Light exposure and stress in pregnancy: Effects of blue-blocking glasses on sleep, mood and melatonin

Randi Liset

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2022

UNIVERSITY OF BERGEN

Light exposure and stress in pregnancy: Effects of blue-blocking glasses on sleep, mood and melatonin

Randi Liset

Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 26.08.2022

Year: 2022

Title: Light exposure and stress in pregnancy: Effects of blue-blocking glasses on sleep, mood and melatonin

Name: Randi Liset

Print: Skipnes Kommunikasjon / University of Bergen

Scientific environment

This doctoral thesis is based on work conducted and written at the Department of Psychosocial Science, Faculty of Psychology, University of Bergen. The candidate took the Ph.D. education program through the Graduate School of Clinical and Developmental Psychology at the University of Bergen.

The project included collaboration with the Municipality of Bergen with help to recruit appropriate participants in the research. The scientific fellowship and environment was the Bergen Stress and Sleep Group at the Department of Biological and Medical Psychology, Faculty of Psychology, University of Bergen, and the Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen.

The candidate was affiliated with the Bergen Sleep and Chronobiology Network, University of Bergen and Reproductive Health, and Health Promotion Work in a Life Course Perspective, Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen.

The dissertation is funded by the Faculty of Psychology, University of Bergen. The candidate also received funding from the Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, and the Norwegian Association of Midwives, Norway.

Main supervisor Ståle Pallesen, professor at the Department of Psychosocial Science, Faculty of Psychology, University of Bergen.

Co-supervisor Janne Grønli, professor at the Department of Biological and Medical Psychology, Faculty of Psychology, University of Bergen.

Co-supervisor Roger E. Henriksen, associate professor, Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen.

Co-supervisor Tone E.G. Henriksen, MD PhD, Consultant Psychiatrist, Valen Hospital, Division of Mental Health Care, Fonna Local Health Authority, Valen.

Acknowledgements

First, I want to thank all the pregnant women in Bergen participating in this study, and the consulting midwives at antenatal healthcare centers in the Municipality of Bergen helping recruit appropriate participants to this research. Their contribution provided valuable and necessary data for this dissertation.

Thank you to my main supervisor Ståle Pallesen for your patience, precise guidance, quick response and support during my PhD, and for always making time available for all my questions. I am very grateful that you have shared your knowledge and insight with me. I want to thank my co-supervisors Janne Grønli, Roger Ekeberg Henriksen and Tone Elise Gjøtterud Henriksen. They have been encouraging throughout the processes, guiding and willingly shared their knowledge with me. Roger, you were there from the beginning introducing me to the idea. Tone, you provided insight in how light affects basic sleep and Janne, you opened the door to a PhD grant and shared your dedication to sleep research. I appreciate the respect the team have shown for midwifery and the pregnant women.

I also want to thank Roy Miodini Nilsen for excellent statistical support, guidance and patience.

I am grateful to the Department of Psychosocial Science, Faculty of Psychology, which gave me the opportunity to take a PhD at the University of Bergen. Thank you for letting me be a part of the environment, also at the Department of Biological and Medical Psychology. To my co-PhD-candidate Erlend Sunde, thank you for assisting me in randomizing the participants in this project, and for always being helpful.

I want to thank all my colleagues at the Western Norway University of Applied Sciences, Midwifery education, for being positive and supportive. A special thank to Katrine Aasekjær for connecting me to Roger and his idea, and to Vigdis Aasheim, Anne-Britt Vika Nilsen and Erica Schytt for valuable guidance at the very beginning of my project. I am also grateful to Eline Skirnisdottir Vik, Tone Engen and Linn

Marie Sørbye for all support. I am looking forward to collaborating with all of you again.

I am very proud to be a midwife! I want to thank all the skillful and talented midwives I have met. You have inspired me through the process of writing this thesis. A special thanks to Ingrid Lid Nordø and Wenche Førde for sharing your clinical insights about pregnancy.

Thanks to my family, family in law and friends! Thanks for your support and encouragement in these years. A special thank to my sister Petra for encouraging me and for being proud of my work, to Leni for coaching me, and to Wenche for guiding me using NLP.

Thank you to my three precious children Martin, Christina and Benedicte. You remind me of what's important in life. Thanks for taking part in discussions of my project, where blue-blocking glasses is a natural part of your life. Thank you for your patience, support and being proud of me.

Finally, I want to thank my wonderful husband Dagfinn, my best friend, soulmate and my safe harbor. Thank you for being my technical research assistant, and for always encourage, support me and still having faith in me!

Abstract

Background and Objective: Sleep disturbances are common during pregnancy, with an increasing prevalence in the third trimester. Insomnia is the most frequent sleep disorder reported by 62% of pregnant women. Poor sleep quality and insomnia may influence both the maternal and fetal health, and are associated with preeclampsia, elevated serum glucose, depression, prolonged labour, caesarean birth, intrauterine growth restriction and preterm birth.

Light exposure in the evening and at night has an acute alerting effect, can reduce evening and night sleepiness, may suppress melatonin excretion, and are also associated with later bedtime and shorter sleep time.

Sleep is closely linked to the circadian rhythm and light is the most important zeitgeber entraining the circadian system. Darkness allows production of melatonin, a hormone which regulates the circadian rhythm, and induce sleep. Suprachiasmatic nucleus is the master clock in the brain and controls the circadian rhythm of melatonin synthesised in the pineal gland. Evening and night-time exposure to light of short wavelength, blue light, supresses the melatonin production, delay the circadian rhythms and inhibit sleep.

There is a need of effective and safe non-pharmacological treatments for sleep disturbances in pregnancy. Blue blocking glasses (BB-glasses) may represent such an intervention, by preventing alertness, improve sleep and maintain the melatonin production.

The objective for this thesis was to investigate sleep patterns, sleep behaviour, perceived stress, prevalence of insomnia and evening light exposure in women in the third trimester. Furthermore, the study aimed to investigate the effect of wearing BB-glasses in the evening and at night, on sleep outcomes and melatonin profile.

Methods: This thesis is based on a sample of healthy nulliparous women in the third trimester of the pregnancy who were included in a double blind randomized controlled trial conducted at the University of Bergen, Norway. The study lasted for three weeks,

where the first week was a baseline week, followed by two weeks of intervention. The intervention comprised orange tinted BB-glasses. The control condition consisted of grey partial blue-blocking control glasses. In both conditions the glasses were worn three hours before bedtime.

Paper 1 was an observational study of 61 pregnant women, using data from the baseline week, and compared with data of sleep and light exposure from 69 non-pregnant female students. The aim of this first paper was to assess sleep pattern, sleep behavior, prevalence of insomnia and evening light exposure in the pregnant women and compare the data with those in the non-pregnant group. Further, Paper 1 aimed to investigate how perceived stress and evening light exposure were associated with sleep outcomes among the pregnant women. Sleep was measured by actigraphy, sleep diaries and the Bergen Insomnia Scale. Stress was assessed by the Relationship Satisfaction Scale, the Perceived Stress Scale and the Pre-Sleep Arousal Scale. Total white light exposure three hours prior to bedtime was measured by wrist-worn actigraphy.

Questionnaires measured sleep, insomnia, and stress. Actigraphy monitored sleep and light exposure.

Papers 2 and 3 present the results from a randomizes controlled trial, including 60 healthy nulliparous women in the third trimester of the pregnancy.

In Paper 2 the main aim was to evaluate the effect of blocking the blue light in the evening and night on sleep outcomes assessed with sleep diaries and actigraphy, further on insomnia (Bergen Insomnia Scale), sleepiness (Karolinska Sleepiness Scale) and arousal (Pre-Sleep Arousal Scale).

Paper 3 aimed to investigate the effect of blocking the blue light in the evening on the melatonin profile. The third paper assessed sleep by sleep diaries, and melatonin was measured based on saliva samples.

Results: Paper 1 reported an insomnia prevalence of 38% of the pregnant women, compared to 51% in the non-pregnant group. Sleep diary data showed lower sleep

efficiency, and actigraphy data showed longer total sleep time and higher exposure to evening light in pregnant women, compared to the non-pregnant women. In the pregnant women, the stress variables were not associated with sleep outcomes, while light exposure in the evening was inversely associated with total sleep time and sleep efficiency measured by actigraphy.

Paper 2 found no effect of blue-blocking glasses on neither of the sleep outcomes total sleep time, midpoint of sleep, sleep efficiency and daytime functioning, nor on insomnia, sleepiness and arousal.

In Paper 3 we estimated the melatonin profile in 47 pregnant women (data for some participants were discarded as their values were out of range). This paper showed that blocking the blue light in the evening resulted in an earlier onset of melatonin in the evening, and higher melatonin levels at some evening time points. Following the intervention, the phase angle (time interval) increased between melatonin onset and bedtime and sleep onset time within the blue blocking group only. Still the difference between the two conditions in terms of phase angle changes were not significant.

Conclusion: The present thesis found that the participating healthy pregnant women in the third trimester slept quite well. Evening light exposure was associated with shorter sleep duration. Blocking blue light in the evening did not show statistically significant effects on sleep outcomes. However, b**y** using BB-glasses in the evening we found a positive effect on the circadian system by preventing suppression of melatonin. Melatonin is a clinically important hormone for both mother and fetus. It is concluded that BB-glasses may be an effective and safe non-pharmacological chronobiological intervention during pregnancy, still more research is needed on this intervention.

List of Publications

Liset, R., Grønli, J., Henriksen, R.E., Henriksen, T.E.G., Nilsen, R.M., Pallesen, S. (2021): Sleep, evening light exposure and perceived stress in healthy nulliparous women in the third trimester of pregnancy. PLoS ONE 16(6): e0252285.

Liset, R., Grønli, J., Henriksen, R.E., Henriksen, T.E.G., Nilsen, R.M., Pallesen, S. (2022): A randomized controlled trial on the effects of blue-blocking glasses compared to partial blue-blockers on sleep outcomes in the third trimester of pregnancy. PLoS ONE 17(1):e0262799.

Liset, R., Grønli, J., Henriksen, R.E., Henriksen, T.E.G., Nilsen, R.M., Pallesen, S. (2021): A randomized controlled trial on the effect of blue-blocking glasses compared to partial blue-blockers on melatonin profile among nulliparous women in third trimester of the pregnancy. Neurobiology of Sleep and Circadian Rhythms 12:100074.

List of abbreviations

ADHD	Attention-deficit hyperactive disorder
ANCOVA	Analysis of covariance
BB	Blue-blocking
BIS	Bergen Insomnia Scale
CBT-i	Cognitive behavioral therapy for insomnia
CPAP	Continuous positive airway pressure
DLMO	Dim light melatonin onset
DSPS	Delayed sleep phase syndrome
EEG	Electroencephalography
EMG	Electromyography
EMR	Electromagnetic radiation
EOG	Electrooculography
HCG	Human choriogonadotropin
HCS	Human chorion somatomammotropin
HPA	Hypothalamic pituitary adrenal
ICSD-3	International Classification of Sleep Disorders, 3rd edition
ipRGC	Intrinsically photosensitive retinal ganglion cell
KSS	Karolinska Sleepiness Scale
LED	Light-emitting diodes
NREM	Non-rapid eye movement
OSA	Obstructive sleep apnea
PRC	Phase-response curve
PSAS	Presleep Arousal Scale
PSG	Polysomnography

PSS	Perceived Stress Scale
REM	Rapid eye movement
RLS	Restless legs syndrome
RSS	Relationship Satisfaction Scale
SCN	Suprachiasmatic nucleus
SD	Standard deviation
SDB	Sleep-disordered breathing
SE	Sleep efficiency
SOL	Sleep onset latency
SPSS	Statistical Package for the Social Sciences
TST	Total sleep time
WASO	Wake after sleep onset

Contents

1. Introduction

Approximately 60,000 (2016) infants are born annually in Norway, although some decrease has been observed in recent years. In 2020, 53,626 infants (43.8 per 1,000 women) were born [1]. Pregnancy is a vulnerable time for women, as it involves physical, hormonal and psychological changes that may influence sleep.

Sleep disruption can start early in pregnancy, when a frequent need to urinate may arise, caused by the increasing level of progesterone and glomerular filtration. Also, discomfort such as nausea and esophageal reflux may cause wakenings. In addition, social factors such as disturbances from bed partner and children may also cause sleep disruptions [2].

Later in pregnancy, fetal movements may start to disrupt sleep. As the pregnancy progresses, more specific biologically based factors such as lower backpain, pelvic pain, nocturia, oedema, esophageal reflux and a growing uterus may negatively affect sleep quality and quantity [3, 4]. Regarding different types of pain, there is a strong association between pain and insomnia in pregnancy [5, 6]. In addition, chronic pain is also associated with depression in pregnant women [6]. When esophageal reflux is expected, the common symptoms of heartburn and acid taste may affect sleep negatively. The incidence of esophageal reflux ranges from 30-80% during normal pregnancies, and typically peaks in the third trimester due to the growing abdominal weight, as well as anatomical and hormonal changes [7].

Sleep disturbances common during pregnancy and may influence both maternal- and fetal outcomes [8]. Sleeping at night and being awake during the day is one representation of circadian rhythms in humans [9], which is highly regulated by light, especially light with short wavelengths (blue light) [10]. This thesis investigates how the sleep in the pregnant women is disrupted in the third trimester, and weather filtering out light containing blue light could ameliorate changes in circadian rhythms and ease the sleep disruptions. More specifically, the aims were to investigate sleep patterns, sleep related behavior, perceived stress, prevalence of insomnia, melatonin

onset and the effect of wearing blue-blocking glasses (BB-glasses) during the evening and at night. The details will be presented later in this thesis.

1.1 Sleep

For the general population of Norway, the prevalence of insomnia increased from 11.9% in 2000 to 15.5% in 2010 [11], and a similar increase of 21.7% has been shown in a recent healthy student population [12]. A related development pattern can be considered to apply to pregnant women. Although sleep problems seem to be on the rise among the general population, worldwide studies do not show any evidence of a reduction in sleep time for adults during the last 60 years [13]. However, the timing of sleep has changed for Norwegians since 1980, which is manifested by later bedtime and rising times [14].

Sleep is defined as a rapidly reversible behavioral state associated with reduced response to stimuli and a loss of awareness of the environment [15, 16]. Sleep is regarded as important in order to achieve and maintain good health [17]. The gold standard method for measuring sleep is polysomnography (PSG), which includes records of electroencephalography (EEG), electromyography (EMG) and electrooculography (EOG). These metrics provide objective information about sleep stages, wakefulness and sleep quality [16, 18]. PSG is quite invasive and is normally used in laboratories and hospital settings. Actigraphy, questionnaires and sleep diaries estimate sleep more or less non-invasively and are better suited to naturalistic settings. An actigraph is a wristwatch-like device that registers movements by an accelerometer, and defines wakefulness and sleep based on algorithms that take activity/inactivity into account. Actigraphy may be sufficient to assess sleep-wake pattern, and some sleep disorders, such as circadian rhythm sleep-wake disorders [19]. Self-reported sleep using questionnaires and sleep diaries is an introspective method of measuring various aspects of sleep, such as daytime sleepiness, perceived sleep quality, sleep duration, sleep habits and the like [20, 21].

Estimating sleep using actigraphy and self-reporting questionnaires, as we have done in this thesis, does not provide information about the specific sleep stages such as the amount of Non-Rapid Eye Movement (NREM) sleep and Rapid Eye Movement (REM) sleep. The natural distribution of sleep stages through the night, as illustrated in Figure 1, shows that sleep stages occur in cycles of approximately 90 minutes, where one sleep cycle consists of time spent in NREM sleep and ends in time spent in REM sleep. During a normal night, we typically go through 4-6 sleep cycles. The first part of the night is dominated by deep NREM sleep (slow wave sleep, stage N3), while the last part of the night is dominated by REM sleep and light NREM sleep (stage N2) [22]. The quality of sleep is reflected in changes in EEG oscillations: slow and synchronous cortical oscillations during NREM, especially during N3, and fast, desynchronous oscillations during REM sleep [15].

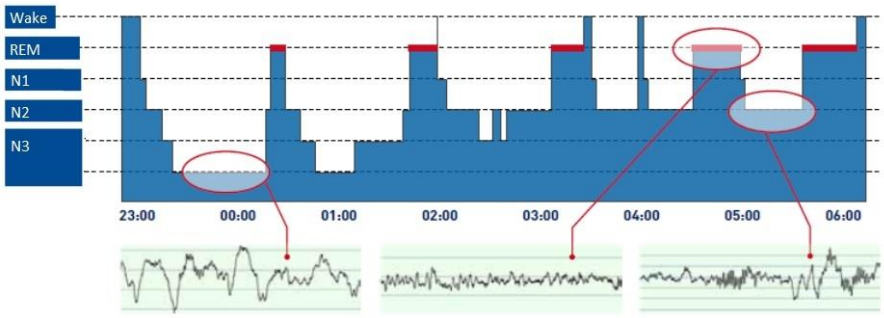


Figure 1. *A typical distribution of sleep stages during the night, measured by PSG. EEG shows the activation of the brain in different sleep stages. Figure made by and reused with permission from Grønli & Saxvig [23].*

1.2 Sleep wake regulation

Sleep is a complex process regulated by sleep homeostasis (the sleep need), circadian rhythms and environmental factors [9]. Ambient light influences both the homeostatic and the circadian aspects of sleep [24]. Below is an outline of how sleep is regulated.

1.2.1 Circadian system

The 24-hour cycle created by the rotation of the Earth synchronizes the circadian rhythm (circa=about and dia=day) of all living organisms including plants, animals, humans and even all bacteria and cells. These endogenous near 24-hour cycles enable anticipation of daily changes in light and darkness [25, 26].

The circadian rhythms are generated at a cellular level in all tissues, each managed by a group of core clock genes working together in transcription/translational feedback loop organs [27]. The expression of the clock genes helps to control the activity of cellular and physiological functions [28]. Importantly, a master clock located in the brain coordinates all the biological clocks, like the sleep-wake rhythm, core body temperature, metabolic functions, and secretion of hormones, such as melatonin and cortisol. Moreover, the circadian rhythms are modulated by external factors, zeitgebers. Here, light is the strongest external zeitgeber. Other external factors entraining the circadian rhythms are physical activity, food intake [10, 29], ambient temperature, social interaction, and work schedule [30], although sleeping time is a weak zeitgeber [31].

1.2.2 Suprachiasmatic nucleus

A master clock in the brain coordinates the biological clocks of all mammalians, the suprachiasmatic nucleus (SCN) [26]. SCN communicates with central and peripheral molecular clockworks, via both neuronal and endocrine signaling [32].

SCN is situated in the anterior hypothalamus, just above the optic chiasm at the base of the third ventricle [10]. SCN is the pacemaker of the circadian rhythms that coordinate molecular clocks [32].

1.2.3 Pineal gland

The pineal gland is located in the epithalamus just above the thalamus. Melatonin is the most important substance synthesized and secreted from the pineal gland. [33, 34]. Melatonin is a neurohormone named after the effect melatonin has on frog skin

melanophores. The discovery of melatonin isolated from the pineal gland took place in 1958 [34].

The SCN controls the circadian rhythm of melatonin synthesized in the pineal gland. The melatonin secretion normally starts to rise in response to darkness during the evening, reaching a peak in the middle of the night, with decreasing levels in the morning as exposure to light suppresses nocturnal melatonin secretion. The suppression effect is most sensitive to short wavelength light, typically present in the early morning hours [35-37]. Melatonin expresses a negligible level during the daytime. In natural light and darkness, this pattern is very stable, making the nocturnal melatonin profile a reliable phase marker of the endogenous timing system [33, 34]. Melatonin regulates circadian rhythms and induces sleepiness, besides acting as an endocrine modulator, direct free radical scavenger and an anti-inflammatory and antioxidant factor [38-41].

Stimulation of the pineal gland results in the production of N-acetylserotonin and melatonin [34, 42, 43]. Melatonin is then released into the blood flow and cerebrospinal fluid (high concentration), and conveys signals to central and peripheral organs [44]. The endogenous melatonin rhythm is, as mentioned, a reliable circadian phase marker [39], and reliable measures can be harvested from blood, saliva and urine (6-sulfatoxymelatonin). In addition, melatonin is found in reproduction fluids like preovulatory follicles, amniotic fluid and breast milk [34]. The appropriate way to measure the circadian phase is by estimating the dim light melatonin onset (DLMO) [45], by using dark sunglasses before and during several samples taken in the evening, according to procedure [46]. DLMO is defined when melatonin concentrations reach 3 or 4 pg/ml in saliva [46, 47]. Melatonin production is negatively correlated with age [48], with a significantly higher concentration in younger people [49].

1.2.4 The two-process model

A major conceptual framework for sleep regulation is the two-process model of sleep. This occurs by simulating the intensity and timing of sleep, termed the homeostatic

process and the circadian process. The model was presented by Borbély in the early 1980s [50]. The homeostatic process (process S) reflects the build-up of sleep pressure during wakefulness. Process S decreases during time asleep, as such representing the sleep need or sleep pressure. Sleep pressure is manifested by the depth of NREM sleep in the ensuing sleep period [9, 50].

The circadian process (process C) is endogenously generated by the circadian rhythm of near-24-hour rhythms in all cellular activity [26]. Process C regulates the timing and length of sleep [9, 50]. The circadian rhythm is linked to the core body temperature [26], which typically falls in the evening and continues to drop to its lowest point (nadir) in the early morning hours, after which it rises. The decrease in core body temperature during the evening promotes sleepiness and the initiation of sleep [34, 51, 52]. In adults, sleep normally and most easily occurs from around six hours before nadir to around two hours following nadir [53].

Hence, sleep depends on the length of prior wakefulness, time of sleep onset and the circadian rhythm [9, 50]. However, behavior such as delay of bedtime, activity and exposure to activating stimuli will also influence sleep [24, 53]. Taken together, the three factors, i.e. the homeostatic, circadian and behavioral factors, interact and influence the ability to sleep and stay awake.

1.2.5 Ligh t and the impact on sleep-wake regulation and circadian rhythms

In sleep-wake regulation the amount of light, the light intensity and the time of exposure to light are of importance. As mentioned previously, light is the most important external environmental factor, or “zeitgeber”, affecting the circadian system [10, 29], and especially short wavelengths (< 530 nm) of light [35, 54].

Light passes through the eye to the retina and here stimulates rods, cones and the intrinsically photo-responsive retinal ganglion cells (ipRGCs). Rods and cones project to the visual cortex. The ipRGCs convey non-visual light information widespread throughout the brain, to areas involved in the regulation of wakefulness, sleep, alertness and circadian rhythms. These responses were first termed “non-image-

forming responses to light" to make a clear distinction from circuits producing vision [35, 37, 54, 55].

The ipRGCs are maximally sensitive to short-wavelengths light of 480 nm, the blue light, from the contribution of the photo sensitivity profile of the photopigment melanopsin [36, 56]. IpRGCs also receive some daylight information from rods and cones. This makes the ipRGCs' action spectrum somewhat wider than the photo-sensitivity curve of melanopsin alone [57].

Information about the non-visual aspects of light is projected from ipRGCs and transmitted by the hypothalamic tract to several hypothalamic nuclei, including the SCN [10]. SCN neurons display a sustained response to light, and signals are transmitted via a nerve connection to the pineal gland, which regulates some hormones, of which melatonin is the most important [10]. Light via SCN activation suppresses the melatonin production, and thus corresponds to the wake phase of the sleep/wake cycle. Lockley et al. found in 2003 that blue light (460 nm) suppresses melatonin two times more than green light (555 nm) [56]. Darkness, or the absence of stimulation of the ipRGCs, allows melatonin production. The onset of melatonin production increases sleep propensity [33, 34], and contributes to sleep maintenance via the circadian process (process C) [24].

The timing of exposure to light is of importance, as it can reset the circadian clock [58, 59]. The duration of bright light exposure also impacts the magnitude of phase shift [60], although small flashes of bright light are also sufficient for phase shifts [61]. Prior light history also impacts the effect of light exposure with regard to the circadian system [62]. The effect of light [63], and exogenous melatonin [64] on the circadian rhythms follows a phase-response curve (PRC). Figure 2 shows that light and melatonin have different effects (advancing or delaying) on the circadian rhythms, depending on time/phase of light exposure and melatonin administration in relation to the core body temperature rhythm.

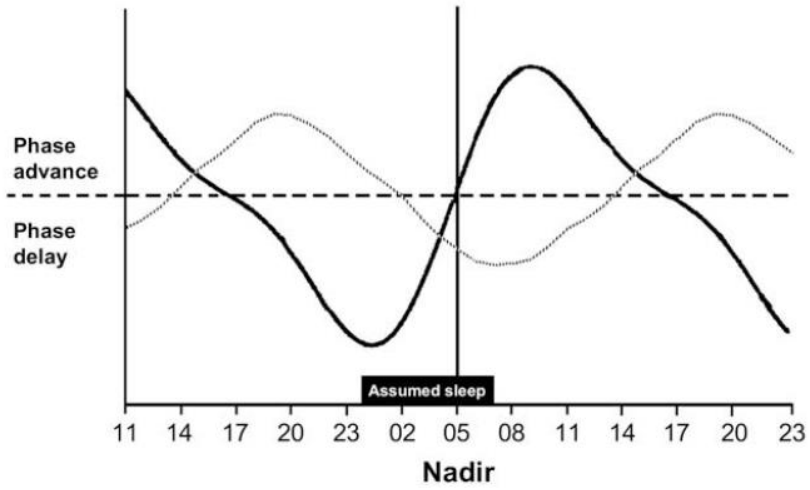


***Figure 2**. Phase-response curve of light (dark line) and melatonin (light line), based on results from Khalsa et al. [63] and Lewy et al. [64]. Figure made by and reused with permission from Bjorvatn and Pallesen [53].*

The nadir (lowest point) of the core body temperature is of importance, as exposure to light before nadir causes phase delay, while light exposure after nadir leads to a phase advance. Normally, evening light exposure delays the phase, while morning light exposure advances the phase [65]. The dose, duration and wavelengths of light, as well as the light exposure history of the individual affect the magnitude of the phase shift [66].

Bright light exposure and light restriction may thus resynchronize the circadian clock and be useful to ameliorate sleep-wake rhythm disturbances [33].

1.2.6 Light and the impact on alertness

Light is also known to have acute alerting effects [67-71], defined as achieving and maintaining high sensitivity to incoming stimuli [72]. Arousal refers to activation related to changes in wakefulness and sleep [73], and is closely related to alertness, [74]. During the daytime it is important to maintain alertness in order to function during daily chores, and regarding cognitive performance and skills [75]. Light exposure, both polychromatic white and monochromatic light, especially in the

evening and at night, has been demonstrated to improve night-time alertness [67, 68, 76]), although other studies report no alerting effects from light at night [77]. It has been indicated that light's effect on alertness depends on the light intensity, duration and wavelength. Prior light history, high light intensity, long light exposure duration and high light energy (assessed in Kelvin terms) all result in increased levels of alertness [69].

1.3 Sleep in pregnancy

Sleep patterns change throughout pregnancy, due to both physiological and psychological changes [78, 79]. In the first trimester it is common to see an increase in total sleep time (TST) [80], compared to before conception [81]. There are also reports of longer sleep onset latency (SOL) and more wake after sleep onset (WASO) [7] at this stage of pregnancy. In line with this, studies using PSG confirm longer sleep durations [80] and increases in wake after sleep onset (WASO) [82], in addition to reduced sleep efficiency in the first part of pregnancy [80]. Compared to pre-pregnant sleep, decreases in deep sleep (slow wave sleep stage 3) [80] and in REM sleep throughout pregnancy have been reported [82].

The second trimester is typically a somewhat better period, where pregnant women report less sleepiness and fatigue, and more energy. Pregnant women also show an increase in SE [81], and less WASO than in the previous trimester [7]. However, deep sleep typically continues to decrease during the second and third trimesters [82]. Yet not all studies are consistent with that (Balsarek, 2017) , but a longitudinal study using PSG showed reduced slow wave sleep compared to the first trimester, while REM sleep did not change [7].

A common sleep pattern in the third trimester is increased TST, but shorter night sleep, compensated by more daytime naps. Studies have shown an average total sleep time of between 6h 26min and 7h19 min in the third trimester [3, 83-86]. Furthermore, typical features are longer SOL, more WASO and reduced SE. PSG studies suggest more time in sleep stages 1 and 2 and reduced slow wave sleep and REM sleep (somewhat

inconsistent findings), compared with the sleep during the first and second trimesters and the sleep of non-pregnant women. [7].

Sleep disorders are also quite prevalent during pregnancy, mainly within three main groups: sleep related breathing disorders, sleep related movement disorders and insomnia (for more details see section 1.4). As pregnancy proceeds, sleep disorders usually worsen and may continue into the postpartum period, especially in nullipara women [80, 87].

1.3.1 Factors influencing sleep in pregnancy

Stress

Prenatal stress in pregnant women comprises psychological distress experienced during pregnancy [88]. In addition to sleep being influenced by pregnancy, this is also regarded as a vulnerable phase in life, which can lead to a stressful time for many women. Pregnant women with stressful pregnancies are at greater risk of developing sleep disturbances [4], and women with stress-related sleep disturbances in pregnancy are more likely to experience insomnia [87].

Pregnancy may be a period associated with increased perceived stress and may affect both the physiological [89] and psychological health of the pregnant woman [90, 91], the fetus (stillbirth, preterm birth, intrauterine growth restriction and developmental delay) [92-94], and the offspring [93, 95]. Furthermore, situational and social factors may trigger underlying vulnerabilities. In pregnant women perceived stress impacts sleep more than in non-pregnant women [96]. Mental preparation for birth might be a stressful factor, like worries about the fetus, the woman's own health, weight gain, appearance and fear of delivery [93]. The latter has been shown to be associated with both insomnia and depressive symptoms [84], although other studies have not found evidence for such relationships [97]. Social factors such as life events, social support, income, education, partner relationship and family relationships may also be influential factors causing stress-responses [4, 88].

Cortisol concentration increases during pregnancy [98], and by up to four times by the end of pregnancy, compared to non-pregnant levels [99]. The increased cortisol level

is essential for the normal development of the fetus and for labor [100]. The physiological stress response system is mainly based on activity in the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis controls the secretion and the concentration of plasma cortisol [101]. From a biological viewpoint, there is a circadian rhythm for the production and secretion of the stress hormone cortisol, with rising levels in the early morning. The cortisol level typically peaks after waking in the morning, with a maximum level after approximately 20-45 minutes, after which the level typically decreases across the day, displaying the lowest point between 18:00 and 02:00 hours [102, 103].

Relationship satisfaction

Relationship with a partner represents an important aspect of social life, and can be a source of support, although relationships may also represent conflicts in life [104]. The transition to parenthood during pregnancy can be characterized by happiness, but also challenges that may lead to a stressful time [105]. Dissatisfaction during the prenatal relationship has been reported to be associated with negative outcomes, such as infectious disease in the infant [95]. Relationship distress may activate the HPA axis and predict adverse stress effects, while satisfaction with the relationship with the partner may reduce stress activation [105]. Social support, especially from the baby's father, plays a major role for the pregnant woman [88]. In the general population, relationship quality has been linked to sleep [106], and is associated with increased REM sleep [107].

Arousal

Arousal is a state of excitement, or feeling energized, and can be achieved both mentally, emotionally and physically. Arousal can either facilitate or debilitate performance, depending on the task at hand. For sleep, arousal will typically impair performance [108], while arousal would normally improve athletic performance. During pregnancy, increased secretion of cortisol can lead to increased arousal and may furthermore result in insomnia. Cortical-related arousal has also been associated with emotional distress, respiratory events and limb movements in the late part of pregnancy [109], and may as such lead to sleep disturbances [7].

1.4 Sleep disorders in pregnancy

Sleep disorders involves disturbances in sleep quality, and the timing and amount of sleep. The International Classification of Sleep Disorders (ICSD-3) categorizes sleep disorders as six major types: insomnia, sleep related breathing disorders, central disorder of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias and sleep related movement disorders [110].

In this thesis we have investigated a proxy of the sleep disorder insomnia, which will be presented in most detail. To provide an overview of typical sleep disorders during pregnancy, a presentation of these will be provided, with focus on the most common, as previously mentioned, i.e. sleep related breathing disorders, sleep related movement disorders and insomnia [8]. Consequently, these will be presented in further detail, while other sleep disorders will be presented more briefly.

Sleep disturbance in pregnancy is associated with neuroendocrine, metabolic, and inflammatory changes, as well as alterations in mental functioning, and in daytime functioning, which may lead to disorders such as depression, hypertension and diabetes [8]. Disturbed sleep is more common among pregnant women, compared to the general population, with 97% of pregnant women reporting this experience [8].

1.4.1 Sleep related breathing disorders in pregnancy

Sleep-disordered breathing (SDB) is characterized by pauses in breathing, irregularity in the quantity of ventilation during sleep, and snoring. The most common sleep related breathing disorder is obstructive sleep apnea (OSA).

Symptoms of SDB are common during pregnancy, with the prevalence of OSA varying between 10-25% in pregnancy, and worsening as the pregnancy progresses [8]. Physiological changes during pregnancy lead to narrowing and increased resistance in the respiratory system. Estrogen and progesterone are increasing which induces capillary engorgement, hypersecretion and mucosal oedema of the upper airway. The narrowed airway results in snoring and obstructed breathing during sleep. [111]. Weight gain and an enlarging uterus contribute further to SDB [8]. SDB is

linked to adverse outcomes such as gestational hypertension, preeclampsia and gestational diabetes [8, 111]. Continuous positive airway pressure (CPAP) is the most effective treatment for OSA [8].

1.4.2 Sleep related movement disorders in pregnancy

Restless legs syndrome (RLS), also known as Willis Ekbom disease, is characterized by unpleasant sensations, normally in the legs, and a strong urge to move the legs, which will relieve the symptoms. RLS occurs during inactivity and follows a circadian pattern primarily in the evening and at night. There is an increased risk of RLS in pregnancy, with an incidence of up to 36% (27-30% reported by Nodine)[8] (3-34% reported by Balserak)[7] (36% reported by Dunietz)[112] in pregnant woman, and this often worsens in the third trimester [8]. RLS typically resolves after birth [7]. Hormonal changes during pregnancy are assumed to be possible etiologies of RLS, but the high prevalence has also been attributed to hemodynamic changes, iron and folate metabolism, as well as psychomotor behaviors [7, 113] family history of RLS, depression and multiparity [7]. Although RLS is linked to delay in sleep onset, sleep deprivation and daytime sleepiness [8], there seems to be no association with delivery outcomes [112].

Sleep related leg cramps are painful involuntary contractions of the lower limbs, and occur during rest, typically at night. Leg cramps are often confused with RLS, but while leg cramp is relieved by stretching the leg, this is not the case for RLS [8]. In pregnancy, up to 50% of pregnant women experience leg cramps, mostly in the third trimester. Although leg cramps cause severe pain and sleep disturbance, this is not related to complications or negative outcomes in pregnancy. Magnesium therapy has been shown to have a positive, albeit weak effect on leg cramp in pregnancy [114].

1.4.3 Insomnia in pregnancy

Insomnia involves difficulty falling asleep, maintaining sleep, early-morning awakening or/and non-restorative sleep affecting daytime functioning with symptoms such as sleepiness, fatigue, irritability, difficulty concentrating and negative mood. To

be diagnosed as chronic insomnia, the sleep difficulties must occur for at least three nights a week for at least three months [110].

Sleep diaries, based on self-reporting, are usually sufficient to diagnose insomnia. Scales used to identify insomnia symptoms are the Pittsburgh Sleep Quality Index (PSQI) [115] and the Insomnia Severity Index (ISI) [116]. Common questionnaires in the Nordic countries are the Bergen Insomnia Scale (BIS) [117] and the Basic Nordic Sleep Questionnaire (BNSQ) [118].

Insomnia is the most common sleep disorder, with a prevalence of 10-15% in the general population. Insomnia and other sleep problems can occur at any age, but problems with falling asleep are more common among young adults, while problems with maintaining sleep are more common among middle-aged and older adults [119, 120].

Similar to the general population, insomnia is also the most frequent sleep disorder during pregnancy, and generally worsens across gestation [3, 8, 83, 109, 121]. According to a recent review, the prevalence of insomnia is 25.3% in the first trimester, 27.2% in the second trimester and 39.7% in the third trimester, respectively [4]. Some report prevalence levels as high as 60% [86] and 62% [84]. Insomnia symptoms are experienced by more than 80% of women during pregnancy [8].

Hormonal and physical changes during pregnancy may cause disrupted sleep. Estrogen and progesterone levels increase during pregnancy. Estrogen causes decreased REM sleep time, and progesterone shares bindings with cortisol, and may thus increase arousal [8]. Pregnancy related physical changes such as various discomforts may be considered to be a secondary risk factor for insomnia. Risk factors for insomnia in pregnancy are age above 30 years [3], nulliparous [122], single mother, pregnancy induced hypertension, preeclampsia [7], pre-pregnancy affective disorder, and depression during the perinatal period [122]. Environmental factors such as noise and light [7], and stressful family interactions may also disturb sleep [4].

Research of the association between insomnia and various outcomes in pregnancy is limited, yet there is evidence suggesting that insomnia and sleep disruption increase adverse outcomes in pregnancies and have been linked to both preterm birth and caesarean delivery [123-125]. A review and meta-analysis support the notion that short sleep duration is associated with preterm birth as well as lower birth weight [126]. Prenatal sleep disruption is further linked to preeclampsia [8], gestational diabetes [89], prolonged labor and increased pain during labor [8, 127], although these outcomes have not been specifically observed to be associated with prenatal insomnia [8]. A cohort study of Norwegian pregnant women in the third trimester showed that depression was strongly associated with insomnia. Further associated factors were previous depression, pain in the lower back, pelvic and other types of chronic pain, as well as smoking [84].

Inflammatory markers may play a role in adverse pregnancy outcomes, and higher levels of proinflammatory cytokines occur in non-pregnant persons with insomnia [128]. Pregnant women with adverse pregnancy outcomes (e.g. preterm birth, postpartum depression) have also shown higher proinflammatory cytokines than those with normal pregnancies [124, 128].

Furthermore, prenatal insomnia has social implications, and may cause disruption in the relationship with the partner and the family [8].

To prevent and better optimize potential adverse pregnancy outcomes there is a need for more knowledge about management and treatment. Management of insomnia includes identifying risk factors, diagnosis and treatment. The latter typically includes sleep hygiene, acupuncture [129], massage and yoga [130]. Cognitive behavioral therapy for insomnia (CBT-i) is regarded as the treatment of choice for the general population [131], as well as among pregnant women with insomnia in the third trimester [132, 133].

If non-pharmacological treatment for insomnia is not sufficient, medication can be considered. Hypnotic medication such as benzodiazepines, some antidepressiva, melatonin and antihistamines are effective for sleep disturbances in the general

population. In pregnancy, however, the potential adverse effects of medication on the fetus have to be considered [134]. Documentation of the safety of such treatments is currently lacking and these treatments are thus not the first line treatment [135]. However, two histamine H1 receptor antagonists with sedative effects; diphenhydramine and doxylamine are categorized as possible for insomnia during pregnancy and are probably harmless for the fetus [7].

1.4.4 Narcolepsy in pregnancy

Narcolepsy is characterized by excessive daytime somnolence, cataplexy, hypnagogic hallucinations and sleep paralysis (AASM, 2005). The prevalence of narcolepsy is low, and onset usually occurs during adolescence or young adulthood. Pregnant women probably follow the same prevalence of narcolepsy as nonpregnant women, although the symptoms may either exacerbate or attenuate during pregnancy. Narcolepsy during pregnancy can be stressful and there is a risk of developing obesity, which increases the risk of pregnancy complications. The possible effect of narcolepsy on pregnancy is not well known, but the condition should be treated by maintaining good sleep hygiene and adequate sleep time, and if needed a sick leave. In severe cases pharmacologic agents are administered [7].

1.4.5 Circadian rhythm sleep-wake disorders in pregnancy

Circadian rhythm sleep-wake disorders are caused by changes in the circadian time-keeping system, or misalignment between the endogenous circadian rhythm and the external environment [110]. The diagnoses include diseases such as delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, non-24-hour sleep-wake rhythm disorder, jet lag disorder, irregular sleep-wake rhythm disorder, and shift work disorder [53]. Alterations in circadian rhythms are not uncommon during pregnancy. Circadian rhythm sleep-wake disorders are frequently observed in pregnant women, with a prevalence of around 3-10% and are most common in shift working pregnant women. Circadian sleep-wake disorders may alter several circadian rhythms, e.g., body temperature and melatonin [136]. Treatment of circadian rhythm sleep-wake disorders typically comprises bright light therapy and melatonin administration [53]. However, in pregnancy melatonin treatment is not recommended [136].

1.4.6 Parasomnias during pregnancy

Parasomnias are unwanted physical events occurring during sleep. Common parasomnias include sleepwalking, sleep terrors and sleep related eating disorders occurring during NREM sleep. Nightmare disorder is another parasomnia, which occurs during REM sleep. The affected person is usually unaware that an NREM sleep parasomnic episode has taken place [7]. A study showed that symptoms of sleep walking and hypnagogic hallucinations, in addition to sleep related conditions like sleep talking, and sleep bruxism generally declined compared to the 3-month prepregnancy period [137]. It is common to have more vivid dreams during pregnancy, and frightening dreams about pregnancy or the fetus have been reported by at least 25% of women during pregnancy [7].

1.5 Endocrine changes in pregnancy

During pregnancy there are dramatic changes in a number of hormones, e.g. melatonin, estrogen, progesterone, cortisol and the growth hormone Human chorion somatomammotropin (HCS), which all increase throughout pregnancy. These hormonal changes affect the sleep-wake cycles and sleep archistructure, and thus may influence several physiological processes which, in turn, can affect the risk of sleep disorders [7].

Human choriogonadotropin (HCG) is normally only produced in pregnancy, has the highest level/concentration in pregnancy weeks 4-12, and stimulates the continuous production of estrogen and progesterone.

Estrogen is produced in the placenta, increasing significantly throughout pregnancy, and peaks before delivery. Maternal estrogen production follow a 24-hour rhythm at pregnancy week 35, showing an opposite circadian profile to cortisol.

Progesterone is also produced in the placenta and the level increases 10 – 500 times from prepregnancy to term. Progesterone follows a circadian rhythm, with an

increased level in the evening, leading to increased NREM sleep, sometime shortened sleep onset and reduced REM sleep. Furthermore, progesterone has a thermogenetic effect due to increasing the body's temperature. In addition, progesterone has an inhibitory effect on smooth muscles which, in turn, will affect the gastrointestinal tractus and urine bladder.

Cortisol, the glucocorticoid stress hormone, peaks in the morning and has the lowest concentration in the evening. It follows almost the same circadian regulation in pregnancy, but the peak in the morning is lower, due to the influence from other hormones. Cortisol increases significantly after gestational week 25, with doubled values at the end of the pregnancy.

HCS acts as a growth hormone, starts being produced at gestational week 8 and peaks at about week 35. HCS is closely related to slow wave sleep and plays an important role in sleep regulation [7].

1.5.1 Melatonin in pregnancy

Figure 3 shows melatonin secretion changes during pregnancy, with the nocturnal peak serum melatonin level decreasing between the first and second trimesters, followed by an increase after 24 gestation weeks. By the end of the pregnancy, the melatonin level reaches the maximum, and by the second day of post-partum the melatonin level decreases to the pre-pregnant value [41, 138].

