regular use at each time point are shown in Table 4. Baseline scores on outcome scales in the intervention and control groups are presented in Table 5. Notably, the intervention group median on the CSDD was 11, while the control group median was 6. On the NPI-NH, the intervention group median was 24, whereas the control group median was 12.5 (Table 5).

Light measurements

The mean vertical illuminance was 1039 lx (range 722–1242 lx) in the intervention condition and 242 lx (range 134–368 lx) in the control group. Mean CCT was 5369 K (range 5088–5641 K) in the intervention group and 3049 K (range 2707–3622 K) in the control group. In terms of melanopic EDI, the mean illuminance was 779 lx in the intervention group and 124 lx in the control group [45]. Although there was some variability between intervention units in the illuminance achieved, both illuminance and CCT were consistently higher in the intervention than in the control condition.

The Cornell scale for depression in dementia

Using a total score of 8 as a cut-off for depression on the CSDD [53], 14 patients in the control group and 24 in the intervention group could be categorized as clinically depressed at baseline. In week 16, this was reduced to 8 patients in the control group and 11 patients in the intervention group. Analyses of the total CSDD score (Table 6) found a significant interaction between week (baseline to week 16) and condition (B = – 3.2, 95% CI = – 6.0 – -0.3, $P = 0.029$) when controlling for the CSDD total at baseline and dementia severity (FAST score). The week by condition interaction indicates a difference between the control group and the intervention group in terms of change from baseline. This result therefore suggests that the intervention group had a larger change from baseline to week 16 than the control group. The estimated marginal mean (see Fig. 4), i.e., the mean adjusted for the influence of other variables in the model, was reduced from 10.3 (95% CI = 8.7–11.8) at baseline to 6.3 (95% CI = 4.6–8.0) at week 16 for the intervention group. In the control group, the estimated marginal mean was reduced from 8.2 (95% CI = 6.7–9.7) at baseline to 7.4 (95% CI = 5.6–9.3) at week 16. Thus, the CSDD total score was estimated to decrease with about 3.2 points (the coefficient for the interaction) more in the intervention group during the 16-week time span.

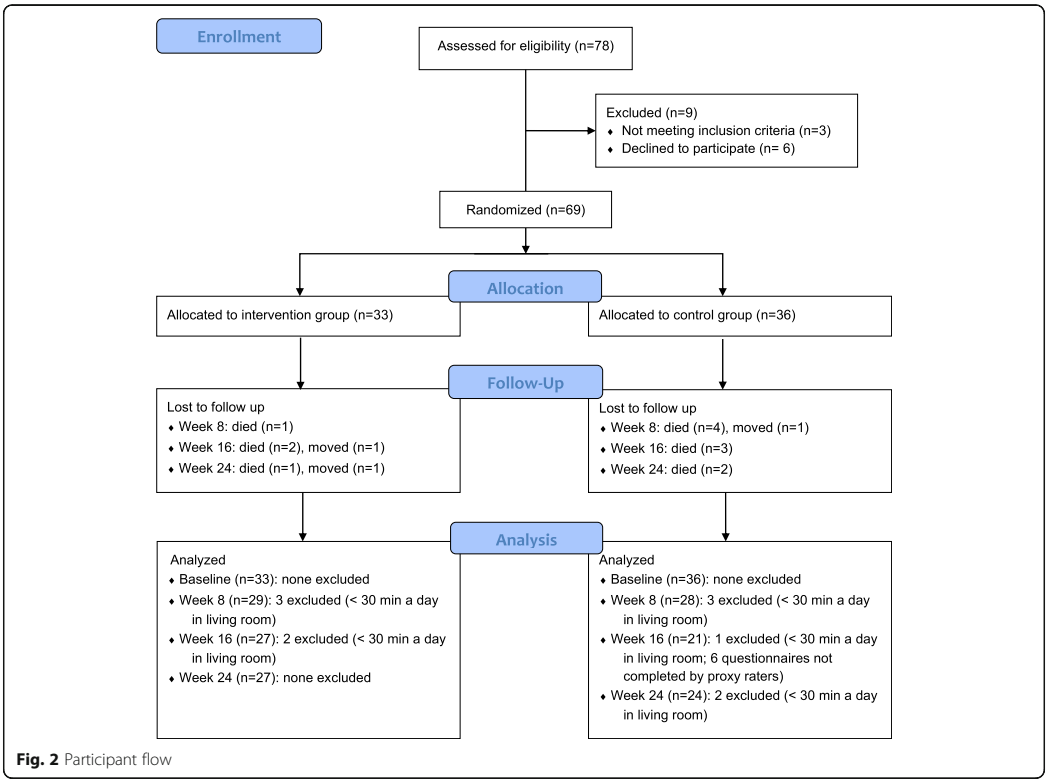

Fig. 2 Participant flow

When using FDR correction, this interaction failed to remain significant, indicating that there is a chance of this result being a false positive.

Sub-scale scores

The interaction between week and condition on the CSDD Mood-related signs was significant ($P < 0.01$) at week 16 with and without FDR correction (B = – 1.8, 95% CI = – 2.7 – – 0.8). This indicates that the intervention group scores were reduced with 1.8 points compared to the control group between baseline and week 16 when controlling for Mood-related signs at baseline and dementia severity (FAST score). The estimated marginal mean for Mood-related signs in the intervention group changed from 3.2 (95% CI = 2.7–3.7) at baseline to 1.8 (95% CI = 1.2–2.3) at week 16. In the control group, it was 2.6 at baseline (95% CI = 2.1–3.1) and 3.0 (95% CI = 2.4–3.6) at week 16. There were no significant interactions at weeks 8 or 24. There was no significant interaction in any week for the Behavioral disturbance or Cyclic functions sub-scales.

The NPI-NH inventory nursing home version

The interaction between week and condition was significant at week 16 (B = – 1.1, 95% CI = – 2.2 – -0.1, $P = 0.031$, transformed scores) for the NPI-NH total score (Table 7) when controlling for the NPI-NH total score at baseline and dementia severity (FAST score). The estimated marginal mean (back-transformed) for the NPI-NH total score was 20.7 (95% CI = 16.0–25.9) at baseline and 11.4 (95% CI = 7.7–15.9) at week 16 for the intervention group. In the control group at week 16, it was 17.7 (95% CI = 13.6–22.3) at baseline and 17.4 (95% CI = 12.4–23.3). Thus, the estimated reduction in NPI-NH scores was 9.3 in the intervention group and near zero in the control group. With FDR correction, this interaction failed to reach significance, indicating that there is a possibility of this result being a false positive.