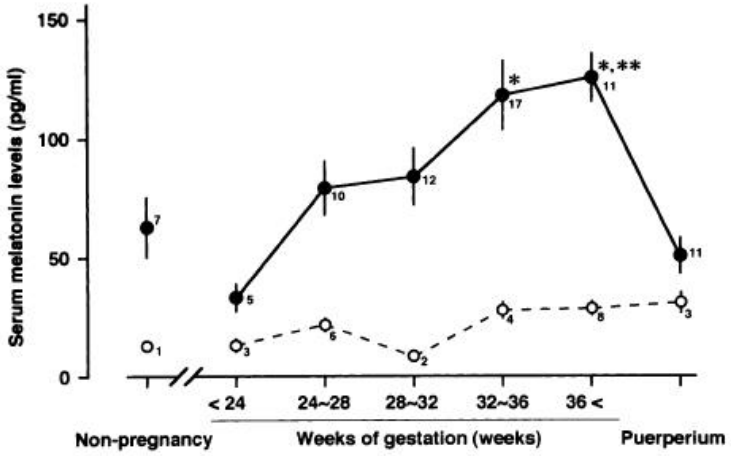


Figure 3. *Maternal serum melatonin levels during night-time (dark line) and daytime (dotted line) in normal singleton pregnancy. Values are presented as means +/- SEM, and the number of participants is indicated beside each dot. A significant rise in melatonin is shown after 24 weeks, peaking at 36 weeks gestation. Reproduced from [Changes of serum melatonin level and its relationship to feto-placental unit during pregnancy, Nakamura et al., 30:29-33, 2001] with permission from John Wiley and Sons.*

Melatonin is mainly produced by the pineal gland also in pregnancy. However, the placenta and the fetus may be involved in regulating the melatonin synthesis in pregnancy. The placenta synthesizes melatonin [40], which may increase the maternal plasma melatonin, and thus cross into the maternal bloodstream. The maternal plasma melatonin can also pass unaltered into the placenta [98]. There is a free exchange of melatonin between maternal and fetal circulation, due to the permeability of the feto-placental barrier [38, 139]. Plasma melatonin concentrations have accordingly been shown to be similar in the maternal and umbilical veins [140], and this provides photoperiodic information to the fetus [38]. Maternal melatonin seems to be important for entraining fetal circadian rhythms, as well as to protect the fetus against oxidative stress, influenced by neurodevelopment. In the last part of pregnancy, when the peak melatonin is highest, this mechanism may be especially important [98].

Melatonin is involved in the placental function and in this regard is thought to protect regeneration of mononuclear villous cytotrophoblasts and further maintain a healthy syncytiotrophoblast layer. Maternal blood is in direct contact with this syncytiotrophoblast layer that mediates the exchange of gases, nutrients and wastes [98].

Melatonin plays further important roles in placental and fetal development and functions. Figure 4 shows melatonin levels in normal and complicated pregnancies.

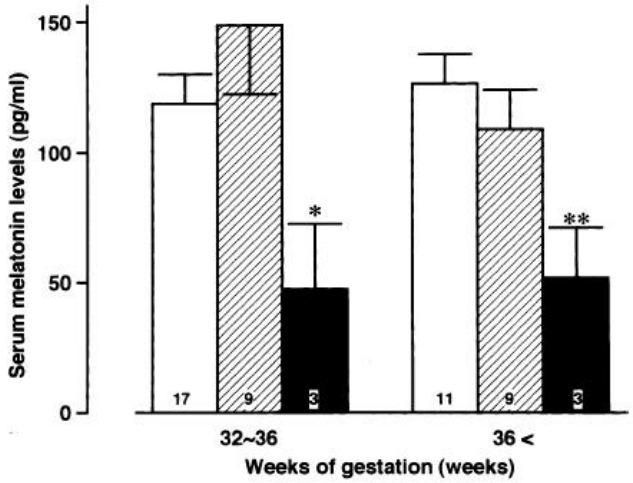


Figure 4. *Maternal serum melatonin levels in normal pregnancy (white column), mild preeclampsia (hatched column) and severe preeclampsia (black column). Data is presented as means +/- SEM. Number of participants is indicated at each column. Reproduced from [Changes of serum melatonin level and its relationship to feto-placental unit during pregnancy, Nakamura et al., 30:29-33, 2001] with permission from John Wiley and Sons.*

Altered melatonin secretion rhythms may affect pregnancy outcomes. Low levels in maternal plasma and/or saliva melatonin can contribute to pregnancy complications such as preeclampsia [41, 141, 142] and gestational diabetes mellitus [39, 142].

1.6 Blue light

Light is electromagnetic radiation (EMR), consisting of the electromagnetic spectrum that is visible for the human eye. The energy of the electromagnetic waves is called a photon and indicates the quanta of light. Photons with short wavelengths (violet-blue) contain more energy than those with long wavelengths [143]. Sunlight consists of polychromatic light and contains all visible wavelengths, including blue light [144]. Visible light is usually defined with wavelengths in the range of 400 -700 nanometers (nm), with monochromatic short-wavelengths (430 nm) violet light, (460 nm) blue light and longer wavelengths (555 nm) green light and (625 nm) red light [145]. Electromagnetic radiation outside the visible wavelength spectrum entails gamma rays, X-rays, ultraviolet red, infra-red, microwaves and radio waves. The impact of EMR depends on its wavelengths [143].

In 2001, researchers found that light exposure in the blue part of the spectrum suppressed melatonin production, through the newly discovered ipRGCs cells in the retina [35, 37]. IpRGCs cells are sensitive to light with short wavelengths between 446 and 484 nm (blue light) [56, 146], and have a stronger impact on the circadian system [70, 147], showing the greatest melatonin suppression [148], in addition to a greater influence on alertness, compared to longer wavelengths [70, 76, 149].

1.6.1 How blue light affects sleep and arousal in the evening and night

Blue light input is conveyed by ipRGCs, projected directly to the SCN, which suppresses pineal melatonin production, the natural hormone that promotes sleep, and may also suppress sleepiness [10]. On the following nights excretion of melatonin may not begin at the normal time, which can cause difficulties with falling asleep and may shift the timing of sleep [70, 147]. Artificial light exposure, typically from electronic sources, in the evening, with a high proportion of blue light, has been reported to delay bedtime [150, 151]. Exposure to blue light in the evening and at night has been shown to delay the circadian rhythm and inhibit sleep [152, 153], and by influencing the arousal system [71], to increase alertness [145]. Pregnant women may need to get up during the night, due to nocturia. This is the time when melatonin is normally flowing,

and exposure to light through the eyes at these times can cut this flow and decrease sleepiness [151], thereby making it harder to return to sleep. These notions are supported by a study that examined nocturnal light exposure in pregnant women and found an association between light and reduced sleep length in the first and last trimesters [154]. Exposure to blue light in the evening or at night, can thus enhance arousal [71, 145] and thereby attenuate subjective sleepiness and impair sleep [151].

1.6.2 How blue light affects the melatonin level

Exposure to blue light, with short wavelengths, has demonstrated acute effects in terms of melatonin suppression [56, 149, 150, 152, 153, 155], interfering with the natural process of increasing production in the evening soon after dark onset [34]. The melatonin suppression shows a dose-response relationship [34], although even a small dose of light can trigger significant melatonin suppression [35, 156].

In a modern society, the use of electronic devices such as smart-phones, computers, tablets and TV is very common. These devices emit a large proportion of blue light, resulting in suppression of melatonin production [150, 151].

The time and intensity of light exposure are of importance. Dim light (low light intensity) exposure during the daytime has been reported to sensitize the person to the melatonin suppression effect of nocturnal light [62, 157]. On the other hand, data shows that early morning blue-white light exposure attenuates the melatonin suppression and phase-shifting response to light exposure in the evening [158].

In pregnancy, melatonin production increases after gestational week 24, and plays an important role in placental and fetal functions and development [138]. Bright light therapy in the early morning has been reported to phase advance the melatonin rhythm for pregnant women with depression [159]. A study of pregnant women who worked at night in the third trimester, reported lower production of nocturnal melatonin than daytime workers [160].

Disruption of melatonin secretion in the early evening may lead to sleep disturbances [33, 34, 161]. Disturbed sleep during pregnancy can affect both pregnancy and

offspring outcomes and might be related to light suppressed melatonin production [160]. Increased exposure to light at night in pregnancy may, as such, affect the health negatively [161], and cause changes in melatonin levels and their impact on circadian rhythms [70, 147].

1.6.3 Blocking the evening blue light

Interventions to reduce exposure to bright light, particularly blue light, are aimed at restoring sleep by reinstating natural circadian rhythms [162]. Orange tinted glasses are suitable to filter/block the blue wavelength of light [163, 164].

There are limited studies of the effects of BB-glasses in pregnancy. In a non-pregnant population, BB-glasses worn in the evening before sleep time, exposed to light-emitting diodes (LED) sources, prevented melatonin suppression, increased subjective sleepiness and decreased alertness [68], which might indicate a reduction of the signals to the SCN. Studies to investigate the effects of wearing BB-glasses while using blue-light emitting screens have shown to prevent increased alertness [163, 164].

Several studies of the use of BB-glasses have reported improvements for insomnia [164, 165], sleep disturbances [166], delayed sleep phase syndrome (DSPS) [167], mood [164], bipolar disorder [168] and attention-deficit hyperactive disorder (ADHD)[169]. In a group suffering from major depressive disorders, however, Esaki et al. [170] did not find significant differences between intervention and control conditions for sleep quality and mood, although half of the intervention group did improve in terms of sleep quality.

Further studies using BB-glasses have reported such use to protect melatonin production from light-suppression in the evening or/and at night [68, 75, 152, 171]. However, Esaki et al. [167] found no statistically significant advance in dim light melatonin onset (DLMO) in individuals with DSPS following BB-glass treatment.

Another study found that participants working in bright light conditions during the night, and wearing BB- glasses, produced melatonin at the same levels as those in

darkness. Furthermore, working in bright light conditions without glasses resulted in suppressed melatonin production [155].

One study demonstrated that blocking the blue light at night showed that women suffering from postpartum depression recovered more quickly than those with no blue-light blocking intervention [163]. By wearing BB-glasses in the evening and at night, when pregnant women often need to get up, they can avoid exposure to LED-induced blue light or blue light emitted from other sources. BB-glasses thereby seem to prevent the suppression of melatonin and allow a natural cycle of light and darkness to govern the melatonin secretion. [68]. This is of importance regarding knowledge of the unrestricted exchange of melatonin between maternal and fetal circulation, and the beneficial roles melatonin plays in terms of placenta and fetal functions [38].

Studies on light exposure and stress, and the effects of blocking the blue light in pregnancy on sleep outcomes, mood and melatonin onset remain to be conducted and will accordingly be a focus in the current thesis.

2. Aims

The overall aim of this thesis was to investigate sleep patterns, sleep related behavior, the prevalence of sleep disturbances, stress, and the effect of BB-glasses in the evening and at night on sleep outcomes, insomnia, evening sleepiness and evening alertness and melatonin onset and levels in pregnant women in the third trimester.

Specific aims were as follows:

I. Paper I

1) To identify sleep patterns, sleep related behavior and the prevalence of sleep disturbances in a sample of pregnant women in the third trimester.

2) To compare the pregnant group to a group of non-pregnant women in terms of sleep patterns, sleep related behavior and the prevalence of sleep disturbances.

3) To investigate the level of evening light exposure and perceived stress and how these are associated with sleep characteristics in the pregnant group.

II. Paper II

1) To investigate the effect of BB-glasses, compared to partially blue-blocking glasses, on subjectively and objectively assessed sleep, insomnia, evening sleepiness and evening alertness, in pregnant women in the third trimester.

III. Paper III

1) To investigate the effect of BB-glasses in the evening, compared to partially blue-blocking glasses, on melatonin onset.

2) To investigate the blue-blocking effect on melatonin profile for clock time and sample number in a sample of pregnant women. A further aim was to investigate the effect of BB-glasses on the phase angle between melatonin onset and bedtime and sleep onset.

3. Methods

3.1 Design and procedures

This thesis is based on a randomized double blind parallel group-controlled trial, pre-registered at ClinicalTrials.gov (NCT03114072). The trial lasted for three consecutive weeks: one baseline week followed by two intervention/control weeks. The trial was randomized into two groups: either BB-glasses (orange) or partial blue-blocking glasses (grey), and investigated whether the intervention altered sleep outcomes, mood and the evening melatonin profile in pregnant women in the third trimester. In addition, we used data already collected from a non-pregnant female group, for comparison with the pregnant group at baseline.

Paper I was an observational study, based on data at baseline collected as part of the randomized clinical trial, where data for sleep and light exposure in pregnant women in the third trimester was compared with a group of female non-pregnant university students. Furthermore, perceived stress and evening light exposure were investigated in terms of how these variables were associated with sleep characteristics among the pregnant women.

Papers II and III were based on the intervention study and presented data from the trial to investigate the effect of BB-glasses on sleep outcomes and melatonin profile.

Recruitment to this trial took place in Bergen, Norway between May 2017 and April 2019. Bergen Municipality has 285,601 inhabitants [172] and had 4,553 births at Haukeland University Hospital in 2020 [1]. There are eight antenatal healthcare centers in Bergen [173], distributed in different districts, and all of them were invited and trained to participate in the recruitment. During the study period, the researcher was in regular contact with the consulting midwives, at short meetings or by email, and conveyed motivation and information about the study.

The consulting midwives at the antenatal healthcare centers mediated the recruitment of pregnant women at around gestational week 24. The midwives provided

information about the study, both orally and in writing, in a brochure/written form, to relevant participants. If a pregnant woman agreed to participate or required further information, the midwife put the pregnant woman in contact with the researcher (Randi Liset). The researcher would then call the participant, give a presentation of the study, present what it would entail for the pregnant woman and set up an appointment for the first meeting. The first meeting, which defined the start of the study protocol, took place at the beginning of the third trimester, around gestational week 28. Week 1 indicated the baseline, and the participants were assessed by subjective and objective measures for 7 days, followed by 14 days of intervention/control condition. Figure 5 shows the scheduled procedures during the study period.

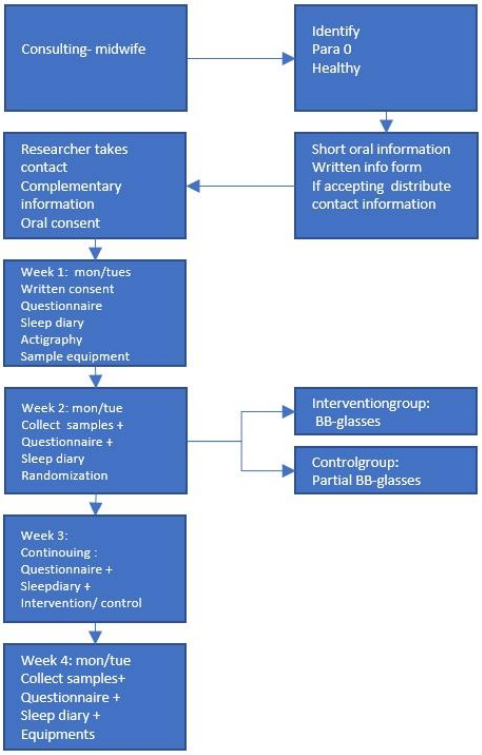


Figure 5 *Flow diagram of scheduled procedures during the study period.*

3.2 Participants

This thesis is based on the same sample of pregnant women as the data from this group presented in all papers. A sample of 60 pregnant women was planned to be recruited during the standard control at around gestational week 24, via consulting midwives at the antenatal healthcare center in the Municipality of Bergen. We continued recruiting until 60 participants had completed the protocol.

In total, 125 pregnant women were eligible for enrollment. Twenty-one were excluded because they did not meet the inclusion criteria. Thirty-seven declined further participation after receiving more information. Seven withdrew before the protocol was completed because of: preterm birth, fire in own home, severe malaise as a side-effect of the glasses, allergic reaction to the actigraph, lack of capacity to participate and discomfort wearing the glasses.

Paper I included data from 61 pregnant women in the analyses. One of the participants solely completed the baseline registration, without taking part in the entire intervention, and hence her data was included in Paper 1 only. Data from a comparative group of 69 non-pregnant female students recruited from the University of Bergen was also included in this paper.

Papers II and III include data from 60 pregnant women.

3.2.1 Inclusion criteria

Participants were eligible for the trial if they were:

- Nulliparous women
- Expecting one child
- In the third trimester of a normal pregnancy
- Able to wear an actigraph during daytime and night-time for the entire study period
- Able to complete a questionnaire in Norwegian

3.2.2 Exclusion criteria

Participants were excluded if they were:

- Suffering from somatic or psychiatric disorders
- Suffering from fever and other health conditions affecting sleep
- Working at night during the study protocol
- Suffering from any eye-condition affecting the translucency of the eyes

Translucency of the eyes reflects the ability to allow light into the eyes, which may be affected by some eye diseases. Eliciting the red reflex is a useful and technically simple clinical test of translucency, performed with an ophthalmoscope [174]. At the first meeting, the red reflex of both eyes was assessed by a researcher using an ophthalmoscope, so as to exclude women with serious eye conditions affecting translucency of the eyes. No participants were excluded based on the translucency of the eyes test.

3.2.3 Inclusion criteria for the non-pregnant comparative group

Students were included as a comparative group if they were:

- Healthy women
- Not pregnant
- Able to wear an actigraph during daytime and night-time for the study period for about one week
- Able to complete a questionnaire in Norwegian

If the students reported sickness during the study-period, they were excluded.

Baseline assessment at week 1 included demographic data, as well as administration of the Bergen Insomnia Scale (BIS), and the sleep variables total sleep time (TST), sleep efficiency (SE) and midtime of sleep, all assessed with sleep diaries. In addition, objective (actigraphy) sleep measures of TST, SE and midpoint of sleep, and light exposure, assessed by actigraphy for 7 days, were included.

3.3 Intervention

The RCT design included two conditions: intervention with BB-glasses and a control condition comprising partially blue-blocking glasses. The consenting participants were randomized by www.randomizer.org for either intervention or control condition. Randomization and masking procedures were carried out as follows: A research

assistant packed the intervention and control glasses into brown paper bags and created a unique number, unknown to the researchers, by using the randomization key. The research assistant was not further involved in the study. Condition was revealed to the researcher when the participants had completed the protocol at the last meeting and when all the completed instruments, questionnaires and saliva samples had been handed in. To ensure blinding of condition, the researcher did not know the identity of the participants and their conditions when data from questionnaires was plotted into the statistical software. Furthermore, scoring of actigraphy recordings and melatonin was performed after completion of all data collection. All participants were given the same information about the study in terms of purpose, which was said to be to investigate the effects of two types of glasses filtering different wavelengths of light on sleep, mood and melatonin secretion. Participants were instructed not to search the topic of light and sleep, and not to reveal details about their glasses if they needed to contact the research team. In the case of participants with previous knowledge of BB-glasses, they were not excluded, since both glasses filtered out some wavelengths shorter than 530 nm. We thus regarded the placebo effect to also be preserved in cases of prior knowledge of effects of blue-filtering glasses.

BB-glasses or control glasses were worn from three hours before self-chosen bedtime, and until the lights were turned off when going to sleep. If the pregnant women needed to get up at night and risked light exposure, they were instructed to wear the glasses.

3.3.1 Blue blocking glasses

The intervention glasses comprised orange-tinted BB-glasses (Uvex Skyper S1933X, by Honeywell, Smithfield, RI, USA. www.uvex.us). The light blocking capacity was assessed by transmittance measurements, using a Ramses hyperspectral radiometer from Trios and a Lions xenon light source. The intervention glasses blocked 99% of wavelengths shorter than 530nm, and approximately 15% of the remaining light spectrum.

3.3.2 Partially blue-blocking glasses

The control condition consisted of grey glasses (Uvex Skyper S1905, by Honeywell, Smithfield, RI, USA. www.uvex.us). The light blocking capacity were assessed as above (3.3.1), and the control glasses blocked approximately 50% of wavelengths shorter than 530 nm, and about 30-50% of light in the remaining visual spectrum. We chose to use partial blue-blocking as control glasses instead of clear glasses. The rationale for this concerned possible knowledge of the orange-tinted blue-blocking glasses, due to media exposure, and to avoid influence on blinding the participants, regarding the placebo effect.

3.4 Measures and instruments

Table 1. *Overview of instruments and procedures.*

Week	**1**			**2**		**3**		
Day	**1**	**2–6**	**7**	**8**	**9-14**	**15**	**16-20**	**21**
Question-naires								
Morning	Sleep diary	Sleep diary	Sleep diary	Sleep diary	Sleep diary	Sleep diary	Sleep diary	Sleep diary
During the day	Demo-graphic RSS BIS PSS			PSS				BIS PSS
Evening	KSS PSAS	KSS PSAS	KSS PSAS	KSS PSAS	KSS PSAS	KSS PSAS	KSS PSAS	KSS PSAS
Actigraphy	Actigraphy/ light recorder	Actigraphy/ light recorder	Actigraphy/ light recorder	Actigraphy/ light recorder	Actigraphy/ light recorder	Actigraphy/ light recorder	Actigraphy/ light recorder	Actigraphy/ light recorder
Saliva sampling			Melatonin					Melatonin
Inter-vention				Randomize: BB-glasses/ control-glasses	BB-glasses/ control-glasses	BB-glasses/ control-glasses	BB-glasses/ control-glasses	BB-glasses/ control-glasses End of inter-vention

Notes: RSS = Relationship Satisfaction Scale; BIS = Bergen Insomnia Scale; PSS = Perceived Stress Scale; KSS = Karolinska Sleepiness Scale; PSAS = Presleep Arousal Scale; BB = Blue-blocking.

3.4.1 Actigraphy and sleep diaries

For objective measurement of sleep and light exposure we used a commercial actigraph, the Actiwatch Spectrum (Philips Respironics). This actigraph looks like a watch and the participants were instructed to wear it on their non-dominant wrist, and continuously during the study period. The participants were further instructed to press an event marker at the time that they turned out the light to go to sleep, and again

when they finally woke up in the morning. Actiwatch Spectrum is constructed to register motor activity by a piezo-electric accelerometer, and has a light sensor that records light exposure, expressed in illuminance (lux). The epoch length was set to 30 seconds, the sensitivity for wakefulness was set to medium, and a cut-off of 10 minutes inactivity was set to score sleep onset and wake up time. Data was scored as sleep or wake and as such was converted to various sleep parameters by the Actiware version 6.0.9 (Philips Respironics) software.

Actiware requires a definition of rest interval to estimate periods of sleep, and the rest interval onset and offset can be changed manually based on an inspection of the raw data and sleep diary data. Actigraphy and sleep diaries are thus often used in combination. Rest interval onset was set at a marked decrease in activity (<50/min), and event marker registration was followed by a sustained decrease in activity or marked sustained decreases in light exposure (<8 lux) in the evening. Furthermore, rest interval termination was set at a marked sustained increase in activity (>50/min), event marker registration and/or sustained increases in light exposure (>8 lux) in the morning [18].

We used actigraph data in Papers I and II.

Sleep diaries are subjective measures of sleep episodes. The sleep diaries estimated the number and duration of naps during the day, use of sleep medication (yes/no), bedtime (hh.mm), lights-out time (hh.mm), sleep onset latency (SOL; min), number of nocturnal wakenings, wake after sleep onset (WASO), and waking and rise time (hh.mm). In addition, items to assess sleep quality and daytime sleepiness were also included [21]. The participants self-monitored and recorded the sleep diary each morning.

Data from sleep diaries was used in all three papers.

3.4.2 Salivary melatonin

To measure the melatonin profile, we used salivary measurement of melatonin. Salivary assessment is a reliable and validated tool and compares well to measurement

in plasma [175]. The participants conducted the sampling at-home in their natural environment. This approach has been validated by in-lab measurement [46]. Saliva sampling should be by protocol, and should be conducted in dim light to determine the dim light melatonin onset. This would entail that the pregnant women would have to wear dark glasses from 18:00 hours, followed by wearing BB-glasses or control glasses until bedtime. Since this entailed enforcing a rather intrusive assessment of the pregnant women, we decided to take the samples in natural conditions (without light blocking).

The participants were instructed to adhere to a protocol concerning food, drink, teeth brushing, etc., of which a detailed description is presented in Paper 3. Saliva was sampled every 30 minutes in the evening on day 7 (baseline) and day 21 (post-treatment). On day 21, the pregnant women also wore intervention or control glasses as from three hours before bedtime. The participants started the saliva sampling about three hours before normal bedtime, using Salivette tubes (Sarstedt AG&Co, Germany). The samples were stored and analyzed (further details in Paper 3) at the laboratory at the Department of Biological and Medical Psychology, Faculty of Psychology, University of Bergen, Norway.

Melatonin-onset was defined as the time when salivary melatonin levels crossed 4.0 pg/mL. Linear interpolation was used between adjacent samples, and linear extrapolation was used if melatonin levels reached 3 pg/mL, but not 4 pg/mL [47, 176]. Melatonin levels are presented as different clock times and sample number.

Melatonin measurements were only used in Paper III.

3.4.3 The Bergen Insomnia Scale

The Bergen Insomnia Scale (BIS) (6 items) is a self-reporting scale for assessing insomnia symptoms. BIS was administered at study initiation (day 1) and at study end (day 21). BIS originally has the time frame of the last month, but due to rapid changes in pregnancy, we changed the time frame to the last week. The first four items pertain to sleep onset, maintenance, early morning awakening insomnia, and not feeling restored after sleep. The last two items measure the level of daytime impairment due to

poor sleep and dissatisfaction with sleep. The cut-off for diagnosing insomnia is a score of 3 or above for at least one of the first four items, and a score of 3 or above for at least one of the last two items. Each item is rated on a scale ranging from 0 to 7 days per week (composite score ranging from 0 to 42) [117].

Papers I and II include data from BIS.

3.4.4 Pre-Sleep Arousal Scale

The Pre-Sleep Arousal Scale (PSAS) (16 items) assesses the state of psychophysiological arousal and weas completed every evening before sleep. PSAS measures cognitive (e.g. worry about falling asleep, depressing or anxious thoughts, mentally alert) and somatic (e.g. heart racing, shortness of breath, stomach upset) components of arousal. Each item is scored on a five-point Likert-scale ranging from 1 (not at all) to 5 (extremely) (composite score ranging from 16 to 80). Higher scores indicate higher states of arousal [177].

Papers I and II include data from PSAS.

3.4.5 Perceived Stress Scale

The Perceived Stress Scale (PSS) (10 items) was used to assess how often the participant had considered a situation in her life to be stressful during the previous week (e.g., ". . .upset of unexpected happening" and ". . .nervous and stressed"). The PSS was administered at study initiation (day 1). Responses were recorded on a five-point Likert scale ranging from 1 (never) to 5 (very often) (total score ranging from 10 to 50), and higher scores indicate higher levels of stress. Four items are reversed [108].

Data from PSS was used in Paper I.

3.4.6 Relationship Satisfaction Scale

The Relationship Satisfaction Scale (RSS) (10 items) was used to measure marital satisfaction (e.g. "…close relationship with my spouse/partner") and relationship quality (e.g. "…have problems in our relationship"). RSS was administered at study initiation (day 1). Unfortunately, one response option was inadvertently lost in the final process of creating the questionnaire, so that the response alternatives range from

1 (strongly agree) to 5 (strongly disagree) resulting in a composite score ranging from 10 to 50 (instead of a 6-point scale). Three items were reversed, and higher scores represent lower levels of relationship satisfaction [178].

Data from RSS was used in Paper I.

3.4.7 Karolinska Sleepiness Scale

The Karolinska Sleepiness Scale (KSS) was used to assess the state of subjective sleepiness, measured at two hours intervals throughout the day. The level of alertness-sleepiness was indicated on a 9-point Likert scale ranging from 1 (extremely alert) to 9 (extremely sleepy - fighting sleep), while higher scores indicate higher levels of sleepiness [179].

Data from KSS was used in Paper II, by calculating a mean score across four time points (20:00, 22:00, midnight, 02:00).

3.5 Statistics

Statistical analyses for all papers were performed using IBM SPSS Statistics version 25 (SPSS, Chicago, IL, USA) and Stata IC version 16 (StataCorp, College Station, TX) for Windows. In addition, we used R version 3.5.1 for statistical analyses in Paper 2 and 3.

In all papers, descriptive statistics were used to summarize demographic characteristics of the sample, presented as means and percentages.

3.5.1 Paper I

Independent sample t-tests were used to examine differences in age, alcohol and BIS-scores between the pregnant and the non-pregnant groups. Linear mixed effects models were used to compare the sleep outcomes TST, SE, midpoint of sleep, and total white light between pregnant and non-pregnant women. All analyses were performed crude and with adjustment for age, weekday and calendar month. Linear mixed effects models were used to examine whether the exposure composite score of RSS, PSS, PSAS and total white light was associated with the sleep outcomes TST, SE

and midpoint of sleep measures, both assessed by sleep diaries and actigraphy. These analyses were carried out for the pregnant women only. The analysis of each exposure on each outcome was performed crude (unadjusted) and adjusted for age, weekday and calendar month, and a random intercept for the individual was specified, to account for repeated measures and intra-individual correlation across weekdays.

3.5.2 Paper II

Independent two-sample t-tests were used to investigate the participants' compliance with the use of glasses. Chi square test was used to examine changes in insomnia (worse, unchanged, improved), based on cut-off points of BIS.

A descriptive analysis was used to calculate subjective measured TST, midpoint of sleep and SE for each day of the second intervention week. Analysis of covariance (ANCOVA) was used to examine the effect of BB-glasses on the primary outcomes TST, SE, midpoint of sleep and daytime functioning, and the secondary outcomes KSS, PSAS and BIS. The baseline outcome measures were used as covariates in regression models. Participants with mean TST <200 minutes per week were defined as outliers and their data was consequently excluded from the analysis.

3.5.3 Paper III

ANCOVA was used to examine the effect of BB-glasses on melatonin onset by including the baseline melatonin onset measure as a covariate in linear regression models. Paired t-tests were used to investigate the changes between baseline and posttreatment measures of melatonin onset within the groups.

ANCOVA and paired t-test analyses were also performed for bedtime and sleep onset, in addition to the secondary outcome, which entailed the phase angle between melatonin onset and bedtime and sleep onset time, respectively, at baseline and post-treatment, specifically.

To investigate how salivary melatonin varied by evening hours and sample numbers for both the BB-group and the control group, we performed generalized additive models for evening hours and cubic splines regression for sample numbers.

The Mann-Whitney U test was used to test for group difference in salivary melatonin at each evening hour and sample number.

3.6 Ethical considerations

The study protocol concerning all three papers was approved by the Regional Committee for Medical and Health Research Ethics in Western Norway (No.2016/1394/REKvest). Consent was obtained from all participants, both orally and in writing, before inclusion in the study. The participants were informed about possible transient discomfort from the glasses, e.g. headache, known from other studies. When participation was completed, the participants received information about the aim of the study and were offered BB-glasses as compensation.

4. Summary of results

4.1 Paper I

The study explored the prevalence of sleep disturbances among pregnant nulliparous women. Among 61 healthy nulliparous women included at the beginning of the third trimester, the prevalence of insomnia was 38%. The comparative group of 69 non-pregnant young women reported an insomnia prevalence of 51%. In both samples, insomnia was measured by BIS.

To identify sleep pattern and sleep related behavior, sleep diary data and actigraphic data were analyzed, and TST, SE and Midtime of sleep were reported. The pregnant women subjectively reported lower total sleep time of 444.2 (SD 5.9) minutes, compared to actigraphy objective data that showed 463.0 (SD 5.5) minutes. The corresponding results for the non-pregnant group were 461.9 (SD 5.8) minutes and 448.4 (SD 7.0) minutes, respectively. Even though the pregnant group reported subjectively less sleep time than the non-pregnant group, the difference was not statistically significant. In terms of the objective actigraphy data, however, the pregnant group showed statistically significant ($p<.001$) longer total sleep time than the non-pregnant group.

Furthermore, the pregnant women reported lower SE of 86.2 % (SD 0.7) with regard to sleep diary data, compared to the non-pregnant women, who reported an SE of 89.6 % (SD 0.8). This difference was significant (p .033), although actigraphic data showed quite equal SE between the groups.

There was no significant difference between the two groups in terms of Midpoint of sleep, neither in sleep diary data nor actigraphic data.

To identify light exposure in the evening, actigraphic data measured white light (polychromatic light). According to the actigraphic data, the pregnant women were exposed to more white light (log transformed) 8.4 (SD 0.1) for the three last hours

before bedtime, compared to the non-pregnant women (log transformed) 7.0 (SD 0.1) (p .002).

Questionnaires measuring stress variables RSS, PSS and PSAS were assessed among the pregnant women only. The analysis investigated how these were associated with sleep outcomes such as TST, SE and Midpoint of sleep, recorded by both sleep diaries and actigraphy. The stress variables showed overall low scores, and were not related to sleep outcomes, when assessed by either subjective or objective measures. However, light exposure before bedtime was inversely related to TST (mean difference = -8.1, p = .016) and midpoint of sleep (mean difference = -10.3, p = <.001), measured by actigraphy data, which suggests that a high level of illumination may curtail sleep.

4.2 Paper II

In this paper, an RCT investigated the effect of blocking evening blue light during a two-week intervention on sleep variables measured by sleep diary, sleep questionnaires and actigraphy. Sixty randomized participants of healthy nulliparous women at the beginning of the third trimester, with 30 women in each condition (BB-glasses or control condition comprising grey glasses), where sleep, insomnia, evening sleepiness and evening alertness constituted the dependent variables.

Sleep-diary measured TST, SE, midpoint of sleep and daytime functioning analyzed for group differences did not show significant differential effects between BB-glasses and control glasses at post-treatment. In total 50 participants had valid actigraphy data and were consequently included in the analyses. There were no significant differences between the BB-glasses and control glasses in terms of TST, midpoint of sleep and SE, from baseline to post-treatment for the actigraphy data.

Insomnia measured by BIS showed a prevalence of 38.3% at baseline, and 49.2% at posttreatment, in total for both groups. We investigated the change in insomnia diagnosis (worse, unchanged, improved) from baseline to posttreatment. In the BB-

group, 6 (20%) pregnant women, compared to 1 (3.3%) in the control group, improved from baseline to post-treatment. However, 4 (13.3%) pregnant women in the BB-group worsened from baseline to post-treatment, compared to 9 (30%) in the control group. However, the different development over time across the two conditions did not reach significance.

Evening sleepiness and evening alertness assessed by KSS and the PSAS did not show statistically significant effects between the conditions.

4.3 Paper III

Due to missing data, 47 out of 60 healthy pregnant women enrolled in the RCT were eligible for analysis of saliva measured melatonin. Saliva was sampled at baseline (day 7) and posttreatment (day 21). This paper investigated the effect of blocking the blue light in the evening during two weeks of intervention, on melatonin onset, phase angle (between melatonin onset - bedtime, and melatonin onset – sleep onset time), in addition to melatonin profile in terms of clock time and sample number.

The group allocated to wear BB-glasses showed a significant advance of 43 minutes (p=<.001) in melatonin onset (earlier onset) from baseline to posttreatment. The group receiving control glasses, with a partially blue-blocking effect, showed an advance of 11 minutes in melatonin onset, also a significant change from baseline (p=.002). The group difference of 28 minutes at posttreatment was statistically significant (p=.019).

Median salivary melatonin was measured and tested for group differences at each clock time and sample number. For clock time, median melatonin showed a significant group difference at 20:00 hours (p=.034) at baseline. However, at post-treatment the group differences were significant at 20:00 hours (p=.001), 21:00 hours (p=.003) and 22:00 hours (p=<.001), all in favor of the BB-group. For sample number there was no significant difference between the intervention and control group at baseline for median melatonin. However, at post-treatment the BB-group showed higher median

melatonin levels at sample number 3 (p=.038) and 4 (p=.025), compared to the control group.

Furthermore, the BB-glass group increased the phase angle (time) between melatonin onset and bedtime by 45 minutes (p=.007), and between melatonin onset and sleep onset time by 41 minutes (p=.037). There were thus no significant difference changes in any of the phase angle times for the control group. Nor were there any significant differences between the two groups.

The results suggest that blue-blocking intervention was beneficial in terms of an earlier onset of melatonin excretion, and higher levels of evening melatonin.

5. Discussion

The main aim of this thesis was to investigate whether BB-glasses can improve sleep outcomes, insomnia, evening sleepiness and evening alertness, and alter melatonin onset/levels in healthy pregnant women in the third trimester of pregnancy. In addition, we wanted to identify the sleep patterns, sleep related behavior and sleep disturbances among a sample of pregnant women. The most important findings of this thesis are presented as follows. Paper 1 reported a prevalence of insomnia in 38%, but still overall good sleep for the group of pregnant women, with an approximate mean total sleep time of 7.5 hours. Evening light exposure was inversely associated with sleep duration. Paper 2 reported that the use of BB-glasses in the evening did not show an effect on sleep outcomes, insomnia, evening sleepiness, or evening alertness. Paper 3 demonstrated that BB-glasses showed an effect in advancing melatonin onset, with a significant group difference, and by increasing the phase angle (time) between melatonin onset and bedtime, and sleep onset time. For phase angle no change in the control group was found, nor was any significant difference found between the two groups. However, melatonin profile at clock time and sample number showed a significant group difference for some of the samples, in favor of the BB-group.

5.1 Discussion of the key findings

In the following, evening and nocturnal light exposure in the third trimester of pregnancy, with focus on blue-blocking glasses as an intervention to ease sleep disturbances and mood, and change melatonin onset, will be discussed.

5.1.1 The association of light exposure with sleep in pregnancy

The literature is scarce concerning studies to investigate light exposure in pregnancy. We thus wanted to identify light exposure, in the three last hours before bedtime, in pregnant women in the third trimester of their pregnancy, and to compare our sample with a comparative group. Paper 1 showed that the pregnant women were exposed to more white light (including blue light) compared to a group of non-pregnant young women, with a statistically significant mean difference of log transformed total white

light of -0.7 (95% CI-1.2, -0.3) (p=.002). This may be due to an earlier midpoint of sleep (albeit the significant difference between the groups was only found in the crude analysis) in the pregnant group, which can reflect an earlier bedtime, which in turn can indicate a higher level of total white light before bedtime, as the latter occurred earlier in the evening when the natural illumination was at a higher level. This notion is supported by the fact that we also investigated light exposure during the three hours before bedtime on weekdays, where we found exposure to light to be higher than at weekends, when the women went to bed later (results not shown). We investigated whether evening light exposure would affect sleep outcomes in our sample of pregnant women. In non-pregnant samples, evening light exposure was demonstrated to reduce evening and nocturnal sleepiness [68, 77, 145, 151], and to induce later bedtime and shorter sleep time [180]. However, there is limited knowledge from previous studies to investigate how light exposure influence sleep outcomes in pregnancy.

In Paper 1, for actiwatch-measured sleep outcomes, we found that light exposure in pregnant women at baseline week was inversely associated with TST (mean difference -8.1 minutes), and earlier midpoint of sleep (mean difference 10.3 minutes), which are both statistically significant compared to the non-pregnant group. These findings suggest that increased light exposure may affect some sleep parameters and are in line with other studies showing that light exposure at night is associated with shorter sleep duration in pregnant women [154, 161].

Furthermore, in Paper 1 we did not find any association between light exposure and SE measured by actigraphy, or between light exposure and sleep outcomes for self-reported data. Based on actigraphy data, the pregnant women reported lower SE (mean difference 3.8%) and longer TST (mean difference 59 minutes) compared to the non-pregnant group.

The impact of blue light on sleep in pregnancy

By nature, we should not be exposed to blue light in the evening and at night, but in our modern surroundings we are still typically exposed to artificial light with a high proportion of blue light, typically from different media sources. This is also the case

for pregnant women. These artificial light sources have been shown to delay bedtime [150, 151], and circadian rhythms and to inhibit sleep [152, 153, 155].

It is of interest to investigate how blue light affects pregnant women, as pregnancy is a vulnerable phase in life. To our knowledge, no previous studies have investigated the effect of BB-glasses on sleep outcomes during pregnancy.

In Paper 2 we investigated the effect of blocking out the blue light in the evening (three hours before normal bedtime) on pregnant women for two weeks, where various sleep variables comprised the outcomes. We found a small increase in TST for pregnant women wearing BB-glasses (8 minutes) and for pregnant women wearing control glasses (4 minutes) for sleep diary measured data. For actigraph data the pregnant women using BB-glasses also had a small increase in TST of 5 minutes, whereas an opposite pattern was shown for the control group, with a decrease of 35 minutes. None of these findings were statistically significant, however.

For the other sleep variables comprising SE, midpoint of sleep and daytime functioning, no differential effects between BB-glasses and control glasses were found, neither for sleep diary nor for actigraphy data.

Even if we did not find any effect of blocking the blue light on sleep outcomes, it has previously been found that illumination with a high amount of blue light, wavelength shorter than 530 nm, in the evening and at night can delay circadian rhythms and inhibit sleep [152, 153, 155]. Some studies have also shown that such illumination delays the onset of deep sleep [150, 151].

In line with our findings in Paper 2, some former studies also found no significant difference between the group using BB-glasses or control condition, on sleep outcomes [68, 170]. In contrast to our findings in Paper 2, however, several other RCTs and crossover studies have shown that use of BB-glasses resulted in improved sleep quality [164, 165, 169, 181], reduced SOL [166, 167], increased TST [165, 181], and increased SE [166, 168].

We expected a worsening of sleep in the third trimester, compared with the previous trimesters, in line with findings from previous studies in this field [3, 83, 109]. Furthermore, we hypothesized to find effects of blue-blocking glasses. The pregnant women in our sample initiated participation in the study when they were in the third trimester, so that we had no information about how sleep had developed up to this point in time. It is possible that the lack of significant effect of the intervention on sleep outcomes reported in Paper 2 is related to the sample, which in the current thesis comprised overall good sleepers. A review by Schechter et al. supports this, as they reported the greatest effect of BB-glasses in groups with strong symptoms of sleep problems [162]. Paper 1 and Paper 2 show an approximate total sleep time of 7.5 hours at baseline, which is in line with recommendations for total sleep time among women at this age group [20]. Furthermore, SE is commonly used as an indicator of sleep quality, and in Paper 1 the baseline mean SE was above the suggested cut-off of 85% [182], so that it would be difficult to detect any improvements in SE in our study.

In Paper 1, we investigated the sleep pattern during all weekdays and found that the pregnant women tended to extend their sleep at the weekend, compared to a non-pregnant group. This may reflect that the pregnant women had accumulated a sleep deficit during the weekdays. It is not conceivable to expect a significant improvement in sleep in a group of pregnant women with average normal sleep patterns. In contrast to this, several studies have shown improvements in sleep quality [183] and advanced sleep onset [171] following use of BB-glasses, even in samples comprising healthy adults without sleep complaints, similar to our study.

In Paper 1, we did not find any association between the stress variables (RSS, PSS and PSAS) and sleep outcomes (TST, SE and midpoint of sleep), neither when measured subjectively nor objectively, even though previous research has shown that pregnant women who report high levels of stress are more likely to experience insomnia than those with moderate to low stress levels [87]. Evening sleepiness was measured by KSS, which showed normal levels, thereby indicating that they were neither sleepy during the daytime nor alert in the evening. Hence, in Paper 2 we found no significant effect of blocking blue light on KKS, between the groups. In contrast to this, studies of

non-pregnant populations have shown that users of BB-glasses have reported greater sleepiness, compared to those in control conditions [68, 166].

In Paper 2, we reported findings based on PSAS and found no significant effect on alertness from blocking the blue light. This may be related to the fact that the sample of pregnant women had low baseline scores for PSAS. Even so, in contrast to our findings, Van der Lely et al. [68] found less alertness in the BB-condition, compared to the controls. Hence, illumination with a high amount of blue light has been shown to increase alertness [150, 151], compared to light with less short-wavelength energy [147]. BB-glasses have been shown to attenuate light induced activating effects on subjective alertness cognitive performance [68].

5.1.2 The association of light with melatonin secretion in pregnancy

Melatonin is important for, among other things, the induction of sleep for pregnant women and as a regulator of the fetal circadian rhythm. In normal pregnancies night-time melatonin levels increase after 24 weeks' gestation, compared to earlier in the pregnancy, and reach a peak at around 36 weeks of gestation [138, 140]. Paper 1 identified that the pregnant women were exposed to more white light before bedtime than a comparative group of non-pregnant women, and this is discussed under 5.5.1. It is a well-known finding that environmental light exposure has an acute suppressive, dose-dependent effect [147] on endogenous melatonin production, and that evening light exposure can phase delay the melatonin rhythm [67].