Sub-syndrome scores

The interaction between week and condition on the Affective symptoms sub-syndrome was significant ($P < 0.01$) at week 16, both with and without FDR correction (B = – 0.9, 95% CI = – 1.6 – – 0.2, transformed scores)

Table 3 Baseline descriptive statistics

	Control (*N* = 36)	Intervention (*N* = 33)	Total (*N* = 69)
Gender			
Female	22 (61.1%)	25 (75.8%)	47 (68.1%)
Male	14 (38.9%)	8 (24.2%)	22 (31.9%)
Age			
Median (Q1, Q3)	82.5 (77.5, 88.0)	86.0 (83.0, 88.0)	85.0 (79.0, 88.0)
FAST			
Missing	1	1	2
4	1 (2.9%)	2 (6.2%)	3 (4.5%)
5	1 (2.9%)	2 (6.2%)	3 (4.5%)
6	24 (68.6%)	25 (78.1%)	49 (73.1%)
7	9 (25.7%)	3 (9.4%)	12 (17.9%)
Charlson			
Median (Q1, Q3)	1.0 (1.0, 2.0)	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)
MMSE			
Missing	6	3	9
Median (Q1, Q3)	3.0 (1.0, 6.8)	6.0 (2.0, 10.0)	4.0 (1.0, 9.2)
No. of psychotropic drugs			
Mean (range)	2.91 (1–6)	2.78 (0–5)	2.85 (0–6)
SDI			
Median (Q1, Q3)	3.0 (0.0, 18.0)	3.0 (0.0, 12.5)	3.0 (0.0, 17.5)
WASO			
Median (Q1, Q3)	73.9 (34.8, 106.6)	56.5 (32.9, 85.2)	62.7 (32.9, 95.0)

Q1 25th percentile, *Q3* 75th percentile, *FAST* Functional Assessment Staging Test, *Charlson* Charlson Comorbidity Index, *MMSE* Mini-Mental State Exam, *SDI* Sleep Disorder Inventory, *WASO* Wake After Sleep Onset

when controlling for Affective symptoms at baseline and dementia severity (FAST score). The estimated marginal mean (back-transformed) for Affective symptoms in the intervention group changed from 3.2 (95% CI = 1.7–5.1) at baseline to 1.1 (95% CI = 0.3–2.5) in week 16. In the control group, it was 1.6 at baseline (95% CI = 0.6–3.0) and 2.1 (95% CI = 0.8–4.0) in week 16. Thus, there was an estimated reduction of 2.1 points in the intervention group, and a slight increase of 0.5 points in the control group. There was no significant interaction at weeks 8 or 24. There was no significant interaction in any week for the sub-syndromes Psychosis or Agitation.

A comparison of the standardized interaction coefficients for all BPSD outcome scales (indicating relative treatment effect) is shown in Fig. 5. When controlling for time spent in the living room, having an Alzheimer's diagnosis, gender, eye disease, age, melanopic EDI, psychotropic medications, the use of sedatives or hypnotics, or score on the Charlson Comorbidity Index, coefficients remained the same or changed only marginally, not affecting significance levels. The only exception was that the Cornell total score coefficient for week 8 just reached significance ($p = 0.047$) before FDR correction with the addition of most covariates, indicating that this score was borderline significant before correcting for multiple measures. The sample size was not sufficient to perform sub-group analyses based on the variables controlled/adjusted for.

Correlations with sleep and other outcome scales at baseline

Spearman correlations at baseline are shown in Fig. 6. There was a significant correlation between the NPI-NH and CSDD total scores at baseline (rho = 0.63). CSDD Mood-related signs and NPI-NH Affective symptoms were highly correlated at 0.70, whereas NPI-NH Agitation and CSDD Behavioral disturbance only correlated at 0.28. WASO only correlated significantly with CSDD Cyclic functions (rho =0.29) and with the NPI-NH total (rho = 0.25), whereas the SDI total correlated with the CSDD Cyclic functions (rho = 0.62), the CSDD total (rho = 0.28), the NPI-NH Agitation (rho = 0.33), and NPI-NH total (rho = 0.49).

Discussion

The present study provides some support for our hypothesis that BPSD can be improved by ceiling mounted BLT, specifically affective symptoms. Results showed significant improvements from baseline to week 16 in the intervention group as compared to the control group on the total scores of both the NPI-NH and CSDD, although not with false discovery rate correction. Only the NPI-NH Affective symptoms sub-scale and the CSDD Mood related signs showed significant group differences in change from baseline to week 16 after FDR correction. In short, the intervention group had an improvement in affective symptoms after 16 weeks of BLT compared to the control group. Our findings suggest that light has a potential clinical application in the management of mood related symptoms in people with dementia, with possible implications for the planning and design of dementia units.

The NPI-NH Affective symptoms and the CSDD Mood-related signs contain questions about depression and anxiety (see Table 2 for an overview of the scales). Although all items of the CSDD are designed to capture various symptoms of depression, mood-related symptoms may be less affected by difficulties with assessing ideation and somatic symptoms than the composite score. Reductions in expressions of affective symptoms, such as sadness and anxiety, are in line with previous research recommending BLT as an intervention for affective disorders [27–30]. However, the present findings diverge from a number of previous studies on BLT in dementia that have reported reduced agitation [10, 66, 67]. We could not replicate these findings using

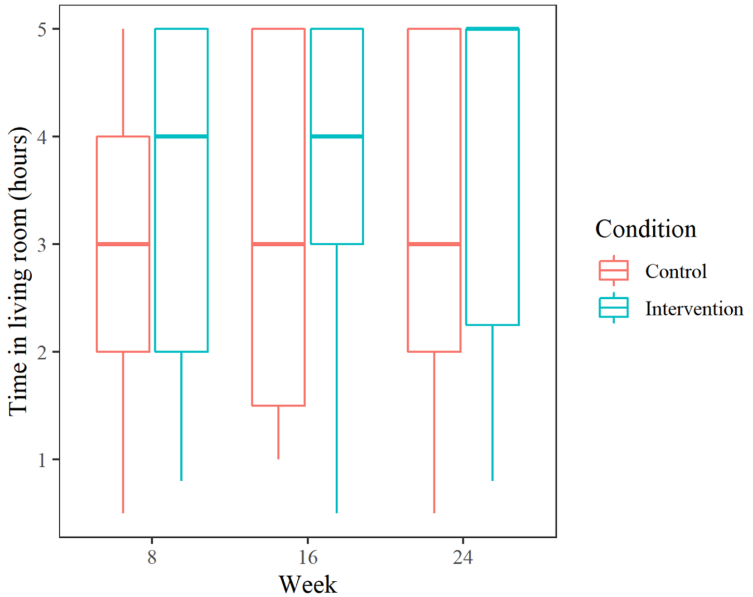

Fig. 3 Time spent in living room (daily average) between 10 a.m. and 3 p.m.* since the previous data collection. *Corresponding to the period of peak illumination (1000 lx and 6000 K) for the intervention group. Horizontal line = median, boxes = 25. – 75. percentiles, ends of whiskers = min / max. After exclusion of patients who spent < 30 min in the living room in this time period

NPI-NH Agitation, or CSDD Behavioral disturbance scores. One reason for this discrepancy could be that previous studies have utilized different outcome measures for agitation [10, 66, 67].

Results on some sub-scales may have been impacted by the fact that certain symptoms are less common. The median scores on NPI-NH Psychosis were 0 in almost all weeks for both groups, and never above 1. Hence, detecting change on sub-syndromes or sub-scales comprising symptoms with very low frequency may require a larger sample size. In contrast, a relatively large number of patients had symptoms of depression, with 38 (55%) classified as depressed according to the CSDD.

The group difference in affective symptoms was only apparent at week 16, corresponding to the winter months of January/February. A possible explanation for this could be variations in availability of natural daylight. As week 24 occurred during springtime (April), week 16 represents the assessment point at which participants would have experienced the shortest period of daily natural illumination. This interpretation is in line with studies showing that seasonal affective disorder peak between December and February [68]. However, if the main effect of the BLT was to prevent deterioration during winter, we may have expected the control group to deteriorate, while the intervention group remained at

Table 4 Types of psychotropic medications prescribed for regular use at each time point

	Week 0 (baseline)		Week 8		Week 16		Week 24	
	Control (N = 36)	Intervention (N = 33)	Control (*N* = 28)	Intervention (*N* = 29)	Control (*N* = 21)	Intervention (*N* = 27)	Control (*N* = 24)	Intervention (*N* = 27)
Hypnotics and sedatives[a]	3 (8.3%)	6 (18.2%)	4 (14.3%)	4 (13.8%)	3 (14.3%)	4 (14.8%)	4 (16.7%)	2 (7.4%)
Benzodiazepines[b]	10 (27.8%)	13 (39.4%)	5 (17.9%)	13 (44.8%)	3 (14.3%)	12 (44.4%)	5 (20.8%)	9 (33.3%)
Antidepressants[c]	21 (58.3%)	16 (48.5%)	16 (57.1%)	11 (37.9%)	12 (57.1%)	11 (40.7%)	14 (58.3%)	11 (40.7%)
Antipsychotics[d]	20 (55.6%)	16 (48.5%)	17 (60.7%)	14 (48.3%)	12 (57.1%)	12 (44.4%)	12 (50.0%)	12 (44.4%)
Anti-dementia drugs[e]	7 (19.4%)	6 (18.2%)	5 (17.9%)	5 (17.2%)	2 (9.5%)	4 (14.8%)	4 (16.7%)	5 (18.5%)

Nmber of people who were prescribed each type of medication for regular use. [a]Anatomical Therapeutic Chemical (ATC) classification N05C. [b]ATC N05BA, benzodiazepine derivatives classified as anxiolytics. [c]ATC N06A. [d]ATC N05A. [e]ATC N06D

Table 5 Outcome variables raw scores, all weeks. Median (Q1, Q3)

	Week 0 (baseline)		Week 8		Week 16		Week 24		
	Control (N = 36)	Intervention (N = 33)	Control (N = 28)	Intervention (N = 29)	Control (N = 21)	Intervention (N = 27)	Control (N = 24)	Intervention (N = 27)	Total (*N* = 225)
CSDD total	6.0 (4.0, 11.0)	11.0* (7.0, 14.0)	7.0 (4.0, 11.2)	10.0* (7.0, 13.0)	5.0 (1.0, 10.0)	6.0 (5.0, 9.0)	4.5 (1.8, 7.2)	8.0* (5.5, 12.5)	8.0 (4.0, 12.0)
CSDD Mood-related signs	2.0 (1.0, 3.0)	4.0* (2.0, 5.0)	2.5 (1.0, 4.0)	3.0 (2.0, 4.0)	2.0 (0.0, 4.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	3.0* (2.0, 4.0)	3.0 (1.0, 4.0)
CSDD Behavioral disturbance	1.5 (0.8, 3.0)	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)	3.0 (1.0, 4.0)	1.0 (0.0, 2.0)	2.0 (0.5, 3.0)	0.5 (0.0, 1.2)	3.0* (1.0, 4.0)	2.0 (1.0, 3.0)
CSDD Cyclic functions	1.0 (0.0, 2.0)	2.0 (0.0, 4.0)	2.0 (0.0, 3.0)	2.0 (1.0, 3.0)	0.0 (0.0, 2.0)	1.0 (0.0, 2.5)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)
NPI-NH total	12.5 (5.8, 41.8)	24.0 (11.0, 42.0)	17.0 (5.8, 30.0)	19.0 (9.0, 34.0)	14.0 (6.0, 34.0)	13.0 (6.0, 26.2)	10.0 (5.0, 21.0)	20.0 (10.0, 28.0)	16.0 (6.0, 34.0)
NPI-NH Agitation	4.5 (0.0, 14.2)	6.0 (0.0, 12.0)	6.0 (2.0, 12.5)	4.0 (2.0, 14.0)	2.0(0.0, 14.0)	2.5 (0.2, 5.8)	4.0 (0.0, 8.0)	3.0 (1.0, 11.0)	4.0 (0.0, 12.0)
NPI-NH Affective symptoms	0.5 (0.0, 4.0)	2.0 (0.0, 10.0)	0.5 (0.0, 4.5)	1.0 (0.0, 6.0)	1.0 (0.0, 8.0)	1.0 (0.0, 4.0)	0.0 (0.0, 0.0)	2.0* (0.0, 6.0)	1.0 (0.0, 6.0)
NPI-NH Psychosis	0.0 (0.0, 8.0)	1.0 (0.0, 8.0)	0.0 (0.0, 3.0)	0.0 (0.0, 5.0)	0.0 (0.0, 4.0)	0.0 (0.0, 2.0)	0.0 (0.0, 4.0)	1.0 (0.0, 4.0)	0.0 (0.0, 6.0)