The impact of light exposure on melatonin in pregnancy has been demonstrated in a few small studies. A study of healthy night workers in the third trimester of pregnancy showed lower night-time melatonin production in their natural environment, compared to daytime workers [160], and an RCT with preliminary melatonin data of pregnant women exposed to blue/green light showed lower melatonin concentration than the control group (red light) [184]. Light exposure is known to suppress melatonin production, and this has been supported by a large range of studies [35, 37, 66, 67, 146, 147].

Paper 3 investigated the impact of light exposure on melatonin in pregnant women. The main aim was to elucidate the effect of BB-glasses on melatonin onset in the evening. It was therefore hypothesized that a reduction of the short wavelength light exposure by using BB-glasses would prevent the suppression of melatonin.

In Paper 3 we found that use of BB-glasses in the evening advanced melatonin onset by 43 minutes (p=<.001), compared to the control glasses, where this was advanced by 11 minutes (p=.002) from baseline to post-treatment. The group difference of 28 minutes at post-treatment was statistically significant (p=.019).

This suggests that exposure to blue light in the evening and at night affects melatonin production negatively. It is known that the circadian photoreceptor system, via ipRGCs cells in the retina, shows peak sensitivity to short wavelengths between 446-484 nm (the blue light) [35, 54], and hence light within this spectral range accounts for suppression of the melatonin secretion [70]. The findings of the present thesis support the notion that the use of BB-glasses in the evening allows melatonin-production to follow the natural cycle of light and darkness more closely. Considering that the control group used glasses with a partial blue-blocking effect, the effects found seem particularly convincing. We expected to find an earlier secretion of melatonin in the BB-group compared to the control group, which was confirmed by a 28-minute difference between the groups. This means that BB-glasses may be effective to use in the evening and at night in terms of preventing disturbance to the circadian rhythms, like circadian delay, by reducing blue-light energy input to ipRGCs. Melatonin modulates not only circadian rhythms, but also the endocrine system, the immunological system, acts as a direct free radical scavenger and exhibits an indirect antioxidant and cytoprotective agent in human pregnancy. There is a free exchange of melatonin between maternal and fetal circulation [38], and also plays an important role in the development and functions of the placenta and fetus [98]. Moreover, and importantly, melatonin is found to be crucial for successful pregnancy and plays a basic role to reduce complications during pregnancy like abortion, pre-eclampsia and fetal brain damage[38]. By preventing melatonin suppression, as we found in Paper 3, there is reason to assume altered rhythms of melatonin secretion, which may be

beneficial for pregnancy outcomes [39, 141]. However, we do not have information about how the BB-glasses affected melatonin levels during the night or in the morning [181].

To our knowledge, the present study presented in Paper 3 is the first to assess the effects of blue light blocking intervention on melatonin onset in pregnancy.

Similar to the findings reported in Paper 3, previous RCT and cross-over studies of non-pregnant populations have already shown that blocking blue light protects the endogenous melatonin production from light-suppression at night [68, 75, 152, 166, 171, 181]. However, some studies have failed to show such effects [167, 183].

Evening light exposure during the hours preceding normal bedtime, from normal ambient room lighting [185], as well as artificial light sources such as smartphones, tablet, computers and TVs, is normal. These light sources can cause a reduction of and delay in melatonin secretion [67, 150], and hence exposure to wavelengths shorter than 530 nm (blue light) suppresses the melatonin production [94, 152, 155].

Another aim of Paper 3 was to investigate the phase angle (the time interval from a phase marker of the master circadian clock and until another circadian driven event occurs), between melatonin onset and bedtime and sleep onset time, respectively. Paper 3 showed a significantly increased phase angle in the BB-group, which increased from baseline to post-treatment, with 45 minutes for the phase angle between melatonin onset and bedtime ($p=.007$), and with 41 minutes between melatonin onset and sleep onset ($p=.037$). Yet neither the changes within the control group nor the difference between the groups reached significance. The fact that the phase angle variables showed within group effect in the BB-group, shows that exposure to blue light in the evening affected the phase angle time. However, there was no time x group interaction effect, so that the two conditions did not seem to impact the phase angles differently. One reason for this may be that the pregnant women could sleep ad libitum. Previous studies have shown a stable relationship between melatonin onset and sleep onset, even though a specific bedtime is enforced [186].

The findings in Paper 3 are in line with previous research in non-pregnant populations, where Van der Lely et al. [68] did not find significant differences between the conditions in terms of phase angles between melatonin onset (DLMO) and sleep onset. In contrast, however, Zerbini et al. [171] showed a significant decrease in phase angle between melatonin onset (DLMO) and sleep onset in the BB-group for the first, but not the second, week of intervention.

The present study followed the pregnant women in their natural setting, and they went to bed according to their own preference. The participants used the BB-glasses from three hours prior to individual bedtimes, which means the melatonin samples were measured at different clock times for each participant. However, as the participants were randomized, no group difference in bedtime would be expected at baseline. The group melatonin difference for clock time at post-treatment was statistically significantly different, with higher melatonin levels in the BB-group at 20:00, 21:00 and 22:00 hours, compared to the control group. Even though the samples were measured at different clock times (range 18:00 to 02:00 hours), the sample number (n=1-6) was equal for all participants, and sample numbers 3 and 4 showed a statistically significant group difference in melatonin levels, in favor of the BB-group.

Even if Paper 2 showed that we did not find statistically significant effects of BB-glasses on sleep parameters, Paper 3 was based on the same sample of a group of relatively well-sleeping and healthy pregnant women who did show effects on melatonin outcomes. The findings of Papers 2 and 3, are partial, in contrast to the findings by Ayaki et al. [166] and Ostrin et al. [181], who reported an improvement in sleep outcomes and advanced melatonin onset. Still, two other studies by Esaki et al. [167] (objectively, sleep onset time) and Nagai et al. [183] (subjectively, sleep quality) reported improved sleep measurements following BB-glass use, but not on melatonin outcomes, which were thus quite opposite to our findings. In Paper 2, BB-glasses did not show a significant effect on evening alertness. These findings are in contrast to the findings by Van der Lely et al. [68], who reported decreased alertness before bedtime in the BB-condition, in addition to significantly higher melatonin levels, although not significantly different between the conditions.

To understand the circadian system in pregnancy, there is a need for knowledge of how blue light impacts melatonin production in pregnant women, as this may have clinical relevance.

5.1.3 Are BB-glasses an effective non-pharmacological treatment for sleep disturbances in pregnancy?

Based on the findings from Paper 2, there were no statistically significant group differences in the changes for BIS from pre- to post-treatment. Still, it might be of clinical interest that 6 of the pregnant women wearing BB-glasses improved, relative to 1 of the pregnant women wearing control glasses. However, this improvement should be interpreted with caution, as we have no firm evidence to claim that BB-glasses are an effective treatment for insomnia in pregnant women, as reported in Paper 2. However, there are several studies that have investigated the effect of blocking blue light on insomnia [164, 165]. In contrast to our study, these studies only had participants with insomnia, which may play an important role in terms of the potential for significant clinical findings. Paper 1 (baseline) and Paper 2 reported the prevalence of insomnia to be 38.3% at baseline, and 49.2% at post-treatment, across both groups. By gaining knowledge from studies of groups other than pregnant women, there may be reason to believe that pregnant women with insomnia symptoms may experience an effect from blue-blocking glasses in terms of insomnia. In a review, Faulkner et al. [187] concluded that behavioral interventions, such as evening light avoidance, seem to have high effectiveness for sleep problems. Another review by Shechter et al. [162] concluded that there was evidence of treatment effects from blocking the blue light in the evening/at night for individuals with insomnia, bipolar disorder, DSPS or ADHD. This might suggest that BB-glasses have potential as a treatment for insomnia in pregnant women. However, this needs to be supported by firm empirical evidence.

BB-glasses represent a safe, affordable and easily implemented therapeutic intervention, and have shown significant effect for the non-pregnant population with insomnia symptoms [165].

In the meantime, while waiting for other studies to assess whether BB-glasses are an effective treatment for insomnia in pregnant women, we have to lean on other existing treatment options. Sleep medication is not recommended as a first-line treatment for sleep disorders in pregnancy, due to potential adverse effects, especially for the fetus [134]. Non-pharmaceutical treatment options do exist, however [188]. Sleep hygiene counseling and cognitive behavior therapy for insomnia (CBT-I) are important treatments and have been shown to be effective during pregnancy [132], and are thus the preferred choice rather than medication [189], although some reviews have expressed doubts about the clinically significant effect of these interventions on the pregnant population [8, 135]. Furthermore, such counselling treatment is also relatively time-consuming, costly and might not be readily available. However, studies have demonstrated the effectiveness of digital CBT-I [190] for pregnant women with insomnia [191], which can increase the availability of this treatment.

5.1.4 Maternal health during pregnancy and possible impact on the fetus and future health

Whatever affects the pregnant woman may also affect the fetus. Lifestyle factors such as nutrition and physical activity are known to have a major impact on maternal health during pregnancy [192, 193], with an impact on the fetus and subsequently on the child's health [194]. Prenatal stress has been related to adverse obstetric [89, 91] and neonatal outcomes [93]. The pregnant women as a whole (Paper 1), reported low exposure to stressors, however, both more generally and in terms of their relationship with a partner.

Sleep disturbances during pregnancy are related to adverse pregnancy outcomes such as preeclampsia, increased serum glucose, depression, prolonged labor, caesarean birth, intrauterine growth restriction and preterm birth [8, 91, 195]. Both indirectly and directly, the sleep of the pregnant woman may affect the fetus and possibly also the child's future health. A large cohort study of maternal tryptophan, a precursor for both melatonin and kynurenine, showed that obese pregnant women had an accumulation of kynurenic acid before they developed preeclampsia [196]. Okatani et al. [140] reported equal plasma melatonin concentration in both the maternal and the umbilical vein,

which provides photoperiodic information to the fetus [38]. This is in line with a study of night workers that found some adverse effect on pregnancy and negative offspring outcomes and concluded that this could be related to light-induced suppression of melatonin during night work [160]. In Paper 3 we demonstrated that blocking out the blue wavelengths had a protective effect on the endogenous melatonin production from evening light suppression. We did not investigate the possible effect on the fetus or the offspring, but BB-glasses might improve circadian function for the offspring as well.

In a clinical perspective, the focus is often on nutrition and physical activity, but less often on sleep. Maternal sleep quality during pregnancy also affects the fetus and the future health of the child [8, 91, 195]. Poor sleep is one of the most underestimated public health problems in Norway [197]. There is consequently a need for more knowledge about sleep in pregnancy, both for pregnant women and for professional healthcare providers. A place to start might be to increase the focus on sleep in education programs at institutions for midwifery, nursing, medicine and psychology. Furthermore, screening of sleep disturbances during pregnancy could pave the way for preventive interventions, as well as early interventions in pregnancy.

We also need to consider health in a generational perspective. What happens in maternal health (life) might be important for the health of the future child.

Suggestions for future research include investigating the effect of blocking evening blue light in pregnant women with insomnia. Furthermore, investigation of effects of blue-blocking intervention on melatonin in pregnant women, and the effect on the offspring, including fetal development, is also warranted.

5.2 Methodological consideration and limitations

This section presents and discusses the methodological considerations and limitations of the studies in this thesis, and further discusses how limitations may have influenced our findings.

5.2.1 Design

Paper 1 in this thesis was designed as an observational study, using data from the baseline week (week 1), where data from the pregnant group was compared to a comparative group of non-pregnant women. Papers 2 and 3 were based on an RCT. A main strength of the two latter papers comprises the randomized controlled design, which is regarded as the best design to draw conclusions about the effect of interventions. The RCTs specifically assessed the causal effect of blocking blue light where the outcomes were sleep variables and melatonin onset and levels.

The present studies investigated the pregnant women in their natural setting. This entailed that light condition could differ greatly among the participants. This could be regarded as an asset for study 1, as its aim was to investigate how evening light was associated with sleep. Regarding Papers 2 and 3, however, individual variations in light levels could be considered an error variance, although the randomization ensured that this factor was evenly distributed between conditions. Still, laboratory settings could have made the environmental influences, e.g. light exposure and seasonal variations, more stable.

Randomization and blinding in Papers 2 and 3

The allocation was randomly performed by www.randomizer.org to either intervention (BB-glasses) or control (grey glasses) condition. An independent research assistant organized the randomization key and packed the glasses into similar bags. The groups were similar, except for physical activity and relaxing activity, where the BB-group reported the highest scores.

This RCT was double blinded, so that neither participants nor researcher had any knowledge of which specific condition each participant was allocated to. A concern related to blinding of the intervention for participants was knowledge of BB-glasses among people in general. Post-treatment, only two of the women reported such knowledge. Furthermore, the control condition also had some light blocking effect, which was a strength considering that this comprised the placebo condition.

This was an effectiveness study in a naturalistic environment, which might entail many uncontrolled influences from the environment, increasing the risk of type 2 errors. However, such studies also become more generalizable than an efficacy study, which is typically characterized by a limited demographic spread, and with more controlled conditions, as typically conducted in a laboratory setting.

Another design which could have been considered relevant is a cross-over design, with the advantage of requiring fewer participants and adjustment within subject characteristics. A disadvantage of a cross-over design would, however, be the need for a washout period, a longer total study period and an increased risk of attrition.

Intervention and control in Papers 2 and 3

The choice of intervention with BB-glasses was based on previous studies demonstrating effect on sleep outcomes [164, 169] and melatonin onset [166]. No previous studies have investigated the effects of BB-glasses in pregnant women, which precludes direct comparisons with previous studies. In this thesis, we used an intervention with 99% blue-blocking filtration and a control group with 50% blue-blocking filtration.

The fact that pregnant women suffer from sleep difficulties, particularly in the last stage of pregnancy, and a desire to explore the effects of non-pharmacological treatment, prompted the interest of the present thesis. In 2016, when planning the study, most people might conceivably have some knowledge about orange-tinted BB-glasses, after several news articles about this topic. We chose to solve this threat to the condition blinding by choosing a control lens with a partially blue-blocking effect. It was essential for the study design to treat the participants as similarly as possible, and they were told that the study aimed to block different wavelengths of light. We thus considered the placebo effect to be maintained, also in cases where the participants had previous knowledge of the effect of the blue-filtering devices.

However, by choosing control glasses that also had some blue-blocking effect, we weakened the difference between the conditions and the potential for a differential change, which may have affected the power negatively. We could have resolved this

issue by using clear control glasses, instead of partially blue-blocking glasses, or have included them as a third group, and in this way obtained a “purer" placebo.

Another concern is whether two weeks of intervention was sufficient time to detect effects. BB-glasses presumably involve mechanisms producing rapid changes, and previous studies [164, 165, 168, 169] have reported la great effect on sleep outcomes when using 1 or 2-week intervention period only. Hence, it can be argued that the present intervention had sufficient duration.

A specific concern is compliance (was the intervention used as prescribed). A requirement for investigating the effect of an intervention is that the intervention is actually implemented, in terms of both frequency and duration. Analysis of compliance data showed high compliance in both the intervention and control groups, respectively.

5.2.2 Participants/samples

Pregnant women

Pregnant women in the Municipality of Bergen were recruited during their standard health examination (check-up) by consulting midwives, which is a strength because the midwives had information about the participants’ health status, and could thus more precisely consider the inclusion and exclusion criteria.

When planning the study, due to the high prevalence of insomnia in the third trimester of pregnancy, we assumed that, as a group, pregnant women in the third trimester would benefit from participating. Hence, we did not deem it necessary to use insomnia symptoms as inclusion criteria. A limitation of the study is the relatively small sample, and in addition, somewhat surprisingly, they reported a low degree of sleep difficulties. This limited the power, as the potential for change/improvement was restricted. The power analysis conducted prior to study start showed that we needed 34 participants, when expecting changes suggestive of a moderate effect size (d=0.50). Due to the healthy sleep status of the sample, a larger sample and/or more stringent inclusion criteria in terms of sleep difficulties might have increased our chances of detecting more effects of the interventions. The need for such adjustment might

possibly have been revealed by performing an interim analysis during the data collection. In fact, we conducted a preliminary analysis of 54 pregnant women, and found a statistically significant effect on some sleep outcomes. However, this effect was reversed after we had included 60 participants, in accordance with the protocol. Another option to increase the chances of achieving more significant effects would have been to use a placebo condition with no light blocking effects. Overall, the small sample size, the healthy status of the participants and the limited difference between the conditions most likely all contributed to an increased likelihood of Type II error.

Selection bias may have occurred in terms of interest in and previous knowledge of BB-glasses, due to media information and exposure. We did not exclude participants with BB-glass knowledge. Still, as mentioned previously, only two participants reported such knowledge. Another concern in terms of selection bias related to those who declined to participate. Although we have no specific clinical information about these non-participants, some declined to participate due to a lack of time and energy. Overall, it seems reasonable to assume that non-participants had fewer resources or a more stressful everyday life. as such, this is in line with many other reports, showing that research participants in general are healthier and more resourceful than non-participants [198, 199].

Another related concern is self-selection. Participants in this study belonged to a relatively well-off group in terms of their socioeconomic status, which is often the case in research [198]. Pregnant women with lower socioeconomic status were thus underrepresented in the studies under this thesis, so that the findings may, as such, have limited generalizability.

Target validity may have been a challenge in this study, since only 38.3% fulfilled the criteria for insomnia. Still, this prevalence is close to the prevalence of insomnia (39.7%) in the third trimester reported in a recent review [4]. Other studies have shown an insomnia prevalence as high as 62% in a group of pregnant women [84], suggesting potential for a greater effect of BB glasses.

Inclusion and exclusion criteria might secure a homogenous sample, and might reduce the potential impact of confounding factors, thereby increasing the internal validity. The selection of nulliparous pregnant women was made to avoid bias in terms of number of children, and sleep and health issues, which are all of importance in a study of sleep during pregnancy. We did not set inclusion criteria for any specific age group. The final sample of participants ranged from 24–43 years of age, which may have strengthened the external validity of the findings. However, the age difference could have affected the results, but this was considered by treating age as a confounding variable in the analysis in Paper 1 and by using randomization in Papers 2 and 3. Even though there are factors possibly threatening the external validity of the findings, the results in this thesis may conceivably be generalized to healthy pregnant women with a low burden of sleep disturbance.

A limitation of this thesis concerns how the pregnant women were recruited throughout the year during two whole years, so that the results could have been influenced by seasonal variations. This may be an issue as seasonal variations in light conditions are relatively substantial this far north (60.4^{O} N). However, a recent study in Norway found no differences in sleep duration across different seasons [200]. A possible reason for the rather stable sleep duration reported in that study is that artificial indoor lighting provides a relatively stable amount of light during all seasons. Still, it cannot be ruled out that seasonal variations may have influenced the findings, as daylight time varies from 5:44 hours to 19:01 hours across the year (https://www.timeanddate.com/sun/norway/bergen), and also when taking into consideration that prior light history significantly impacts the effects of light [66].

The analysis in the studies was admittedly adjusted for the months, but comparing effect by seasons could have strengthened the findings.

Comparative group

A limitation of Paper 1 is the concerns regarding the differences between the pregnant group and the comparative group of younger, non-pregnant female students, who probably also have a different lifestyle. Still, age is an important confounder and was

controlled for in the analysis. Even so, we are aware that the differences between the groups need to be interpreted with caution, and a comparative group of the same age and with the same demographic characteristics as the intervention group could have increased the homogeneity between the groups.

5.2.3 Measures

A strength of this thesis is the repeated administration of several instruments. The measurements and instruments used in this thesis were standard measures and validated tools. Another strength is the use of both subjective and objective measures of sleep variables and circadian parameters. A current concern is, however, whether the magnitude of the instruments to be completed represented an unreasonable toll on the participants.

Questionnaires

The standard questionnaires of sleep diaries, BIS, PSAS, PSS, RSS and KSS, used in this thesis are validated measurements that are commonly used in previous studies.

We calculated Cronbach's alpha for BIS, PSAS, PSS and RSS and received support for their reliability, although the reliability of PSS was somewhat low. To further test reliability, we could have used e.g. test-retest and split half and corrected item-total correlational analyses.

In Paper 1, both the pregnant and the comparative group completed the same questionnaires to measure insomnia (BIS) and sleep diary to measure sleep. This increased the validity of our comparative findings. There were some challenges regarding missing data in the comparative group, due to failure to report or outliers, which could potentially have led to information bias. The instruments PSAS, PSS and RSS were not completed by the contrast group and therefore could not be compared between the two groups, but were used to explain variance in sleep variables within the pregnant group. Another limitation concerning the use of subjective measures is that the scores could have suffered from recall bias and inaccurate reports [201], and

social desirability bias [202], as well as some common method bias [203]. A strength of using a randomization process is that such biases are prevented from affecting the results. Chronotype is an important factor for sleep and may affect sleep outcomes [204, 205]. In order to reduce the burden on the pregnant women of many questionnaires, we did not include measurements of chronotype, e.g. Morning Evening Questionnaire. The lack of inclusion of such instruments is a limitation, as data from this could have moderated the results.

Actigraphy

Actigraphy devices were used to measure light exposure in Paper 1, and for objective measurement of the sleep outcomes we used actigraphy in Paper 1 and paper 2. The device was worn on the non-dominant wrist, measuring movements and exposure to light, and did not limit the participant in her everyday activities.

A limitation is the crude measures of light intensity. The Actiwatch Spectrum has a built-in light sensor consisting of color sensitive photodiodes to measure illuminance of full spectrum white light in units of lux (0.1 to 200,000 lux), and the irradiance of the 'blue' (400–500 nm), 'green' (500–600 nm) and 'red' (600–700 nm) components. However, the latter is not deemed to be of sufficient quality to differentiate reliably between the ('colored') wavelengths' different photon density (in photons/cm^2/s) and as such represents a notable limitation. Moreover, actigraph devices typically underestimate illuminance (both artificial and natural) [206]. We therefore decided to report the estimated light exposure based on recordings of full spectrum white light in Paper 1. Notably, the actigraph is worn on the wrist and thus represents a crude measure of the light reaching the retina. In addition, the actigraph may become covered by sleeves etc., which further impairs its function as a light measurement.

Actigraphy is regarded as a valid and reliable method of measuring sleep and wakefulness [207], and correlates well with PSG [19]. However, the actigraphy algorithm has a limitation in terms of low specificity (detection of wakefulness and wakefulness as detected by PSG). Overestimation of sleep can thus occur if a participant is lying quietly in bed while still awake [207, 208]. To consider any

misinterpretations when estimating sleep intervals, we inspected the raw data and manually set the rest interval as onset and offset, in accordance with recommendations [18]. Increasing consistency in actigraphy scoring and further reporting of the data should thus be considered as a strength.

The actigraph device could potentially cause irritation or affect compliance, and thereby influence the research. Ideally, we should have measured any discomfort experienced due to the device, but we only followed this up orally at the meeting appointments. There were some challenges with regard to useless data from Actiwatch recordings, which resulted in a lack of inclusion of the data in the analysis and thereby a risk of information bias. It is also appropriate to discuss whether there are other useful measurement methods for sleep, wakefulness and light exposure. PGS is the gold standard for measuring sleep, but it is an intrusive measure, especially for pregnant women. It is also expensive and time consuming to hook up participants, as well as scoring the protocols. Somnofy is a fairly new tool for sleep assessment, based on non-contact radar technology [209], which could avoid the harm and discomfort of using a physical device like actigraphy. Its furthermore a validated sleep stage classification tool [210]. Somnofy has a high specificity, which could have been beneficial, compared to the challenges with actigraphy.

Saliva melatonin

A strength of the study in Paper 3 is the use of the objective measurement of saliva melatonin, and the home-based sample collection procedure is considered to correlate well with laboratory sampling [46].

A limitation of the study in Paper 3 is that we only measured saliva melatonin three hours prior to bedtime. By omitting a wider sampling timespan, we lack information about a possible continuing rise of melatonin levels during the night.

A concern related to measuring saliva melatonin is that we did not establish the dim light melatonin onset (DLMO), which is the standard protocol for assessment of the

endogenous circadian rhythm and entails using dark goggles prior to and during saliva sampling. If the participants had followed the DLMO procedure by wearing dark sunglasses from 18:00 hours and until the BB-glasses were used, the exposure to light would have been reduced to less than 50 lux, and participants might have started to increase melatonin secretion earlier in the evening, which could have reduced missing data from 13 participants due to melatonin levels being out of range. However, this could have been compensated for by adding more sample collection points. In the case of inadequate sampling procedures, the issue of missing data might also have been reduced if the saliva sampling had been conducted by a researcher, and at constant light conditions in a laboratory. However, we wanted to measure the circadian phase by sampling saliva melatonin in pregnant women in their natural and home-based setting, in order to detect the direct effect of BB-glasses on melatonin secretion. This choice might have strengthened the generalizability.

5.2.4 Statistical considerations

A relevant consideration is that analysis was conducted of per protocol set, and not of intention-to-treat. Per protocol is an analysis method that only includes data from the participants who completed the treatment to which they were originally allocated, whereas intention-to-treat analyses include all participants originally allocated to specific conditions following randomization [211]. Of 67 participants, 7 withdrew from the study after randomization, which gives a low attrition rate of 10.4%. The 7 excluded participants were not included in the analysis, and this dropout may be related to the effect of the intervention and thereby lead to Type I errors. It could be argued that an intention-to-treat approach would have provided a more realistic assessment of the intervention [211].

The research in all three papers involved a relatively low number of subjects, which may make the research prone to Type II errors. Although, several studies with a lower number of subjects have shown a positive effect of BB-glasses on sleep outcomes

[164-166, 168, 169], mood [68, 164] and melatonin onset [68, 75, 152, 166]. Normally, the demographic variables of the participants are not tested for statistically significant group differences, due to the randomized controlled procedure of allocation, which secured random group assignment. In the event of differences in demographic variables, this would be a by-chance event.

Another concern is that we did not include any measure to assess clinically significant improvement. A finding that is statistically significant minimize the possibility of Type I error, but does not in itself convey information about the clinical significance or clinical meaning of the finding. Jacobson-Truax developed a common method of evaluating clinical significance that involves calculating a Reliability Change Index (RCI). The formula for RCI is shown in Figure 6, where x_2 is the score at time 2, x_1 is the score at time 1, s is the standard deviation at time 1 and r_{xx} is the test-retest reliability of the measurement in question.

$$RCI = \frac{x_2 - x_1}{\sqrt{2(s\sqrt{1-r_{xx}})^2}}$$

Figure 6 *Formula for Reliability Change Index.*

An RCI above 1.96 is considered to reflect a clinically significant change [212]. Accordingly, including measures of clinically significant change would have facilitated evaluation of the intervention investigated in the present thesis.

Type II error is related to the power of the statistical test. We included measures of power analysis to ensure a sufficient sample size to further strengthen the effect size, and thereby avoid Type II errors. [212]. Still, the sample in the thesis were so well-functioning that Type II errors could have occurred.

5.3 Ethical considerations

Research of light exposure, sleep outcomes, mood and melatonin onset in pregnant women is of public, clinical and academic importance. Informed consent is an

important ethical consideration, and all the pregnant women were able to withdraw from the study at any time, in accordance with the Helsinki Declaration [213].

Concerns may relate to the number of questionnaires and amount of measurements that were included in the study, as these may have represented a burden, especially with regard to a vulnerable group like pregnant women. In relation to this issue, there was dialogue with the participants throughout the study period, and they were informed that they could contact the research team at any time. In addition, they had regular appointments with the researcher from the team during the study period. Due to the chosen methodological and double blinded randomization, the intervention had to be hidden. The pregnant women were thus not informed about the blue light and the function of the glasses until the participation in the study was completed.

Another concern is whether it is unethical to have such a small difference between the conditions, as this may increase the probability of not finding a difference in the outcome measures between the conditions.

Importantly, we used a non-invasive, simple and low-cost intervention. The pregnant women were notified to contact the researcher if they experienced side effects while wearing the intervention and control glasses, respectively. After completion of the study, the participants were further probed for side effects. Six participants reported side effects (malaise, headache, lowered mood and anxiety). The conditions were equally represented (n=3 in each condition) in terms of the side effects and were transient in five of the six cases. One participant in the control group reported severe malaise, and after one more day wearing the glasses without improvement she dropped out, at her own request. The side effects reported here had not previously been reported in term of use of BB-glasses and are thereby of clinical importance. It cannot be ruled out that pregnant women are more susceptible to developing such side effects than other groups. This should accordingly be addressed in future studies. All in all, it still seems fair to conclude that the intervention had few side effects. Elucidating the effect of a non-pharmacological intervention was regarded as an ethical asset of the present study, as sleep medication is not recommended during pregnancy [135].

6. Conclusion

Paper 1 showed that healthy Norwegian pregnant women at the beginning of the third trimester overall enjoy good sleep. The pregnant women had significant lower SE in sleep diary data, higher TST, and were exposed to more light (actigraphic data) in the evening, compared to a non-pregnant group. Light exposure in the evening was associated with shorter TST and earlier midpoint of sleep on actigraphic data. Stress variables did not show any association with sleep outcomes in pregnant women.

Paper 2 showed that use of BB-glasses compared to control glasses with partially blue-blocking effect did not reveal a statistically significant difference in TST, midpoint of sleep, SE (neither assessed by self-report nor actigraphy), daytime functioning or for BIS, KSS, PSAS between the groups. The transient side-effects of the intervention or control glasses were low in both groups.

Paper 3 showed a positive effect of blocking the blue light on the circadian system with an earlier onset and higher evening levels of melatonin in pregnant women in the last part of pregnancy. The findings indicate that BB-glasses advanced melatonin onset. Furthermore, the BB-group only increased the phase angle (time) between melatonin onset and bedtime and sleep onset time.

The findings of this thesis suggest that evening light exposure is related to shorter sleep duration among pregnant women. Blocking blue light in the evening may have a positive effect on the circadian system in terms of an earlier melatonin onset and rise for healthy nulliparous pregnant women. This indicates the effectiveness and feasibility of a simple and low-risk non-pharmacological chronobiological intervention during pregnancy.

7. Implications and future perspectives

This research project has brought new knowledge about light exposure effects on pregnant women. Further research of the effects of blue-blocking glasses for pregnant women with sleep-problems or circadian disturbances is warranted.

Sleep disturbances are common in pregnancy and are associated with adverse pregnancy outcomes. The cost of not treating sleep disturbances in pregnancy may be of great importance for both mother and fetus, as well as the offspring.

Screening is the first step to prevent the harmful effect of low sleep quality. The Norwegian public health service needs to adapt its focus on screening and treatment to sleep problems/disorders in pregnancy, and this needs to be designed in both primary and specialized health care services. I dream of increased interdisciplinary collaboration between different professional groups in the follow-up of pregnant women with sleep problems, to offer them proper treatment for their burdensome sleep problems. To achieve this, we need more research into prevalence, predictors, preventive measures and treatment of different sleep disorders in pregnancy. In addition to insomnia, sleep related breathing disorders and sleep related movement disorders (restless legs) are the most common sleep disorders during pregnancy.

The hypothesis to be tested more stringently than in the present thesis is that a blue-blocking intervention in the evening and during the night and some simple CBT-i interventions for pregnant women with insomnia will improve sleep significantly.

The study should use a randomized controlled design, and furthermore apply both subjective and objective measures, and should be based on a longitudinal design. Furthermore, long-term follow-up could also be useful for investigating outcomes for the fetus and future health of the offspring.

In the present thesis, we found a clear protective effect of BB-glasses in the evening, on endogenous production of melatonin. Melatonin is a clinical important hormone for both mother and fetus. Light in the evening seemed to suppress melatonin in the present sample and was associated with shorter sleep in these normal pregnancies.

Based on that, the advice concerning BB-glasses for pregnant women has been strengthened. In the meantime, while waiting for future studies, pregnant women may benefit from using glasses and light bulbs that block blue light during the evening and night.

8. Source of data

1. Medical Birth Registry of Norway. Medical Birth Registry's bank of statistics. Norwegian Institute of Public Health. 2022. [Accessed 22.02.2022]. http://statistikkbank.fhi.no/mfr/.
2. Baratte-Beebe KR, Lee K. Sources of midsleep awakenings in childbearing women. Clin Nurs Res. 1999;8(4):386-97.
3. Facco FL, Kramer J, Ho KH, et al. Sleep disturbances in pregnancy. Obstetrics and Gynecology. 2010;115(1):77-83.
4. Sedov ID, Anderson NJ, Dhillon AK, Tomfohr-Madsen LM. Insomnia symptoms during pregnancy: A meta-analysis. Journal of sleep research. 2021;30(1):e13207.
5. Sivertsen B, Petrie KJ, Skogen JC, Hysing M, Eberhard-Gran M. Insomnia before and after childbirth: The risk of developing postpartum pain-A longitudinal population-based study. Eur J Obstet Gynecol Reprod Biol. 2017;210:348-54.
6. Sivertsen B, Krokstad S, Overland S, Mykletun A. The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. J Psychosom Res. 2009;67(2):109-16.
7. Balserak BI, Lee KA. Sleep and Sleep Disorders Associated with Pregnancy. In: Kryger M, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. 6th ed: Elsevier; 2017. p. 1525-39.
8. Nodine PM, Matthews EE. Common sleep disorders: management strategies and pregnancy outcomes. J Midwifery Womens Health. 2013;58(4):368-77.
9. Borbely AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. Journal of sleep research. 2016;25(2):131-43.
10. Buijs RM, Kalsbeek A. Hypothalamic integration of central and peripheral clocks. Nat Rev Neurosci. 2001;2(7):521-6.
11. Pallesen S, Sivertsen B, Nordhus IH, Bjorvatn B. A 10-year trend of insomnia prevalence in the adult Norwegian population. Sleep medicine. 2014;15(2):173-9.
12. Sivertsen B, Hysing M, Harvey AG, Petrie KJ. The Epidemiology of Insomnia and Sleep Duration Across Mental and Physical Health: The SHoT Study. Front Psychol. 2021;12:662572.
13. Youngstedt SD, Goff EE, Reynolds AM, Kripke DF, Irwin MR, Bootzin RR, et al. Has adult sleep duration declined over the last 50+ years? Sleep Med Rev. 2016;28:69-85.
14. Sivertsen B, Overland S, Pallesen S. Trends in timing of sleep in the general population of Norway: 1980 to 20001. Percept Mot Skills. 2011;113(2):509-18.
15. Carskadon MA, Dement WC. Normal human sleep: An overview. In: Kryger M, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. 6th ed: Elsevier; 2017. p. 15-24.
16. Keenan S, Hirshkowitz M. Sleep Stage Scoring. In: Kryger M, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. 6th ed: Elsevier; 2017. p. 1567-75.

17. Norwegian Institute of Public Health. Sleep and sleep disorders. 2022. [Accessed 22.02.2022]. https://www.fhi.no/en/mp/sleep-and-sleep-disorders/.
18. Smith MT, McCrae CS, Cheung J, Martin JL, Harrod CG, Heald JL, et al. Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. J Clin Sleep Med. 2018;14(7):1209-30.
19. Stone KL, Ancoli-Israel S. Actigraphy. In: Kryger M, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine 6th ed: Elsevier; 2017. p. 1671-8.
20. Hirshkowitz M, Sharafkhaneh A. Evaluating Sleepiness. In: Kryger M, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. 6th ed: Elsevier; 2017. p. 1651-8.
21. Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012;35(2):287-302.
22. Berry RB, Gamaldo CE, Harding SM, Brooks R, Lloyd RM, Vaughn BV, et al. AASM Scoring Manual Version 2.2 Updates: New Chapters for Scoring Infant Sleep Staging and Home Sleep Apnea Testing. J Clin Sleep Med. 2015;11(11):1253-4.
23. Grønli J, Saxvig IW. Hvordan sover vi-egentlig? SØVN Nasjonalt Kompetansesenter for Søvnsykdommer SOVno. 2011;3(1):10-2.
24. Hubbard J, Ruppert E, Gropp CM, Bourgin P. Non-circadian direct effects of light on sleep and alertness: lessons from transgenic mouse models. Sleep Med Rev. 2013;17(6):445-52.
25. Foster RG, Kreitzman L. The rhythms of life: what your body clock means to you! Exp Physiol. 2014;99(4):599-606.
26. Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Rimmer DW, et al. Stability, precision, and near-24-hour period of the human circadian pacemaker. Science. 1999;284(5423):2177-81.
27. Morris CJ, Aeschbach D, Scheer FA. Circadian system, sleep and endocrinology. Mol Cell Endocrinol. 2012;349(1):91-104.
28. Reppert SM, Weaver DR. Molecular analysis of mammalian circadian rhythms. Annu Rev Physiol. 2001;63:647-76.
29. Arendt J. Shift work: coping with the biological clock. Occup Med (Lond). 2010;60(1):10-20.
30. Grosbellet E, Challet E. Central and Peripheral Circadian Clocks. In: Kryger M, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. 6th ed: Elsevier; 2017. p. 396-404.
31. Danilenko KV, Cajochen C, Wirz-Justice A. Is sleep per se a zeitgeber in humans? J Biol Rhythms. 2003;18(2):170-8.
32. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. Nature. 2002;418(6901):935-41.
33. Czeisler CA, Buxton OM. Human Circadian Timing System and Sleep-Wake Regulation. In: Kryger M, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. 6th ed: Elsevier; 2017. p. 362-76.
34. Macchi MM, Bruce JN. Human pineal physiology and functional significance of melatonin. Front Neuroendocrinol. 2004;25(3-4):177-95.

35. Brainard GC, Hanifin JP, Greeson JM, Byrne B, Glickman G, Gerner E, et al. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. J Neurosci. 2001;21(16):6405-12.
36. Berson DM, Dunn FA, Takao M. Phototransduction by retinal ganglion cells that set the circadian clock. Science. 2002;295(5557):1070-3.
37. Thapan K, Arendt J, Skene DJ. An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. J Physiol. 2001;535(Pt 1):261-7.
38. Tamura H, Nakamura Y, Terron MP, Flores LJ, Manchester LC, Tan DX, et al. Melatonin and pregnancy in the human. Reprod Toxicol. 2008;25(3):291-303.
39. Laste G, Silva AAD, Gheno BR, Rychcik PM. Relationship between melatonin and high-risk pregnancy: A review of investigations published between the years 2010 and 2020. Chronobiol Int. 2021;38(2):168-81.
40. Lanoix D, Beghdadi H, Lafond J, Vaillancourt C. Human placental trophoblasts synthesize melatonin and express its receptors. J Pineal Res. 2008;45(1):50-60.
41. Lanoix D, Guerin P, Vaillancourt C. Placental melatonin production and melatonin receptor expression are altered in preeclampsia: new insights into the role of this hormone in pregnancy. J Pineal Res. 2012;53(4):417-25.
42. Skene DJ, Arendt J. Human circadian rhythms: physiological and therapeutic relevance of light and melatonin. Ann Clin Biochem. 2006;43(Pt 5):344-53.
43. Brzezinski A. Melatonin in humans. N Engl J Med. 1997;336(3):186-95.
44. Reiter RJ, Tan DX, Kim SJ, Cruz MH. Delivery of pineal melatonin to the brain and SCN: role of canaliculi, cerebrospinal fluid, tanycytes and Virchow-Robin perivascular spaces. Brain Struct Funct. 2014;219(6):1873-87.
45. Lewy AJ, Sack RL. The dim light melatonin onset as a marker for circadian phase position. Chronobiol Int. 1989;6(1):93-102.
46. Pullman RE, Roepke SE, Duffy JF. Laboratory validation of an in-home method for assessing circadian phase using dim light melatonin onset (DLMO). Sleep medicine. 2012;13(6):703-6.
47. Keijzer H, Smits MG, Peeters T, Looman CW, Endenburg SC, Gunnewiek JM. Evaluation of salivary melatonin measurements for Dim Light Melatonin Onset calculations in patients with possible sleep-wake rhythm disorders. Clin Chim Acta. 2011;412(17-18):1616-20.
48. Wetterberg L, Bratlid T, von Knorring L, Eberhard G, Yuwiler A. A multinational study of the relationships between nighttime urinary melatonin production, age, gender, body size, and latitude. Eur Arch Psychiatry Clin Neurosci. 1999;249(5):256-62.
49. Keijzer H, Smits MG, Duffy JF, Curfs LM. Why the dim light melatonin onset (DLMO) should be measured before treatment of patients with circadian rhythm sleep disorders. Sleep Med Rev. 2014;18(4):333-9.
50. Borbely AA. A two process model of sleep regulation. Hum Neurobiol. 1982;1(3):195-204.
51. Krauchi K. The thermophysiological cascade leading to sleep initiation in relation to phase of entrainment. Sleep Med Rev. 2007;11(6):439-51.
52. Gilbert SS, van den Heuvel CJ, Ferguson SA, Dawson D. Thermoregulation as a sleep signalling system. Sleep Med Rev. 2004;8(2):81-93.

53. Bjorvatn B, Pallesen S. A practical approach to circadian rhythm sleep disorders. Sleep Med Rev. 2009;13(1):47-60.
54. Berson DM. Phototransduction in ganglion-cell photoreceptors. Pflugers Arch. 2007;454(5):849-55.
55. LeGates TA, Fernandez DC, Hattar S. Light as a central modulator of circadian rhythms, sleep and affect. Nat Rev Neurosci. 2014;15(7):443-54.
56. Lockley SW, Brainard GC, Czeisler CA. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. J Clin Endocrinol Metab. 2003;88(9):4502-5.
57. Prayag AS, Munch M, Aeschbach D, Chellappa SL, Gronfier C. Light Modulation of Human Clocks, Wake, and Sleep. Clocks Sleep. 2019;1(1):193-208.
58. Smith MR, Revell VL, Eastman CI. Phase advancing the human circadian clock with blue-enriched polychromatic light. Sleep medicine. 2009;10(3):287-94.
59. Smith MR, Eastman CI. Phase delaying the human circadian clock with blue-enriched polychromatic light. Chronobiol Int. 2009;26(4):709-25.
60. Chang AM, Santhi N, St Hilaire M, Gronfier C, Bradstreet DS, Duffy JF, et al. Human responses to bright light of different durations. J Physiol. 2012;590(13):3103-12.
61. Zeitzer JM, Ruby NF, Fisicaro RA, Heller HC. Response of the human circadian system to millisecond flashes of light. PLoS One. 2011;6(7):e22078.
62. Hebert M, Martin SK, Lee C, Eastman CI. The effects of prior light history on the suppression of melatonin by light in humans. J Pineal Res. 2002;33(4):198-203.
63. Khalsa SB, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. J Physiol. 2003;549(Pt 3):945-52.
64. Lewy AJ, Cutler NL, Sack RL. The endogenous melatonin profile as a marker for circadian phase position. J Biol Rhythms. 1999;14(3):227-36.
65. Minors DS, Waterhouse JM, Wirz-Justice A. A human phase-response curve to light. Neurosci Lett. 1991;133(1):36-40.
66. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. J Physiol. 2000;526 Pt 3:695-702.
67. Cajochen C, Frey S, Anders D, Spati J, Bues M, Pross A, et al. Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. J Appl Physiol (1985). 2011;110(5):1432-8.
68. van der Lely S, Frey S, Garbazza C, Wirz-Justice A, Jenni OG, Steiner R, et al. Blue blocker glasses as a countermeasure for alerting effects of evening light-emitting diode screen exposure in male teenagers. J Adolesc Health. 2015;56(1):113-9.
69. Cajochen C, Zeitzer JM, Czeisler CA, Dijk DJ. Dose-response relationship for light intensity and ocular and electroencephalographic correlates of human alertness. Behav Brain Res. 2000;115(1):75-83.
70. Cajochen C, Munch M, Kobialka S, Krauchi K, Steiner R, Oelhafen P, et al. High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. J Clin Endocrinol Metab. 2005;90(3):1311-6.
71. Cajochen C. Alerting effects of light. Sleep Med Rev. 2007;11(6):453-64.
72. Posner MI. Measuring alertness. Ann N Y Acad Sci. 2008;1129:193-9.