** p < 0.05, Kruskal-Wallis rank sum test for the difference between the control and intervention group. Q1* 25th percentile, *Q3* 75th percentile, *CSDD* The Cornell Scale for Depression in Dementia, *NPI-NH* The Neuropsychiatric Inventory Nursing Home Version

Table 6 Cornell Scale for Depression in Dementia predicted by week, condition, dementia severity and baseline total using multilevel regression

Predictors	Total		Mood-related signs		Behavioral disturbance		Cyclic functions	
	Estimates (CI)	*Std. betas (SD)*	*Estimates (CI)*	*Std. betas (SD)*	*Estimates (CI)*	*Std. betas (SD)*	*Estimates (CI)*	*Std. betas (SD)*
Week (8)	1.6 (− 0.3–3.5)	0.3 (1.6)	0.6 (− 0.1–1.2)	0.3 (1.8)	0.5 (− 0.2–1.1)	0.3 (1.3)	0.4 (− 0.3–1.0)	0.2 (1.1)
Week (16)	-0.8 (−2.8–1.3)	-0.1 (− 0.7)	0.3 (− 0.3–1.0)	0.2 (1.0)	− 0.6 (− 1.3–0.1)	− 0.4 (− 1.7)	− 0.6 (− 1.3–0.1)	− 0.3 (− 1.6)
Week (24)	− 1.2 (−3.2–0.8)	− 0.2 (− 1.2)	0.1 (− 0.5–0.8)	0.1 (0.5)	−0.4 (− 1.1–0.3)	−0.2 (− 1.1)	−0.6 (− 1.3–0.1)	−0.3 (− 1.7)
Condition [Intervention]	2.1 (− 0.1–4.2)	0.4 (1.9)	0.6 (− 0.1–1.3)	0.3 (1.6)	0.4 (− 0.3–1.1)	0.2 (1.1)	0.5 (−0.1–1.2)	0.3 (1.6)
Interactions (indicating treatment effect)								
Week (8) * [Intervention]	−2.7 (−5.4–0.0)	−0.5 (− 1.9)	− 1.0 *(− 1.9 – − 0.1)	− 0.5 (− 2.3)	−0.4 (− 1.4–0.5)	−0.2 (− 0.9)	−0.6 (− 1.5–0.3)	−0.3 (− 1.3)
Week (16) * [Intervention]	− 3.2 *(−6.0 – − 0.3)	− 0.6 (− 2.2)	*−1.8 ***(− 2.7 – − 0.8)*	−0.9 (− 3.8)	−0.0 (− 1.0–0.9)	−0.0 (− 0.1)	−0.1 (− 1.1–0.8)	−0.1 (− 0.3)
Week (24) * [Intervention]	−1.0 (− 3.8–1.8)	−0.2 (− 0.7)	−0.8 (− 1.6–0.1)	−0.4 (− 1.7)	0.4 (− 0.5–1.4)	0.3 (0.9)	−0.5 (− 1.5–0.4)	−0.3 (− 1.1)
Covariates								
FAST	0.2 (−0.9–1.2)	0.0 (0.3)	−0.3 (− 0.6–0.1)	−0.1 (− 1.5)	0.1 (− 0.3–0.4)	0.0 (0.3)	0.2 (− 0.1–0.6)	0.1 (1.4)
Baseline DV	*0.6 ***(0.4–0.7)*	0.6 (8.6)	*0.6 ***(0.5–0.8)*	0.7 (8.8)	*0.5 ***(0.4–0.6)*	0.5 (7.4)	*0.5 ***(0.4–0.6)*	0.6 (9.6)
Model information								
ICC (id)	0.25		0.32		0.18		0.11	
Marginal R^2 / Conditional R^2	0.423 / 0.567		0.436 / 0.614		0.334 / 0.454		0.415 / 0.480	

** p < 0.05, ** p < 0.01, *** p < 0.001. In italics: significant after Benjamini-Hochberg correction for false discovery rate with all eight models. Std. betas* standardized regression coefficients, *SD* standard deviation, *CI* 95% confidence interval, *SD* standard deviation, *FAST* Functional Assessment Staging Test, *DV* dependent variable, *ICC* intraclass correlation coefficient

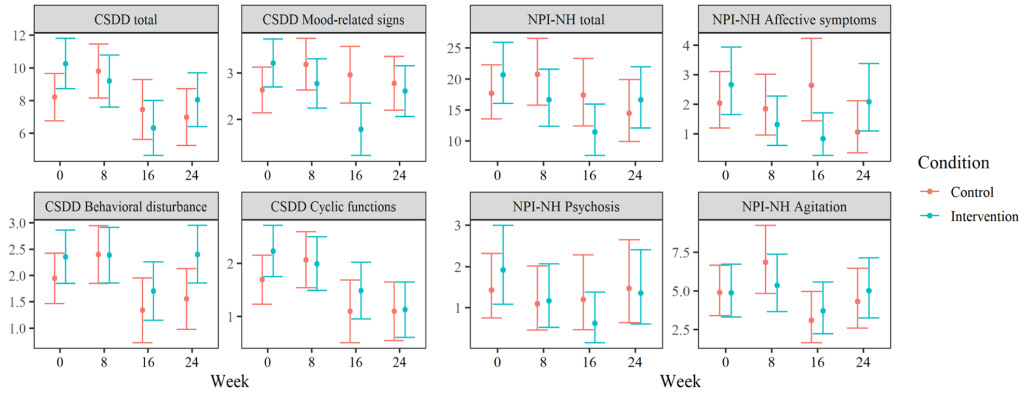

Fig. 4 Estimated marginal means for all outcome measures by week. Scale of y-axis adapted to each outcome separately. Scaled for visibility, not reflective of the full range of possible scores. CSDD = The Cornell Scale for Depression in Dementia, NPI-NH = The Neuropsychiatric Inventory Nursing Home Version

Table 7 Neuropsychiatric Inventory - Nursing Home Version (transformed scores) predicted by week, condition, dementia severity and baseline total using multilevel regression

Predictors	**Total**		**Affective symptoms**		**Psychosis**		**Agitation**	
	Estimates (CI)	***Std. betas (SD)***	***Estimates (CI)***	***Std. betas (SD)***	***Estimates (CI)***	***Std. betas (SD)***	***Estimates (CI)***	***Std. betas (SD)***
Week (8)	0.4 (− 0.3–1.0)	0.2 (1.0)	−0.1 (− 0.5–0.4)	−0.1 (− 0.3)	−0.1 (− 0.6–0.3)	−0.1 (− 0.7)	0.4 (− 0.1–0.9)	0.2 (1.6)
Week (16)	−0.0 (− 0.8–0.7)	−0.0 (− 0.1)	0.2 (− 0.3–0.7)	0.1 (0.8)	−0.1 (− 0.6–0.4)	−0.1 (− 0.4)	−0.5 (− 1.0–0.1)	−0.3 (− 1.7)
Week (24)	−0.4 (− 1.1–0.4)	−0.2 (− 1.0)	−0.4 (− 0.9–0.1)	−0.3 (− 1.6)	0.0 (− 0.5–0.5)	0.0 (0.1)	−0.1 (− 0.7–0.4)	−0.1 (− 0.5)
Condition [Intervention]	0.3 (− 0.4–1.1)	0.2 (0.9)	0.2 (− 0.3–0.7)	0.1 (0.8)	0.2 (−0.3–0.7)	0.1 (0.8)	−0.0 (− 0.5–0.5)	−0.0 (− 0.0)
Interactions (indicating treatment effect)								
Week (8) * [Intervention]	− 0.8 (− 1.8–0.1)	− 0.4 (− 1.7)	− 0.4 (− 1.1–0.2)	−0.3 (− 1.3)	−0.2 (− 0.8–0.4)	−0.1 (− 0.5)	−0.3 (− 1.0–0.4)	−0.2 (− 0.8)
Week (16) * [Intervention]	−1.1 *(− 2.2 – − 0.1)	−0.5 (− 2.2)	*−0.9 **(− 1.6 – − 0.2)*	−0.7 (− 2.6)	−0.5 (− 1.2–0.1)	−0.4 (− 1.5)	0.2 (− 0.6–0.9)	0.1 (0.5)
Week (24) * [Intervention]	−0.1 (− 1.1–1.0)	−0.0 (− 0.1)	0.2 (− 0.5–0.9)	0.2 (0.6)	−0.2 (− 0.9–0.4)	−0.2 (− 0.7)	0.2 (− 0.6–0.9)	0.1 (0.5)
Covariates								
FAST	− 0.3 (− 0.7–0.1)	− 0.1 (− 1.6)	0.0 (−0.2–0.3)	0.0 (0.4)	−0.1 (− 0.3–0.1)	−0.0 (− 0.8)	−0.2 (− 0.5–0.1)	−0.1 (− 1.6)
Baseline DV	*0.7 ***(0.6–0.8)*	0.7 (11.8)	*0.6 ***(0.5–0.7)*	0.7 (12.0)	*0.6 ***(0.5–0.7)*	0.7 (10.8)	*0.7 ***(0.6–0.9)*	0.8 (14.3)
Model information								
ICC	0.24		0.56		0.60		0.70	
Marginal R^2 / Conditional R^2	0.516 / 0.630		0.037 / 0.580		0.019 / 0.610		0.013 / 0.701	

** p < 0.05, ** p < 0.01, *** p < 0.001. In italics: significant after Benjamini-Hochberg correction for false discovery rate) with all eight models. Std. betas* standardized regression coefficients, SD standard deviation, *CI* 95% confidence interval, *SD* standard deviation, *FAST* Functional Assessment Staging Test, *DV* dependent variable, *ICC* intraclass correlation coefficient

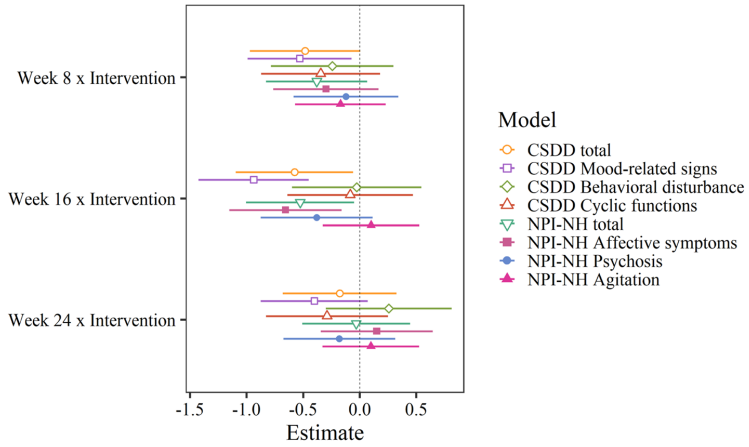

Fig. 5 Standardized coefficients* and confidence intervals for the interaction between group (intervention vs. control) and time since baseline (week).*Predictors mean-centered, and dependent variable scaled. CSDD = The Cornell Scale for Depression in Dementia, NPI-NH = The Neuropsychiatric Inventory Nursing Home Version

pre-intervention levels. Rather, we found a reduction in scores from baseline to week 16 in the intervention group, and scores that either stayed the same or only slightly worsened in the control group.

The absence of an effect in week 8 could also indicate that the effects of BLT take a while to develop. This may be particularly true for patients suffering from severe dementia, because age and neurological disorders cause physiological changes that may affect circadian photoreception [69, 70]. A recent review reported that trials of at least 8 weeks appeared more effective at reducing depression and agitation in people with dementia compared to shorter trials [35]. It is also possible that the study did not have the statistical power to detect changes from baseline to week 8, as a non-significant reduction in the NPI-NH Affective symptoms and the CSDD Mood-related signs in the intervention group was seen already at week 8 in the present study.