73. Oken BS, Salinsky MC, Elsas SM. Vigilance, alertness, or sustained attention: physiological basis and measurement. Clin Neurophysiol. 2006;117(9):1885-901.
74. Lok R, Smolders K, Beersma DGM, de Kort YAW. Light, Alertness, and Alerting Effects of White Light: A Literature Overview. J Biol Rhythms. 2018;33(6):589-601.
75. Figueiro MG, Overington D. Self-luminous devices and melatonin suppression in adolescents. Lighting Res Technol. 2016;48:966-75.
76. Lockley SW, Evans EE, Scheer FA, Brainard GC, Czeisler CA, Aeschbach D. Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. Sleep. 2006;29(2):161-8.
77. Souman JL, Tinga AM, Te Pas SF, van Ee R, Vlaskamp BNS. Acute alerting effects of light: A systematic literature review. Behav Brain Res. 2018;337:228-39.
78. Mindell JA, Cook RA, Nikolovski J. Sleep patterns and sleep disturbances across pregnancy. Sleep medicine. 2015;16(4):483-8.
79. Lee KA. Alterations in sleep during pregnancy and postpartum: a review of 30 years of research. Sleep Med Rev. 1998;2(4):231-42.
80. Lee KA, Zaffke ME, McEnany G. Parity and sleep patterns during and after pregnancy. Obstet Gynecol. 2000;95(1):14-8.
81. Vietheer A, Kiserud T, Lie RT, Haaland OA, Kessler J. Sleep and physical activity from before conception to the end of pregnancy in healthy women: a longitudinal actigraphy study. Sleep medicine. 2021;83:89-98.
82. Garbazza C, Hackethal S, Riccardi S, Cajochen C, Cicolin A, D'Agostino A, et al. Polysomnographic features of pregnancy: A systematic review. Sleep Med Rev. 2020;50:101249.
83. Abbott SM, Attarian H, Zee PC. Sleep disorders in perinatal women. Best Pract Res Clin Obstet Gynaecol. 2014;28(1):159-68.
84. Dorheim SK, Bjorvatn B, Eberhard-Gran M. Insomnia and depressive symptoms in late pregnancy: a population-based study. Behav Sleep Med. 2012;10(3):152-66.
85. Tsai SY, Lin JW, Kuo LT, Thomas KA. Daily sleep and fatigue characteristics in nulliparous women during the third trimester of pregnancy. Sleep. 2012;35(2):257-62.
86. Sivertsen B, Hysing M, Dorheim SK, Eberhard-Gran M. Trajectories of maternal sleep problems before and after childbirth: a longitudinal population-based study. BMC Pregnancy Childbirth. 2015;15:129.
87. Palagini L, Cipollone G, Masci I, Novi M, Caruso D, Kalmbach DA, et al. Stress-related sleep reactivity is associated with insomnia, psychopathology and suicidality in pregnant women: preliminary results. Sleep medicine. 2019;56:145-50.
88. Gurung RAR, Dunkel-Schetter C, Collins N, Rini C, Hobel CJ. Psychosocial predictors of prenatal anxiety. Journal of Social and Clinical Psychology. 2005;24(4):497-519.
89. Pauley AM, Moore GA, Mama SK, Molenaar P, Symons Downs D. Associations between prenatal sleep and psychological health: a systematic review. J Clin Sleep Med. 2020;16(4):619-30.

90. Kaasen A, Helbig A, Malt UF, Naes T, Skari H, Haugen G. Acute maternal social dysfunction, health perception and psychological distress after ultrasonographic detection of a fetal structural anomaly. BJOG. 2010;117(9):1127-38.
91. Palagini L, Gemignani A, Banti S, Manconi M, Mauri M, Riemann D. Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome. Sleep medicine. 2014;15(8):853-9.
92. Kinsella MT, Monk C. Impact of maternal stress, depression and anxiety on fetal neurobehavioral development. Clin Obstet Gynecol. 2009;52(3):425-40.
93. Levine TA, Alderdice FA, Grunau RE, McAuliffe FM. Prenatal stress and hemodynamics in pregnancy: a systematic review. Arch Womens Ment Health. 2016;19(5):721-39.
94. Van den Bergh BRH, Van den Heuvel MI, Lahti M, Braeken M, de Rooij SR, Entringer S, et al. Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. Neuroscience and Biobehavioral Reviews. 2017.
95. Henriksen RE, Thuen F. Marital Quality and Stress in Pregnancy Predict the Risk of Infectious Disease in the Offspring: The Norwegian Mother and Child Cohort Study. PLoS One. 2015;10(9):e0137304.
96. Ko SH, Chang SC, Chen CH. A comparative study of sleep quality between pregnant and nonpregnant Taiwanese women. J Nurs Scholarsh. 2010;42(1):23-30.
97. Storksen HT, Eberhard-Gran M, Garthus-Niegel S, Eskild A. Fear of childbirth; the relation to anxiety and depression. Acta Obstet Gynecol Scand. 2012;91(2):237-42.
98. McCarthy R, Jungheim ES, Fay JC, Bates K, Herzog ED, England SK. Riding the Rhythm of Melatonin Through Pregnancy to Deliver on Time. Front Endocrinol (Lausanne). 2019;10:616.
99. Allolio B, Hoffmann J, Linton EA, Winkelmann W, Kusche M, Schulte HM. Diurnal salivary cortisol patterns during pregnancy and after delivery: relationship to plasma corticotrophin-releasing-hormone. Clin Endocrinol (Oxf). 1990;33(2):279-89.
100. Benfield RD, Newton ER, Tanner CJ, Heitkemper MM. Cortisol as a biomarker of stress in term human labor: physiological and methodological issues. Biol Res Nurs. 2014;16(1):64-71.
101. La Marca-Ghaemmaghami P, Ehlert U. Stress During Pregnancy. Experienced Stress, Stress Hormones and Protective Factors. . European Psychologist. 2015;20(2):102-19.
102. Levine A, Zagoory-Sharon O, Feldman R, Lewis JG, Weller A. Measuring cortisol in human psychobiological studies. Physiol Behav. 2007;90(1):43-53.
103. Chida Y, Steptoe A. Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis. Biol Psychol. 2009;80(3):265-78.
104. Bradbury TN, Fincham FD, Beach SRH. Research on the Nature and Determinants of Marital Satisfaction: A Decade in Review. Journal of Marriage and the Family. 2000;62:964-80.
105. Pepping CA, Halford WK. Attachment and relationship satisfaction in expectant first-time parents: The mediating role of relationship enhancing behaviors. Journal of Research in Personality. 2012;46:770-4.
106. Gunn HE, Buysse DJ, Hasler BP, Begley A, Troxel WM. Sleep Concordance in Couples is Associated with Relationship Characteristics. Sleep. 2015;38(6):933-9.

107. Drews HJ, Drews A. Couple Relationships Are Associated With Increased REM Sleep-A Proof-of-Concept Analysis of a Large Dataset Using Ambulatory Polysomnography. Front Psychiatry. 2021;12:641102.
108. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.
109. Wilson DL, Barnes M, Ellett L, et al. Decreased sleep efficiency, increased wake after sleep onset and increased cortical arousals in late pregnancy. ANZJOG. 2011;51(1):38-46.
110. American Academy of Sleep Medicine. International Classification of Sleep Disorders (ICSD-3). In: Medicine AAoS, editor. Darien, IL: 3rd ed; 2014.
111. Facco F, Louis J, Knavert MP, Izci-Balserak B. Sleep-Disordered Breathing in Pregnancy. In: Kryger M, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. 6th ed: Elsevier; 2017. p. 1540-6.
112. Dunietz GL, Lisabeth LD, Shedden K, Shamim-Uzzaman QA, Bullough AS, Chames MC, et al. Restless Legs Syndrome and Sleep-Wake Disturbances in Pregnancy. J Clin Sleep Med. 2017;13(7):863-70.
113. Gupta R, Dhyani M, Kendzerska T, Pandi-Perumal SR, BaHammam AS, Srivanitchapoom P, et al. Restless legs syndrome and pregnancy: prevalence, possible pathophysiological mechanisms and treatment. Acta Neurologica Scandinavica. 2016;133(5):320-9.
114. Sebo P, Cerutti B, Haller DM. Effect of magnesium therapy on nocturnal leg cramps: a systematic review of randomized controlled trials with meta-analysis using simulations. Fam Pract. 2014;31(1):7-19.
115. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.
116. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep medicine. 2001;2(4):297-307.
117. Pallesen S, Bjorvatn B, Nordhus IH, Sivertsen B, Hjornevik M, Morin CM. A new scale for measuring insomnia: the Bergen Insomnia Scale. Percept Mot Skills. 2008;107(3):691-706.
118. Partinen M, Gislason T. Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. Journal of sleep research. 1995;4(S1):150-5.
119. National Sleep Foundation. Women and Sleep. Washington, DC. National Sleep Foundation. 2007. [Accessed 22.02.2022]. https://www.sleepfoundation.org/professionals/sleep-americar-polls/2007-women-and-sleep.
120. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th ed. ed. Washington, DC.: APA, 2013.; 2013.
121. Sedov ID, Cameron EE, Madigan S, Tomfohr-Madsen LM. Sleep quality during pregnancy: A meta-analysis. Sleep Med Rev. 2018;38:168-76.
122. Dorheim SK, Bjorvatn B, Eberhard-Gran M. Can insomnia in pregnancy predict postpartum depression? A longitudinal, population-based study. PLoS One. 2014;9(4):e94674.

123. Okun ML, Schetter CD, Glynn LM. Poor sleep quality is associated with preterm birth. Sleep. 2011;34(11):1493-8.
124. Micheli K, Komninos I, Bagkeris E, Roumeliotaki T, Koutis A, Kogevinas M, et al. Sleep patterns in late pregnancy and risk of preterm birth and fetal growth restriction. Epidemiology. 2011;22(5):738-44.
125. Li R, Zhang J, Zhou R, Liu J, Dai Z, Liu D, et al. Sleep disturbances during pregnancy are associated with cesarean delivery and preterm birth. J Matern Fetal Neonatal Med. 2017;30(6):733-8.
126. Warland J, Dorrian J, Morrison JL, O'Brien LM. Maternal sleep during pregnancy and poor fetal outcomes: A scoping review of the literature with meta-analysis. Sleep Med Rev. 2018;41:197-219.
127. Reichner CA. Insomnia and sleep deficiency in pregnancy. Obstet Med. 2015;8(4):168-71.
128. Chang JJ, Pien GW, Duntley SP, Macones GA. Sleep deprivation during pregnancy and maternal and fetal outcomes: is there a relationship? Sleep Med Rev. 2010;14(2):107-14.
129. da Silva JB, Nakamura MU, Cordeiro JA, Kulay LJ. Acupuncture for insomnia in pregnancy--a prospective, quasi-randomised, controlled study. Acupunct Med. 2005;23(2):47-51.
130. Beddoe AE, Lee KA, Weiss SJ, Kennedy HP, Yang CP. Effects of mindful yoga on sleep in pregnant women: a pilot study. Biol Res Nurs. 2010;11(4):363-70.
131. Morin CM, Hauri PJ, Espie CA, Spielman AJ, Buysse DJ, Bootzin RR. Nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine review. Sleep. 1999;22(8):1134-56.
132. Manber R, Bei B, Simpson N, Asarnow L, Rangel E, Sit A, et al. Cognitive Behavioral Therapy for Prenatal Insomnia: A Randomized Controlled Trial. Obstet Gynecol. 2019;133(5):911-9.
133. Kalmbach DA, Cheng P, O'Brien LM, Swanson LM, Sangha R, Sen S, et al. A randomized controlled trial of digital cognitive behavioral therapy for insomnia in pregnant women. Sleep medicine. 2020;72:82-92.
134. Okun ML, Ebert R, Saini B. A review of sleep-promoting medications used in pregnancy. Am J Obstet Gynecol. 2015;212(4):428-41.
135. Bacaro V, Benz F, Pappaccogli A, De Bartolo P, Johann AF, Palagini L, et al. Interventions for sleep problems during pregnancy: A systematic review. Sleep Med Rev. 2020;50:101234.
136. Moretti P, Menculini G, Gonfia L. Sleep Disorders in Pregnancy. Sleep Medicine and the Evolution of Contemporary Sleep Pharmacotherapy: IntechOpen; 2021.
137. Hedman C, Pohjasvaara T, Tolonen U, Salmivaara A, Myllyla VV. Parasomnias decline during pregnancy. Acta Neurol Scand. 2002;105(3):209-14.
138. Nakamura Y, Tamura H, Kashida S, Takayama H, Yamagata Y, Karube A, et al. Changes of serum melatonin level and its relationship to feto-placental unit during pregnancy. J Pineal Res. 2001;30(1):29-33.
139. Reiter RJ, Tan DX, Qi W, Manchester LC, Karbownik M, Calvo JR. Pharmacology and physiology of melatonin in the reduction of oxidative stress in vivo. Biol Signals Recept. 2000;9(3-4):160-71.

140. Okatani Y, Okamoto K, Hayashi K, Wakatsuki A, Tamura S, Sagara Y. Maternal-fetal transfer of melatonin in pregnant women near term. J Pineal Res. 1998;25(3):129-34.
141. Dou Y, Lin B, Cheng H, Wang C, Zhao M, Zhang J, et al. The reduction of melatonin levels is associated with the development of preeclampsia: a meta-analysis. Hypertens Pregnancy. 2019;38(2):65-72.
142. Shimada M, Seki H, Samejima M, Hayase M, Shirai F. Salivary melatonin levels and sleep-wake rhythms in pregnant women with hypertensive and glucose metabolic disorders: A prospective analysis. Biosci Trends. 2016;10(1):34-41.
143. Sand O, Sjaastad ØV, Haug E. Sansene. Menneskets fysiologi. 1 ed ed: Gyldendal Akademiske; 2001. p. 154-97.
144. Peyvandi S, Hernandez-Andres J, Olmo FJ, Nieves JL, Romero J. Colorimetric analysis of outdoor illumination across varieties of atmospheric conditions. J Opt Soc Am A Opt Image Sci Vis. 2016;33(6):1049-59.
145. Sasseville A, Martin JS, Houle J, Hebert M. Investigating the contribution of short wavelengths in the alerting effect of bright light. Physiol Behav. 2015;151:81-7.
146. Berson DM. Strange vision: ganglion cells as circadian photoreceptors. Trends Neurosci. 2003;26(6):314-20.
147. Brainard GC, Hanifin JP, Warfield B, Stone MK, James ME, Ayers M, et al. Short-wavelength enrichment of polychromatic light enhances human melatonin suppression potency. J Pineal Res. 2015;58(3):352-61.
148. Wright HR, Lack LC, Partridge KJ. Light emitting diodes can be used to phase delay the melatonin rhythm. J Pineal Res. 2001;31(4):350-5.
149. Revell VL, Arendt J, Fogg LF, Skene DJ. Alerting effects of light are sensitive to very short wavelengths. Neurosci Lett. 2006;399(1-2):96-100.
150. Figueiro MG, Wood B, Plitnick B, Rea MS. The impact of light from computer monitors on melatonin levels in college students. Neuro Endocrinol Lett. 2011;32(2):158-63.
151. Gronli J, Byrkjedal IK, Bjorvatn B, Nodtvedt O, Hamre B, Pallesen S. Reading from an iPad or from a book in bed: the impact on human sleep. A randomized controlled crossover trial. Sleep medicine. 2016;21:86-92.
152. Sasseville A, Paquet N, Sevigny J, Hebert M. Blue blocker glasses impede the capacity of bright light to suppress melatonin production.(Author abstract). Journal of Pineal Research. 2006;41:73-8.
153. van de Werken M, Gimenez MC, de Vries B, Beersma DG, Gordijn MC. Short-wavelength attenuated polychromatic white light during work at night: limited melatonin suppression without substantial decline of alertness. Chronobiol Int. 2013;30(7):843-54.
154. Wada K, Nagata C, Nakamura K, Iwasa S, Shiraki M, Shimizu H. Light exposure at night, sleep duration and sex hormone levels in pregnant Japanese women. Endocr J. 2012;59(5):393-8.
155. Kayumov L, Casper RF, Hawa RJ, Perelman B, Chung SA, Sokalsky S, et al. Blocking low-wavelength light prevents nocturnal melatonin suppression with no adverse effect on performance during simulated shift work. J Clin Endocrinol Metab. 2005;90(5):2755-61.

156. Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. Science. 1980;210(4475):1267-9.
157. Smith KA, Schoen MW, Czeisler CA. Adaptation of human pineal melatonin suppression by recent photic history. J Clin Endocrinol Metab. 2004;89(7):3610-4.
158. Munch M, Nowozin C, Regente J, Bes F, De Zeeuw J, Hadel S, et al. Blue-Enriched Morning Light as a Countermeasure to Light at the Wrong Time: Effects on Cognition, Sleepiness, Sleep, and Circadian Phase. Neuropsychobiology. 2016;74(4):207-18.
159. Epperson CN, Terman M, Terman JS, Hanusa BH, Oren DA, Peindl KS, et al. Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J Clin Psychiatry. 2004;65(3):421-5.
160. Nehme PA, Amaral FG, Middleton B, Lowden A, Marqueze E, Franca-Junior I, et al. Melatonin profiles during the third trimester of pregnancy and health status in the offspring among day and night workers: A case series. Neurobiol Sleep Circadian Rhythms. 2019;6:70-6.
161. Argys LM, Averett SL, Yang M. Light Pollution, Sleep Deprivation, and Infant Health at Birth. In: Economics IIoL, editor. Discussion paper series. Discussion paper series ed. Initiated by Deutsche Post Foundation2018. p. 1-53.
162. Shechter A, Quispe KA, Barbecho JSM, Slater C, Falzon L. Interventions to reduce short-wavelength ("blue") light exposure at night and their effects on sleep: A systematic review and meta-analysis. Sleep Advances. 2020:1-13.
163. Bennett S, Alpert M, Kubulins V, Hansler RL. Use of modified spectacles and light bulbs to block blue light at night may prevent postpartum depression. Med Hypotheses. 2009;73(2):251-3.
164. Burkhart K, Phelps JR. Amber lenses to block blue light and improve sleep: a randomized trial. Chronobiol Int. 2009;26(8):1602-12.
165. Shechter A, Kim EW, St-Onge MP, Westwood AJ. Blocking nocturnal blue light for insomnia: A randomized controlled trial. J Psychiatr Res. 2018;96:196-202.
166. Ayaki M, Hattori A, Maruyama Y, Nakano M, Yoshimura M, Kitazawa M, et al. Protective effect of blue-light shield eyewear for adults against light pollution from self-luminous devices used at night. Chronobiol Int. 2016;33(1):134-9.
167. Esaki Y, Kitajima T, Ito Y, Koike S, Nakao Y, Tsuchiya A, et al. Wearing blue light-blocking glasses in the evening advances circadian rhythms in the patients with delayed sleep phase disorder: An open-label trial. Chronobiol Int. 2016;33(8):1037-44.
168. Henriksen TEG, Gronli J, Assmus J, Fasmer OB, Schoeyen H, Leskauskaite I, et al. Blue-blocking glasses as additive treatment for mania: Effects on actigraphy-derived sleep parameters. Journal of sleep research. 2020;29(5):e12984.
169. Fargason R, Preston T, Hammond E, May R, Gamble K. Treatment of attention deficit hyperactivity disorder insomnia with blue wavelength light-blocking glasses. ChronoPhysiology and Therapy; 2013. Contract No.: 3.
170. Esaki Y, Kitajima T, Takeuchi I, Tsuboi S, Furukawa O, Moriwaki M, et al. Effect of blue-blocking glasses in major depressive disorder with sleep onset insomnia: A randomized, double-blind, placebo-controlled study. Chronobiol Int. 2017;34(6):753-61.

171. Zerbini G, Kantermann T, Merrow M. Strategies to decrease social jetlag: Reducing evening blue light advances sleep and melatonin. Eur J Neurosci. 2020;51(12):2355-66.
172. Bergen Municipality. Folkemengde per 1.januar 2021. In: Kommune. B, editor. [Accessed 22.02.2022]. https://www.bergen.kommune.no/omkommunen/fakta-om-bergen/befolkning/folkemengde-per-1-januar-2021.
173. Bergen Municipality. Helsestasjoner i Bergen. In: Kommune. B, editor. [Accessed 22.02.2022]. https://www.bergen.kommune.no/omkommunen/avdelinger/helsestasjoner?navnFilter=.
174. McLaughlin C, Levin AV. The red reflex. Pediatr Emerg Care. 2006;22(2):137-40.
175. Voultsios A, Kennaway DJ, Dawson D. Salivary melatonin as a circadian phase marker: validation and comparison to plasma melatonin. J Biol Rhythms. 1997;12(5):457-66.
176. Pandi-Perumal SR, Smits M, Spence W, Srinivasan V, Cardinali DP, Lowe AD, et al. Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(1):1-11.
177. Nicassio PM, Mendlowitz DR, Fussell JJ, Petras L. The phenomenology of the pre-sleep state: The development of the pre-sleep arousal scale. Behav Res Ther. 1985;23(3):263-71.
178. Røysamb E, Vittersø J, Tambs K. The Relationship Satisfaction scale-psychometric properties. Norsk Epidemiologi. 2014;24((1/2)):187-94.
179. Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. Int J Neurosci. 1990;52(1-2):29-37.
180. Bartel KA, Gradisar M, Williamson P. Protective and risk factors for adolescent sleep: a meta-analytic review. Sleep Med Rev. 2015;21:72-85.
181. Ostrin LA, Abbott KS, Queener HM. Attenuation of short wavelengths alters sleep and the ipRGC pupil response. Ophthalmic Physiol Opt. 2017;37(4):440-50.
182. Lacks P, Morin CM. Recent advances in the assessment and treatment of insomnia. J Consult Clin Psychol. 1992;60(4):586-94.
183. Nagai N, Ayaki M, Yanagawa T, Hattori A, Negishi K, Mori T, et al. Suppression of Blue Light at Night Ameliorates Metabolic Abnormalities by Controlling Circadian Rhythms. Invest Ophthalmol Vis Sci. 2019;60(12):3786-93.
184. Klerman E, Rahman SA, Robinson JN, Olcese J. Light exposure, endogenous melatonin concentrations, and contractions in late stage pregnancy. Poster. Poster Session IV ed. American Journal of Obstetrics & Gynecology2016. p. S336-S7.
185. Gooley JJ, Chamberlain K, Smith KA, Khalsa SB, Rajaratnam SM, Van Reen E, et al. Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. J Clin Endocrinol Metab. 2011;96(3):E463-72.
186. Sletten TL, Vincenzi S, Redman JR, Lockley SW, Rajaratnam SM. Timing of sleep and its relationship with the endogenous melatonin rhythm. Front Neurol. 2010;1:137.

187. Faulkner SM, Bee PE, Meyer N, Dijk DJ, Drake RJ. Light therapies to improve sleep in intrinsic circadian rhythm sleep disorders and neuro-psychiatric illness: A systematic review and meta-analysis. Sleep Med Rev. 2019;46:108-23.
188. Carroll JE, Teti DM, Hall MH, Christian LM. Maternal Sleep in Pregnancy and Postpartum Part II: Biomechanisms and Intervention Strategies. Curr Psychiatry Rep. 2019;21(3):19.
189. Sedov I, Madsen JW, Goodman SH, Tomfohr-Madsen LM. Couples' treatment preferences for insomnia experienced during pregnancy. Fam Syst Health. 2019;37(1):46-55.
190. Zachariae R, Lyby MS, Ritterband LM, O'Toole MS. Efficacy of internet-delivered cognitive-behavioral therapy for insomnia - A systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev. 2016;30:1-10.
191. Felder JN, Epel ES, Neuhaus J, Krystal AD, Prather AA. Efficacy of Digital Cognitive Behavioral Therapy for the Treatment of Insomnia Symptoms Among Pregnant Women: A Randomized Clinical Trial. JAMA Psychiatry. 2020;77(5):484-92.
192. Walsh JM, McAuliffe FM. Impact of maternal nutrition on pregnancy outcome--does it matter what pregnant women eat? Best Pract Res Clin Obstet Gynaecol. 2015;29(1):63-78.
193. Melzer K, Schutz Y, Boulvain M, Kayser B. Physical activity and pregnancy: cardiovascular adaptations, recommendations and pregnancy outcomes. Sports Med. 2010;40(6):493-507.
194. Moreno-Fernandez J, Ochoa JJ, Lopez-Frias M, Diaz-Castro J. Impact of Early Nutrition, Physical Activity and Sleep on the Fetal Programming of Disease in the Pregnancy: A Narrative Review. Nutrients. 2020;12(12).
195. Ding XX, Wu YL, Xu SJ, Zhang SF, Jia XM, Zhu RP, et al. A systematic review and quantitative assessment of sleep-disordered breathing during pregnancy and perinatal outcomes. Sleep Breath. 2014;18(4):703-13.
196. Nilsen RM, Bjorke-Monsen AL, Midttun O, Nygard O, Pedersen ER, Ulvik A, et al. Maternal tryptophan and kynurenine pathway metabolites and risk of preeclampsia. Obstet Gynecol. 2012;119(6):1243-50.
197. The Norwegian Directorate of Health. Søvn og søvnvansker (Sleep and sleep disorders). Helsedirektoratet, Oslo. 2017. [Accessed 22.02.2022]. https://www.helsedirektoratet.no/tema/sovn/sovn-og-sovnvansker.
198. Nilsen RM, Vollset SE, Gjessing HK, Skjaerven R, Melve KK, Schreuder P, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. Paediatr Perinat Epidemiol. 2009;23(6):597-608.
199. Carter KN, Imlach-Gunasekara F, McKenzie SK, Blakely T. Differential loss of participants does not necessarily cause selection bias. Aust N Z J Public Health. 2012;36(3):218-22.
200. Sivertsen B, Friborg O, Pallesen S, Vedaa O, Hopstock LA. Sleep in the land of the midnight sun and polar night: The Tromso study. Chronobiol Int. 2021;38(3):334-42.
201. Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemiol. 1990;43(1):87-91.

202. Dodou D, de Winter JCF. Social desirability is the same in offline, online, and paper surveys: A meta-analysis. Computers in Human Behavior. 2014;36:487-95.
203. Podsakoff PM, MacKenzie SB, Lee JY, Podsakoff NP. Common method biases in behavioral research: a critical review of the literature and recommended remedies. J Appl Psychol. 2003;88(5):879-903.
204. Roenneberg T, Pilz LK, Zerbini G, Winnebeck EC. Chronotype and Social Jetlag: A (Self-) Critical Review. Biology (Basel). 2019;8(3).
205. Kerkkof GA. Differences between morning-types and evening-types in the dynamics of EEG slow wave activity during night sleep. Electroencephalogr Clin Neurophysiol. 1991;78(3):197-202.
206. Joyce DS, Zele AJ, Feigl B, Adhikari P. The accuracy of artificial and natural light measurements by actigraphs. Journal of sleep research. 2020;29(5):e12963.
207. Van de Water AT, Holmes A, Hurley DA. Objective measurements of sleep for non-laboratory settings as alternatives to polysomnography--a systematic review. Journal of sleep research. 2011;20(1 Pt 2):183-200.
208. Sivertsen B, Omvik S, Havik OE, Pallesen S, Bjorvatn B, Nielsen GH, et al. A comparison of actigraphy and polysomnography in older adults treated for chronic primary insomnia. Sleep. 2006;29(10):1353-8.
209. Pallesen S, Gronli J, Myhre K, Moen F, Bjorvatn B, Hanssen I, et al. A Pilot Study of Impulse Radio Ultra Wideband Radar Technology as a New Tool for Sleep Assessment. J Clin Sleep Med. 2018;14(7):1249-54.
210. Toften S, Pallesen S, Hrozanova M, Moen F, Gronli J. Validation of sleep stage classification using non-contact radar technology and machine learning (Somnofy(R)). Sleep medicine. 2020;75:54-61.
211. Sussman JB, Hayward RA. An IV for the RCT: using instrumental variables to adjust for treatment contamination in randomised controlled trials. BMJ. 2010;340:c2073.
212. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol. 1991;59(1):12-9.
213. World Medical Association. WMA Declaration of Helsinki - Ethical Principles of Medical Research involving Human Subjects. 2018. [Accessed 22.02.2022]. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

I

PLOS ONE

RESEARCH ARTICLE

Sleep, evening light exposure and perceived stress in healthy nulliparous women in the third trimester of pregnancy

Randi Liset[1]*, Janne Grønli[2], Roger E. Henriksen[3], Tone E. G. Henriksen[4,5], Roy M. Nilsen[3], Ståle Pallesen[1,6,7]

1 Department of Psychosocial Science, Faculty of Psychology, University of Bergen, Bergen, Norway, **2** Department of Biological and Medical Psychology, Faculty of Psychology, University of Bergen, Bergen, Norway, **3** Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen, Norway, **4** Division of Mental Health Care, Valen Hospital, Fonna Local Health Authority, Valen, Norway, **5** Department of Clinical Medicine, Section for Psychiatry, Faculty of Medicine, University of Bergen, Bergen, Norway, **6** Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway, **7** Optentia, The Vaal Triangle Campus of the North-West University, Vanderbijlpark, South-Africa

* Randi.Liset@uib.no

OPEN ACCESS

Citation: Liset R, Grønli J, Henriksen RE, Henriksen TEG, Nilsen RM, Pallesen S (2021) Sleep, evening light exposure and perceived stress in healthy nulliparous women in the third trimester of pregnancy. PLoS ONE 16(6): e0252285. https://doi.org/10.1371/journal.pone.0252285

Editor: Federica Provini, IRCCS Istituto Delle Scienze Neurologiche di Bologna, ITALY

Received: August 28, 2020

Accepted: May 12, 2021

Published: June 3, 2021

Data Availability Statement: A dataset underlying the results reported in the manuscript are now submitted as Supporting Information files to this resubmission, "S1" – "S11". To ensure de-identification and reverse path identification of personal data, we have removed the variables age, marital status and household.

Funding: The study was supported by a PhD grant for RL, and a grant for graphical design and printing of questionnaire, all funded by Faculty of Psychology, University of Bergen, Norway. The

Abstract

Objective

Sleep disturbances are common in pregnancy, and the prevalence increases during the third trimester. The aim of the present study was to assess sleep patterns, sleep behavior and prevalence of insomnia in pregnant women in the third trimester, by comparing them to a group of non-pregnant women. Further, how perceived stress and evening light exposure were linked to sleep characteristics among the pregnant women were examined.

Methods

A total of 61 healthy nulliparous pregnant women in beginning of the third trimester (recruited from 2017 to 2019), and 69 non-pregnant women (recruited in 2018) were included. Sleep was monitored by actigraphy, sleep diaries and the Bergen Insomnia Scale. The stress scales used were the Relationship Satisfaction Scale, the Perceived Stress Scale and the Pre-Sleep Arousal Scale. Total white light exposure three hours prior to bed-time were also assessed.

Results

The prevalence of insomnia among the pregnant women was 38%, with a mean score on the Bergen Insomnia Scale of 11.2 (SD = 7.5). The corresponding figures in the comparing group was 51% and 12.3 (SD = 7.7). The pregnant women reported lower sleep efficiency (mean difference 3.8; 95% CI = 0.3, 7.3), longer total sleep time derived from actigraphy (mean difference 59.0 minutes; 95% CI = 23.8, 94.2) and higher exposure to evening light (mean difference 0.7; 95% CI = 0.3, 1.2), compared to the non-pregnant group. The evening light exposure was inversely associated with total sleep time derived from actigraphy (B = -8.1; 95%

funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: REH and TEGH are share-holders in Chrono Chrome AS. TEGH has received speaker honorarium from H. Lundbeck AS. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

CI = -14.7, -1.5), and an earlier midpoint of sleep (B = -10.3, 95% CI = -14.7, -5.9). Perceived stressors were unrelated to self-reported and actigraphy assessed sleep.

Conclusion

In healthy pregnant participants sleep in the third trimester was preserved quite well. Even so, the data suggest that evening light exposure was related to shorter sleep duration among pregnant women.

Introduction

Pregnancy represents a time of several significant changes in terms of physical, hormonal, and psychological alterations, all which may influence sleep. Accordingly, disturbed sleep is frequent during pregnancy [1]. Some sleep characteristics seem to be more frequently occurring in specific phases of the pregnancy; such as increased demand for sleep in the first trimester, and disrupted sleep in the third trimester. By the start of gestational week 40 a high percentage (75–98%) report multiple nocturnal awakening [2–4] Further, sleep quality has been found to worsen with age of the pregnant women [5]. Overall, there seems to be three main groups of sleep disturbances which predominate during pregnancy; 1) obstructive sleep apnea (OSA), 2) restless legs syndrome (RLS) and 3) insomnia. The latter is characterized by difficulty initiating sleep, nocturnal awakenings, or early-morning awakenings, occurring for at least three nights per week [1].

Insomnia has been reported by 62% of pregnant women, a number that is significantly higher than found in the general population (10–15%) [6]. Disrupted sleep among pregnant women may be caused by several hormonal and mechanical influences, and factors such as nocturia, dyspnea, nasal congestion, muscular aches and pelvic pains, fetal activity, leg cramps as well as gastric reflux [1]. There is evidence suggesting that poor sleep quality and insomnia negatively could influence the health of mother and offspring, e.g. in terms of preeclampsia [1], gestational diabetes mellitus, preterm birth [7], prolonged labor, increased pain during labor, Caesarean section, low birth weight [1, 8], depressive reactions [6, 8], and postnatal depression [9]. Thus, assessment of sleep and identifying predictors of poor sleep in pregnancy are clearly warranted.

Sleep is closely linked to circadian rhythms [10]. The central pacemaker, the suprachiasmatic nucleus (SCN) situated in the hypothalamus, is the master clock, and influences not only the sleep-wake rhythm, but also a vast array of physiological (e.g. hormonal) and behavioral (e.g. feeding) rhythms [11]. Light is the strongest "zeitgeber" and entrains the SCN to the 24-hour dark-light cycle. Information about environmental illumination is signaled to the SCN by melanopsin-containing intrinsically photoresponsive retinal ganglion cells (ipRGC) [12]. The SCN projects further to the pineal gland, producing the sleep promoting night hormone melatonin. Exposure to nocturnal light has been found to suppress melatonin secretion, a signal of darkness and marker for circadian rhythms [13]. A recent review reported that circadian rhythm disturbances, in both mother and infant in the postpartum period, are strongly correlated with maternal exposure to light [14]. Preclinically observations find that constant light exposure in pregnant rats reduced melatonin level and affected the pregnant progress negatively [15]. Especially light exposure in the evening and during the night increases alertness, disturbs sleep and delays the circadian rhythm [16]. In line with this, a review showed

that avoidance of evening light was associated with less sleep disturbance and increased total sleep time in a non-pregnant population [17].

There is so far dearth of knowledge about how light exposure in pregnancy influence sleep and the circadian rhythm. A study of primipara pregnant women exposed for ocular blue/green light for two hours prior to and after bedtime (total of four hours) showed lower melatonin concentration than the control group (red light) [18]. Natural light exposure at night showed an inversely association with sleep duration in pregnant women, assessed at first and third trimester [19]. Further, in agreement with this, a study of nocturnal artificial outdoor light (skyglow, light pollution) found a negative association with sleep duration in pregnant women [20].

Pregnancy is regarded as a vulnerable phase in life. Several aspects of pregnancy may increase perceived stress. One study showed that 78% of pregnant women experienced low to moderate levels and 6% reported high levels of psychosocial stress [21]. In agreement with this, a cohort study reported that women perceived more stress during pregnancy than during the postpartum period [22]. Stress affects sleep, and women with stress-related sleep disturbances during pregnancy are more likely to experience insomnia [23] and psychiatric disorders, compared to women without stress related sleep disturbance [23, 24]. Maternal prenatal stress can affect the physiological [7] and psychological health [25] of the pregnant women, and has been associated with negative fetal outcome such as stillbirth, preterm birth, intrauterine growth restriction and developmental delay [26–28], neurodevelopment [7, 29] as well as infectious disease in the offspring [30]. Pregnancy typically include worries about the health of the fetus, diet, weight gain, appearance, labor and delivery [27]. It can also be influenced by many other factors, including life events, social support, income level, educational background and partner relationship quality [31]. Marital distress may activate the central stress response system, the hypothalamic-pituitary-adrenal (HPA) axis and predict adverse stress effects. Satisfaction with partner on the other hand, may reduce stress activation [32].

Although some studies have attested to worsening of sleep in the third trimester, most of these studies are based on questionnaires. Few studies have combined sleep diaries with objective measures, such as actigraphy, when assessing sleep during pregnancy. Further, there is a dearth of knowledge when it comes to how light exposure in pregnancy is related to sleep disturbances. In addition, few studies have assessed how sleep in pregnant women are affected by different perceived stressors.

Against this background, the aim of the present study was to describe sleep patterns and sleep related behavior as well as the prevalence of sleep disturbances in population of pregnant women in the third trimester. Secondly, we aimed to compare them to a contrast group of non-pregnant women. Thirdly, we aimed to investigate how evening light exposure and perceived stress were associated with sleep characteristics among the pregnant women.

Method

Study population and design

The current study was observational, based on data collected as part of a randomized clinical trial, registered at ClinicalTrials.gov (NCT03114072), comparing sleep and light exposure data in pregnant women in the third trimester with female non-pregnant students.

Fig 1 presents a flowchart of enrollment of the pregnant women to the present study. Between May 2017 and April 2019 healthy nulliparous women were recruited during their standard health control about gestational week 24 by consulting midwives at antenatal-health-care centers in the Municipality of Bergen, Norway. The midwives provided oral and written information about the study. If the pregnant women consented to receive more information

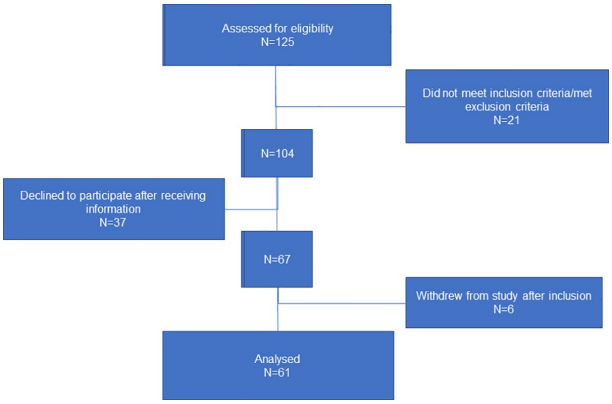


Fig 1. Flowchart of enrollment of pregnant women in the study.

https://doi.org/10.1371/journal.pone.0252285.g001

or participate, further information was provided by the research team. Inclusion criteria were: 1) Nulliparous women, 2) expecting one child, 3) being in the third trimester of a normal pregnancy, 4) able to wear an actigraph during daytime and nighttime for the study period (one week) and, 5) able to complete a questionnaire in Norwegian. Exclusion criteria were; 1) somatic or psychiatric disorders, 2) fever and other health conditions affecting sleep, 3) working at night during the study protocol or 4) having an eye-condition affecting the translucency of the eyes. A total of 125 pregnant women were assessed for eligibility. After excluding those who declined participation, a final sample of 61 pregnant women were retained (Fig 1). The pregnant women finally started their participation with data collection between pregnancy week 28 to 32, mean week 29+0.

To compare sleep data and light exposure data with a non-pregnant population, we used data from a group of 69 healthy young women who were students at University of Bergen, during the period of February/March, August/September and October/November in 2018. Inclusion criteria were: 1) healthy women, 2) not pregnant, 3) able to wear an actigraph during daytime and nighttime for the study period (about one week) and, 5) able to complete questionnaires in Norwegian. We excluded those reporting sicknesses during the study-period.

Variables

Demographic. Self-report questions were used to obtain information about maternal age, marital/partner status (married, cohabitating, single, separated/divorced, widow), level of education (high school and below, college and above), income (NOK<150 000–399 999, 400 000–599 999, 600 000–799 999, 800 000–1 mill and above; 10 NOK ≈ 1 US $), number of people living together in the household (partner, parents, parents in law, children, none, other) and smoking (daily, less than daily, never).

Subjective measure of sleep. *A sleep diary* was completed every morning. The sleep diary included items on number and duration of naps during the day, use of sleep medication (yes/no), bedtime (hh.mm), lights-out time (hh.mm), sleep latency (min), number of nocturnal awakenings, wake after onset sleep (WASO), waking and rise time (hh.mm). Included were also items assessing sleep quality and daytime sleepiness [33]. The outcomes used in the present study were total sleep time (TST), sleep efficiency (SE%) (total sleep time/ time in bed * 100) and midpoint of sleep (TST:2).

The Bergen Insomnia Scale (BIS) was administered at study initiation. Originally the time frame was last month, but this was changed to last week in order to capture the rapid change in sleep that may occur during pregnancy and also to align the BIS with the time frame for the sleep diary and actigraphy measures. The BIS consists of six items. The first four pertain to sleep onset, maintenance, early morning wakening insomnia, and not feeling restored after sleep. The last two assess level of daytime impairment due to poor sleep and dissatisfaction with sleep. Each item is rated on a scale ranging from 0 to 7 days per week, providing a composite score ranging from 0 to 42. An insomnia diagnosis was made if the participant scored at least 3 points on at least one of the first four items of the BIS, and scored at least 3 points on at least one of the last two items of the BIS [34]. Cronbachs alpha for the BIS was .80 for pregnant and .82 for non-pregnant women.

Objective measure of sleep and light. *Actigraphy*. To objectively estimate sleep patterns and light, each participant was asked to wear a commercially available wrist actigraph (Actiwatch Spectrum; Philips Respironics Inc.), on their non-dominant wrist, continuously throughout the study period. The actigraph registered movements by a piezoelectric accelerometer and epoch length was set to thirty seconds and the sensitivity was set to medium. An embedded light sensor in the actigraph recorded and determined the light exposure, expressed in illuminance (lux). The participants were instructed to press the event button on the actigraph to indicate when they turned off the light and tried to sleep, and when they finally woke up in the morning. Data was converted to objective sleep parameters through the Actiware (version 6.0.9, Philips Respironics Inc.) software. Rest intervals were manually scored based on raw data, reflecting motor activity, light exposure, event button presses and also supported by sleep diary data according to description of the criteria for defining the duration of the sleep episode [35]. Duration of the sleep episode is the sum of sleep onset latency (SOL) + total sleep time (TST) + time awake after sleep onset but before final awakening (WASO) + time in bed after the final awakening [36]. In cases where event button markers were not pressed or discrepancies between the sleep diary data and actigraph data were evident, duration of the sleep episode was set based on motor- activity. Three sleep related outcome variables were derived: Total sleep time (TST), sleep efficiency (SE) and midpoint of sleep. Midpoint of sleep provides an indirect measure of circadian phase [37]. Data on the total white light exposure during the three last hours before bedtime, were also retained and analyzed. Total white light refers to the total light illuminance (lux/m2). In the Actiwatch Spectrum device this measure is calculated from the integration of data from three color diode sensors detecting ambient light in the range from 400 nm to 700 nm [38].

Measure of stress. *Pre-Sleep Arousal Scale (PSAS)* was completed every night before bedtime. The PSAS assesses the state of psychophysiological arousal before sleep. The scale consists of 16 items and measures somatic (e.g. heart racing, shortness of breath, stomach upset) as well as cognitive (e.g. worry about falling asleep, depressing or anxious thoughts, mentally alert) components of arousal. Responses are recorded on a five-point Likert scale ranging from 1 (not at all) to 5 (extremely), providing a composite score ranging from 16 to 80. Higher scores indicate higher states of arousal [39]. Cronbachs alpha for the PSAS scale was on average for all the seven days .76.

Perceived Stress Scale (PSS) was measured at study initiation. The PSS measures how often a situation in one's life has been considered stressful during the previous week and consists of 10 items (e.g. ". . .upset of unexpected happening" and ". . .nervous and stressed"). Each item is scored on a five-point Likert-scale ranging from 1 (never) to 5 (very often), with a total score ranging from 10 to 50. Four items are reversed, and higher scores indicate higher levels of stress [40]. Cronbachs alpha for the PSS was .64 in the present study.

Relationship Satisfaction Scale (RSS) was also administered at the start of the data collection. This instrument measures marital satisfaction and relationship quality. It consists of 10-items (e.g. "Have a close relationship with my spouse/partner" and "My partner and I have problems in our relationship"). One response option was by inadvertence lost in the process of finalizing the questionnaire, hence, a 5-point scale ranging from 1 (strongly agree) to 5 (strongly disagree), providing a composite score ranging from 10 to 50 where used rather a 6-point scale. Three items were reversed, and higher scores represent lower levels of relationship satisfaction [41]. Cronbachs alpha for the RSS scale was .74.

Statistical methods

All analyses were performed using IBM SPSS Statistics version 25 (SPSS, Chicago, IL, USA), and Stata IC version 16 (Stata Statistical Software, College Station, TX, USA) and R version 3.5.1 [42]. Notably, data on TST, SE, and midpoint of sleep were collected both from sleep diary and actigraphy, whereas data on white light were exclusively collected from actigraphy. In terms of actigraphy there were valid data for 54 pregnant and 58 non-pregnant women, yielding a somewhat lower sample size compared with the sample with valid sleep diary data. Descriptive statistics were used to summarize demographic characteristics of the sample, presented as means and percentages, and differences in age, alcohol and BIS-scores between pregnant and non-pregnant women were examined by independent samples t-tests and presented as means (SDs) and p-values.

Linear mixed effects models were used for comparing the outcomes TST, SE, midpoint of sleep, and total white light between pregnant and non-pregnant women. All models included pregnancy group, weekday, and a group-by-weekday interaction as independent categorical terms. To account for repeated measures and the intra-individual correlation across weekdays, we specified a random intercept for the individual using the individual's unique study number. For some outcomes, we also added a first-order autoregressive error term to account for lagged correlation not captured by the random intercept alone. The group difference for each outcome was estimated for each weekday as well as across all weekdays overall. For the overall analysis, the group-by-weekday interaction was omitted from the models. To examine potential group-by-weekday interactions, we further used likelihood ratio tests. All analyses were performed crude and with adjustment for age, weekday and calendar month.

We also used linear mixed effects models to examine if the exposures RSS, PSS, PSAS, and total white light were associated with the outcomes TST, SE and midpoint of sleep measures, both with sleep diaries and actigraphy. These analyses were carried out only for data on the pregnant women. The analysis of each exposure on each outcome was performed crude and with adjustment for age, weekday and calendar month and a random intercept for the individual was specified to account for the repeated measures and intra-individual correlation across weekdays. Note, that in all abovementioned analyses, we excluded outliers in both outcomes and exposures. In addition, total white light was strongly right-skewed and was therefore log-transformed before entering the models. Furthermore, consistency for total scores on RSS, PSS, and PSAS was estimated by Cronbach's alpha.

Ethical considerations

The study was approved by the Regional Committee for Medical and Health Related Ethics, in Western Norway (2016/1394/REK vest). All participants provided written informed consent before inclusion in the study.

Results

In the 61 healthy primipara pregnant women, the mean age was 30.6 years (SD 4.0, range 24–43), whereas the mean age of the 69 healthy non-pregnant group age was 23.1 years (SD 2.8, range 19–33), $p < .001$.

Sample characteristics in terms of marital status, education, economics (total income in the household), number of adults and children living in the household for the pregnant women are displayed in Table 1. In all, 96.7% of the primipara women were married or living with a partner, 84% had education at least at college level, 72% had an income of 800 000 NOK (≈ 80 000 US $) or more, and 95% were living with their partner. Only one pregnant woman reported she was smoking. None of the pregnant women reported consumption of alcohol during the study week, compared to 9 of the non-pregnant group.

The pregnant group had a mean score of 11.2 (SD 7.5) on the BIS, whereas the mean BIS score for the non-pregnant group was 12.3 (SD 7.7) which did not amount to a significant difference neither before nor after adjusting for age. In the pregnant group, 38% scored above cut-off for insomnia compared to 51% in the non-pregnant group.

Table 2 displays the results from linear mixed models regarding sleep and evening light exposure variables for each weekday. The sleep diary data showed no significant difference

Table 1. Demographic factors among pregnant and non-pregnant women, self-reported data.

Factor	Level	Pregnant	Non-pregnant	P-value
N		61	69	
Age, mean (SD)		30.6 (4.0)	23.1 (2.8)	< .001
Marital status, n (%)	Married	18 (30%)		
	Cohabitating/partner	41 (67%)		
	Single	2 (3%)		
Education, n (%)	< = Senior high school	10 (16%)		
	College and above	51 (84%)		
Economics, n (%)	<150 000–399 999 NOK	6 (10%)		
	400 000–599 999 NOK	4 (7%)		
	600 000–799 999 NOK	7 (11%)		
	800 000–1mill. NOK or above	44 (72%)		
Adult, total in Household, n (%)	1	2 (3%)		
	2	58 (95%)		
	4	1 (2%)		
Children, total in household, n (%)	0	59 (97%)		
	1	1 (2%)		
	3	1 (2%)		
Smoking, n (%)	Daily	1 (2%)		
	Not at all	60 (98%)		
Alcohol, n (%)	Units 1–6	0 (0)	9 (6.2)	< .001
Physical activity, minutes, mean (SD)		20.9 (27.5)		
Relaxing activity, minutes, mean (SD)		4.5 (13.3)		
Bergen Insomnia Scale, mean (SD)		11.2 (7.5)	12.3 (7.7)	.943[b]
Insomnia, (%)		(38%)	(51%)	.136

N = number of participants; SD = standard deviation; NOK = Norwegian kroner; 10 NOK ≈ 1 US $.

[a]N = 67

[b]Adjusted for age.

https://doi.org/10.1371/journal.pone.0252285.t001

Table 2. Sleep and light exposure variables for each weekday, and the association between pregnant and non-pregnant women.

		Pregnant		Non pregnant	Crude model:	Adjusted model:
	N	Mean (SE)	N	Mean (SE)	Mean difference (95% CI) [P-value]	Mean difference (95% CI) [P-value][a]
Total sleep time (Self-report)						
Average across week	61	444.2 (5.9)	52	461.0 (5.8)	16.6 (0.3, 32.9) [.046]	-14.1 (-40.8, 12.6) [.301]
Sleep efficiency (Self-report)						
Average across week	61	86.2 (0.7)	52	89.6 (0.8)	3.4 (1.3, 5.6) [.002]	3.8 (0.3, 7.3) [.033]
Midpoint of sleep (Self-report)						
Average across week	61	03:52 (00:05)	52	04:40 (00:08)	00:47 (00:27, 01:08) [< .001]	00:21 (-00:14, 00:56) [.225]
Total sleep time (Actigraph)						
Average across week	55	463.0 (5.5)	58	448.4 (7.0)	-14.7 (-32.3, 2.9) [.102]	-59.0 (-94.2, -23.8) [< .001]
Sleep efficiency (Actigraph)						
Average across week	55	85.9 (0.7)	58	85.0 (0.7)	-1.0 (-3.0, 1.1) [.357]	-0.3 (-4.3, 3.6) [.862]
Midpoint of sleep (Actigraph)						
Average across week	55	04:24 (00:03)	58	05:01 (00:06)	00:36 (00:21, 00:51) [< .001]	-00:04 (-00:33, 00:26) [.831]
Total white light log transformed						
Average across week	54	8.4 (0.1)	58	7.0 (0.1)	-1.4 (-1.6, -1.1) [< .001]	-0.7 (-1.2, -0.3) [.002]

Estimated by linear mixed effects models without the group-by-weekday interaction were used for comparing the outcomes TST, SE, Midpoint of sleep, Total White light between pregnant and non-pregnant women. N = number of participants; SE = standard error; CI = confidence interval.

[a] Adjusted for age, weekday and calendar month.

https://doi.org/10.1371/journal.pone.0252285.t002

between the non-pregnant women and the pregnant women in terms of TST or midpoint of sleep after adjustment for age, weekday and calendar month. However, the pregnant group had lower SE compared to the non-pregnant group, both in the crude, mean difference = 3.4 (95% CI = 1.3, 5.6), and in the adjusted analysis, mean difference = 3.8 (95% CI = 0.3, 7.3).

In terms of the actigraph data, the non-pregnant women had 59 minutes shorter TST than the pregnant women in the adjusted analysis (Table 2). No group differences were found for SE or midpoint of sleep after adjustment for age, weekday and calendar month. Compared to the non-pregnant women, the pregnant women were exposed to more total white light, the three last hours before bedtime, also after adjustment for age, weekday and calendar month.

Daily change in sleep, and evening light exposure in pregnant and non-pregnant women, are displayed in Figs 2 and 3, analyzed by linear mixed models, and adjusted for age and

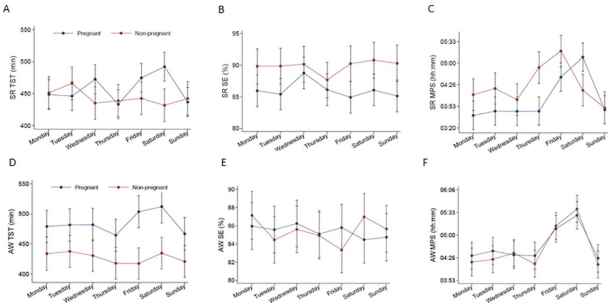


Fig 2. Daily sleep, in pregnant and non-pregnant women. Estimated by linear mixed effects models including group-by-weekday interaction. The p value for time-by-group interaction was (A) p < .001 for Self-reported (SR) total sleep time (TST), (B) p = .192 for Self-reported sleep efficiency (SE), (C) p < .001 for Self-reported midpoint of sleep (MPS) was, (D) p = .183 derived from actigraphy (AW) for total sleep time (TST), (E) p = .027 derived from actigraphy for sleep efficiency (SE), (F) p = .408 derived from actigraphy for midpoint of sleep.

https://doi.org/10.1371/journal.pone.0252285.g002

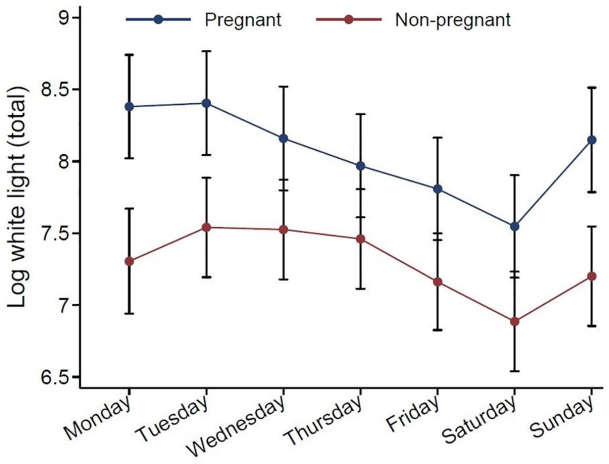


Fig 3. Daily evening light exposure, in pregnant and non-pregnant women. Estimated by linear mixed effects models including group-by-weekday interaction. The p value for time-by-group interaction was p = .307 derived from actigraphy for total white light (log transformed).

https://doi.org/10.1371/journal.pone.0252285.g003

calendar month. Self-reported data TST and midpoint of sleep showed a different pattern over the days for the two groups (p for interaction < .001), but not in SE. For actigraph data, SE showed a different between the groups (p for interaction .027), but daily change in TST, midpoint of sleep and total white light showed a similar pattern in the two groups.

Table 3 displays the association between the exposures RSS, PSS, PSAS and the outcomes TST, SE and midpoint of sleep, in pregnant women, analyzed by linear mixed model. When using self-reported data, an association between PSAS and midpoint of sleep was only detected

Table 3. Association between sleep and different types of perceived stressors in pregnant women.

	Self-reported				Actigraphy			
	Crude model:		Adjusted model:[a]		Crude model:		Adjusted analysis:[a]	
	Beta	95% CI [P]	Beta	95% CI [P]	Beta	95% CI [P]	Beta	95% CI [P]
Total sleep time								
RSS	-3.3	-8.1, 1.5 [.178]	-2.7	-7.4, 2.0 [.265]	-2.8	-7.4, 1.7 [.226]	-2.6	-7.0, 1.7 [.238]
PSS	-0.2	-2.8, 2.4 [.868]	-0.6	-3.0, 1.9 [.646]	0.3	-2.1, 2.7 [.785]	1.2	-1.0, 3.5 [.270]
PSAS	-2.0	-4.3, 0.2 [.078]	-1.9	-4.1, 0.2 [.075]	-0.7	-2.7, 1.3 [.468]	-0.7	-2.6, 1.2 [.461]
Sleep efficiency								
RSS	-0.04	-0.6, 0.6 [.908]	0.09	-0.7, 0.5 [.779]	0.2	-0.5, 0.8 [.597]	0.2	-0.4, 0.9 [.451]
PSS	-0.1	-0.5, 0.2 [.382]	-0.2	-0.5, 0.1 [.126]	0.02	-0.3, 0.3 [.919]	0.1	-0.2, 0.4 [.422]
PSAS	0.1	-0.2, 0.3 [.604]	0.03	-0.2, 0.3 [.824]	0.1	-0.1, 0.2 [.364]	0.1	-0.1, 0.2 [.424]
Midpoint of sleep								
RSS	-0.8	-5.9, 4.2 [.753]	-0.7	-6.0, 4.6 [.788]	-1.3	-4.6, 2.1 [.462]	-0.7	-4.0, 2.6 [.658]
PSS	-1.5	-4.0, 1.0 [.240]	-2.2	-4.7, 0.2 [.070]	-0.9	-2.6, 0.8 [.303]	-1.1	-2.7, 0.4 [.163]
PSAS	-2.8	-4.7, -0.9 [.004]	-1.2	-2.8, 0.3 [.124]	-0.6	-2.0, 0.9 [.464]	-0.5	-1.8, 0.9 [.500]

Estimated by linear mixed effects models. CI = confidence interval; RSS = relationship satisfaction scale; PSS = perceived stress scale; PSAS = pre-sleep arousal scale.

[a] Adjusted for age, weekday and calendar month.

https://doi.org/10.1371/journal.pone.0252285.t003

Table 4. Association between sleep and evening light exposure in pregnant women.

	Self-reported				Actigraphy			
	Crude model:		Adjusted model:[a]		Crude model:		Adjusted model:[a]	
	Beta	95% CI [P]	Beta	95% CI [P]	Beta	95% CI [P]	Beta	95% CI [P]
Total sleep time								
Total white light	-2.0	-9.8, 5.8 [.608]	-2.4	-10.3, 5.5 [.558]	-11.4	-17.9, -4.9 [.001]	-8.1	-14.7, -1.5 [.016]
Sleep efficiency								
Total white light	0.7	-0.1, 1.6 [.088]	0.5	-0.4, 1.4 [.263]	0.2	-0.3, 0.8 [.364]	0.1	-0.4, 0.7 [.667]
Midpoint of sleep								
Total white light	-3.5	-9.6, 2.6 [.256]	-0.2	-5.2, 4.8 [.935]	-15.3	-20.0, -10.6 [< .001]	-10.3	-14.7, -5.9 [< .001]

Estimated by linear mixed effects models. CI = confidence interval; RSS = relationship satisfaction scale; PSS = perceived stress scale; PSAS = pre-sleep arousal scale.
[a] Adjusted for age, weekday and calendar month.

https://doi.org/10.1371/journal.pone.0252285.t004

before, but not after adjustment for age, weekday and calendar month. The exposures RSS, PSS, PSAS did not show any relationship with any of the sleep variables TST, SE and midpoint of sleep, neither on sleep diary nor actigraphy data before or after adjustment.

Exposure of total white light in the pregnant women, displayed in Table 4, was not associated with self-reported TST, SE or midpoint of sleep. For the actigraphy data, total white light was inversely associated with TST (B = -8.1, 95% CI = -14.7, -1.5) and earlier midpoint of sleep (B = -10.3, 95% CI = -14.7, -5.9). Total white light was not associated with SE.

Discussion

The aim of this study was to assess sleep disturbance, sleep patterns and sleep related behavior in healthy pregnant women in the third trimester by comparing them to non-pregnant women. Further, the aim was also to investigate how evening light exposure and perceived stress were linked to the sleep of the pregnant women.

Sleep in late pregnancy

According to sleep diary data the pregnant women had significant lower SE compared to the non-pregnant women in the adjusted analyses. According to the actigraphic data the pregnant women had higher TST and were exposed to more light the three last hours before bedtime compared to the non-pregnant group. None of the investigated stress variables were related to sleep outcomes, neither assessed by sleep diary or actigraphy among the pregnant women. Light exposure the three last hours before bedtime was inversely related to TST and midpoint of sleep according to the actigraphic data.

This study showed no difference between the two groups in terms of insomnia scores. The mean BIS scores of the two groups were actually quite comparable to national norm data for women in the relevant age groups [34]. Still, a relatively high proportion of the two groups fulfilled the criteria for insomnia, albeit no group differences emerged.

The non-pregnant group had a shorter total sleep time than the pregnant group measured by the actigraph, however this was not corroborated by self-reported data. This may reflect that the non-pregnant women overestimated sleep subjectively and/or that the pregnant women underestimated sleep. The time x group interaction for self-reported TST and midpoint of sleep suggested that the pregnant women slept relatively longer and later during the weekend compared to the non-pregnant women, hence they seemed to accumulate a greater sleep debt during the week compared to the non-pregnant women. Such a sleep pattern is common in working populations [43]. As the non-pregnant women comprised university

students who probably have few early lectures and few mandatory tasks, the results may also reflect that this group to a large extent can sleep ad libitum many days per week [44]. The pregnant women reported significant lower SE than the non-pregnant women on the sleep diary, but not according to the actigraph. Sleep efficiency is often used as an indicator of sleep quality. Decreased sleep quality during pregnancy compared with a non-pregnant population has been reported previously [1]. The fact that this was not detected by actigraphy may suggest that movement during pregnancy is reduced. This is in line with studies suggesting that actigraphy may overestimate TST and SE in pregnancy when using default settings [45]. It should be noted that the mean age of the pregnant women was 30.6 years, compared to 23.7 years in the non-pregnant group.

The pregnant women were exposed to a higher level of total white light in the three last hours before bedtime compared to the non-pregnant women. This might reflect an earlier midpoint of sleep (although not significant difference between the groups in adjusted analysis), which can be an indicator of light exposure occurring earlier in the evening when natural illumination is at a higher level. The fact that the exposure of light was lower in the weekends, when the pregnant women went to bed later (results not shown), support this interpretation. In the pregnant women exposure to light according to actigraph data showed an inversely association with TST and midpoint of sleep, but not with SE. We did not find any association between light exposure and self-reported sleep variables.

The inverse relationship between light exposure before bedtime and TST suggests that high level of illumination may curtail sleep. This is in line with studies showing that light exposure in the evening may reduce sleepiness [16] and studies showing that light exposure disturbs sleep and circadian rhythms in mothers and their offspring [14].

In terms of stress, none of the stress scales (RSS, PSS and PSAS) showed any association with the sleep variables TST, SE and midpoint of sleep, both when assessed with sleep diary and actigraphy. Still, previous research has shown that psychosocial stress during pregnancy is associated with elevated risk of negative maternal health and birth outcomes [46] and women with stress-related sleep disturbances during pregnancy are more likely to experience insomnia [23]. Conversely, previous studies have shown that poor sleep quality can cause stress in pregnant women [7], both during second and third trimester of pregnancy [7, 47]. The present sample of pregnant women reported as a group, low scores on relationship-stress and other stress-related variables. A good relationship with partner contributes to low levels of perceived stress [32], which generally seems to protect against sleep problems [23, 24, 48]. In line with this, the present sample of healthy pregnant women in the first part of the third trimester slept overall quite well. Their overall sleep duration, both according to sleep diary and actigraphy was in line with the recommended amount for adults [49]. The mean SE was also above the suggested cut-off of 85%, commonly used to distinguish between sleep of acceptable quality and suboptimal sleep [50].

Overall, in the present sample of healthy pregnant participants we found that sleep was quite well preserved, in contrast to findings from several previous studies [1, 6]. However, the present sample was on average quite economical resourceful and reported low levels of exposure to stressors, which may explain the discrepancies with other studies. The data were collected in an early part of the third trimester, which in term of mechanical discomfort may be less challenging than closer to term.

Limitations and strength

A limitation of the present study is the relatively small number of participants. Overall, the pregnant group reported good sleep and low exposure to stressors, either from their

relationship with their partner and in general. Due to the low scores on sleep problems and stress the odds of finding a relationship between sleep and stress are assumingly quite low.

As chronotype might have moderated the findings, it is a limitation that subjects in the present study were not assessed by such measure. Mid-sleep time on weekend corrected for sleep debt on workdays is normally regarded as the best indirect subjective measure of circadian phase [51]. In the present study however, some had weekend work, some were on sick leave and some were students. We therefore used mid-sleep time averaged over the whole week as an indirect measure of circadian phase.

Only small and inconsistent differences were found between the sleep of the pregnant and the non-pregnant group, which shows that the pregnant group did not have poorer sleep than this non-pregnant group. Hence, the pregnant group seems healthier than other pregnant groups studied in terms of sleep and health. In this realm it is worth noticing that the pregnant group had higher education, higher income and had fewer minority members than in the general population. Thus, the generalizability of the findings may be limited. The comparative group comprised female students at the University of Bergen who were younger and likely have a different lifestyle than the pregnant women. This may pose a challenge when using these as a comparison group. Still, it should be noted that age was controlled for in the analyses. Also, a recent study [52], has shown a high prevalence of sleep problems among Norwegian students, hence the comparison group do probably not comprise good sleepers only.

Data on several clinical-demographic characteristics (marital status, education, economics, smoking and physical and relaxing activity) were unfortunately not collected in the student sample, precluding group comparisons on these variables. The comparative group did not complete the instruments PSAS, PSS and RSS. However, the scores on these instruments were not associated with sleep in the pregnant sample. The reliability in some instruments, like the PSS, was somewhat lower than ideally, with an alpha of .64. Some of the data in the present study were based on self-report which may render the data vulnerable to recall bias [53], social desirability bias [54], and common method bias [55]. Although actigraphy in many studies have shown low specificity [56], actigraphy has still shown to be sufficiently sensitive to detect changes in sleep duration in several studies [35]. A strength of the present study is the combination of subjective and objective sleep assessment, and an observation period of a full week. Despite that the light measure was not of sufficient quality to differentiate between different wavelengths and the fact that actigraph devices typically underestimates illuminance (both artificial and natural) [57], the inclusion of light measurement and analyses of associations with sleep parameters were of importance. Light was the only environmental factor showing association with sleep in the present study.

Another asset of the present study is that it contributes with knowledge suggesting that sleep, even at the end of pregnancy, may be fairly good in healthy and resourceful women. This is an important message to convey. In terms of future research there is a need for more knowledge about light exposure and its effects during pregnancy. Studies following sleep in pregnant women throughout the whole pregnancy would be an asset to the field. As sleep problems generally are common in pregnant women, more studies investigating the effects of non-pharmacological interventions are warranted.

Conclusions

This study of healthy Norwegian pregnant women in the beginning of the third trimester showed that they as a group overall slept quite well. Compared to a non-pregnant group, there were few differences between the groups. In the present sample of pregnant women, light

exposure in the evening was associated with shorter sleep duration. Perceived stress did not show any association with sleep parameters of pregnant women in the present study.

Supporting information

S1 Dataset. Table 1; demographic factors from selfreported data.
(XLSX)

S2 Dataset. Table 2; total sleep time, sleep efficiency and midpoint of sleep from selfreported data.
(XLSX)

S3 Dataset. Table 2; total sleep time from actiware data.
(XLSX)

S4 Dataset. Table 2; sleep efficiency from actiware data.
(XLSX)

S5 Dataset. Table 2; midpoint of sleep from actiware data.
(XLSX)

S6 Dataset. Table 2; total white light from actiware data.
(XLSX)

S7 Dataset. Table 3; total sleep time from selfreported and actiware data, and the stressors RSS, PSS and PSAS.
(XLSX)

S8 Dataset. Table 3; sleep efficiency from selfreported and actiware data, and the stressors RSS, PSS and PSAS.
(XLSX)

S9 Dataset. Table 3; midpoint of sleep from selfreported and actiware data, and the stressors RSS, PSS and PSAS.
(XLSX)

S10 Dataset. Table 4; total sleep time, sleep efficiency and midpoint of sleep from selfreported data, and total white light from actiware data.
(XLSX)

S11 Dataset. Table 4; total sleep time, sleep efficiency and midpoint of sleep, and total white light, all from actiware data.
(XLSX)

Acknowledgments

We are grateful to all the participating pregnant women who took part in study, as well as the consulting midwifes at antenatal-healthcare centers in the Municipality of Bergen, Norway, for recruiting participants. We are also grateful to the students participating as a comparative group. We would further like to thank Alex Craven for providing advice and assistance in processing of the actigraphy data.

Author Contributions

Conceptualization: Randi Liset, Janne Grønli, Roger E. Henriksen, Tone E. G. Henriksen, Ståle Pallesen.

Data curation: Randi Liset, Janne Grønli.

Formal analysis: Randi Liset, Roy M. Nilsen, Ståle Pallesen.

Investigation: Randi Liset, Janne Grønli.

Methodology: Randi Liset, Janne Grønli, Roger E. Henriksen, Tone E. G. Henriksen, Ståle Pallesen.

Project administration: Randi Liset.

Resources: Janne Grønli, Tone E. G. Henriksen, Ståle Pallesen.

Software: Roy M. Nilsen, Ståle Pallesen.

Supervision: Janne Grønli, Roger E. Henriksen, Tone E. G. Henriksen, Roy M. Nilsen, Ståle Pallesen.

Writing – original draft: Randi Liset.

Writing – review & editing: Janne Grønli, Roger E. Henriksen, Tone E. G. Henriksen, Roy M. Nilsen, Ståle Pallesen.

References

1. Nodine PM, Matthews EE. Common sleep disorders: management strategies and pregnancy outcomes. J Midwifery Womens Health. 2013; 58(4):368–77. https://doi.org/10.1111/jmwh.12004 PMID: 23855316
2. Facco FL, Kramer J, Ho KH, et al. Sleep disturbances in pregnancy. Obstetrics and Gynecology. 2010; 115(1):77–83. https://doi.org/10.1097/AOG.0b013e3181c4f8ec PMID: 20027038
3. Abbott SM, Attarian H, Zee PC. Sleep disorders in perinatal women. Best Pract Res Clin Obstet Gynaecol. 2014; 28(1):159–68. https://doi.org/10.1016/j.bpobgyn.2013.09.003 PMID: 24144530
4. Wilson DL, Barnes M, Ellett L, et al. Decreased sleep efficiency, increased wake after sleep onset and increased cortical arousals in late pregnancy. ANZJOG. 2011; 51(1):38–46. https://doi.org/10.1111/j.1479-828X.2010.01252.x PMID: 21299507
5. Sedov ID, Cameron EE, Madigan S, Tomfohr-Madsen LM. Sleep quality during pregnancy: A meta-analysis. Sleep Med Rev. 2018; 38:168–76. https://doi.org/10.1016/j.smrv.2017.06.005 PMID: 28866020
6. Dorheim SK, Bjorvatn B, Eberhard-Gran M. Insomnia and depressive symptoms in late pregnancy: a population-based study. Behav Sleep Med. 2012; 10(3):152–66. https://doi.org/10.1080/15402002.2012.660588 PMID: 22742434
7. Pauley AM, Moore GA, Mama SK, Molenaar P, Symons Downs D. Associations between prenatal sleep and psychological health: a systematic review. J Clin Sleep Med. 2020; 16(4):619–30. https://doi.org/10.5664/jcsm.8248 PMID: 32003734
8. Reichner CA. Insomnia and sleep deficiency in pregnancy. Obstet Med. 2015; 8(4):168–71. https://doi.org/10.1177/1753495X15600572 PMID: 27512475
9. Pietikainen JT, Polo-Kantola P, Polkki P, Saarenpaa-Heikkila O, Paunio T, Paavonen EJ. Sleeping problems during pregnancy-a risk factor for postnatal depressiveness. Arch Womens Ment Health. 2019; 22(3):327–37. https://doi.org/10.1007/s00737-018-0903-5 PMID: 30121844
10. Borbely AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. Journal of sleep research. 2016; 25(2):131–43. https://doi.org/10.1111/jsr.12371 PMID: 26762182
11. Merrow M, Spoelstra K, Roenneberg T. The circadian cycle: daily rhythms from behaviour to genes. EMBO Rep. 2005; 6(10):930–5. https://doi.org/10.1038/sj.embor.7400541 PMID: 16222241
12. Buijs RM, Kalsbeek A. Hypothalamic integration of central and peripheral clocks. Nat Rev Neurosci. 2001; 2(7):521–6. https://doi.org/10.1038/35081582 PMID: 11433377
13. Brainard GC, Hanifin JP, Warfield B, Stone MK, James ME, Ayers M, et al. Short-wavelength enrichment of polychromatic light enhances human melatonin suppression potency. J Pineal Res. 2015; 58(3):352–61. https://doi.org/10.1111/jpi.12221 PMID: 25726691

14. Gallaher KGH, Slyepchenko A, Frey BN, Urstad K, Dorheim SK. The Role of Circadian Rhythms in Postpartum Sleep and Mood. Sleep Med Clin. 2018; 13(3):359–74. https://doi.org/10.1016/j.jsmc.2018.04.006 PMID: 30098753

15. Berbets AM, Barbe AM, Yuzko OM. Constant light exposure terminates pregnancy in rats with pineal gland dysfunction, low melatonin level and pro-inflammatory response. Melatonin Research. 2019; 2 (4):9–24.

16. Gronli J, Byrkjedal IK, Bjorvatn B, Nodtvedt O, Hamre B, Pallesen S. Reading from an iPad or from a book in bed: the impact on human sleep. A randomized controlled crossover trial. Sleep medicine. 2016; 21:86–92. https://doi.org/10.1016/j.sleep.2016.02.006 PMID: 27448477

17. Faulkner SM, Bee PE, Meyer N, Dijk DJ, Drake RJ. Light therapies to improve sleep in intrinsic circadian rhythm sleep disorders and neuro-psychiatric illness: A systematic review and meta-analysis. Sleep Med Rev. 2019; 46:108–23. https://doi.org/10.1016/j.smrv.2019.04.012 PMID: 31108433

18. Klerman E, Rahman SA, Robinson JN, Olcese J. Light exposure, endogenous melatonin concentrations, and contractions in late stage pregnancy. Poster. Poster Session IV ed. American Journal of Obstetrics & Gynecology2016. p. S336–S7.

19. Wada K, Nagata C, Nakamura K, Iwasa S, Shiraki M, Shimizu H. Light exposure at night, sleep duration and sex hormone levels in pregnant Japanese women. Endocr J. 2012; 59(5):393–8. https://doi.org/10.1507/endocrj.ej11-0325 PMID: 22333297

20. Argys LM, Averett SL, Yang M. Light Pollution, Sleep Deprivation, and Infant Health at Birth. In: Economics IIoL, editor. Discussion paper series. Discussion paper series ed. Initiated by Deutsche Post Foundation2018. p. 1–53. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3234226

21. Woods SM, Melville JL, Guo Y, Fan MY, Gavin A. Psychosocial stress during pregnancy. Am J Obstet Gynecol. 2010; 202(1):61 e1–7. https://doi.org/10.1016/j.ajog.2009.07.041 PMID: 19766975

22. Tegethoff M, Greene N, Olsen J, Schaffner E, Meinlschmidt G. Stress during pregnancy and offspring pediatric disease: A National Cohort Study. Environ Health Perspect. 2011; 119(11):1647–52. https://doi.org/10.1289/ehp.1003253 PMID: 21775267

23. Palagini L, Cipollone G, Masci I, Novi M, Caruso D, Kalmbach DA, et al. Stress-related sleep reactivity is associated with insomnia, psychopathology and suicidality in pregnant women: preliminary results. Sleep medicine. 2019; 56:145–50. https://doi.org/10.1016/j.sleep.2019.01.009 PMID: 30803833

24. Sanchez SE, Friedman LE, Rondon MB, Drake CL, Williams MA, Gelaye B. Association of stress-related sleep disturbance with psychiatric symptoms among pregnant women. Sleep medicine. 2020; 70:27–32. https://doi.org/10.1016/j.sleep.2020.02.007 PMID: 32193051

25. Palagini L, Gemignani A, Banti S, Manconi M, Mauri M, Riemann D. Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome. Sleep medicine. 2014; 15(8):853–9. https://doi.org/10.1016/j.sleep.2014.02.013 PMID: 24994566

26. Kinsella MT, Monk C. Impact of maternal stress, depression and anxiety on fetal neurobehavioral development. Clin Obstet Gynecol. 2009; 52(3):425–40. https://doi.org/10.1097/GRF.0b013e3181b52df1 PMID: 19661759

27. Levine TA, Alderdice FA, Grunau RE, McAuliffe FM. Prenatal stress and hemodynamics in pregnancy: a systematic review. Arch Womens Ment Health. 2016; 19(5):721–39. https://doi.org/10.1007/s00737-016-0645-1 PMID: 27329120

28. Van den Bergh BRH, Van den Heuvel MI, Lahti M, Braeken M, de Rooij SR, Entringer S, et al. Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. Neuroscience and Biobehavioral Reviews. 2017. https://doi.org/10.1016/j.neubiorev.2017.07.003 PMID: 28757456

29. Ibrahim SM, Lobel M. Conceptualization, measurement, and effects of pregnancy-specific stress: review of research using the original and revised Prenatal Distress Questionnaire. J Behav Med. 2020; 43(1):16–33. https://doi.org/10.1007/s10865-019-00068-7 PMID: 31183596

30. Henriksen RE, Thuen F. Marital Quality and Stress in Pregnancy Predict the Risk of Infectious Disease in the Offspring: The Norwegian Mother and Child Cohort Study. PLoS One. 2015; 10(9):e0137304. https://doi.org/10.1371/journal.pone.0137304 PMID: 26422017

31. Gurung RAR, Dunkel-Schetter C, Collins N, Rini C, Hobel CJ. Psychosocial predictors of prenatal anxiety. Journal of Social and Clinical Psychology. 2005; 24(4):497–519.

32. Pepping CA, Halford WK. Attachment and relationship satisfaction in expectant first-time parents: The mediating role of relationship enhancing behaviors. Journal of Research in Personality. 2012; 46:770–4.

33. Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012; 35(2):287–302. https://doi.org/10.5665/sleep.1642 PMID: 22294820

34. Pallesen S, Bjorvatn B, Nordhus IH, Sivertsen B, Hjornevik M, Morin CM. A new scale for measuring insomnia: the Bergen Insomnia Scale. Percept Mot Skills. 2008; 107(3):691–706. https://doi.org/10.2466/pms.107.3.691-706 PMID: 19235401

35. Smith MT, McCrae CS, Cheung J, Martin JL, Harrod CG, Heald JL, et al. Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. J Clin Sleep Med. 2018; 14(7):1209–30. https://doi.org/10.5664/jcsm.7228 PMID: 29991438

36. Reed DL, Sacco WP. Measuring Sleep Efficiency: What Should the Denominator Be? J Clin Sleep Med. 2016; 12(2):263–6. https://doi.org/10.5664/jcsm.5498 PMID: 26194727

37. Martin SK, Eastman CI. Sleep logs of young adults with self-selected sleep times predict the dim light melatonin onset. Chronobiology International. 2002; 19(4):695–707. https://doi.org/10.1081/cbi-120006080 PMID: 12182497

38. Philips respironics. Characterization of Light Sensor Performance for Three Models of Actiwatch 2008 [cited 2021 Mar 30]. Available from: http://www.actigraphy.respironics.com/assets/ActiwatchLightSensorPerformance-71c44d6474b549abcd85a903695855d6989fa3d8b2c5aa046bd972289f716fd8.pdf.

39. Nicassio PM, Mendlowitz DR, Fussell JJ, Petras L. The phenomenology of the pre-sleep state: The development of the pre-sleep arousal scale. Behav Res Ther. 1985; 23(3):263–71. https://doi.org/10.1016/0005-7967(85)90004-x PMID: 4004706

40. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983; 24(4):385–96. PMID: 6668417

41. Røysamb E, Vittersø J, Tambs K. The Relationship Satisfaction scale-psychometric properties. Norsk Epidemiologi. 2014; 24((1/2)):187–94.

42. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/. 2018.

43. Hashizaki M, Nakajima H, Kume K. Monitoring of Weekly Sleep Pattern Variations at Home with a Contactless Biomotion Sensor. Sensors (Basel). 2015; 15(8):18950–64. https://doi.org/10.3390/s150818950 PMID: 26247948

44. Ramirez C, Garcia A, Valdez P. Sleep disorders and sleep-wake cycle in undergraduate students attending morning and afternoon school shifts. In: Laboratory of Psychophysiology SoP, Universidad Autònoma de Nuevo Leòn, Mexico, editor. Sleep Medicine2017. p. 274–5.

45. Zhu B, Calvo RS, Wu L, Simon L, Shah K, Piano M, et al. Objective sleep in pregnant women: a comparison of actigraphy and polysomnography. Sleep Health. 2018; 4(5):390–6. https://doi.org/10.1016/j.sleh.2018.07.011 PMID: 30241652

46. Christian LM. Stress and Immune Function during Pregnancy: An Emerging Focus in Mind-Body Medicine. Curr Dir Psychol Sci. 2015; 24(1):3–9. https://doi.org/10.1177/0963721414550704 PMID: 25745279

47. Gao M, Hu J, Yang L, Ding N, Wei X, Li L, et al. Association of sleep quality during pregnancy with stress and depression: a prospective birth cohort study in China. BMC Pregnancy Childbirth. 2019; 19(1):444. https://doi.org/10.1186/s12884-019-2583-1 PMID: 31775666

48. Warlick C, Williams N, Hale L, Killgore WDS, Alfonso-Miller P. Is Relationship Satisfaction Associated with Habitual Sleep? In: University of Arizona U, editor. Abstract, Scholarly Journals ed. Sleep suppl.; Westchester2019. p. 371–2.

49. Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. Sleep Health. 2015; 1(1):40–3. https://doi.org/10.1016/j.sleh.2014.12.010 PMID: 29073412

50. Lacks P, Morin CM. Recent advances in the assessment and treatment of insomnia. J Consult Clin Psychol. 1992; 60(4):586–94. https://doi.org/10.1037//0022-006x.60.4.586 PMID: 1506506

51. Roenneberg T, Pilz LK, Zerbini G, Winnebeck EC. Chronotype and Social Jetlag: A (Self-) Critical Review. Biology (Basel). 2019; 8(3). https://doi.org/10.3390/biology8030054 PMID: 31336976

52. Sivertsen B, Vedaa O, Harvey AG, Glozier N, Pallesen S, Aaro LE, et al. Sleep patterns and insomnia in young adults: A national survey of Norwegian university students. Journal of sleep research. 2019; 28(2):e12790. https://doi.org/10.1111/jsr.12790 PMID: 30515935

53. Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemiol. 1990; 43(1):87–91. https://doi.org/10.1016/0895-4356(90)90060-3 PMID: 2319285

54. Dodou D, de Winter JCF. Social desirability is the same in offline, online, and paper surveys: A meta-analysis. Computers in Human Behavior. 2014; 36:487–95.

55. Podsakoff PM, MacKenzie SB, Lee JY, Podsakoff NP. Common method biases in behavioral research: a critical review of the literature and recommended remedies. J Appl Psychol. 2003; 88(5):879–903. https://doi.org/10.1037/0021-9010.88.5.879 PMID: 14516251

56. Quante M, Kaplan ER, Cailler M, Rueschman M, Wang R, Weng J, et al. Actigraphy-based sleep estimation in adolescents and adults: a comparison with polysomnography using two scoring algorithms. Nat Sci Sleep. 2018; 10:13–20. https://doi.org/10.2147/NSS.S151085 PMID: 29403321

57. Joyce DS, Zele AJ, Feigl B, Adhikari P. The accuracy of artificial and natural light measurements by actigraphs. Journal of sleep research. 2020; 29(5):e12963. https://doi.org/10.1111/jsr.12963 PMID: 31860938

II

PLOS ONE

RESEARCH ARTICLE

A randomized controlled trial on the effects of blue-blocking glasses compared to partial blue-blockers on sleep outcomes in the third trimester of pregnancy

Randi Liset[1]*, Janne Grønli[2], Roger E. Henriksen[3], Tone E. G. Henriksen[4], Roy M. Nilsen[3], Ståle Pallesen[1,5,6]

1 Department of Psychosocial Science, Faculty of Psychology, University of Bergen, Bergen, Norway, **2** Department of Biological and Medical Psychology, Faculty of Psychology, University of Bergen, Bergen, Norway, **3** Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen, Norway, **4** Division of Mental Health Care, Fonna Local Health Authority, Valen Hospital, Valen, Norway, **5** Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway, **6** Optentia, The Vaal Triangle Campus of The North-West University, Vanderbijlpark, South-Africa

* randi.liset@uib.no

OPEN ACCESS

Citation: Liset R, Grønli J, Henriksen RE, Henriksen TEG, Nilsen RM, Pallesen S (2022) A randomized controlled trial on the effects of blue-blocking glasses compared to partial blue-blockers on sleep outcomes in the third trimester of pregnancy. PLoS ONE 17(1): e0262799. https://doi.org/10.1371/journal.pone.0262799

Editor: Marquis S. Hawkins, University of Pittsburgh Graduate School of Public Health, UNITED STATES

Received: December 12, 2020

Accepted: December 15, 2021

Published: January 28, 2022

Data Availability Statement: All relevant data are within the paper and its Supporting information files.

Funding: Funding was provided by a PhD grant for RL, and a grant for graphical design and printing of questionnaire, all funded by Faculty of Psychology, University of Bergen, Norway. The Norwegian Competence Center for Sleep Disorders and the

Abstract

Objective

Sleep disturbances are common in pregnancy. Blocking blue light has been shown to improve sleep and may be a suitable intervention for sleep problems during pregnancy. The present study investigated the effects of blue light blocking in the evening and during nocturnal awakenings among pregnant women on primary sleep outcomes in terms of total sleep time, sleep efficiency and mid-point of sleep.

Methods

In a double-blind randomized controlled trial, 60 healthy nulliparous pregnant women in the beginning of the third trimester were included. They were randomized, using a random number generator, either to a blue-blocking glass intervention (n = 30) or to a control glass condition constituting partial blue-blocking effect (n = 30). Baseline data were recorded for one week and outcomes were recorded in the last of two intervention/control weeks. Sleep was measured by actigraphy, sleep diaries, the Bergen Insomnia Scale, the Karolinska Sleepiness Scale and the Pre-Sleep Arousal Scale.

Results

The results on the primary outcomes showed no significant mean difference between the groups at posttreatment, neither when assessed with sleep diary; total sleep time (difference = .78[min], 95%CI = -19.7, 21.3), midpoint of sleep (difference = -8.9[min], 95% CI = -23.7, 5.9), sleep efficiency (difference = -.06[%], 95%CI = -1.9, 1.8) and daytime functioning (difference = -.05[score points], 95%CI = -.33, .22), nor by actigraphy; total sleep time (difference = 13.0[min], 95%CI = -9.5, 35.5), midpoint of sleep (difference = 2.1[min], 95%CI = -11.6, 15.8) and sleep efficiency (difference = 1.7[%], 95%CI = -.4, 3.7). On the

Norwegian Association of Midwifes supported by a grant.