A delay in effect would still not explain why symptoms return to pre-intervention levels in the intervention group at week 24. It may be that the onset of spring in week 24 introduced additional illumination both in the intervention area and in the patients' bedrooms. Some researchers have raised concerns that excessive illumination may cause increased levels of agitation [38]. However, we did not find that scores on the NPI-NH Agitation or the CSDD Behavioral disturbance in the intervention group at week 24 were elevated above baseline levels.

Increased illumination in week 24 might have impacted BPSD indirectly by affecting circadian rhythms or sleep, but we found no significant change in daytime sleep or the total amount of sleep as measured by actigraphy as a result of the intervention [41]. Furthermore, the proxy-rated SDI showed significant improvements in sleep both at weeks 16 and 24 following BLT [41], indicating that caregiver perceptions of sleep problems did not increase prior to or at the same time as CSDD and NPI-NH assessed symptoms. At baseline, SDI correlated positively with the CSDD and NPI-NH totals but not with NPI-NH Affective symptoms or CSDD Mood-related signs. Taken together, this may suggest that the association between affective symptoms and measures of sleep are weak in this population, but research focusing on the relationship between these outcomes over time is needed. This is an issue that also needs to be addressed in future studies by controlling the light exposure from windows and other sources of artificial illumination outside of the main intervention area. Examination of individual variability in melatonin production and mid-winter activity levels would also be a valuable addition for exploration of why results varied over time.

The estimated group differences in change from baseline may have been inflated by the fact that scores on the CSDD and the NPI-NH were not equal between the conditions at baseline. The intervention group, with median score of 11 on the CSDD and 24 on the NPI-NH, had more room for improvement than the control group with a median score of 6 on the CSDD and 12.5 on the NPI-NH. Although baseline levels were included as predictors in the regression models, there is a possibility that changes in the intervention group could be attributed to a regression to the mean. The fact that group differences mainly resulted from symptom reduction in

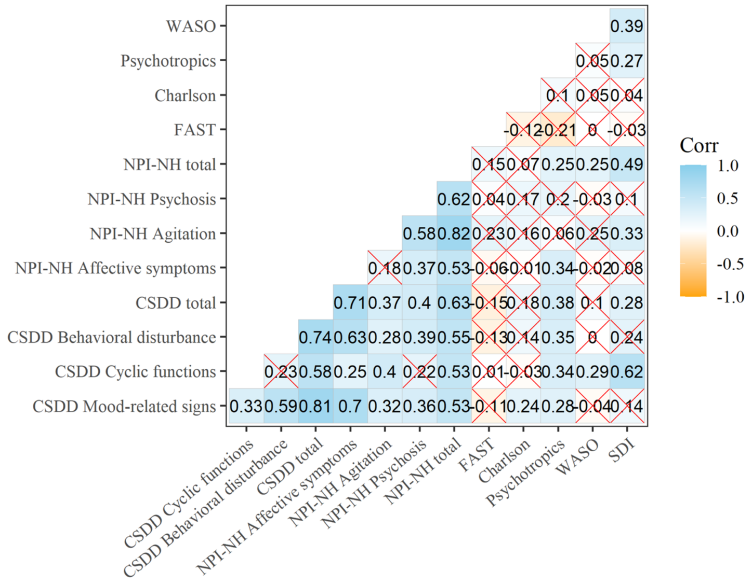

Fig. 6 Spearman correlations at baseline. Non-significant ($p > 0.05$) correlations crossed out. CSDD = The Cornell Scale for Depression in Dementia, NPI-NH = The Neuropsychiatric Inventory Nursing Home Version

the intervention group, and not increased symptoms in the control group, further supports the notion that group differences at baseline influenced the present results.

Some studies on BLT have reported side-effects, although they are normally mild and transient [71]. We did not find evidence that any symptoms (including agitation) worsened during the 24-week period in the intervention group compared to the control group.

Strengths and limitations of the study

The present study investigated short- and long-term effects of BLT, allowing for an investigation of both acute responses and of delayed effects. The 24-week time span of the trial exceeds most previous studies on BLT, allowing us to investigate the effects of BLT as well as the development of symptoms over time.

The participants represent a section of the population that is likely to experience a number of behavioral and psychological symptoms, but frequently excluded from trials due to the high occurrence of possible confounding factors such as multimorbidity and polypharmacy.

Using ceiling mounted light installations greatly reduces the demand on staff compared to the use of light boxes which require constant monitoring, and reduces the confounding impact such administration implies in terms of social interaction. Utilizing an intervention that conceivably could be implemented in dementia units also adds to the clinical relevance of the study. Resident medical practitioners and other staff were asked to continue treatment as usual, and daily routines were minimally disrupted, further adding to the ecological validity of the trial and the generalizability of the findings to clinical settings.

The use of ambient light installations also involves certain limitations. The intervention was not tailored to each individual, but rather provided a fixed schedule in terms of time and exposure. The optimal delivery of light treatment depends on individual circadian rhythms [72] and might therefore be more effective if timed according to each person's sleep-wake rhythm. This would be a demanding approach, however, and may not be feasible in dementia units with limited available staff resources. Furthermore, the daily exposure time comprised a rough estimate. Still, the current design investigated the average effect of installing dynamic light fixtures under naturalistic conditions, albeit did not estimate the ideal duration of light exposure for each patient. Continuation of treatment as usual also involves the potential for confounding effects of psychopharmacological treatments, which could mask symptoms, lead to improvements independently of the BLT, or interact with the treatment effect. Investigating such an impact would

require a considerably larger sample or a more selective screening of participants.

Inclusion mainly of very old and frail individuals with a high degree of cognitive impairment makes assessment of symptoms challenging. Our findings raise the possibility that treatment effect in this population might only be evident on questions relating to observable or overt symptoms. Future research with this population may thus consider utilizing assessment tools that to a larger extent evaluate observable behaviors. The rather small sample size is another limitation of the study. A larger sample size would have allowed for greater certainty regarding the reported results, and provided adequate power to perform subgroup-analyses, for instance by gender, depression scores at baseline, or dementia subtype. A larger number of clusters (nursing homes) would have allowed us to better account for the effect of clustering in regression models, and a larger sample of patients would be less vulnerable to group differences as baseline. Despite controlling for baseline scores in the analyses, differences in group scores at baseline raises questions about the internal validity of the present study, as the comparison group may not have provided an adequate control.