Competing interests: We have read the journal's policy and the authors of this manuscript have the following competing interests to report: REH and TEGH are share-holders in Chrono Chrome AS. TEGH has received speaker honorarium from H. Lundbeck AS. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

secondary outcomes, the Bergen Insomnia Scale, the Karolinska Sleepiness Scale and the Pre-Sleep Arousal Scale the blue-blocking glasses no statistically significant difference between the groups were found. Transient side-effects were reported in both groups (n = 3).

Conclusions

The use of blue-blocking glasses compared to partially blue-blocking glasses in a group of healthy pregnant participants did not show statistically significant effects on sleep outcomes. Research on the effects of blue-blocking glasses for pregnant women with sleep-problems or circadian disturbances is warranted.

Trial registration

The trial is registered at ClinicalTrials.gov (NCT03114072).

Introduction

Sleep changes occur throughout pregnancy. Pregnant women typically experience increased need for sleep in the first trimester and increased sleep disturbances during the third trimester [1]. By gestational week 40, as many as 75–98% report multiple nocturnal awakenings [2–5].

Insomnia is the most frequent sleep disorder in pregnancy reported by 62% of pregnant women, which is significantly higher than found in the general population (10–15%) [1, 6, 7]. Insomnia manifests as difficulties falling asleep, maintaining sleep, or early morning awakenings, occurring for at least three nights per week [8]. Several hormonal and mechanical influences can cause insomnia during pregnancy, including nocturia (a frequent need to rise and urinate at night), dyspnea (shortness of breath), nasal congestion, muscular aches and pelvic pains, fetal activity, leg cramps as well as reflux [1].

Sleep disturbances during pregnancy are associated with adverse pregnancy outcomes including preeclampsia, elevated serum glucose, depression, prolonged labor, cesarean birth, intrauterine growth restriction and preterm birth [1, 9, 10]. Insomnia is also a significant risk factor for development of depression during the prenatal and postpartum period, in particular if it debuts in the third trimester of pregnancy [6].

Effective treatments for sleep disturbances, which are documented as safe for use during pregnancy are currently lacking [11]. Hypnotic medications such as benzodiazepines, some antidepressants, melatonin and antihistamines are available as for the general population. However, there is a dearth of research on the effects and potential side-effects of such medications, especially for the fetus, when used during pregnancy [12]. Still, some evidence suggest that such drugs are linked with adverse neonatal outcomes [13]. Hence, medication is not a recommended first-line treatment for sleep problems during pregnancy [1, 11]. Non-pharmaceutical treatments such as sleep hygiene counselling or cognitive behavior therapy for insomnia [14] may have a treatment potential, but the evidence for a clinically significant effect on the pregnant population is scarce [1, 11, 12]. In addition, such treatments are relatively time-consuming, costly, and often not readily available. Hence, effective treatment options should be explored.

One assumingly harmless intervention would be to reduce evening and night light exposure, promoting natural mechanisms for sleep initiation and maintenance. Even though studies on acute alerting effects of artificial light exposure in the evening and night have used small sample sizes which make it difficult to draw definitive conclusions [15], light has been shown

to reduce evening and night sleepiness [15–18]. Moreover, a meta-analysis shows that evening light is associated with later bedtime and shorter sleep time [19]. Light at night can reduce the quality of sleep in terms of repeated awakenings [20], interrupting sleep [21], and reduce quality of the deep, restorative sleep [16]. Conversely, behavioural interventions for sleep problems in terms of evening light avoidance seem to have highest effectiveness [21].

Light is known to be the principal environmental factor (zeitgeber) regulating circadian rhythms [22]. Darkness allows production of melatonin, a hormone which regulates the circadian rhythm, and facilitate sleep. Non-visual effects of light are conveyed by sensitive special photoreceptors of the retina, intrinsically photoresponsive retinal ganglion cells (ipRGCs) which project to the suprachiasmatic nucleus (SCN) of the hypothalamus [22]. IpRGCs are most sensitive to the frequencies between 446 and 484 nm [23, 24]. Evening and nighttime exposure to wavelength shorter than 530 nm (blue light), suppresses the melatonin production, delay circadian rhythms and inhibit sleep [25–27].

Studies investigating the relationship between light exposure and sleep in pregnant women are limited. One study found that light exposure at night was associated with reduced sleep duration in the first and third trimester [28]. A more recent study showed that evening light exposure in pregnant women was related to shorter total sleep time and earlier midpoint of sleep as measured by actigraphy [29]. There is a dearth of knowledge regarding the burden light exposure might have on pregnant women and if blocking such light improves sleep in this population.

Artificial light-sources such as smart-phones, tablet, computers and TV often have illumination with a relative high amount of blue light and some studies have shown that such illumination increases alertness, delay onset of the deep restorative sleep stage and suppresses the melatonin production [16, 30]. Glasses that block blue light (BB-glasses) have accordingly shown to prevent alertness caused by blue-light emitting screens [31, 32].

Studies have further shown that use of BB-glasses are able to relieve sleep disturbances [33], particular with individuals with insomnia [32, 34, 35], bipolar disorder [36] and attention-deficit hyperactive disorder (ADHD) [37]. These treatment effects have further been attested to by a recent review [38].

In terms of fertile women BB-glasses may speed recovery for postpartum depression sufferers [31]. To our knowledge, no previous studies have investigated the effect of BB-glasses on sleep outcomes during pregnancy.

Blue blocking glasses have previously been shown to produce rapid effects on sleep and activation [31, 35–37], and exploring nonpharmacologic treatment of insomnia in pregnancy is warranted [11, 13].

The present study initiates new research by investigating the effects of a blue light blocking intervention in the evening and during nocturnal awakenings, in pregnant women. A low cost, safe treatment for sleep problems in pregnant women will have high public health interest, as available treatments are either hard to access or might carry risks. In the present study we investigated how two weeks use of BB-glasses affected sleep, subjectively and objectively, from pre- to posttreatment among women pregnant in the third trimester, compared to partially blue-blocking grey glasses. Also, symptoms of insomnia, evening sleepiness and evening activation were examined.

Method

Trial design

This study was a randomised double blind parallel group controlled trial, registered at ClinicalTrials.gov (NCT03114072), investigating an intervention to improve sleep in pregnant women in the third trimester.

The trial was conducted over three consecutive weeks, one baseline week followed by two intervention/control weeks.

Participants

Healthy nulliparous women, about 24 gestation weeks, were recruited between May 2017 and April 2019, during their standard health control. Recruitment was mediated by consulting midwives at antenatal-healthcare centers in the Municipality of Bergen, Norway. All participants were provided information about the study (oral and written form) by the consulting midwife. If the pregnant women consented to receive more information or participate, further information was provided by the researcher (first author). Inclusion criteria were: 1) nulliparous women, 2) expecting one child, 3) being in the third trimester of a normal pregnancy (free from obstetrical complications), 4) able to wear an actigraph during daytime and nighttime for all three weeks and, 5) able to complete questionnaires in Norwegian. Exclusion criteria were: 1) somatic or psychiatric disorders, 2) fever and other health conditions affecting sleep, 3) working nights during the study protocol or 4) having a condition affecting the translucency of the eyes To be able to exclude women with serious eye-conditions affecting the translucency of the eyes, the red reflex [39] of both eyes was assessed. The participating pregnant women started the data collection between pregnancy week 27 to 32, mean week 29+0 days. For baseline data, the participants were assessed with subjective and objective measures for 7 days.

Participant characteristics

Self-reported questions were administered to obtain information about maternal age, marital/partner status (married/cohabitating, single, separated/divorced, widow), level of education (high school and below, college and above), income (NOK$<$600 000, NOK $>$600 000; 10 NOK $\approx$ 1 US $), number of people living together in the household (partner, parents, parents in law, children, none, other), smoking (daily, less than daily, never), physical- and relaxing activity.

Interventions

The interventions comprised of BB-glasses (Uvex Skyper S1933X, by Honeywell, Smithfield, RI, USA. www.uvex.us) blocking 99% of wavelengths shorter than 530 nm, and circa 15% of the light were in the remaining visual spectrum. The control condition were light grey glasses (Uvex Skyper S1905, by Honeywell, Smithfield, RI, USA. www.uvex.us) blocking approximately 50% of wavelengths shorter than 530 nm, and 30–50% of light were keeping in the remaining visual spectrum. A partial blue-blocking control group was used as this was assumed to maintain the placebo effect also in cases of knowledge of BB-glassesParticipants in both groups were instructed to wear the glasses from three hours before normal bedtime at night, and if needed, also when going to the bathroom etc. during the night until final awakening in the morning. They were instructed to report if they could not adhere to these instructions.

The participants were informed to contact the research team if they experienced any side-effects after start wearing the glasses, and were also probed for side-effects after study completion.

Outcomes

The primary outcomes were total sleep time (TST), midpoint of sleep, sleep efficiency (SE) and daytime functioning, measured subjectively and objectively. The secondary outcomes were

subjective symptoms of insomnia (Bergen Insomnia Scale; BIS), sleepiness prior to turning the lights off (Karolinska Sleepiness Scale; KSS), and evening activation (Pre-Sleep Arousal Scale; PSAS).

Subjective measure of sleep. *A sleep diary* was completed every morning. The sleep diary included items on number and duration of naps during the day, use of sleep medication (yes/no), bedtime, lights-out time, sleep latency, number of nocturnal awakenings, wake after sleep onset (WASO), waking and rise time. Included were also items assessing sleep quality and daytime sleepiness [40]. The outcomes used in the present study were total sleep time (TST)(min), sleep efficiency (SE%) (total sleep time/time in bed *100%), midpoint of sleep (TST:2)(hh:mm) and daytime functioning (score points).

The Bergen Insomnia Scale (BIS) was administered at study initiation and at day 21, the last day of participation. Originally the time frame was last month, but this was changed to last week in order to capture the rapid change in sleep that may occur during pregnancy and also to align the BIS with the time frame for the sleep diary and actigraphy measures. The BIS consists of six items. The first four pertain to sleep onset, maintenance, early morning wakening insomnia, and not feeling restored after sleep. The last two assess level of daytime impairment due to poor sleep and dissatisfaction with sleep. Each item is rated on a scale ranging from 0 to 7 days per week, providing a composite score point ranging from 0 to 42. Cut-offs of BIS indicating insomnia are scoring 3 or above on at least one of the first four items, and scoring of 3 or above on at least one of the last two items [41]. Cronbachs alpha for the BIS was .80 at study initiation and .78 at day 21.

Karolinska Sleepiness Scale (KSS) was completed every night before bedtime. The KSS was used to assess subjective sleepiness at two hours intervals from 8pm until sleep onset, measured latest at 2 am every night, and responses are provided on a 9-point Likert scale ranging from 1 (extremely alert) to 9 (extremely sleepy–fighting sleep) [42]. The mean score across four-time points (8pm, 10pm, midnight, 2am) in the evening/night was used.

Pre-Sleep Arousal Scale (PSAS) was completed every night before bedtime. The PSAS assesses psychophysiological arousal before sleep. The scale consists of 16 items and measures somatic (e.g. heart racing, shortness of breath, stomach upset) as well as cognitive (e.g. worry about falling asleep, depressing or anxious thoughts, mentally alert) components of arousal. Responses are recorded on a five-point Likert scale ranging from 1 (not at all) to 5 (extremely), providing a composite score ranging from 16 to 80. Higher scores indicate higher states of arousal [43]. Cronbachs alpha for the PSAS scale ranged across the 14 days between .65 (day 7) to .85 (day 2).

Objective measure of sleep. *Actigraphy*. To objectively estimate sleep patterns, each participant was asked to wear a commercially available wrist actigraph (Actiwatch Spectrum; Philips Respironics Inc.) on their non-dominant wrist, continuously throughout the study period. The actigraph registered movements by a piezoelectric accelerometer and epoch length was set to thirty seconds and the sensitivity was set to medium. The participants were instructed to press the event button on the actigraph to indicate when they turned off the light and tried to sleep, and when they finally woke up in the morning. Data were converted to objective sleep parameters through the Actiware software (version 6.0.9, Philips Respironics Inc.). Rest intervals were manually set based on visual determination of raw data, by the use of motor activity, light exposure, event-markers and also supported by sleep diary data. This approach was in line with international recommendations for the use of actigraphy data in sleep research [44]. Rest interval onset was set at marked decrease in activity (<50/min), event-marker followed by a sustained decrease in activity, or marked sustained decreases in light exposure (<8 lux). Rest interval termination was set at marked sustained increase in activity (>50/min), event-marker and/or sustained increases in light exposure (>8 lux). In cases where the event button

was not pressed or where discrepancies between the sleep diary data and actigraph data were evident, duration of the sleep episode was set based on motor activity. Duration of the sleep episodes reflects time in bed minus sleep onset latency (SOL), time awake after sleep onset (WASO) and time in bed after final morning awakening [45]. Three sleep related outcome variables were derived: Total sleep time (TST)(min), sleep efficiency (SE)(%) and midpoint of sleep (hh:mm). Midpoint of sleep comprised a proxy of circadian phase [46].

Sample size

The estimated sample size was based on effect sizes reported in previous studies that have used BB-glasses as treatment for sleep-disorders. These studies showed strong effects on sleep quality in one group of healthy individuals [32] and in persons diagnosed with ADHD [37]. Because sleep problems during late pregnancy also may be caused by various hormonal and mechanical factors, we expected a medium effect size (Cohens d = 0.50) for the BB-intervention. Setting the alpha to .05 (two-tailed), power to .80, correlation between repeated assessments to .50 revealed that a minimum of 34 participants in total were needed to detect statistically significant time (pre vs. post) x group (BB vs. control condition) interaction effects [47].

Randomization and blinding

The included participants were randomized by www.randomizer.org to either intervention (BB-glasses) or control condition (grey glasses). A research assistant packed the glasses into an opaque brown paperbags. Based on unique numbers on the paper bags a randomization key not available to the researchers were made. Condition was first revealed to the first author when participants were handling in completed post-treatment questionnaires and the actigraph. All participants received the same oral and written information about the purpose of the study; testing glasses filtering different wavelengths of light on sleep and mood. They were instructed to refrain from researching the topic of light and sleep, and in case they needed to contact the research team not to describe their glasses. Participants with knowledge of BB glasses were not excluded, since both glasses eliminated some wavelengths shorter than 530 nm. This way we regarded that the placebo-effect were preserved also in the cases of some previous knowledge on effects of blue-filtering devices.

Statistical methods

Characteristics of the study participants were presented as means and standard deviations or numbers and percentages as appropriate. Participant compliance of use of glasses were tested by independent two-sample t-test. Based on cut-off points of BIS, number and percentage of participants were calculated for insomnia, and a chi square test was used to examine the changes in insomnia (worse, unchanged, improved).

A descriptive analysis of the pattern of change were calculated with mean and standard deviations of subjective measured TST, midpoint of sleep and SE for each day of the second intervention week. To examine the effect of BB-glasses on the primary outcomes TST, SE, midpoint of sleep, daytime functioning and secondary outcomes KSS and PSAS and BIS, analysis of covariance (ANCOVA) were performed by including the baseline outcome measure as a covariate in regression models. The effect estimates were calculated as difference in means with 95% confidence intervals (95% CI) between BB-glasses and control glasses. The p-values for within group change in outcomes were calculated by paired t-test. Further, effect sizes (Cohens d) for both within and between groups were calculated. Analysis was conducted on per protocol set, hence excluded participants were not included in the analysis. Participants

with mean TST <200 minutes per week were defined as outliers, and were excluded from the analysis.

All statistical analyses were performed using IBM SPSS Statistics version 25 (SPSS, Chicago, IL, USA), Stata IC version 16 (Stata Statistical Software, College Station, TX, USA) and R version 3.5.1 [48].

Ethical considerations

The Regional Committee for Medical and Health Related Ethics, in Western Norway, approved the study (2016/1394/REK vest). All participants provided written informed consent before inclusion. After completed participation, all participants were debriefed about the aim of the study, and also offered BB-glasses as a compensation.

Results

Fig 1 presents a flowchart of enrollment. In total, 125 pregnant women were assessed for eligibility. After adherence to the inclusion and exclusion criteria and following elimination of those who refused to participate, a sample of 60 pregnant women were enrolled. The sample of pregnant women were evenly assigned to the two groups (BB group n = 30, control group n = 30). The reasons for exclusion of 7 participants were: preterm birth, fire in own home, severe malaise as a side-effect of the glasses, allergic reaction to the actigraph, not capacity to participate and discomfort wearing glasses. There were no missing data for the self-reported primary and secondary outcomes, except one missing follow-up value for the BIS. Actigraphy

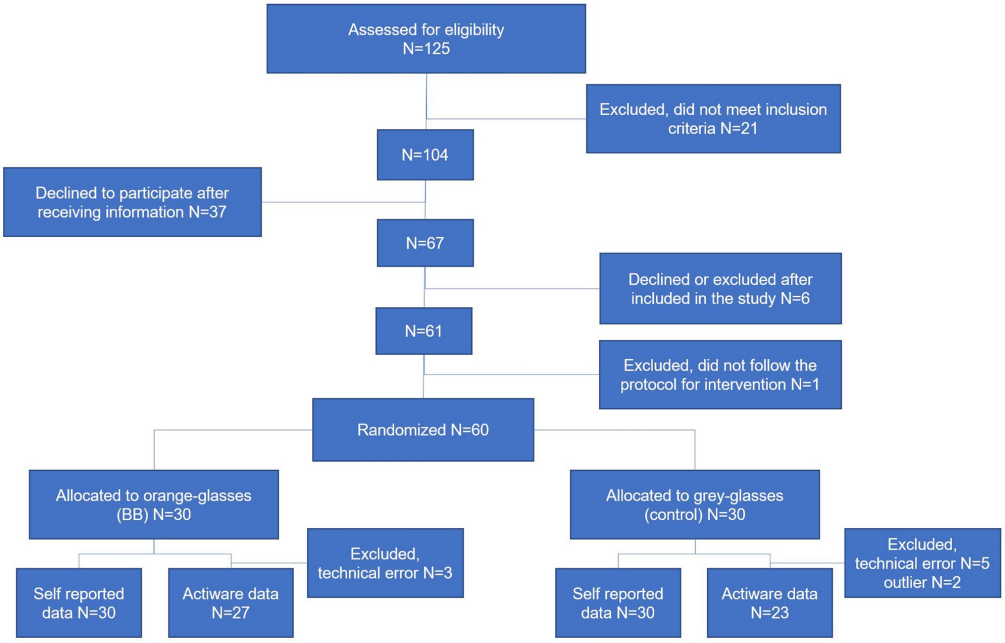


Fig 1. Flowchart of enrollment of pregnant women in the study.

https://doi.org/10.1371/journal.pone.0262799.g001

data from 8 women were excluded from the analyses because of technical errors, and data from further 2 were eliminated because of outliers. Accordingly, data from these individuals were not included in the regression analyses.

Participant characteristics for each group are presented in Table 1. The mean age for the intervention group was 30.0 (SD 3.7) years and 31.0 (SD 4.2) years for the control group; for the whole sample it was 30.5 (SD 4.0) years. In all, 96.7% of the primipara women were married or living with a partner, 83.3% had education at college level or above, 83.4% had an income of 600 000 NOK (≈ 60 000 US $) or more. Only one pregnant woman reported she was smoking. None of the pregnant women reported consumption of alcohol during the study weeks.

During the second intervention week, the glasses were on average worn for 173 min per evening (SD 28.9) in the BB-group and for 165 min (SD 45.5) in the control group. This difference was not significant (t = .81, df = 58, p = .420). About one third of the sample (N = 23)

Table 1. Demographic factors for the blue-blocking- and control-group (self-reported data).

Characteristics	Total, both groups	Blue blocking group	Control group
N	60	30	30
Age, mean (SD)	30.5 (4.0)	30.0 (3.7)	31.0 (4.2)
Marital status, N (%)			
Married/ Cohabitating	58 (96.7)	30 (100%)	28 (93.3%)
Single	2 (3.3)	0	2 (6.7%)
Education, N (%)			
< = Senior high school	10 (16.7)	6 (20%)	4 (13.3%)
College and above	50 (83.3)	24 (80%)	26 (86.7%)
Income, N (%)			
< 600 000 NOK	10 (16.7)	5 (16.7%)	5 (16.7%)
>600 000 NOK	50 (83.4)	25 (83.3%)	25 (83.3%)
Adult, total in household, N (%)			
1	2 (3.3)	0	2 (6.7%)
2	57 (95.0)	29 (96.7%)	28 (93.3%)
4	1 (1.7)	1 (3.3%)	0
Children, total in household, N (%)			
0	58 (96.7)	30 (100%)	28 (93.3%)
1	1 (1.7)	0	1 (3.3%)
3	1 (1.7)	0	1 (3.3%)
Smoking, N (%)			
Daily	1 (1.7)	1 (3.3%)	0
Not at all	59 (98.3)	29 (96.7%)	30 (100%)
Physical activity (min), mean (SD)	23.8 (33.8)	29.7 (39.0)	18.0 (26.5)
Relaxing activity (min), mean (SD)	5.9 (18.0)	7.0 (19.5)	4.8 (16.4)
Pregnancy week, mean (SD)	29.1 (1.2)	28.9 (1.1)	29.3 (1.3)
Participant compliance, use of glasses (min), mean (SD)[a]	169 (38.3)	173 (28.9)	165 (45.5)
Insomnia (BIS), N (%)			
Baseline	23 (38.3)	16 (53.3)	7 (23.3)
Week 3	29 (49.2)	14 (46.7)	15 (51.7)

Note. N = Number of participants; SD = standard deviation; NOK = Norwegian kroner; 10 NOK ≈ 1 United States dollar (US $); min = minutes.

[a]The difference were tested by unpaired t-test: t = .81, df = 58, p = .420.

Number of participants using the glasses less than instructed (180 min): ≤ 160 min = 23, ≤ 90 min = 23, 0 min = 11 (occurred once).

https://doi.org/10.1371/journal.pone.0262799.t001

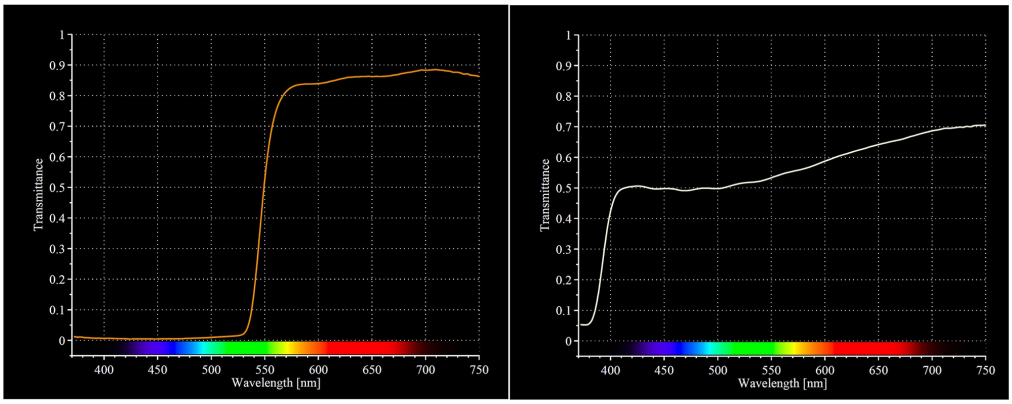


Fig 2. Irradiance spectra from intervention- and control glasses. Note the near complete filtering of blue light spectral irradiance (< 530 nm) of the BB-glasses.

https://doi.org/10.1371/journal.pone.0262799.g002

reported they wore the glasses for a shorter time than instructed (range 0–160 min). For those reporting an event of non-adherence for an entire evening, this happened only once (N = 11). The irradiance spectra for the respective glasses are illustrated in Fig 2.

At baseline, in total 38.3% scored above cut-off for insomnia compared to 49.2% posttreatment. Within the BB-group 53.3% (baseline) and 46.7% (posttreatment) scored above cut-off compared to 23.3% (baseline) and 51.7% (posttreatment) within the control group. A change in insomnia diagnosis (worse, unhanged, improved) from baseline to posttreatment was investigated, showed in Supporting information (S1 Table). A total of 6 (20%) of the pregnant women in the BB-group improved, compared to 1 (3.3%) in the control group, and 4 (13.3%) in the BB-group compared to 9 (30%) in the control group worsen. A chi square test showed these changes were not significant ($X^2 = 5.5$, df = 2, p = .064).

Only two participants reported they had some previous knowledge about the effect of BB glasses.

Table 2 displays the results of mean difference of outcome measure before and after intervention as well as from the ANCOVA analyses regarding the effects of BB-glasses and control glasses on the primary sleep outcomes variables and secondary outcomes KSS, PSAS and BIS. Within group change showed a significant decrease only for SE in actigraphy data in both groups, and an increase for the BIS score in the control group. The effect sizes were low for all outcome variables, both within and between groups. The BB-group showed for subjective TST an increase of 8 minutes and for control glasses 4 minutes. The corresponding actigraphy data showed a 5 minutes increase in the BB-group and a decrease of 35 minutes in control group. Regarding actigraphy data SE was above the suggested cut-off limit for baseline, but not at posttreatment. The control group lead to a decrease of SE from 85.5% (SD 5.5) to 79.0% (SD 16.6). The corresponding values for the BB-glass group were 85.6% (SD 5.6) and 84.9% (SD 5.7), respectively.

The analyses for self-reported data for primary sleep outcomes showed no statistically significant difference between the groups at posttreatment in terms of TST (difference .78 [min], 95%CI = -19.7, 21,3), midpoint of sleep (difference -8.9 [min], 95%CI = -23.7, 5.9), SE (difference -.06 [%], 95%CI = -1.9, 1.8) and daytime functioning (difference -.05 [score points], 95%

Table 2. Outcome at posttreatment.

Outcome	Blue blocking group		Control group		Effect size between groups [a]	Estimated mean Difference (95%CI)[b]	P value
	N	Mean (SD)	N	Mean (SD)			
Self-reported data:							
Total sleep time (min)							
Baseline	30	439.0 (38.2)	30	450.0 (54.2)			
Week 3	30	447.7 (55.7)	30	454.5 (45.5)	-.134	.78 (-19.7, 21.3)	.939
P value within groups		.314		.505			
Effect size[c]		.175		.087			
Midpoint of sleep (hh:mm)							
Baseline	30	03:55 (00:42)	30	03:51 (00:46)			
Week 3	30	03:47 (00:45)	30	03:52 (00:50)	.116	-8.9 (-23.7, 5.9)	.234
P value within groups		.196		.786			
Effect size[c]		.192		-.023			
Sleep efficiency (%)							
Baseline	30	85.6 (11.1)	30	85.8 (10.3)			
Week 3	30	86.7 (6.0)	30	87.1 (5.9)	-.067	-.06 (-1.9, 1.8)	.948
P value within groups		.070		.099			
Effect size[c]		.193		.216			
Daytime functioning (score points)							
Baseline	30	3.2 (.6)	30	3.3 (.7)			
Week 3	30	3.3 (0.7)	30	3.5 (.6)	-.307	-.05 (-.33, .22)	.703
P value within groups		.119		.198			
Effect size[c]		.152		.304			
Bergen Insomnia Scale (score points)							
Baseline	30	13.4 (8.0)	29	8.9 (6.5)			
Week 3	30	11.8 (6.8)	29	11.2 (7.8)	.082	-2.4 (-5.6, .72)	.128
P value within groups		.176		.034			
Effect size[c]		.213		-.359			
Karolinska Sleepiness Scale (score points)							
Baseline	30	5.9 (.8)	30	5.8 (.9)			
Week 3	30	5.9 (1.1)	30	5.6 (1.1)	-.273	.25 (-.15, .66)	.218
P value within groups		.751		.141			
Effect size[c]		< .001		.193			
Presleep Arousal Scale (score points)							
Baseline	30	21.9 (3.2)	30	20.7 (4.0)			
Week 3	30	21.3 (3.6)	30	20.4 (3.5)	-.253	.05 (-.95, 1.0)	.922
P value within groups		.100		.346			
Effect size[c]		.173		.078			
Actigraph data:							
Total sleep time (min)							
Baseline	27	440.8 (43.0)	23	450.9 (39.1)			
Week 3	27	445.2 (53.4)	22	415.2 (93.2)	.115	13.0 (-9.5,35.5)	.251
P value within groups		.604		.137			
Effect size[c]		.089		-.302			
Midpoint of sleep (hh:mm)							
Baseline	27	04:26 (00:25)	23	04:27 (00:32)			
Week 3	27	04:28 (00:35)	22	04:18 (00:50)	-.010	2.1 (-11.6, 15.8)	.754

(*Continued*)

Table 2. (Continued)

Outcome	Blue blocking group		Control group		Effect size between groups [a]	Estimated mean Difference (95%CI)[b]	P value
	N	Mean (SD)	N	Mean (SD)			
P value within groups		.694		.913			
Effect size[c]		-.061		.014			
Sleep efficiency (%)							
Baseline	27	85.6 (5.6)	23	85.5 (5.5)			
Week 3	27	84.9 (5.7)	22	79.0 (16.6)	.244	1.7 (-.4, 3.7)	.115
P value within groups		.049		.033			
Effect size[c]		-.124		-.342			

Note: N = Number of participants; SD = standard deviation; CI = confidence interval; min = minutes; hh:mm = hours and minutes; % = percent.

[a]Estimated with Cohens d, negative effect size indicating a negative trend at post value, or the control group are doing better than the blue blocking group.

[b] Estimated by using analysis of covariance (ANCOVA) by including the baseline outcome measure as a covariate in linear regression models.

[c]Estimated with Cohens d, by paired t-test for within group change.

https://doi.org/10.1371/journal.pone.0262799.t002

CI = -.33, .22) after using the baseline outcome measure as a covariate in regression models. Likewise, regression analyses showed no group difference in actigraphy data for the primary sleep outcomes TST (difference 13.0 [min], 95%CI = -9.5, 35.5), midpoint of sleep (difference 2.1 [min], 95%CI = -11.6, 15.8) and SE (difference 1.7 [%], 95%CI = -.4, 3.7) or for the secondary outcome measures BIS (difference -2.4 [score points], 95%CI = -5.6, .72), KSS (difference .25 [score points], 95%CI = -.15, .66) and PSAS (difference .05 [score points], 95%CI = -.95, 1.0). The pattern of daily change in subjective sleep through the last intervention week are presented in Fig 3, and shows a similar pattern, with some variation throughout the week.

There were some side-effects reported from use of both the intervention and control glasses. Reported side-effects of BB-glasses were: malaise (n = 2) restored after about 5 minutes, and headache, anxiety and depressive mood (n = 1) which lasted for 1.5 hour the first evening and 30 minutes the second evening while still wearing the glasses, and absent the third night. Side-effects reported by the control group comprised severe malaise (n = 1) in such a way that exclusion was necessary; headache (n = 1) the first evening, then restored; experienced watching double text/subtitles on the TV some evenings (n = 1).

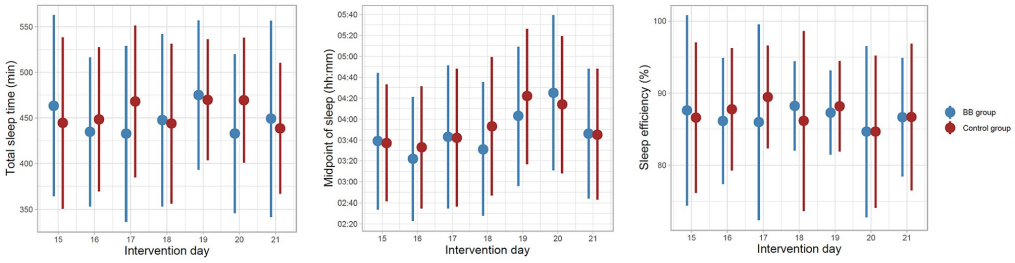


Fig 3. Daily sleep during the second intervention period (subjective data). The pattern of daily changes in total sleep time, midpoint of sleep and sleep efficiency presented with mean and standard deviation for the second intervention week.

https://doi.org/10.1371/journal.pone.0262799.g003

Discussion

The aim of the present study was to assess the effect of BB-glasses compared to partially blue-blocking grey glasses on sleep outcomes among nulliparous women in the third trimester of the pregnancy as such intervention previously never has been investigated in this population.

In terms of sleep, none of the sleep variables TST, SE, midpoint of sleep and daytime functioning showed any differential effects of BB-glasses and control glasses, neither when assessed with sleep diary nor by actigraphy. According to the score on the BIS, the KSS and the PSAS the BB-glasses did not show any statistically significant effect between the groups. The results suggested that compliance was high in both groups. Hence, lack of differential effects between conditions can probably not be attribute to lack of compliance.

Although a decrease in insomnia score for the BB-group and an increase for the control group posttreatment were shown on the BIS this was not statistically significant, even the control group improved significant within group. The change in the categorized insomnia diagnosis (worse, unchanged, improved) showed a trend toward improvement of insomnia status in the BB-group from baseline to posttreatment, whereas the opposite was the case for the control group, though not significant. At baseline the sample showed a mean total sleep time of approximately 7.5 hours based on sleep diary and actigraphy data, which were quite comparable to recommendations for total sleep time for women in the relevant age group [49]. Also, the pregnant women part taking in the intervention slept longer during baseline than a comparative group of non-pregnant women according to actigraphy data. In the weekend they tended to extend their sleep more than the non-pregnant group, hence they seemed to accumulate a sleep deficit during the week [29]. This indicate that this group of pregnant women slept overall quite well, and followed a sleep pattern which is common in working populations [50].

In the present study from pre to post-treatment the BB-group showed a small increase on TST both assessed with sleep diary and actigraphy, whereas this was only the case for TST assessed with sleep diary for the control group. Still the difference between the groups were statistically non-significant. Related to previous studies of healthy pregnant women, we would expect worsening of sleep in the third trimester compared to the two first trimesters [2–4]. This may have occurred in our sample but the women were not recruited before they were in the third trimester. However, other studies have shown a shorter average TST (range 6h 26 min-7h 19 min) [2, 3, 6, 51, 52] in the third trimester, than the present study (range 7h 25–34 min), except of the control group for actigraph data (6h 55 min). It is worth noting that the discrepancies between some of these studies and the present one in terms of TST were small (9–18 min), although the prevalence of insomnia were higher in other studies than the present [6, 52].

This study showed an earlier mean midpoint of sleep assessed with sleep diary in the BB-group and in actigraphy data for the control group, though not significant. The mean SE assessed with sleep diary was above the suggested cut-off of 85%, used as an indicator of adequate sleep quality, both at baseline and post-treatment for the BB-group and the control group. In regard of the actigraphy data SE was above the suggested cut-off at baseline, but not at posttreatment for both groups. Within group analyzes did show significance decrease in SE for both groups, although between groups neither of these findings were statistically significant. Previous studies show lower SE than our study [4]. Another study of pregnant women in Norway reported a lower SE but a small discrepancy in TST (9–18 minutes) compared to the present results [6, 52]. A possible explanation could be that our sample had shorter time in bed which typically result in higher SE. An SE above 85% indicates that this sample of pregnant women had good sleep quality. The reduction (not statistically significant) of SE in actigraphy data may reflect a decrease of sleep quality because of a further advanced pregnancy.

It could be argued that we could not expect the pregnant women in this study to improve sleep due to the intervention, as their baseline sleep overall was quite good. Still, pregnancy normally causes several physical and psychological changes, including poor sleep. Sleep deteriorates especially during the third trimester, characterized by longer sleep latency, decreased SE, longer WASO [4] and decreased TST [3] at night, compared to the two first trimesters. In previous research using BB-glasses in people with insomnia, TST has shown to be increased following use [35, 53]. It is well known that light exposure in the evening, can cause suppressed secretion of melatonin [30, 54], circadian disturbance and increased alertness [55, 56], even though some studies also report no alerting effects [15]. By blocking blue wavelengths from reaching the retina, BB-glasses prevent these such negative effects [18, 25]. Use of blue-blocking glasses (BB-glasses) in the evening allows the melatonin-production to follow the natural cycle of light and darkness, even when electric light and light-sources such as smart-phones, tablet, computers and TV are used [18]. In this regard it should be noted that the sample in the present study belongs to a group that usually uses electronic devices, also in the evening, even in bed [16, 33].

The mean score of daytime functioning and mean score of the KSS was within normal levels, which means they were neither sleepy in daytime nor alert during evenings. In addition, the low scores on the PSAS indicated low arousal in the evening right before bedtime. However, several aspects of pregnancy may increase stress, which may negatively affect sleep, especially if occurring close to bedtime. Women with stress-related sleep disturbances during pregnancy are more likely to experience insomnia [10]. In addition, pregnant women are known to be more sensitive to stressors, and elevated mood and depressive symptoms are common in pregnancy [6]. Mood changes are often associated with bidirectional alterations in sleep. It has further been shown that individuals with mood disorders seem to have elevated sensitivity to light [32]. Against this backdrop, we expected, despite relatively good sleep at baseline, that the BB-glasses would prevent negative development of sleep or even would improve sleep during the third trimester. Except for sleep efficiency, both groups did show a small improvement in sleep outcomes from pre- to posttreatment, although the between group changes were non-significant.

However, the present study cannot serve as basis for a general recommendation of BB-glasses as a sleep aid to pregnant women in general. Clinically there was a tendency for the women in the BB-group to fare better than those in the control group from baseline to posttreatment in terms of insomnia status. We suggest that effects of BB-glasses should be investigated in pregnant women with more sleep problems than in the present sample. Further, future trials should also include a control condition with no blocking of blue light.

The observed side effects (malaise, headache, lowered mood and anxiety) were transient, and equally represented in both groups (n = 3) except for severe malaise reported by one participant in the control-group causing drop-out. The frequency of side-effects is similar to that reported by Henriksen [57], while other studies have reported no adverse effects [32]. Our findings is in line with the previous conclusions from the literature that BB-glasses is a safe intervention when used in the evening and night [34, 38, 57]. It is of note that the side effects in five of the six cases disappeared during continued use, a notion that is of practical clinical value.

Limitations and strength

The sample in this study reported good sleep overall, with 53.3% in the BB group and 23.3% in the control group fulfilling the criteria of insomnia at baseline. Thus, it is reasonable to assume that the presents sample may not be representative of pregnant women in general, and

therefore limits the generalizability and the target validity of the present findings. Target validity might be limited in the present study [58], as only 38.3% of total sample initially fulfilled the criteria for insomnia. Another limitation of the present study concerns the relatively low number of subjects, making the study susceptible to type II errors. Still, a priori power analysis was calculated based on a previous study of sleep quality [32], and also based on persons diagnosed with ADHD [37]. Even so, several studies with a lower number of participants have shown positive effects of BB-glasses on sleep outcomes [32, 33, 35–37], which may be due to chance, although significant effects were reported. A common factor for these studies however was that the subjects reported strong symptoms of sleep-problems [38]. Also, replication based on a larger sample and with subjects fulfilling criteria for insomnia should also be conducted.

The sample of pregnant women in this study seems healthier than reported in previous studies of pregnant women in terms of sleep [1, 6]. It should also be noted that a vast majority of the participants were married or cohabitating, as well as had higher education and income than the general population, which might is a protective factor for poor sleep the link between insomnia and low socioeconomic status is demonstrated [59].

The present study is partly based on self-report data which may lead to recall bias [60], social desirability bias [61] and some common method bias [62]. Still, the randomization processes would prevent such biases to influence the results. Although actigraphy has shown low specificity in many studies [63], it has still shown to be sufficiently sensitive to detect changes in sleep duration in several studies [44]. A strength of the present study is the combination of subjective and objective sleep assessment, and an observation of a full week with baseline data and treatment effect data.

The control glasses used in the present study blocked 50% of blue wavelengths, which may also have provided some effect on the human melanopsin system. In order to take measures to counteract personal knowledge about blue light-filtering glasses among study participants, we considered that the control glasses should also have some blue-blocking filtering effect, and this way strengthen blinding of the participants. Two participants reported they had some previous knowledge about the effect of BB glasses. Future studies on effects of BB-glasses should avoid or keep to a minimum the reduction of melanopic lux yielded by the control condition.

Conclusions

In this study of 60 healthy Norwegian pregnant women in the beginning of the third trimester the participants had overall well-preserved sleep. The use of BB-glasses compared to grey partially blue-blocking glasses did not show a statistically significant difference in sleep outcomes between the groups, neither assessed by self-report or actigraphy. Side effects were low-frequent and mostly transient.

Supporting information

S1 Table. Changes in insomnia diagnosis from baseline to posttreatment (self-reported data).
(DOCX)

S1 Checklist. CONSORT 2010 checklist of information to include when reporting a randomised trial*.
(DOC)

S1 Protocol. Nightly light exposure in pregnancy: Blue-blocking glasses as an intervention to ease sleep disturbances and to improve mood.
(DOCX)

S1 Dataset. Table 1, supporting table and Fig 3.
(XLSX)

S2 Dataset. Table 2.
(XLSX)

Acknowledgments

We are grateful to all the participating pregnant women who took part in study, as well as the consulting midwifes at antenatal-healthcare centers in the Municipality of Bergen, Norway, for recruiting participants. We are also thankful to Børge Hamre for testing and measurement of the irradiance spectra from the intervention- and control glasses, and thanks to Erlend Sunde for assisting in randomization and blinding of the participants.

Author Contributions

Conceptualization: Randi Liset, Janne Grønli, Roger E. Henriksen, Tone E. G. Henriksen, Ståle Pallesen.

Data curation: Randi Liset, Janne Grønli, Ståle Pallesen.

Formal analysis: Randi Liset, Roy M. Nilsen.

Investigation: Randi Liset.

Methodology: Randi Liset, Janne Grønli, Roger E. Henriksen, Tone E. G. Henriksen, Roy M. Nilsen, Ståle Pallesen.

Project administration: Randi Liset.

Supervision: Janne Grønli, Roger E. Henriksen, Tone E. G. Henriksen, Ståle Pallesen.

Writing – original draft: Randi Liset.

Writing – review & editing: Janne Grønli, Roger E. Henriksen, Tone E. G. Henriksen, Roy M. Nilsen, Ståle Pallesen.