Furthermore, as light is a visible intervention, blinding of the staff to the condition assignment could not be achieved in the same way as with pharmacological trials. Although we strived to achieve a single blind design, some degree of response bias can therefore not be ruled out.

Conclusions

The results of this 24-week trial indicate that ambient BLT may be effective at ameliorating affective symptoms after 16 weeks, but not after 8 or 24 weeks, among nursing home patients with dementia. The effects were especially evident on the CSDD Mood-related signs and NPI-NH Affective symptoms, which reflect observable signs of mood disorders such as sadness, crying, anhedonia and anxiety. This may indicate that BLT is effective mainly for affective symptoms during mid-winter in this population. There were no significant effects on other BPSD or sub-scales, and no indications of negative effects. We conclude that ambient BLT shows promise as a safe and non-invasive way to reduce affective symptoms, but future research is needed to determine why the effect was not observed after 8 or 24 weeks of BLT.

Abbreviations

BPSD: Behavioral and psychological symptoms of dementia; BLT: Bright light treatment; CCT: Correlated color temperature; NPI-NH: The Neuropsychiatric Inventory Nursing Home version; CSDD: The Cornell Scale for Depression in Dementia; MMSE: The Mini-Mental State Examination; FAST: The Functional Assessment Staging Test; SDI: The Sleep Disorder Inventory; WASO: Wake After Sleep Onset; FDR: False discovery rate

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Authors' contributions

EF, SP and IHN conceived of, and secured funding for, the trial presented in the present manuscript. GJH, EK, EF, SP, IHN, and ET planned the trial. EK and GJH coordinated and implemented the trial, and collected the data with assistance from ET. EK conducted analyses and wrote the manuscript with critical feedback from all authors. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to the risk of compromising the privacy of participating individuals but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was provided by the Regional Committee for Medical and Health Research Ethics, Health Region South East (project no. 2016/2246). Legal guardians provided consent on behalf of the patients after being informed verbally and in writing. Patients who were potentially able to understand or provide consent were approached by researchers and informed in a personally adapted manner. During the trial, any verbal and non-verbal expressions of distress or unwillingness to participate in data collection procedures expressed by the patients were regarded as withdrawal of consent at that time point. Because light panels were only installed in the living rooms, patients were able to withdraw to other areas if they were uncomfortable with the light.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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	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.
	Hynninen, Kia Minna Johanna	Anxiety, depression and sleep disturbance in chronic obstructive pulmonary disease (COPD). Associations, prevalence and effect of psychological treatment.
	Flo, Elisabeth	Sleep and health in shift working nurses

	Aasen, Elin Margrethe	From paternalism to patient participation? The older patients undergoing hemodialysis, their next of kin and the nurses: a discursive perspective on perception of patient participation in dialysis units
	Ekornås, Belinda	Emotional and Behavioural Problems in Children: Self-perception, peer relationships, and motor abilities
	Corbin, J. Hope	North-South Partnerships for Health: Key Factors for Partnership Success from the Perspective of the KIWAKKUKI
	Birkeland, Marianne Skogbrott	Development of global self-esteem: The transition from adolescence to adulthood
2013 H	Gianella-Malca, Camila	Challenges in Implementing the Colombian Constitutional Court's Health-Care System Ruling of 2008
	Hovland, Anders	Panic disorder – Treatment outcomes and psychophysiological concomitants
	Mortensen, Øystein	The transition to parenthood – Couple relationships put to the test
	Årdal, Guro	Major Depressive Disorder – a Ten Year Follow-up Study. Inhibition, Information Processing and Health Related Quality of Life
	Johansen, Rino Bandlitz	The impact of military identity on performance in the Norwegian armed forces
	Bøe, Tormod	Socioeconomic Status and Mental Health in Children and Adolescents
2014 V	Nordmo, Ivar	Gjennom nåløyet – studenters læringserfaringer i psykologutdanningen
	Dovran, Anders	Childhood Trauma and Mental Health Problems in Adult Life
	Hegelstad, Wenche ten Velden	Early Detection and Intervention in Psychosis: A Long-Term Perspective
	Urheim, Ragnar	Forståelse av pasientaggresjon og forklaringer på nedgang i voldsrate ved Regional sikkerhetsavdeling, Sandviken sykehus
	Kinn, Liv Grethe	Round-Trips to Work. Qualitative studies of how persons with severe mental illness experience work integration.
	Rød, Anne Marie Kinn	Consequences of social defeat stress for behaviour and sleep. Short-term and long-term assessments in rats.
	Nygård, Merethe	Schizophrenia – Cognitive Function, Brain Abnormalities, and Cannabis Use
	Tjora, Tore	Smoking from adolescence through adulthood: the role of family, friends, depression and socioeconomic status. Predictors of smoking from age 13 to 30 in the "The Norwegian Longitudinal Health Behaviour Study" (NLHB)
	Vangsnes, Vigdis	The Dramaturgy and Didactics of Computer Gaming. A Study of a Medium in the Educational Context of Kindergartens.

	Nordahl, Kristin Berg	Early Father-Child Interaction in a Father-Friendly Context: Gender Differences, Child Outcomes, and Protective Factors related to Fathers' Parenting Behaviors with One-year-olds
2014 H	Sandvik, Asle Makoto	Psychopathy – the heterogenety of the construct
	Skotheim, Siv	Maternal emotional distress and early mother-infant interaction: Psychological, social and nutritional contributions
	Halleland, Helene Barone	Executive Functioning in adult Attention Deficit Hyperactivity Disorder (ADHD). From basic mechanisms to functional outcome.
	Halvorsen, Kirsti Vindal	Partnerskap i lærerutdanning, sett fra et økologisk perspektiv
	Solbue, Vibeke	Dialogen som visker ut kategorier. En studie av hvilke erfaringer innvandrerungdommer og norskfødte med innvandrerforeldre har med videregående skole. Hva forteller ungdommenes erfaringer om videregående skoles håndtering av etniske ulikheter?
	Kvalevaag, Anne Lise	Fathers' mental health and child development. The predictive value of fathers' psychological distress during pregnancy for the social, emotional and behavioural development of their children
	Sandal, Ann Karin	Ungdom og utdanningsval. Om elevar sine opplevingar av val og overgangsprosessar.
	Haug, Thomas	Predictors and moderators of treatment outcome from high- and low-intensity cognitive behavioral therapy for anxiety disorders. Association between patient and process factors, and the outcome from guided self-help, stepped care, and face-to-face cognitive behavioral therapy.
	Sjølie, Hege	Experiences of Members of a Crisis Resolution Home Treatment Team. Personal history, professional role and emotional support in a CRHT team.
	Falkenberg, Liv Eggset	Neuronal underpinnings of healthy and dysfunctional cognitive control
	Mrdalj, Jelena	The early life condition. Importance for sleep, circadian rhythmicity, behaviour and response to later life challenges
	Hesjedal, Elisabeth	Tverrprofesjonelt samarbeid mellom skule og barnevern: Kva kan støtte utsette barn og unge?
2015 V	Hauken, May Aasebø	«*The cancer treatment was only half the work!»* A Mixed-Method Study of Rehabilitation among Young Adult Cancer Survivors
	Ryland, Hilde Katrin	Social functioning and mental health in children: the influence of chronic illness and intellectual function
	Rønsen, Anne Kristin	Vurdering som profesjonskompetanse. Refleksjonsbasert utvikling av læreres kompetanse i formativ vurdering

	Hoff, Helge Andreas	Thinking about Symptoms of Psychopathy in Norway: Content Validation of the Comprehensive Assessment of Psychopathic Personality (CAPP) Model in a Norwegian Setting
	Schmid, Marit Therese	Executive Functioning in recurrent- and first episode Major Depressive Disorder. Longitudinal studies
	Sand, Liv	Body Image Distortion and Eating Disturbances in Children and Adolescents
	Matanda, Dennis Juma	Child physical growth and care practices in Kenya: Evidence from Demographic and Health Surveys
	Amugsi, Dickson Abanimi	Child care practices, resources for care, and nutritional outcomes in Ghana: Findings from Demographic and Health Surveys
	Jakobsen, Hilde	The good beating: Social norms supporting men's partner violence in Tanzania
	Sagoe, Dominic	Nonmedical anabolic-androgenic steroid use: Prevalence, attitudes, and social perception
	Eide, Helene Marie Kjærgård	Narrating the relationship between leadership and learning outcomes. A study of public narratives in the Norwegian educational sector.
2015 H	Wubs, Annegreet Gera	Intimate partner violence among adolescents in South Africa and Tanzania
	Hjelmervik, Helene Susanne	Sex and sex-hormonal effects on brain organization of fronto-parietal networks
	Dahl, Berit Misund	The meaning of professional identity in public health nursing
	Røykenes, Kari	Testangst hos sykepleierstudenter: «Alternativ behandling»
	Bless, Josef Johann	The smartphone as a research tool in psychology. Assessment of language lateralization and training of auditory attention.
	Løvvik, Camilla Margrethe Sigvaldsen	Common mental disorders and work participation – the role of return-to-work expectations
	Lehmann, Stine	Mental Disorders in Foster Children: A Study of Prevalence, Comorbidity, and Risk Factors
	Knapstad, Marit	Psychological factors in long-term sickness absence: the role of shame and social support. Epidemiological studies based on the Health Assets Project.
2016 V	Kvestad, Ingrid	Biological risks and neurodevelopment in young North Indian children
	Sælør, Knut Tore	Hinderløyper, halmstrå og hengende snører. En kvalitativ studie av håp innenfor psykisk helse- og rusfeltet.
	Mellingen, Sonja	Alkoholbruk, partilfredshet og samlivsstatus. Før, inn i, og etter svangerskapet – korrelater eller konsekvenser?
	Thun, Eirunn	Shift work: negative consequences and protective factors

	Hilt, Line Torbjørnsen	The borderlands of educational inclusion. Analyses of inclusion and exclusion processes for minority language students
	Havnen, Audun	Treatment of obsessive-compulsive disorder and the importance of assessing clinical effectiveness
	Slåtten, Hilde	Gay-related name-calling among young adolescents. Exploring the importance of the context.
	Ree, Eline	Staying at work. The role of expectancies and beliefs in health and workplace interventions.
	Morken, Frøydis	Reading and writing processing in dyslexia
2016 H	Løvoll, Helga Synnevåg	Inside the outdoor experience. On the distinction between pleasant and interesting feelings and their implication in the motivational process.
	Hjeltnes, Aslak	Facing social fears: An investigation of mindfulness-based stress reduction for young adults with social anxiety disorder
	Øyeflaten, Irene Larsen	Long-term sick leave and work rehabilitation. Prognostic factors for return to work.
	Henriksen, Roger Ekeberg	Social relationships, stress and infection risk in mother and child
	Johnsen, Iren	«Only a friend» - The bereavement process of young adults who have lost a friend to a traumatic death. A mixed methods study.
	Helle, Siri	Cannabis use in non-affective psychoses: Relationship to age at onset, cognitive functioning and social cognition
	Glambek, Mats	Workplace bullying and expulsion in working life. A representative study addressing prospective associations and explanatory conditions.
	Oanes, Camilla Jensen	Tilbakemelding i terapi. På hvilke måter opplever terapeuter at tilbakemeldingsprosedyrer kan virke inn på terapeutiske praksiser?
	Reknes, Iselin	Exposure to workplace bullying among nurses: Health outcomes and individual coping
	Chimhutu, Victor	Results-Based Financing (RBF) in the health sector of a low-income country. From agenda setting to implementation: The case of Tanzania
	Ness, Ingunn Johanne	The Room of Opportunity. Understanding how knowledge and ideas are constructed in multidisciplinary groups working with developing innovative ideas.
	Hollekim, Ragnhild	Contemporary discourses on children and parenting in Norway. An empirical study based on two cases.
	Doran, Rouven	Eco-friendly travelling: The relevance of perceived norms and social comparison
2017 V	Katisi, Masego	The power of context in health partnerships: Exploring synergy and antagony between external and internal ideologies in implementing Safe Male Circumcision (SMC) for HIV prevention in Botswana

	Jamaludin, Nor Lelawati Binti	The “why” and “how” of International Students’ Ambassadorship Roles in International Education
	Berthelsen, Mona	Effects of shift work and psychological and social work factors on mental distress. Studies of onshore/offshore workers and nurses in Norway.
	Krane, Vibeke	Lærer-elev-relasjoner, elevers psykiske helse og frafall i videregående skole – en eksplorerende studie om samarbeid og den store betydningen av de små ting
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