References

1. Nodine PM, Matthews EE. Common sleep disorders: management strategies and pregnancy outcomes. J Midwifery Womens Health. 2013; 58(4):368–77. https://doi.org/10.1111/jmwh.12004 PMID: 23855316
2. Abbott SM, Attarian H, Zee PC. Sleep disorders in perinatal women. Best Pract Res Clin Obstet Gynaecol. 2014; 28(1):159–68. https://doi.org/10.1016/j.bpobgyn.2013.09.003 PMID: 24144530
3. Facco FL, Kramer J, Ho KH, et al. Sleep disturbances in pregnancy. Obstetrics and Gynecology. 2010; 115(1):77–83. https://doi.org/10.1097/AOG.0b013e3181c4f8ec PMID: 20027038
4. Wilson DL, Barnes M, Ellett L, et al. Decreased sleep efficiency, increased wake after sleep onset and increased cortical arousals in late pregnancy. ANZJOG. 2011; 51(1):38–46. https://doi.org/10.1111/j.1479-828X.2010.01252.x PMID: 21299507
5. Sedov ID, Cameron EE, Madigan S, Tomfohr-Madsen LM. Sleep quality during pregnancy: A meta-analysis. Sleep Med Rev. 2018; 38:168–76. https://doi.org/10.1016/j.smrv.2017.06.005 PMID: 28866020
6. Dorheim SK, Bjorvatn B, Eberhard-Gran M. Insomnia and depressive symptoms in late pregnancy: a population-based study. Behav Sleep Med. 2012; 10(3):152–66. https://doi.org/10.1080/15402002.2012.660588 PMID: 22742434
7. Sedov ID, Anderson NJ, Dhillon AK, Tomfohr-Madsen LM. Insomnia symptoms during pregnancy: A meta-analysis. Journal of sleep research. 2021; 30(1):e13207. https://doi.org/10.1111/jsr.13207 PMID: 33140514

8. American Academy of Sleep Medicine. International Classification of Sleep Disorders. In: Medicine AAoS, editor. Third Edition (ICSD-3) ed. Chicago: Third Edition (ICSD-3); 2014.
9. Ding XX, Wu YL, Xu SJ, Zhang SF, Jia XM, Zhu RP, et al. A systematic review and quantitative assessment of sleep-disordered breathing during pregnancy and perinatal outcomes. Sleep Breath. 2014; 18 (4):703–13. https://doi.org/10.1007/s11325-014-0946-4 PMID: 24519711
10. Palagini L, Gemignani A, Banti S, Manconi M, Mauri M, Riemann D. Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome. Sleep medicine. 2014; 15(8):853–9. https://doi.org/10.1016/j.sleep.2014.02.013 PMID: 24994566
11. Bacaro V, Benz F, Pappaccogli A, De Bartolo P, Johann AF, Palagini L, et al. Interventions for sleep problems during pregnancy: A systematic review. Sleep Med Rev. 2020; 50:101234. https://doi.org/10.1016/j.smrv.2019.101234 PMID: 31801099
12. Okun ML, Ebert R, Saini B. A review of sleep-promoting medications used in pregnancy. Am J Obstet Gynecol. 2015; 212(4):428–41. https://doi.org/10.1016/j.ajog.2014.10.1106 PMID: 25448509
13. Reichner CA. Insomnia and sleep deficiency in pregnancy. Obstet Med. 2015; 8(4):168–71. https://doi.org/10.1177/1753495X15600572 PMID: 27512475
14. Manber R, Bei B, Simpson N, Asarnow L, Rangel E, Sit A, et al. Cognitive Behavioral Therapy for Prenatal Insomnia: A Randomized Controlled Trial. Obstet Gynecol. 2019; 133(5):911–9. https://doi.org/10.1097/AOG.0000000000003216 PMID: 30969203
15. Souman JL, Tinga AM, Te Pas SF, van Ee R, Vlaskamp BNS. Acute alerting effects of light: A systematic literature review. Behav Brain Res. 2018; 337:228–39. https://doi.org/10.1016/j.bbr.2017.09.016 PMID: 28912014
16. Gronli J, Byrkjedal IK, Bjorvatn B, Nodtvedt O, Hamre B, Pallesen S. Reading from an iPad or from a book in bed: the impact on human sleep. A randomized controlled crossover trial. Sleep medicine. 2016; 21:86–92. https://doi.org/10.1016/j.sleep.2016.02.006 PMID: 27448477
17. Sasseville A, Martin JS, Houle J, Hebert M. Investigating the contribution of short wavelengths in the alerting effect of bright light. Physiol Behav. 2015; 151:81–7. https://doi.org/10.1016/j.physbeh.2015.06.028 PMID: 26122037
18. van der Lely S, Frey S, Garbazza C, Wirz-Justice A, Jenni OG, Steiner R, et al. Blue blocker glasses as a countermeasure for alerting effects of evening light-emitting diode screen exposure in male teenagers. J Adolesc Health. 2015; 56(1):113–9. https://doi.org/10.1016/j.jadohealth.2014.08.002 PMID: 25287985
19. Bartel KA, Gradisar M, Williamson P. Protective and risk factors for adolescent sleep: a meta-analytic review. Sleep Med Rev. 2015; 21:72–85. https://doi.org/10.1016/j.smrv.2014.08.002 PMID: 25444442
20. Esaki Y, Kitajima T, Obayashi K, Saeki K, Fujita K, Iwata N. Light exposure at night and sleep quality in bipolar disorder: The APPLE cohort study. J Affect Disord. 2019; 257:314–20. https://doi.org/10.1016/j.jad.2019.07.031 PMID: 31302520
21. Faulkner SM, Bee PE, Meyer N, Dijk DJ, Drake RJ. Light therapies to improve sleep in intrinsic circadian rhythm sleep disorders and neuro-psychiatric illness: A systematic review and meta-analysis. Sleep Med Rev. 2019; 46:108–23. https://doi.org/10.1016/j.smrv.2019.04.012 PMID: 31108433
22. Buijs RM, Kalsbeek A. Hypothalamic integration of central and peripheral clocks. Nat Rev Neurosci. 2001; 2(7):521–6. https://doi.org/10.1038/35081582 PMID: 11433377
23. Berson DM. Phototransduction in ganglion-cell photoreceptors. Pflugers Arch. 2007; 454(5):849–55. https://doi.org/10.1007/s00424-007-0242-2 PMID: 17351786
24. Brainard GC, Hanifin JP, Greeson JM, Byrne B, Glickman G, Gerner E, et al. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. J Neurosci. 2001; 21 (16):6405–12. https://doi.org/10.1523/JNEUROSCI.21-16-06405.2001 PMID: 11487664
25. Sasseville A, Paquet N, Sevigny J, Hebert M. Blue blocker glasses impede the capacity of bright light to suppress melatonin production.(Author abstract). Journal of Pineal Research. 2006; 41:73–8. https://doi.org/10.1111/j.1600-079X.2006.00332.x PMID: 16842544
26. Kayumov L, Casper RF, Hawa RJ, Perelman B, Chung SA, Sokalsky S, et al. Blocking low-wavelength light prevents nocturnal melatonin suppression with no adverse effect on performance during simulated shift work. J Clin Endocrinol Metab. 2005; 90(5):2755–61. https://doi.org/10.1210/jc.2004-2062 PMID: 15713707
27. van de Werken M, Gimenez MC, de Vries B, Beersma DG, Gordijn MC. Short-wavelength attenuated polychromatic white light during work at night: limited melatonin suppression without substantial decline of alertness. Chronobiol Int. 2013; 30(7):843–54. https://doi.org/10.3109/07420528.2013.773440 PMID: 23705821

28. Wada K, Nagata C, Nakamura K, Iwasa S, Shiraki M, Shimizu H. Light exposure at night, sleep duration and sex hormone levels in pregnant Japanese women. Endocr J. 2012; 59(5):393–8. https://doi.org/10.1507/endocrj.ej11-0325 PMID: 22333297

29. Liset R, Gronli J, Henriksen RE, Henriksen TEG, Nilsen RM, Pallesen S. Sleep, evening light exposure and perceived stress in healthy nulliparous women in the third trimester of pregnancy. Plos One. 2021; 16(6):e0252285. https://doi.org/10.1371/journal.pone.0252285 PMID: 34081723

30. Figueiro MG, Wood B, Plitnick B, Rea MS. The impact of light from computer monitors on melatonin levels in college students. Neuro Endocrinol Lett. 2011; 32(2):158–63. PMID: 21552190

31. Bennett S, Alpert M, Kubulins V, Hansler RL. Use of modified spectacles and light bulbs to block blue light at night may prevent postpartum depression. Med Hypotheses. 2009; 73(2):251–3. https://doi.org/10.1016/j.mehy.2009.01.049 PMID: 19329259

32. Burkhart K, Phelps JR. Amber lenses to block blue light and improve sleep: a randomized trial. Chronobiol Int. 2009; 26(8):1602–12. https://doi.org/10.3109/07420520903523719 PMID: 20030543

33. Ayaki M, Hattori A, Maruyama Y, Nakano M, Yoshimura M, Kitazawa M, et al. Protective effect of blue-light shield eyewear for adults against light pollution from self-luminous devices used at night. Chronobiol Int. 2016; 33(1):134–9. https://doi.org/10.3109/07420528.2015.1119158 PMID: 26730983

34. Esaki Y, Kitajima T, Takeuchi I, Tsuboi S, Furukawa O, Moriwaki M, et al. Effect of blue-blocking glasses in major depressive disorder with sleep onset insomnia: A randomized, double-blind, placebo-controlled study. Chronobiol Int. 2017; 34(6):753–61. https://doi.org/10.1080/07420528.2017.1318893 PMID: 28488943

35. Shechter A, Kim EW, St-Onge MP, Westwood AJ. Blocking nocturnal blue light for insomnia: A randomized controlled trial. J Psychiatr Res. 2018; 96:196–202. https://doi.org/10.1016/j.jpsychires.2017.10.015 PMID: 29101797

36. Henriksen TEG, Gronli J, Assmus J, Fasmer OB, Schoeyen H, Leskauskaite I, et al. Blue-blocking glasses as additive treatment for mania: Effects on actigraphy-derived sleep parameters. Journal of sleep research. 2020; 29(5):e12984. https://doi.org/10.1111/jsr.12984 PMID: 31967375

37. Fargason R, Preston T, Hammond E, May R, Gamble K. Treatment of attention deficit hyperactivity disorder insomnia with blue wavelength light-blocking glasses. ChronoPhysiology and Therapy. 2013; 3:1–8.

38. Shechter A, Quispe KA, Barbecho JSM, Slater C, Falzon L. Interventions to reduce short-wavelength ("blue") light exposure at night and their effects on sleep: A systematic review and meta-analysis. Sleep Advances. 2020:1–13.

39. McLaughlin C, Levin AV. The red reflex. Pediatr Emerg Care. 2006; 22(2):137–40. https://doi.org/10.1097/01.pec.0000199567.87134.81 PMID: 16481935

40. Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, et al. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep. 2012; 35(2):287–302. https://doi.org/10.5665/sleep.1642 PMID: 22294820

41. Pallesen S, Bjorvatn B, Nordhus IH, Sivertsen B, Hjornevik M, Morin CM. A new scale for measuring insomnia: the Bergen Insomnia Scale. Percept Mot Skills. 2008; 107(3):691–706. https://doi.org/10.2466/pms.107.3.691-706 PMID: 19235401

42. Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. Int J Neurosci. 1990; 52(1–2):29–37. https://doi.org/10.3109/00207459008994241 PMID: 2265922

43. Nicassio PM, Mendlowitz DR, Fussell JJ, Petras L. The phenomenology of the pre-sleep state: The development of the pre-sleep arousal scale. Behav Res Ther. 1985; 23(3):263–71. https://doi.org/10.1016/0005-7967(85)90004-x PMID: 4004706

44. Smith MT, McCrae CS, Cheung J, Martin JL, Harrod CG, Heald JL, et al. Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. J Clin Sleep Med. 2018; 14(7):1209–30. https://doi.org/10.5664/jcsm.7228 PMID: 29991438

45. Reed DL, Sacco WP. Measuring Sleep Efficiency: What Should the Denominator Be? J Clin Sleep Med. 2016; 12(2):263–6. https://doi.org/10.5664/jcsm.5498 PMID: 26194727

46. Martin SK, Eastman CI. Sleep logs of young adults with self-selected sleep times predict the dim light melatonin onset. Chronobiology International. 2002; 19(4):695–707. https://doi.org/10.1081/cbi-120006080 PMID: 12182497

47. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007; 39(2):175–91. https://doi.org/10.3758/bf03193146 PMID: 17695343

48. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/. 2018.

49. Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. Sleep Health. 2015; 1(1): 40–3. https://doi.org/10.1016/j.sleh.2014.12.010 PMID: 29073412

50. Hashizaki M, Nakajima H, Kume K. Monitoring of Weekly Sleep Pattern Variations at Home with a Contactless Biomotion Sensor. Sensors (Basel). 2015; 15(8):18950–64. https://doi.org/10.3390/s150818950 PMID: 26247948

51. Tsai SY, Lin JW, Kuo LT, Thomas KA. Daily sleep and fatigue characteristics in nulliparous women during the third trimester of pregnancy. Sleep. 2012; 35(2):257–62. https://doi.org/10.5665/sleep.1634 PMID: 22294816

52. Sivertsen B, Hysing M, Dorheim SK, Eberhard-Gran M. Trajectories of maternal sleep problems before and after childbirth: a longitudinal population-based study. BMC Pregnancy Childbirth. 2015; 15:129. https://doi.org/10.1186/s12884-015-0577-1 PMID: 26031504

53. Janku K, Smotek M, Farkova E, Koprivova J. Block the light and sleep well: Evening blue light filtration as a part of cognitive behavioral therapy for insomnia. Chronobiol Int. 2020; 37(2):248–59. https://doi.org/10.1080/07420528.2019.1692859 PMID: 31752544

54. Brainard GC, Hanifin JP, Warfield B, Stone MK, James ME, Ayers M, et al. Short-wavelength enrichment of polychromatic light enhances human melatonin suppression potency. J Pineal Res. 2015; 58(3):352–61. https://doi.org/10.1111/jpi.12221 PMID: 25726691

55. Cajochen C, Frey S, Anders D, Spati J, Bues M, Pross A, et al. Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. J Appl Physiol (1985). 2011; 110(5):1432–8. https://doi.org/10.1152/japplphysiol.00165.2011 PMID: 21415172

56. Chang AM, Aeschbach D, Duffy JF, Czeisler CA. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. Proc Natl Acad Sci U S A. 2015; 112(4): 1232–7. https://doi.org/10.1073/pnas.1418490112 PMID: 25535358

57. Henriksen TE, Skrede S, Fasmer OB, Schoeyen H, Leskauskaite I, Bjorke-Bertheussen J, et al. Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial. Bipolar Disord. 2016; 18(3):221–32. https://doi.org/10.1111/bdi.12390 PMID: 27226262

58. Westreich D, Edwards JK, Lesko CR, Cole SR, Stuart EA. Target Validity and the Hierarchy of Study Designs. Am J Epidemiol. 2019; 188(2):438–43. https://doi.org/10.1093/aje/kwy228 PMID: 30299451

59. Pallesen S, Sivertsen B, Nordhus IH, Bjorvatn B. A 10-year trend of insomnia prevalence in the adult Norwegian population. Sleep medicine. 2014; 15(2):173–9. https://doi.org/10.1016/j.sleep.2013.10.009 PMID: 24382513

60. Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemiol. 1990; 43(1):87–91. https://doi.org/10.1016/0895-4356(90)90060-3 PMID: 2319285

61. Dodou D, de Winter JCF. Social desirability is the same in offline, online, and paper surveys: A meta-analysis. Computers in Human Behavior. 2014; 36:487–95.

62. Podsakoff PM, MacKenzie SB, Lee JY, Podsakoff NP. Common method biases in behavioral research: a critical review of the literature and recommended remedies. J Appl Psychol. 2003; 88(5):879–903. https://doi.org/10.1037/0021-9010.88.5.879 PMID: 14516251

63. Quante M, Kaplan ER, Cailler M, Rueschman M, Wang R, Weng J, et al. Actigraphy-based sleep estimation in adolescents and adults: a comparison with polysomnography using two scoring algorithms. Nat Sci Sleep. 2018; 10:13–20. https://doi.org/10.2147/NSS.S151085 PMID: 29403321

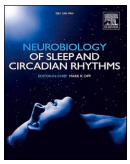
III

Neurobiology of Sleep and Circadian Rhythms 12 (2022) 100074

Contents lists available at ScienceDirect

Neurobiology of Sleep and Circadian Rhythms

journal homepage: www.elsevier.com/locate/



A randomized controlled trial on the effect of blue-blocking glasses compared to partial blue-blockers on melatonin profile among nulliparous women in third trimester of the pregnancy

Randi Liset [a,*], Janne Grønli [b], Roger Ekeberg Henriksen [c], Tone Elise Gjøtterud Henriksen [d], Roy Miodini Nilsen [c], Ståle Pallesen [a,e,f]

[a] Department of Psychosocial Science, Faculty of Psychology, University of Bergen, Bergen, Norway
[b] Department of Biological and Medical Psychology, Faculty of Psychology, University of Bergen, Bergen, Norway
[c] Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen, Norway
[d] Valen Hospital, Division of Mental Health Care, Fonna Local Health Authority, Valen, Norway
[e] Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway
[f] Optentia, The Vaal Triangle Campus of the North-West University, Vanderbijlpark, South Africa

ARTICLE INFO

Keywords:
Blue light
Blue blocking glasses
Melatonin
Sleep
Pregnancy
RCT

ABSTRACT

Objective: In pregnancy melatonin regulates circadian rhythms, induce sleep, and has a neuroprotective positive effect on fetal development. Artificial blue light in the evening delays and suppresses melatonin production. Thus, we investigated the effect of blocking blue light on the melatonin profile.

Methods: A randomized controlled trial (n=30 blue-blocking glasses vs. n=30 control glasses with partial blue-blocking effect) including healthy nulliparous pregnant women in the beginning of the third trimester. Salivary melatonin and subjective sleep were measured before and after two weeks of intervention/control condition. Saliva was sampled at 30-min intervals from 3 h before normal bedtime. Melatonin onset was set at 4.0 pg/ml.

Results: Due to missing data melatonin onset was estimated for 47 participants. At posttreatment, melatonin onset advanced by 28 min in the blue-blocking group compared with the control condition (p=.019). Melatonin levels were significantly higher, favoring the blue-blocking glass condition, at clock time 20:00, 21:00 and 22:00 h, and for sample number 3 and 4. The phase angle (time interval) between melatonin onset and sleep bedtime and sleep onset time increased within the blue blocking group (+45 min and +41 min, respectively), but did not reach statistical significance compared to control condition (+13 min and +26 min, respectively).

Conclusion: Blocking blue light in the evening had a positive effect on the circadian system with an earlier onset and rise of melatonin levels in healthy nulliparous pregnant women. This demonstrated the effectiveness and feasibility of a simple non-pharmacological chronobiological intervention during pregnancy.

1. Introduction

Melatonin is a hormone, mainly produced by the pineal gland and has various important biological functions (Tamura et al., 2008). Melatonin acts as a regulator of circadian rhythms, sleep inducer, endocrine modulator, direct free radical scavenger and as a potent anti-inflammatory and antioxidant factor (Lanoix et al., 2008, 2012; Laste et al., 2021; Tamura et al., 2008).

The pineal melatonin production is mainly regulated by the dark-light cycle (Macchi and Bruce, 2004). Melatonin secretions start to rise soon after the onset of darkness, reach maximum levels in the middle of the night and falls before wake-up time (Czeisler and Buxton, 2017). This pattern is normally very stable, making the melatonin profile a reliable phase marker of the circadian rhythm as the main circadian pacemaker, the suprachiasmatic nucleus (SCN), expresses melatonin receptors peaking at the subjective night (Macchi and Bruce, 2004; Masana et al., 2000).

During pregnancy, the night-time melatonin levels increases in the maternal blood after 24 weeks of gestation (Nakamura et al., 2001) and reaches a peak at term (Lanoix et al., 2012). Melatonin crosses all physiological barriers, including blood-brain barrier and placenta

* Corresponding author.
E-mail address: randi.liset@uib.no (R. Liset).

https://doi.org/10.1016/j.nbscr.2021.100074
Received 21 October 2021; Received in revised form 20 December 2021; Accepted 21 December 2021
Available online 29 December 2021

Abbreviations

ipRGCs	intrincically photo responsive retinal ganglion cells
BB-glasses	blue-blocking glasses
WASO	wake after sleep onset
ANCOVA	analysis of covariance
CI	confidence intervals
DLMO	dim light melatonin onset

(Reiter et al., 2000). Placenta expresses melatonin receptors, indicating that melatonin is involved in the placental function (Lanoix et al., 2008).

Melatonin has beneficial roles in placental and fetal functions and are essential for successful pregnancy (Lanoix et al., 2012; Shimada et al., 2016). In line with melatonin's important biological functions, a diminished maternal plasma and/or saliva melatonin levels are found in complicated pregnancies with preeclampsia (Dou et al., 2019; Lanoix et al., 2012; Shimada et al., 2016) and gestational diabetes mellitus (Laste et al., 2021; Shimada et al., 2016) compared with normal pregnancies. The exchange of melatonin between maternal and fetal circulation is unrestricted, and this circulation provides photoperiodic information to the fetus (Tamura et al., 2008).

Sleep is regulated by circadian rhythms and time spent awake. Hence, disturbances in circadian rhythms often result in disturbed sleep and wakefulness (American Academy of Sleep Medicine, 2014). In this realm, melatonin plays a pivotal role as the hormone transmits information to maintain biorhythms, such as sleep-wake rhythms (Czeisler and Buxton, 2017). Insomnia and other sleep disturbances during pregnancy can affect the perinatal outcomes, and studies indicate that poor sleep increases the risk of preeclampsia, gestational diabetes, perinatal depression, prolonged labor, cesarean birth, intrauterine growth restriction and preterm birth (Ding et al., 2014; Nodine and Matthews, 2013; Palagini et al., 2014).

How well you sleep and how entrained the circadian rhythms are, is closely linked to light exposure. Non-visual effects of light are conveyed by special photoreceptors of the retina, melanopsin-containing intrincically photo responsive retinal ganglion cells (ipRGCs), which via the retinohypothalamic tract, project to the SCN (Buijs and Kalsbeek, 2001). IpRGCs are highly sensitive to a relatively narrow band of wavelengths, specifically to the frequencies between 446 and 484 nm: blue light (Berson, 2007; Brainard et al., 2001). The SCN projects further to the pineal gland, which secrets melatonin (Brainard et al., 2015). Light exposure has an acute suppressive and dose-dependent effect on nocturnal melatonin production (Kayumov et al., 2005; Sasseville et al., 2006; van de Werken et al., 2013). The ipRGC cells also signal both directly and indirectly to brain areas known for its role in regulation arousal and sleep (LeGates et al., 2014). Consequently, artificial light-sources such as smart-phones, computers, tablets and TV with a relative high proportion of blue light illumination, are shown to suppress the melatonin production, increase alertness and delay bedtime (Figueiro et al., 2011; Gronli et al., 2016).

Knowledge of how blue light impact melatonin production in pregnant women has implications for our understanding of the circadian system in pregnancy, as well as clinical relevance. Use of blue-blocking glasses (BB-glasses) in the evening allows the melatonin-production more strongly to follow the natural cycle of light and darkness, even when electric light and light-sources such as smart-phones, computers, tablets and TVs are used (van der Lely et al., 2015). Some studies have already shown that interventions involving blocking the blue light protect endogenous melatonin production from light-suppression at night (Figueiro and Overington, 2016; Sasseville et al., 2006; van der Lely et al., 2015; Zerbini et al., 2020).

Only a few studies have investigated the relationship between light exposure and sleep in pregnant women. One study found that light exposure at night was associated with reduced sleep duration in the first and third trimester (Wada et al., 2012). A more recent study showed that evening light exposure in pregnant women was related to shorter total sleep time and earlier midpoint of sleep as measured by actigraphy (Liset et al., 2021). Early morning bright light therapy for pregnant women with depression, has been found to phase advance the melatonin rhythm (Epperson et al., 2004). A study of healthy night workers in the third trimester of pregnancy showed lower night-time melatonin production in their natural environment, compared to day workers (Nehme et al., 2019). Among night workers an increase in advanced pregnancy and negative offspring outcomes may be related to light-induced suppression of melatonin during night work (Nehme et al., 2019).

Clinical studies on effects of BB-glasses during pregnancy are scarce. One study indicated that BB-glasses may speed recovery from postpartum depression sufferers (Bennett et al., 2009). However, in a previous study, we did not find an effect of BB-glasses on sleep-parameters of healthy nulliparous women (unpublished results). To the best of our knowledge, no study has previously investigated the effect of BB-glasses on melatonin onset, the melatonin profile and the phase angle between melatonin secretion and sleep variables during pregnancy.

Accordingly, the primary objective of the present study was to investigate the effect of blocking blue light in the evening on melatonin onset. The secondary objective was to describe the effect on melatonin profile for clock time and sample number, as well as to investigate the effects on the phase angle (the time interval from a phase marker of the master circadian clock and until another circadian driven event occurs), here assessed by the melatonin onset and bedtime and sleep onset time. We hypothesized that blocking of blue light would result in advancement of melatonin onset. Any effect on the phase angle between melatonin onset and bedtime and sleep onset time was examined.

2. Method

2.1. Trial design

This study was part of a double blinded randomized placebo-controlled trial, registered at ClinicalTrials.gov (NCT03114072). The trial investigated an intervention to improve sleep, and mood and to increase evening melatonin secretion in pregnant women in the third trimester. In the current study melatonin was sampled from saliva.

The trial was conducted over three consecutive weeks, one baseline week followed by two intervention/control weeks.

2.2. Participants

Participants were healthy nulliparous women, recruited between May 2017 and April 2019, during their standard health control (checkup) about 24 gestation weeks. Consulting midwives at antenatal-healthcare centers in the Municipality of Bergen, Norway, mediated the recruitment and provided information about the study (oral and written form) to the relevant participants. If the pregnant women consented to receive more information or participate, further information was provided by the researcher (first author). Inclusion criteria were: 1) nulliparous women, 2) expecting one child, 3) being in the third trimester of a normal pregnancy, 4) able to wear an actigraph during daytime and nighttime for all three weeks (results reported in another paper) and, 5) able to complete questionnaires in Norwegian (results reported in another paper). We recruited nulliparous pregnant women exclusively in order to minimize the risk of their sleep being disturbed by older offspring and to ensure that the participants represented a relatively homogenous group. Exclusion criteria were: 1) somatic or psychiatric disorders, 2) fever and other health conditions affecting sleep, 3) working nights during the study protocol 4) having a condition affecting the translucency of the eyes or 5) melatonin concentrations out of range (either all vaues below 3.0 pg/mL or above 4 pg/mL. The red reflex of both eyes was assessed (McLaughlin and Levin, 2006) to be able

to exclude women with serious eye-conditions affecting translucency. The participating pregnant women started the data collection between pregnancy week 27–32, mean week 29+0 days.

Self-reported questions were used to obtain information about maternal age, marital/partner status (married/cohabitating, single, separated/divorced, widow), level of education (high school and below, college and above), income (NOK<600 000, NOK >600 000; 10 NOK ≈ 1 US $), number of people living together in the household (partner, parents, parents in law, children, none, other), smoking (daily, less than daily, never), physical- and relaxing activity.

2.3. Interventions

The intervention group wore BB-glasses (Uvex Skyper S1933X, by Honeywell, Smithfield, RI, USA. www.uvex.us) blocking 99% of wavelengths shorter than 530 nm, and approximately 15% of the remaining light spectrum. Participants in the control group wore light grey glasses (Uvex Skyper S1905, by Honeywell, Smithfield, RI, USA. www.uvex.us) blocking approximately 50% of wavelengths shorter than 530 nm, and about 30–50% of light in the remaining visual spectrum. We assessed the light blocking capacity of the BB-glasses and the control glasses by transmittance measurements, using a Ramses hyperspectral radiometer from Trios and a Lions xenon light source. In case of knowledge of BB-glasses a partial blue light blocking condition was used as a control, assumed to maintain the placebo effect. Fig. 1 illustrates the irradiance spectra for the respective glasses. The participants were instructed to wear the glasses from 3 h before normal bedtime at night, and until they turned the lights off to go to sleep. If they were exposed to light at night, such as by going to the bathroom etc., they were instructed to wear the glasses on these occasions also, until final awakening in the morning.

The participants were informed to contact the research team if they experienced any side effects after start wearing the glasses, and they were probed for side-effects after study completion.

2.4. Outcomes

The primary outcome was melatonin onset (≥4 pg/mL) measured by saliva samples. The secondary outcome was phase angle (change in latency) between melatonin onset measured by saliva samples and bedtime and sleep onset time assessed by a sleep diary, and melatonin profile for clock time and sample number.

2.4.1. Subjective measure of sleep

A sleep diary was completed every morning. The sleep diary included items on number and duration of naps during the day, use of sleep medication (yes/no), bedtime, lights-out time (trying to sleep), sleep latency, number of nocturnal awakenings, wake after sleep onset (WASO), waking and rise time. Included were also items assessing sleep quality and daytime sleepiness (Carney et al., 2012). The variables used in the present study were bedtime, lights-out time and sleep latency. Sleep onset time was calculated as lights-out time added to sleep latency. The phase angle was calculated as the difference in time between melatonin onset (based on saliva sampling) and bedtime (from sleep diary), and between melatonin onset and sleep onset (from sleep diary), for day 7 and day 21, specifically.

2.4.2. Objective measure of melatonin

Salivette® tubes (Sarstedt AG&Co, Nümbrecht, Germany) were used to collect salivary samples. The participants were instructed to avoid bananas and chocolate the whole sampling day, and in addition to totally avoid drinks with artificial colors, alcohol, caffeine, chewing gum, use of lipstick/lip gloss and tooth brushing during the collection period. They were further recommended not to eat anything during the collection time. In case they needed to eat they were instructed to eat and/or drink right after a sample was taken and then wait for at least 15 min before next sampling.

Saliva was sampled at baseline (day 7) and posttreatment (day 21), at 30-min intervals from 3 h before normal bedtime, overall ranging from 6pm to 2am. Hence, sample number 1 was sampled 3 h before planned bedtime. Participants labeled the samples with id number, date and clock time, and stored the samples in their domestic refrigerator before delivery to a member of the research team, who stored the samples at −70 ℃.

Melatonin-onset was defined as the time the rising concentration curve crossed 4.0 pg/mL in saliva, using linear interpolation between adjacent samples or linear extrapolation if melatonin levels was between (≥) 3.0 pg/mL and >4.0 pg/mL (Keijzer et al., 2011; Pandi-Perumal et al., 2007). Due to missing data, melatonin onset was estimated for 47 participants. For baseline (N=19) and posttreatment (N=13) participants had melatonin concentrations out of range (either all values below 3.0 pg/mL or above 4 pg/mL).

Melatonin levels were presented by melatonin profile at different clock times and sample number.

Samples were analyzed with enzyme-linked immunosorbent assay (ELISA) kit (EK-DSM, Bühlman Laboratories, Schönenbuch, Switzerland), using a Wallac 1420 Multilabel counter (PerkinElmer Inc., United States) and software Workout 2.5. The analytical sensitivity of this kit was 0.5 pg/mL, and the functional sensitivity was 1.6–20.5 pg/mL, with an inter-assay coefficient of variation of 1.5–6.0 pg/mL for the low and 4.6–18.3 pg/mL for the high controls (PerkinElmer Inc., United States).

Power analysis was calculated prior to the study. The power analysis was based on a 2 x 2 ANOVA analysis where one factor reflected a repeated measure, time (pre vs. post) and where the second factor, condition, was a between group factor (BB-glasses vs. control glasses) and where the relevant outcome comprised the time-by-condition

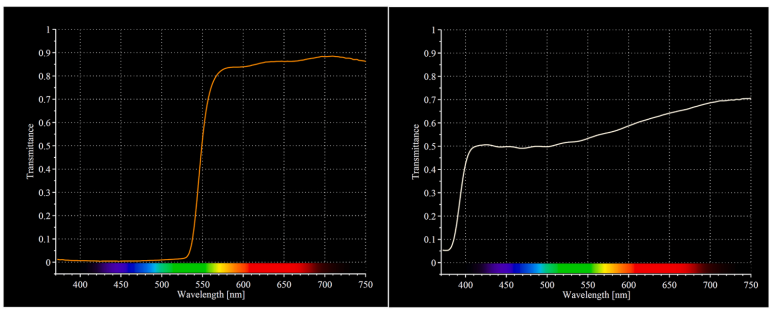


Fig. 1. Irradiance spectra from intervention- and control glasses. Note the near complete filtering of blue light spectral irradiance (<530 nm) of the BB-glasses. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

interaction. The estimated sample size needed was based on effect sizes reported in previous studies that have used BB-glasses as intervention and melatonin onset as outcome. For urine melatonin a study showed strong effects on melatonin onset in a group of healthy adults (Ayaki et al., 2016). We expected a medium effect size (Cohens d = 0.50) for the BB-intervention. Setting the alpha to .05 (two-tailed), power to .80, the correlation between repeated assessments to 0.50 revealed that a minimum of 34 participants in total were needed to detect statistically significant time (pre vs. post) x group (BB vs. control condition) interaction effects (Faul et al., 2007).

2.5. Randomization and blinding

The participants were randomly assigned by www.randomizer.org to either the intervention (BB-glasses) or control condition (grey glasses). A research assistant packed the glasses into opaque brown paper bags, and by using the randomization key a unique number was created, unknown to the researchers. Condition was revealed to the first author not until the participants were handling in the saliva samples. All participants received the same information about the purpose of the study (two types of glasses filtering different wavelengths of light, and the hypothetical impact on sleep and mood). They were instructed to refrain from researching the topic of light and sleep, and in case they needed to contact the research team not to describe their glasses. Participants with knowledge of BB-glasses were not excluded, since both glasses eliminated some wavelengths shorter than 530 nm. This way we regarded that the placebo-effect was preserved also in the cases of some previous knowledge on effects of blue-filtering devices.

2.6. Statistical methods

All statistical analyses were performed using IBM SPSS Statistics version 25 (SPSS, Chicago, IL, USA) and R version 3.5.1 (R Core Team, 2018) and Stata IC version 16 (StataCorp, College Station, TX) for windows.

Characteristics of the study participants are presented as means and standard deviations or numbers and percentages as appropriate.

Melatonin onset was measured at baseline and posttreatment. To examine the effect of BB-glasses on melatonin onset, we used ANCOVA (analysis of covariance) by including the baseline melatonin onset measure as a covariate in linear regression models. The effect estimates were calculated as the difference in melatonin onset means with 95% confidence intervals (CI) between the BB-group and control group, reported in terms of hours and minutes. To further investigate the change in baseline and posttreatment measures of melatonin onset within the BB-group and control group, separately, we used paired *t*-test.

The abovementioned ANCOVA and paired *t*-test analyses were also performed for bedtime and sleep onset, in addition to the secondary outcome, which entailed the phase angle between melatonin onset and bedtime and sleep onset time, respectively, baseline and posttreatment, specifically.

To investigate how salivary melatonin varied by evening hours and sample numbers for both the BB-group and control group, we performed generalized additive models for evening hours and cubic splines regression for sample numbers. The estimated regression lines with corresponding observations points are presented in a graphical format. Because melatonin measures were strongly right-skewed, the regression analyses were performed on log-transformed values to improve model fit.

To test for group difference in salivary melatonin at each evening hour and sample number, we used the Mann-Whitney *U* test. Melatonin values were rounded to nearest hour and observations before 18:30 h and after 24:30 h were excluded (n = 13) due to low numbers.

2.7. Ethical considerations

The Regional Committee for Medical and Health Related Ethics, in Western Norway, approved the study (2016/1394/REK vest). All participants included in the study provided written informed consent. After completed participation, all participants were debriefed about the aim of the study, and they were also offered BB-glasses as a compensation.

3. Results

Fig. 2 presents a flowchart of study enrollment. In total, 125 pregnant women were assessed for eligibility. After adherence to the inclusion and exclusion criteria and following elimination of those who refused to participate, a sample of 60 pregnant women were analyzed (BB-group n=30, control group n=30). The reasons for exclusion of 7 participants were: preterm birth, fire in own home, severe malaise as a side-effect of the glasses, allergic reaction to the actigraph, not capacity to participate and discomfort wearing glasses. Due to melatonin concentration out of range (either all values below 3.0 pg/mL or above 4 pg/mL) a total of 13 women (6 from BB and 7 from control) were excluded from the final analysis, thereby 24 pregnant women in the BB-group and 23 pregnant women in the control group were included in the final analysis.

Sample characteristics for each group are presented in Table 1. The mean age for the BB-group was 30.0 (SD 3.7) years and 31.0 (SD 4.2) years for the control group. Overall, 96.7% of the nulliparous women were married or living with a partner, 83.3% had education at college level or above, 83.4% had an income of 600 000 NOK (≈60 000 US $) or more. Only one pregnant woman reported she was smoking. None of the pregnant women reported consumption of alcohol during the study weeks.

Only two participants reported they had some previous knowledge about the effect of BB glasses.

Table 2 shows the effect of BB-glasses and control glasses on the primary outcome melatonin onset, as well as the secondary outcomes phase angle melatonin onset and bedtime and sleep onset time, in addition to bedtime and sleep onset time. The BB-group showed a significant (p=<.001) advance in melatonin onset by 43 min from baseline to posttreatment period, while the control group with grey glasses showed a significant (p=.002) advance by 11 min. Using ANCOVA with adjustment for baseline values, we detected an estimated 28 min group difference at posttreatment (p=.019).

Fig. 3 visualizes the log-salivary melatonin measures for BB group and control group according to clock time and sample number. In Supplemental Table 1 we also present median salivary melatonin for each group at each clock time and sample number with a corresponding test for difference. For clock time at baseline there were no difference between the groups, except at 20:00 h, which amounted to a statistically significant group difference (p=.034). Posttreatment, the evening rise in median melatonin levels were significantly higher in the BB-glasses than in the control condition at 20:00, 21:00 and 22:00 h with p-values of .001, .003 and <.001, respectively.

For sample number, the melatonin profiles showed no statistically significant difference between the groups, at baseline. At posttreatment, sample number 3 (p=.038) and 4 (p=.025) showed higher median melatonin levels for BB-glasses, compared with the control-glasses.

The phase angle between melatonin onset and bedtime and sleep onset time did not differ significantly between the two groups, according to the ANCOVA. However, from baseline to posttreatment, the BB-group showed an increased difference in 45 min for the phase angle between melatonin onset and bedtime (p=.007) and an increased difference of 41 min for the phase angle between melatonin onset and sleep onset (p=.037). The control group showed similar trends, albeit not significant changes from baseline to posttreatment.

The participants reported side-effects for both the intervention and control glasses. The BB-group reported: malaise (n=2) restored after

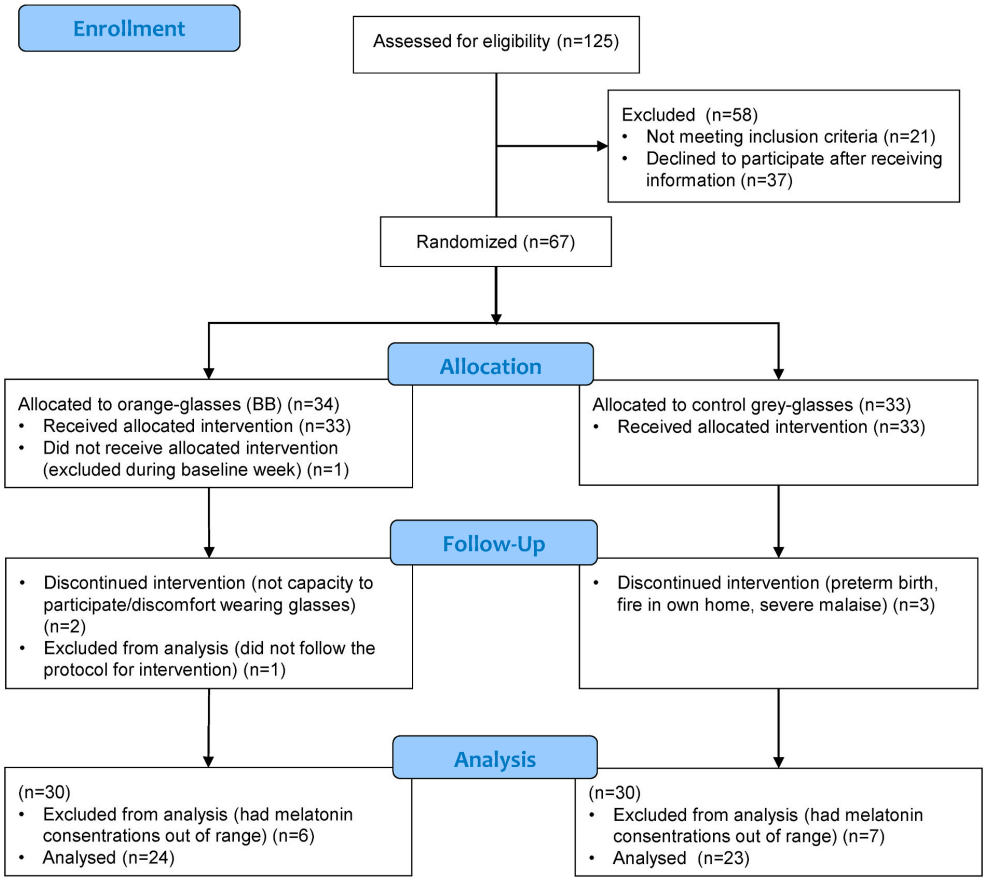


Fig. 2. CONSORT 2010 Flow Diagram of enrollment of pregnant women in the study.

about 5 min, and headache, anxiety and depressive mood (n=1) which lasted for 1.5 h the first evening and 30 min the second evening while still wearing the glasses, and absent the third night. The control group reported severe malaise (n=1) in such a way that exclusion was necessary; headache (n=1) the first evening, then restored; experienced watching double text/subtitles on the TV some evenings (n=1).

4. Discussion

The aim of this study was to investigate the effect of blocking the blue light in the evening on melatonin onset, to investigate the association of melatonin profile with clock time and sample number and phase angle between melatonin onset and bedtime and sleep onset time, among nulliparous women in the beginning of the third trimester of the pregnancy.

The results showed that use of BB-glasses advanced melatonin onset. Melatonin profile at clock time and sample number showed a significant group difference for some of the samples, emerged at posttreatment, in favor of the BB-group. Further, the BB-glasses increased the phase angle (time) between melatonin onset and bedtime and sleep onset time within the BB-group, but not in the control group. However, the difference between the groups at posttreatment, adjusted for baseline values, for the two-phase angle variables were not significant.

4.1. Melatonin onset

The main objective of this study was to test the effectiveness of blue-blocking glasses on melatonin onset. The melatonin onset for the BB-group advanced by 43 min from pre-to post-intervention compared to 11 min advance in the control group. The group difference at post treatment in melatonin onset, adjusted for baseline values, was significant with 28 min advance in the BB-group.

The current findings are in line with previous research showing acute melatonin suppressive effect of nocturnal light exposure (Kayumov et al., 2005; Sasseville et al., 2006; van de Werken et al., 2013). Dim light melatonin onset (DLMO) is a marker of circadian phase, and by blocking the blue light from reaching the ipRGCs in retina the melatonin-production allows more strongly to follow the natural cycle of light and darkness, even when artificial light and electronic light-sources are used (Sasseville et al., 2006; van der Lely et al., 2015).

As expected in the present study, blocking the blue light in the evening led to an earlier secretion of melatonin in the BB-group, of 28 min earlier melatonin onset compared to the control group (p=.019). The participants in the control group used glasses with partial blue-blocking properties, which resulted in some melatonin protective effect.

The results from this first study on effect of BB-glasses on melatonin outcomes for pregnant women are mainly in line with previous research involving BB-interventions (Ayaki et al., 2016; Figueiro and Overington,

Table 1
Demographic factors for the blue-blocking- and control-group.

Characteristics	Both groups, total	Blue blocking group	Control group
N	60	30	30
Age, mean (SD)	30.5 (4.0)	30.0 (3.7)	31.0 (4.2)
Marital status, N (%)			
Married/Cohabitating	58 (96.7)	30 (100%)	28 (93.3%)
Single	2 (3.3)	0	2 (6.7%)
Education, N (%)			
≤Senior high school	10 (16.7)	6 (20%)	4 (13.3%)
College and above	50 (83.3)	24 (80%)	26 (86.7%)
Income, N (%)			
<600 000 NOK	10 (16.7)	5 (16.7%)	5 (16.7%)
>600 000 NOK	50 (83.4)	25 (83.3%)	25 (83.3%)
Adult, total in household, N (%)			
1	2 (3.3)	0	2 (6.7%)
2	57 (95.0)	29 (96.7%)	28 (93.3%)
4	1 (1.7)	1 (3.3%)	0
Children, total in household, N (%)			
0	58 (96.7)	30 (100%)	28 (93.3%)
1	1 (1.7)	0	1 (3.3%)
3	1 (1.7)	0	1 (3.3%)
Smoking, N (%)			
Daily	1 (1.7)	1 (3.3%)	0
Not at all	59 (98.3)	29 (96.7%)	30 (100%)
Physical activity per day (min), mean (SD)	23.8 (33.8)	29.7 (39.0)	18.0 (26.5)
Relaxing activity per day (min), mean (SD)	5.9 (18.0)	7.0 (19.5)	4.8 (16.4)
Pregnancy week, mean (SD)	29.1 (1.2)	28.9 (1.1)	29.3 (1.3)

N=Number of participants; SD = standard deviation; NOK=Norwegian kroner; 10 NOK ≈ 1 United States dollar (US $).

2016; Sasseville et al., 2006; van der Lely et al., 2015; Vethe et al., 2021; Zerbini et al., 2020). In a recent RCT with 12 healthy adults who resided in an evening blue-depleted light environment for 5 days, the melatonin onset (DLMO) was advanced compared with group in usual indoor light (p=.008) (Vethe et al., 2021). In addition, a RCT with 38 young adults, with two weeks intervention, similar to the present study, investigated use of BB-glasses in the evening and showed that BB-glasses significantly advanced melatonin onset (DLMO) compared to the control group with clear lenses (p=<.05). Surprisingly, this only led to advance in melatonin onset (DLMO) in the first but not in the second week of intervention (Zerbini et al., 2020). In contrast to our finding of advanced melatonin onset in the BB-group, in a crossover study with 14 male teenagers, there was no significantly different melatonin onset (DLMO) (p=.351) between the groups (BB-glasses and clear lens-glasses) (van der Lely et al., 2015). The same study however demonstrated a sharper rise of melatonin in the BB-group.

4.2. Melatonin profile at clock time and sample time

The melatonin profile for clock time at posttreatment showed a statistically significant difference between the compared groups, suggesting a larger increase in the melatonin level in the BB- group at 20:00, 21:00 and 22:00 h relative to the control group. However, at baseline the difference reached a significant level only at 20:00 h, favoring the BB-group. The pregnant women in the present study were instructed to use BB-glasses from 3 h prior to bedtime, thus the melatonin samples were not measured at the same clock time (range 18:00 to 02:00 h) for all subjects.

In contrast to sample per clock hour, sample number was similar for all the women. Melatonin profile at posttreatment for sample number 3 and 4 showed a statistically significant group difference, indicating a relatively larger increase in the melatonin level in the BB-group. At baseline it did not appear a difference between the two groups.

Table 2
Effect of blue-blocking glasses on melatonin onset and phase angle.

Outcome	Blue blocking group		Control group		Estimated group difference (95% CI)[a]	P value
	N	Mean (SD)	N	Mean (SD)		
Melatonin onset						
Baseline	23	21:50 (00:56)	18	21:42 (00:49)		
Posttreatment	24	21:07 (01:06)	23	21:31 (00:47)	0 h 28 (0 h 05, 0 h 51)	0.019
P for change[b]		<0.001		0.002		
Bedtime						
Baseline	23	23:04 (00:55)	18	22:54 (00:56)		
Posttreatment	24	23:05 (01:03)	24	22:53 (00:51)	−00:02 (−00:36, 00:31)	0.87
P for change[b]		0.81		0.98		
Phase angle bedtime (in relation to melatonin onset)						
Baseline	23	1 h 12 (0 h 50)	18	1 h 11 (1 h 02)		
Posttreatment	24	1 h 57 (0 h 55)	23	1 h 24 (1 h 02)	−0 h 22 (−0 h 58, 0 h 14)	0.23
P for change[b]		0.007		0.11		
Sleep onset						
Baseline	23	23:54 (01:04)	18	23:33 (01:01)		
Posttreatment	24	23:51 (01:10)	24	23:48 (00:57)	−00:03 (−00:42, 00:36)	0.89
P for change[b]		0.65		0.52		
Phase angle sleep onset (in relation to melatonin onset)						
Baseline	23	2 h 03 (0 h 57)	18	1 h 51 (0 h 56)		
Posttreatment	24	2 h 44 (1 h 07)	23	2 h 17 (0 h 58)	−0 h 20 (−1 h 03, 0 h 22)	0.34
P for change[b]		0.037		0.065		

N = Number of participants; SD = standard deviation; CI = confidence interval; phase angle bedtime = time interval from melatonin onset to bedtime (derived from self-reported data); phase angle sleep onset = time interval from melatonin onset to sleep onset (derived from self-reported data). Baseline = day 7, Posttreatment= day 21.

[a] By ANCOVA.

[b] By paired sample *t*-test.

4.3. Phase angle

A second aim of the study was to estimate the effect of blocking the blue light on phase angle with respect to the time lag between melatonin onset and bedtime and sleep onset time. A statistically significant increase within the BB group were shown (p = .007 and p = .037, respectively). A similar pattern was not shown within the control group, and this were not significant, nor the group difference at posttreatment adjusted for baseline values.

The fact that the difference for the two phase angle variables remained non-significant may reflect that the participants could sleep ad libitum, as previous studies have shown that the relationship between melatonin onset and sleep onset is stable, even when a specific bedtime is enforced (Sletten et al., 2010).

Also, these findings are similarly to results published by Van der Lely (van der Lely et al., 2015) where the phase angle between melatonin onset (DLMO) and sleep onset did not significantly differ between the

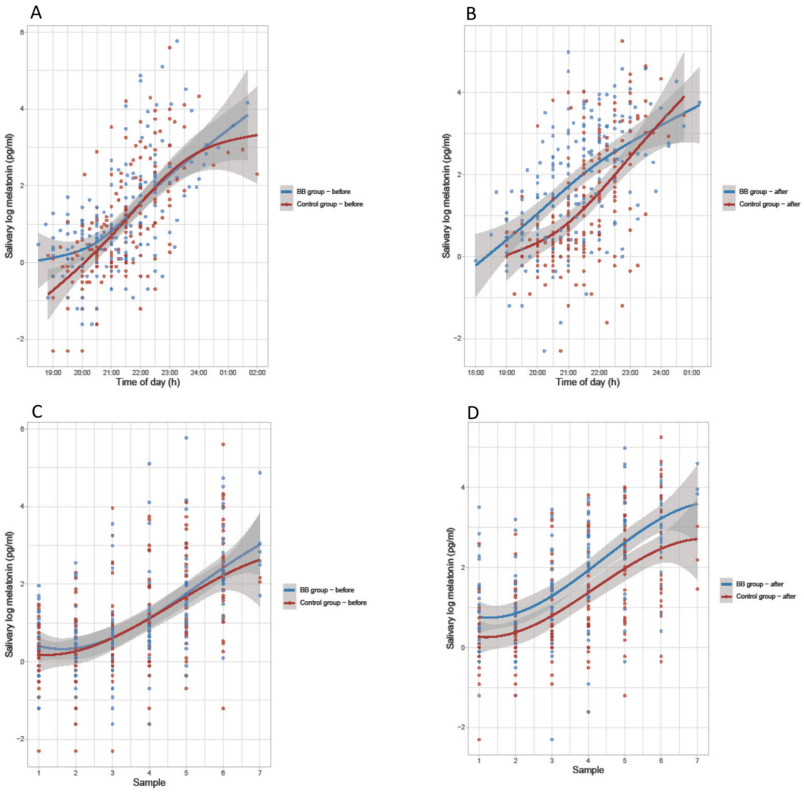


Fig. 3. Difference in saliva log-melatonin at clock time and sample number between blue blocking- and control group, at baseline and posttreatment. Log-melatonin visualized for clock-time for (A) baseline and (B) posttreatment, and for sample number for (C) baseline and (D) posttreatment. Median salivary melatonin for each group at each clock time and sample number with a corresponding test for difference are shown in Supplemental Table 1. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

BB- and the control group. However, Zerbini et al. (2020) showed a significantly decreased phase angle between melatonin onset (DLMO) and sleep onset in the intervention group (p=<.05), but only for the first of two intervention weeks.

A recent study showed that in the same sample as the present study evening light exposure was inversely related to total sleep time and positively related to earlier midpoint of sleep, measured by actigraphy, at baseline (Liset et al., 2021).

Maternal melatonin levels have been shown to be important for adequate fetal development (Lanoix et al., 2012) due to the exposure to the maternal rhythms such as maternal melatonin, which crosses the placenta barrier unaltered (Seron-Ferre et al., 1993). Complicated pregnancies are associated with a decrease in melatonin levels, thus indirectly affects the fetus with occurrence of intrauterine growth restriction (Dou et al., 2019; Lanoix et al., 2012; Laste et al., 2021; Nakamura et al., 2001; Shimada et al., 2016).

The present study showed that BB-glasses were able to increase melatonin levels in the evening, which is promoting normal development of the maternal pregnancy (Nakamura et al., 2001). Findings from other studies have identified a synchronous process between the maternal and fetal melatonin levels (Reiter et al., 2000; Tamura et al., 2008), which fortunate the fetal development (McCarthy et al., 2019). The present study may serve as basis for recommendation of BB-glasses to pregnant women as an increase of melatonin secretion did occur at some time points in the evening, and due to the importance of melatonin levels both for the pregnant women and the fetal development.

The observed side effects of the BB-glasses (malaise, headache, lowered mood and anxiety) were transient, and occurred in both groups equally (n=3) except for severe malaise experienced by one participant in the control-group which led to drop-out. The frequency of side-effects is in line with what was reported by Henriksen (Henriksen et al., 2016), while other studies have reported no side effects (Burkhart and Phelps, 2009). These findings are consistent with the previous conclusions from the literature that BB-glasses are a safe intervention when used in the evening and night (Esaki et al., 2017; Henriksen et al., 2016; Shechter et al., 2020). The side effects in five of the six cases disappeared with further use. This observation is not previously reported in similar studies involving BB-glasses and are thus a clinically valuable notion.

Blue light-rich environment at night is not natural and by using BB-glasses one may simulate natural nocturnal light conditions. BB-glasses are inexpensive, safe, and easy to use.

4.4. Limitations

The sample in the present study included only 30 participants in each group, which may entail a limitation. After exclusion of 13 participants due to melatonin levels out of range, there were 24 pregnant women in the BB-group and 23 pregnant women in the control group, which may be a further limitation as some uncertainties remain regarding melatonin alternations in the sample as a whole. In addition, the majority of the participants were married or cohabitating, had higher education and income than the general population and they reported good sleep (Liset et al., 2021), which may put limits on the generalizability. On the other hand, the pregnant women could freely follow their rhythms, sleep ad libitum and the saliva melatonin samples were self-collected at home. This may be viewed as an asset in terms of generalizability.

Because we wanted to study the effects of BB-glasses and grey control glasses on melatonin profile as compared to the endogenous melatonin in the naturalistic home-based setting, we could not use the ordinary convention of establishing internal circadian rhythm in the participants; the dim light melatonin onset (DLMO). The DMLO protocol involves use of specialized dark sunglasses prior to and during saliva sampling, which would compromise our study design. The consequence was that we do not have a fixed time point as marker for the internal circadian phase for the participants. Instead, we measured their circadian phase in interaction with the naturalistic light exposure at baseline, and with filtered light exposure during the experimental conditions. In this regard however, it should be noted that some previous comparable studies neither followed the conventional DLMO protocol (van der Lely et al., 2015; Zerbini et al., 2020), or replaced dark sunglasses by BB-glasses (van der Lely et al., 2015). Some participants went to bed before natural rise in melatonin concentration (values $>$ 3.0 pg/mL), which resulted in exclusion from analysis, and this may have affected the results.

It is conceivable that self-report data may lead to recall bias (Coughlin, 1990), social desirability bias (Dodou and de Winter 2014) and some common method bias (Podsakoff et al., 2003). However, the randomization processes would prevent such biases to influence the results. In addition, the melatonin data were derived from saliva samples, and hence not influenced by the previously mentioned biases.

A strength of the present study is the use of objective measure of saliva melatonin, measured repeatedly during one evening both before and after the intervention. As the melatonin saliva sampling was home-based, inadequate sampling procedure may have occurred. However, the subjects received detailed instructions in terms of sampling procedure and home-based melatonin sampling/assessment are shown to correlate well with laboratory assessment (Pullman et al., 2012).

The control glasses in the present study had a partial blue blocking effect of the light, and the results showed that they had some melatonin protective effect. If the control condition was use of clear glasses, the difference between the groups in terms of melatonin onset, melatonin profiles and phase angle would likely have been larger. By using two active interventions we aimed to maintain the placebo-effect in both groups and strengthen the blinding of participants. Two participants reported previous knowledge of effects of blue light and that these glasses work by filtering out specific wavelengths of the visual spectrum. Future studies on the effect of BB-glasses should use a control condition with a minimal reduction of melanopic lux.

5. Conclusions

We found that blue-blocking glasses worn 3 h before bedtime protected the melatonin of pregnant women from evening light suppression. Our findings indicate that BB-glasses may serve as an effective non-pharmacological tool for improving circadian function and health for both mother and offspring.

Funding

The study was supported by a PhD grant for RL, and a grant for graphical design and printing of questionnaire, all funded by The Faculty of Psychology, University of Bergen, Norway. The melatonin samples equipment and analyses were supported by a grant from the Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Trial registration

The trial is registered at ClinicalTrials.gov (NCT03114072).

CRediT authorship contribution statement

Randi Liset: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Project administration. **Janne Grønli:** Conceptualization, Methodology, Writing- Reviewing and Editing of the final draft. **Roger Ekeberg Henriksen:** Conceptualization, Methodology, Writing- Reviewing and Editing of the final draft. **Tone Elise Gjøtterud Henriksen:** Conceptualization, Methodology, Writing- Reviewing and Editing of the final draft. **Roy Miodini Nilsen:** Methodology, Formal analysis, Writing- Reviewing and Editing of the final draft. **Ståle Pallesen:** Conceptualization, Methodology, Investigation, and Co-authoring original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are grateful to the participating pregnant women for their generous contribution in the study, and thanks to the consulting midwifes at antenatal-healthcare centers in the Municipality of Bergen, Norway, for recruiting participants. We also thank the University of Bergen for the scholarship to this project, the Norwegian Competence Center for Sleep Disorders for a project grant, and a grant from the Norwegian Association of Midwifes. We are also thankful to Børge Hamre for testing and measurement of the irradiance spectra from the intervention- and control glasses. Further we thank Erlend Sunde for assisting in randomization and blinding of the participants, and Nina Harkestad for giving advice and analyzing the saliva samples.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbscr.2021.100074.

References

American Academy of Sleep Medicine, 2014. In: International Classification of Sleep Disorders. Chicago, third ed. ICSD-3.

Ayaki, M., Hattori, A., Maruyama, Y., Nakano, M., Yoshimura, M., Kitazawa, M., Negishi, K., Tsubota, K., 2016. Protective effect of blue-light shield eyewear for adults against light pollution from self-luminous devices used at night. Chronobiol. Int. 33 (1), 134–139. https://doi.org/10.3109/07420528.2015.1119158.

Bennett, S., Alpert, M., Kubulins, V., Hansler, R.L., 2009. Use of modified spectacles and light bulbs to block blue light at night may prevent postpartum depression. Med. Hypotheses 73 (2), 251–253. https://doi.org/10.1016/j.mehy.2009.01.049.

Berson, D.M., 2007. Phototransduction in ganglion-cell photoreceptors. Pflügers Archiv 454 (5), 849–855. https://doi.org/10.1007/s00424-007-0242-2.

Brainard, G.C., Hanifin, J.P., Greeson, J.M., Byrne, B., Glickman, G., Gerner, E., Rollag, M.D., 2001. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. J. Neurosci. 21 (16), 6405–6412. Retrieved from. http://www.ncbi.nlm.nih.gov/pubmed/11487664.

Brainard, G.C., Hanifin, J.P., Warfield, B., Stone, M.K., James, M.E., Ayers, M., Kubey, A., Byrne, B., Rollag, M., 2015. Short-wavelength enrichment of polychromatic light enhances human melatonin suppression potency. J. Pineal Res. 58 (3), 352–361. https://doi.org/10.1111/jpi.12221.

Buijs, R.M., Kalsbeek, A., 2001. Hypothalamic integration of central and peripheral clocks. Nat. Rev. Neurosci. 2 (7), 521–526. https://doi.org/10.1038/35081582.

Burkhart, K., Phelps, J.R., 2009. Amber lenses to block blue light and improve sleep: a randomized trial. Chronobiol. Int. 26 (8), 1602–1612. https://doi.org/10.3109/07420520903523719.

Carney, C.E., Buysse, D.J., Ancoli-Israel, S., Edinger, J.D., Krystal, A.D., Lichstein, K.L., Morin, C.M., 2012. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep 35 (2), 287–302. https://doi.org/10.5665/sleep.1642.

Coughlin, S.S., 1990. Recall bias in epidemiologic studies. J. Clin. Epidemiol. 43 (1), 87–91. https://doi.org/10.1016/0895-4356(90)90060-3.

Czeisler, C.A., Buxton, O.M., 2017. Human circadian timing system and sleep-wake regulation. In: Kryger, M., Roth, T., Dement, W.C. (Eds.), Principles and Practice of Sleep Medicine, sixth ed. Elsevier, pp. 362–376.

Ding, X.X., Wu, Y.L., Xu, S.J., Zhang, S.F., Jia, X.M., Zhu, R.P., Hao, J.H., Tao, F.B., 2014. A systematic review and quantitative assessment of sleep-disordered breathing

during pregnancy and perinatal outcomes. Sleep Breath. 18 (4), 703–713. https://doi.org/10.1007/s11325-014-0946-4.
Dodou, D., de Winter, J.C.F., 2014. Social desirability is the same in offline, online, and paper surveys: a meta-analysis. Comput. Hum. Behav. 36, 487–495. https://doi.org/10.1016/j.chb.2014.04.005.
Dou, Y., Lin, B., Cheng, H., Wang, C., Zhao, M., Zhang, J., Wu, J., 2019. The reduction of melatonin levels is associated with the development of preeclampsia: a meta-analysis. Hypertens. Pregnancy 38 (2), 65–72. https://doi.org/10.1080/10641955.2019.1581215.
Epperson, C.N., Terman, M., Terman, J.S., Hanusa, B.H., Oren, D.A., Peindl, K.S., Wisner, K.L., 2004. Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J. Clin. Psychiatr. 65 (3), 421–425. https://doi.org/10.4088/jcp.v65n0319.
Esaki, Y., Kitajima, T., Takeuchi, I., Tsuboi, S., Furukawa, O., Moriwaki, M., Fujita, K., Iwata, N., 2017. Effect of blue-blocking glasses in major depressive disorder with sleep onset insomnia: a randomized, double-blind, placebo-controlled study. Chronobiol. Int. 34 (6), 753–761. https://doi.org/10.1080/07420528.2017.1318893.
Faul, F., Erdfelder, E., Lang, A.G., Buchner, A., 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods 39 (2), 175–191. Retrieved from. http://www.ncbi.nlm.nih.gov/pubmed/17695343.
Figueiro, M.G., Overington, D., 2016. Self-luminous devices and melatonin suppression in adolescents. Light. Res. Technol. 48, 966–975. https://doi.org/10.1177/1477153515584979.
Figueiro, M.G., Wood, B., Plitnick, B., Rea, M.S., 2011. The impact of light from computer monitors on melatonin levels in college students. Neuroendocrinol. Lett. 32 (2), 158–163. Retrieved from. https://www.ncbi.nlm.nih.gov/pubmed/21552190.
Gronli, J., Byrkjedal, I.K., Bjorvatn, B., Nodtvedt, O., Hamre, B., Pallesen, S., 2016. Reading from an iPad or from a book in bed: the impact on human sleep. A randomized controlled crossover trial. Sleep Med. 21, 86–92. https://doi.org/10.1016/j.sleep.2016.02.006.
Henriksen, T.E.G., Skrede, S., Fasmer, O.B., Schoeyen, H., Leskauskaite, I., Bjorke-Bertheussen, J., Assmus, J., Hamre, B., Grønli, J., Lund, A., 2016. Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial. Bipolar Disord. 18 (3), 221–232. https://doi.org/10.1111/bdi.12390.
Kayumov, L., Casper, R.F., Hawa, R.J., Perelman, B., Chung, S.A., Sokalsky, S., Shapiro, C.M., 2005. Blocking low-wavelength light prevents nocturnal melatonin suppression with no adverse effect on performance during simulated shift work. J. Clin. Endocrinol. Metab. 90 (5), 2755–2761. https://doi.org/10.1210/jc.2004-2062.
Keijzer, H., Smits, M.G., Peeters, T., Looman, C.W., Endenburg, S.C., Gunnewiek, J.M., 2011. Evaluation of salivary melatonin measurements for Dim Light Melatonin Onset calculations in patients with possible sleep-wake rhythm disorders. Clin. Chim. Acta 412 (17–18), 1616–1620. https://doi.org/10.1016/j.cca.2011.05.014.
Lanoix, D., Beghdadi, H., Lafond, J., Vaillancourt, C., 2008. Human placental trophoblasts synthesize melatonin and express its receptors. J. Pineal Res. 45 (1), 50–60. https://doi.org/10.1111/j.1600-079X.2008.00555.x.
Lanoix, D., Guerin, P., Vaillancourt, C., 2012. Placental melatonin production and melatonin receptor expression are altered in preeclampsia: new insights into the role of this hormone in pregnancy. J. Pineal Res. 53 (4), 417–425. https://doi.org/10.1111/j.1600-079X.2012.01012.x.
Laste, G., Silva, A.A.D., Gheno, B.R., Rychcik, P.M., 2021. Relationship between melatonin and high-risk pregnancy: a review of investigations published between the years 2010 and 2020. Chronobiol. Int. 38 (2), 168–181. https://doi.org/10.1080/07420528.2020.1863975.
LeGates, T.A., Fernandez, D.C., Hattar, S., 2014. Light as a central modulator of circadian rhythms, sleep and affect. Nat. Rev. Neurosci. 15 (7), 443–454. https://doi.org/10.1038/nrn3743.
Liset, R., Gronli, J., Henriksen, R.E., Henriksen, T.E.G., Nilsen, R.M., Pallesen, S., 2021. Sleep, evening light exposure and perceived stress in healthy nulliparous women in the third trimester of pregnancy. PLoS One 16 (6), e0252285. https://doi.org/10.1371/journal.pone.0252285.
Macchi, M.M., Bruce, J.N., 2004. Human pineal physiology and functional significance of melatonin. Front. Neuroendocrinol. 25 (3–4), 177–195. https://doi.org/10.1016/j.yfrne.2004.08.001.
Masana, M.I., Benloucif, S., Dubocovich, M.L., 2000. Circadian rhythm of mt1 melatonin receptor expression in the suprachiasmatic nucleus of the C3H/HeN mouse. J. Pineal Res. 28 (3), 185–192. https://doi.org/10.1034/j.1600-079x.2001.280309.x.
McCarthy, R., Jungheim, E.S., Fay, J.C., Bates, K., Herzog, E.D., England, S.K., 2019. Riding the rhythm of melatonin through pregnancy to deliver on time. Front. Endocrinol. 10, 616. https://doi.org/10.3389/fendo.2019.00616.
McLaughlin, C., Levin, A.V., 2006. The red reflex. Pediatr. Emerg. Care 22 (2), 137–140. https://doi.org/10.1097/01.pec.0000199567.87134.81.
Nakamura, Y., Tamura, H., Kashida, S., Takayama, H., Yamagata, Y., Karube, A., Sugino, N., Kato, H., 2001. Changes of serum melatonin level and its relationship to feto-placental unit during pregnancy. J. Pineal Res. 30 (1), 29–33. https://doi.org/10.1034/j.1600-079x.2001.300104.x.
Nehme, P.A., Amaral, F.G., Middleton, B., Lowden, A., Marqueze, E., Franca-Junior, I., Antunes, J.L.F., Cipolla_Neto, J., Skene, D.J., Moreno, C.R.C., 2019. Melatonin profiles during the third trimester of pregnancy and health status in the offspring among day and night workers: a case series. Neurobiol. Sleep Circadian Rhythms 6, 70–76. https://doi.org/10.1016/j.nbscr.2019.04.001.
Nodine, P.M., Matthews, E.E., 2013. Common sleep disorders: management strategies and pregnancy outcomes. J. Midwifery Wom. Health 58 (4), 368–377. https://doi.org/10.1111/jmwh.12004.
Palagini, L., Gemignani, A., Banti, S., Manconi, M., Mauri, M., Riemann, D., 2014. Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome. Sleep Med. 15 (8), 853–859. https://doi.org/10.1016/j.sleep.2014.02.013.
Pandi-Perumal, S.R., Smits, M., Spence, W., Srinivasan, V., Cardinali, D.P., Lowe, A.D., Kayumov, L., 2007. Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 31 (1), 1–11. https://doi.org/10.1016/j.pnpbp.2006.06.020.
Podsakoff, P.M., MacKenzie, S.B., Lee, J.Y., Podsakoff, N.P., 2003. Common method biases in behavioral research: a critical review of the literature and recommended remedies. J. Appl. Psychol. 88 (5), 879–903. https://doi.org/10.1037/0021-9010.88.5.879.
Pullman, R.E., Roepke, S.E., Duffy, J.F., 2012. Laboratory validation of an in-home method for assessing circadian phase using dim light melatonin onset (DLMO). Sleep Med. 13 (6), 703–706. https://doi.org/10.1016/j.sleep.2011.11.008.
R Core Team, 2018. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/.
Reiter, R.J., Tan, D.X., Qi, W., Manchester, L.C., Karbownik, M., Calvo, J.R., 2000. Pharmacology and physiology of melatonin in the reduction of oxidative stress in vivo. Biol. Signals Recept. 9 (3–4), 160–171. https://doi.org/10.1159/000014636.
Sasseville, A., Paquet, N., Sevigny, J., Hebert, M., 2006. Blue blocker glasses impede the capacity of bright light to suppress melatonin production.(Author abstract). J. Pineal Res. 41, 73–78.
Seron-Ferre, M., Ducsay, C.A., Valenzuela, G.J., 1993. Circadian rhythms during pregnancy. Endocr. Rev. 14 (5), 594–609. https://doi.org/10.1210/edrv-14-5-594.
Shechter, A., Quispe, K.A., Barbecho, J.S.M., Slater, C., Falzon, L., 2020. Interventions to reduce short-wavelength ("blue") light exposure at night and their effects on sleep: a systematic review and meta-analysis. Sleep Adv. 1–13. https://doi.org/10.1093/sleepadvances/zpaa002.
Shimada, M., Seki, H., Samejima, M., Hayase, M., Shirai, F., 2016. Salivary melatonin levels and sleep-wake rhythms in pregnant women with hypertensive and glucose metabolic disorders: a prospective analysis. Biosci. Trends 10 (1), 34–41. https://doi.org/10.5582/bst.2015.01123.
Sletten, T.L., Vincenzi, S., Redman, J.R., Lockley, S.W., Rajaratnam, S.M., 2010. Timing of sleep and its relationship with the endogenous melatonin rhythm. Front. Neurol. 1, 137. https://doi.org/10.3389/fneur.2010.00137.
Tamura, H., Nakamura, Y., Terron, M.P., Flores, L.J., Manchester, L.C., Tan, D.X., Sugino, N., Reiter, R.J., 2008. Melatonin and pregnancy in the human. Reprod. Toxicol. 25 (3), 291–303. https://doi.org/10.1016/j.reprotox.2008.03.005.
van de Werken, M., Gimenez, M.C., de Vries, B., Beersma, D.G., Gordijn, M.C., 2013. Short-wavelength attenuated polychromatic white light during work at night: limited melatonin suppression without substantial decline of alertness. Chronobiol. Int. 30 (7), 843–854. https://doi.org/10.3109/07420528.2013.773440.
van der Lely, S., Frey, S., Garbazza, C., Wirz-Justice, A., Jenni, O.G., Steiner, R., Wolf, S., Cajochen, C., Bromundt, V., Schmidt, C., 2015. Blue blocker glasses as a countermeasure for alerting effects of evening light-emitting diode screen exposure in male teenagers. J. Adolesc. Health 56 (1), 113–119. https://doi.org/10.1016/j.jadohealth.2014.08.002.
Vethe, D., Scott, J., Engstrom, M., Salvesen, O., Sand, T., Olsen, A., Morken, G., Heglum, H.S., Kjørstad, K., Faaland, P.M., Vestergaard, C.L., Langsrud, K., Kallestad, H., 2021. The evening light environment in hospitals can be designed to produce less disruptive effects on the circadian system and improve sleep. Sleep 44 (3). https://doi.org/10.1093/sleep/zsaa194.
Wada, K., Nagata, C., Nakamura, K., Iwasa, S., Shiraki, M., Shimizu, H., 2012. Light exposure at night, sleep duration and sex hormone levels in pregnant Japanese women. Endocr. J. 59 (5), 393–398. https://doi.org/10.1507/endocrj.ej11-0325.
Zerbini, G., Kantermann, T., Merrow, M., 2020. Strategies to decrease social jetlag: reducing evening blue light advances sleep and melatonin. Eur. J. Neurosci. 51 (12), 2355–2366. https://doi.org/10.1111/ejn.14293.

Doctoral Theses at The Faculty of Psychology, University of Bergen

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

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

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

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

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

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

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

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

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

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

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

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

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

2012 H	Danielsen, Yngvild Sørebø	Childhood obesity – characteristics and treatment. Psychological perspectives.
	Horverak, Jøri Gytre	Sense or sensibility in hiring processes. Interviewee and interviewer characteristics as antecedents of immigrant applicants' employment probabilities. An experimental approach.
	Jøsendal, Ola	Development and evaluation of BE smokeFREE, a school-based smoking prevention program
	Osnes, Berge	Temporal and Posterior Frontal Involvement in Auditory Speech Perception
	Drageset, Sigrunn	Psychological distress, coping and social support in the diagnostic and preoperative phase of breast cancer
	Aasland, Merethe Schanke	Destructive leadership: Conceptualization, measurement, prevalence and outcomes
	Bakibinga, Pauline	The experience of job engagement and self-care among Ugandan nurses and midwives
	Skogen, Jens Christoffer	Foetal and early origins of old age health. Linkage between birth records and the old age cohort of the Hordaland Health Study (HUSK)
	Leversen, Ingrid	Adolescents' leisure activity participation and their life satisfaction: The role of demographic characteristics and psychological processes
	Hanss, Daniel	Explaining sustainable consumption: Findings from cross-sectional and intervention approaches
	Rød, Per Arne	Barn i klem mellom foreldrekonflikter og samfunnsmessig beskyttelse
2013 V	Mentzoni, Rune Aune	Structural Characteristics in Gambling
	Knudsen, Ann Kristin	Long-term sickness absence and disability pension award as consequences of common mental disorders. Epidemiological studies using a population-based health survey and official ill health benefit registries.
	Strand, Mari	Emotional information processing in recurrent MDD
	Veseth, Marius	Recovery in bipolar disorder. A reflexive-collaborative exploration of the lived experiences of healing and growth when battling a severe mental illness
	Mæland, Silje	Sick leave for patients with severe subjective health complaints. Challenges in general practice.
	Mjaaland, Thera	At the frontiers of change? Women and girls' pursuit of education in north-western Tigray, Ethiopia
	Odéen, Magnus	Coping at work. The role of knowledge and coping expectancies in health and sick leave.
	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
	Søvik, Margaret Ljosnes	Evaluating the implementation of the Empowering Coaching™ program in Norway
	Tonheim, Milfrid	A troublesome transition: Social reintegration of girl soldiers returning ‘home’
	Senneseth, Mette	Improving social network support for partners facing spousal cancer while caring for minors. A randomized controlled trial.
	Urke, Helga Bjørnøy	Child health and child care of very young children in Bolivia, Colombia and Peru.
	Bakhturidze, George	Public Participation in Tobacco Control Policy-making in Georgia
	Fismen, Anne-Siri	Adolescent eating habits. Trends and socio-economic status.
2017 H	Hagatun, Susanne	Internet-based cognitive-behavioural therapy for insomnia. A randomised controlled trial in Norway.
	Eichele, Heike	Electrophysiological Correlates of Performance Monitoring in Children with Tourette Syndrome. A developmental perspective.
	Risan, Ulf Patrick	Accommodating trauma in police interviews. An exploration of rapport in investigative interviews of traumatized victims.
	Sandhåland, Hilde	Safety on board offshore vessels: A study of shipboard factors and situation awareness
	Blågestad, Tone Fidje	Less pain – better sleep and mood? Interrelatedness of pain, sleep and mood in total hip arthroplasty patients
	Kronstad, Morten	Frå skulebenk til deadlines. Korleis nettjournalistar og journaliststudentar lærer, og korleis dei utviklar journalistfagleg kunnskap
	Vedaa, Øystein	Shift work: The importance of sufficient time for rest between shifts.
	Steine, Iris Mulders	Predictors of symptoms outcomes among adult survivors of sexual abuse: The role of abuse characteristics, cumulative childhood maltreatment, genetic variants, and perceived social support.
	Høgheim, Sigve	Making math interesting: An experimental study of interventions to encourage interest in mathematics

2018 V	Brevik, Erlend Joramo	Adult Attention Deficit Hyperactivity Disorder. Beyond the Core Symptoms of the Diagnostic and Statistical Manual of Mental Disorders.
	Erevik, Eilin Kristine	User-generated alcohol-related content on social media: Determinants and relation to offline alcohol use
	Hagen, Egon	Cognitive and psychological functioning in patients with substance use disorder; from initial assessment to one-year recovery
	Adólfsdóttir, Steinunn	Subcomponents of executive functions: Effects of age and brain maturations
	Brattabø, Ingfrid Vaksdal	Detection of child maltreatment, the role of dental health personnel – A national cross-sectional study among public dental health personnel in Norway
	Fylkesnes, Marte Knag	Frykt, forhandlinger og deltakelse. Ungdommer og foreldre med etnisk minoritetsbakgrunn i møte med den norske barnevernstjenesten.
	Stiegler, Jan Reidar	Processing emotions in emotion-focused therapy. Exploring the impact of the two-chair dialogue intervention.
	Egelandsdal, Kjetil	Clickers and Formative Feedback at University Lectures. Exploring students and teachers' reception and use of feedback from clicker interventions.
	Torjussen, Lars Petter Storm	Foreningen av visdom og veltalenhet – utkast til en universitetsdidaktikk gjennom en kritikk og videreføring av Skjervheims pedagogiske filosofi på bakgrunn av Arendt og Foucault. *Eller hvorfor menneskelivet er mer som å spille fløyte enn å bygge et hus.*
	Selvik, Sabreen	A childhood at refuges. Children with multiple relocations at refuges for abused women.
2018 H	Leino, Tony Mathias	Structural game characteristics, game features, financial outcomes and gambling behaviour
	Raknes, Solfrid	Anxious Adolescents: Prevalence, Correlates, and Preventive Cogntive Behavioural Interventions
	Morken, Katharina Teresa Enehaug	Mentalization-based treatment of female patients with severe personality disorder and substance use disorder
	Braatveit, Kirsten Johanne	Intellectual disability among in-patients with substance use disorders
	Barua, Padmaja	Unequal Interdependencies: Exploring Power and Agency in Domestic Work Relations in Contemporary India
	Darkwah, Ernest	Caring for "parentless" children. An exploration of work-related experiences of caregivers in children's homes in Ghana.
	Valdersnes, Kjersti Bergheim	Safety Climate perceptions in High Reliability Organizations – the role of Psychological Capital

2019 V	Kongsgården, Petter	Vurderingspraksiser i teknologirike læringsmiljøer. En undersøkelse av læreres vurderingspraksiser i teknologirike læringsmiljøer og implikasjoner på elevenes medvirkning i egen læringsprosess.
	Vikene, Kjetil	Complexity in Rhythm and Parkinson's disease: Cognitive and Neuronal Correlates
	Heradstveit, Ove	Alcohol- and drug use among adolescents. School-related problems, childhood mental health problems, and psychiatric diagnoses.
	Riise, Eili Nygard	Concentrated exposure and response prevention for obsessive-compulsive disorder in adolescents: the Bergen 4-day treatment
	Vik, Alexandra	Imaging the Aging Brain: From Morphometry to Functional Connectivity
	Krossbakken, Elfrid	Personal and Contextual Factors Influencing Gaming Behaviour. Risk Factors and Prevention of Video Game Addiction.
	Solholm, Roar	Foreldrenes status og rolle i familie- og nærmiljøbaserte intervensjoner for barn med atferdsvansker
	Baldomir, Andrea Margarita	Children at Risk and Mothering Networks in Buenos Aires, Argentina: Analyses of Socialization and Law-Abiding Practices in Public Early Childhood Intervention.
	Samuelsson, Martin Per	Education for Deliberative Democracy. Theoretical assumptions and classroom practices.
	Visted, Endre	Emotion regulation difficulties. The role in onset, maintenance and recurrence of major depressive disorder.
2019 H	Nordmo, Morten	Sleep and naval performance. The impact of personality and leadership.
	Sveinsdottir, Vigdis	Supported Employment and preventing Early Disability (SEED)
	Dwyer, Gerard Eric	New approaches to the use of magnetic resonance spectroscopy for investigating the pathophysiology of auditory-verbal hallucinations
	Synnevåg, Ellen Strøm	Planning for Public Health. Balancing top-down and bottom-up approaches in Norwegian municipalities.
	Kvinge, Øystein Røsseland	Presentation in teacher education. A study of student teachers' transformation and representation of subject content using semiotic technology.
	Thorsen, Anders Lillevik	The emotional brain in obsessive-compulsive disorder
	Eldal, Kari	Sikkerheitsnettet som tek imot om eg fell – men som også kan fange meg. Korleis erfarer menneske med psykiske lidingar ei innlegging i psykisk helsevern? Eit samarbeidsbasert forskingsprosjekt mellom forskarar og brukarar.

	Svendsen, Julie Lillebostad	Self-compassion - Relationship with mindfulness, emotional stress symptoms and psychophysiological flexibility
2020 V	Albæk, Ane Ugland	Walking children through a minefield. Qualitative studies of professionals' experiences addressing abuse in child interviews.
	Ludvigsen, Kristine	Creating Spaces for Formative Feedback in Lectures. Understanding how use of educational technology can support formative assessment in lectures in higher education.
	Hansen, Hege	Tidlig intervensjon og recoveryprosesser ved førsteepisode psykose. En kvalitativ utforsking av ulike perspektiver.
	Nilsen, Sondre Aasen	After the Divorce: Academic Achievement, Mental Health, and Health Complaints in Adolescence. Heterogeneous associations by parental education, family structure, and siblings.
	Hovland, Runar Tengel	Kliniske tilbakemeldingssystemer i psykisk helsevern – implementering og praktisering
	Sæverot, Ane Malene	Bilde og pedagogikk. En empirisk undersøkelse av ungdoms fortellinger om bilder.
	Carlsen, Siv-Elin Leirvåg	Opioid maintenance treatment and social aspects of quality of life for first-time enrolled patients. A quantitative study.
	Haugen, Lill Susann Ynnesdal	Meeting places in Norwegian community mental health care: A participatory and community psychological inquiry
2020 H	Markova, Valeria	How do immigrants in Norway interpret, view, and prefer to cope with symptoms of depression? A mixed method study
	Anda-Ågotnes, Liss Gøril	Cognitive change in psychosis
	Finserås, Turi Reiten	Assessment, reward characteristics and parental mediation of Internet Gaming Disorder
	Hagen, Susanne	«Helse i alt kommunen gjør? ...» - *en undersøkelse av samvariasjoner mellom kommunale faktorer og norske kommuners bruk av folkehelsekoordinator, fokus på levekår og prioritering av fordelingshensyn blant sosioøkonomiske grupper.*
	Rajalingam, Dhaksshaginy	The impact of workplace bullying and repeated social defeat on health complaints and behavioral outcomes: A biopsychosocial perspective
	Potrebny, Thomas	Temporal trends in psychological distress and healthcare utilization among young people
2021 V	Hjetland, Gunnhild Johnsen	The effect of bright light on sleep in nursing home patients with dementia
	Marquardt, Lynn Anne	tDCS as treatment in neuro-psychiatric disorders. The underlying neuronal mechanisms of tDCS treatment of auditory verbal hallucinations.

	Sunde, Erlend	Effects of light interventions for adaptation to night work: Simulated night work experiments
	Kusztrits, Isabella	About psychotic-like experiences and auditory verbal hallucinations. Transdiagnostic investigations of neurobiological, cognitive, and emotional aspects of a continuous phenomenon.
	Halvorsen, Øyvind Wiik	Aktørskap hjå norsklærarar i vidaregåande skule – Ein sosiokulturell intervjustudie
	Fyhn, Tonje	Barriers and facilitators to increasing work participation among people with moderate to severe mental illness
	Marti, Andrea Rørvik	Shift work, circadian rhythms, and the brain. Identifying biological mechanisms underlying the metabolic and cognitive consequences of work timing, using a rat model.
	Thomassen, Ådne Gabriel	Hardiness and mental health in military organizations. Exploring mechanism and boundary conditions.
	Husabø, Elisabeth Bakke	Implementation of indicated anxiety prevention in schools
	Hagatun, Kari	The Educational Situation for Roma Pupils in Norway. Silenced Narratives on Schooling and Future.
	Herrero-Arias, Raquel	Negotiating parenting culture, identity, and belonging. The experiences of Southern European parents raising their children in Norway.
	Moltudal, Synnøve	Purposeful Actions in Leadership of Learning Processes: A Mixed Methods Study of Classroom Management in Digital Learning Environments
2021 H	Johnsen, Anja	Barn og unge i fattige familier: Selvoppfattet skolekompetanse, etnisitet og akademisk resiliens. Hvilke faktorer kan fremme skoleprestasjoner hos barn og unge i risiko?
	Eilertsen, Silje Elisabeth Hasmo	Who profits from concentrated exposure treatment for obsessive-compulsive disorder (OCD)? A quality assurance project from the OCD-team in Bergen.
	Chegeni, Razieh	Anabolic-Androgenic Steroids and Aggression in Humans: Experimental Studies, Subgroups, and Longitudinal Risk
	Solstad, Stig Magne	Patients' experiences with routine outcome monitoring and clinical feedback systems in psychotherapy
	Oldeide, Olin Blaalid	Local drug prevention - From policy to practice: A qualitative case study of policy makers, outreach social workers and at-risk youths
	Steinkopf, Per Heine	«Being the Instrument of Change» Staff Experiences in Developing Trauma-informed Practice in a Norwegian Child Welfare Residential Care Unit.
	Tsogli, Barbara	When predictions about the "what", "where" and "when" interact with statistical learning, from a behavioural and neural perspective.

2022 V	Simhan, Indra Laetitia	Seeing and being seen: An investigation of video guidance processes with vulnerable parents of infants
	Fekete, Orsolya Réka	Clubhouse Members' Experiences of Being in Recovery in Light of Salutogenesis
	Madsø, Kristine Gustavsen	Momentary well-being in dementia: Observational assessment of psychosocial interventions and music therapy
	Olaniyan, Oyeniyi Samuel	Embracing both sides of the same coin. Work-related psychosocial risks and resources among child welfare workers.
	Harris, Samantha Marie	Mental health encounters between general practitioners and individuals with a refugee background - Help seeking and provision in the resettlement context
	Larsen, Marit Hjellset	Service support and quality of life for youth in foster care
	Vik, Berit Marie Dykesteen dr.philos.	Effects of Music Training on Cortical Plasticity: Cognitive Rehabilitation of Patients with Traumatic Brain Injury
	Abamosa, Juhar Yasin	Pathways to Social Inclusion: The Role of Institutions in the Social Inclusion of Refugees into Higher Education in Norway. Policies and practices in focus.
	Raudeberg, Rune	Improving the Methodology for Assessing Cognitive Impairment in People with Schizophrenia Spectrum Disorders
	Ågotnes, Kari Wik	Work-related risk factors for workplace bullying. The moderating effect of laissez-faire leadership.
	Stokkebekk, Jan Kristian	Navigating Prolonged Conflict: Subject positions and meaning constructions in postdivorce families
	Valle, Roald	Skoleledelse og utdanningspolitikk. Hvordan beskrives skoleledelse etter 1990?
	Woodfin, Vivian Irena	Self-Compassion and Perfectionism
	Aarestad, Sarah Helene	Treating the aftermath of exposure to workplace bullying and preventing exclusion from working life. The effect of individual resilience, return to work self-efficacy and work-focused metacognitive and cognitive treatment.
	Ampim, Gloria Abena	Transforming gender relations? Men's involvement in care for their partners and households at the time of pregnancy in rural and urban Ghana – A qualitative study

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

uib.no

ISBN: 9788230863107 (print)
9788230867280 (PDF)