The effect of cycled light exposure on clinical outcomes of preterm infants admitted in neonatal intensive care units

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BACKGROUND: Hospitalization in neonatal intensive care units (NICU) exposes preterm infants to adverse stimuli, including continuous 24-hour lighting. There is currently no standardized NICU layout advised for the best development of preterm neonates. This meta-analysis aimed to assess the impact of cycled light (CL) exposure on clinical outcomes in premature infants admitted to NICU as synthesized in previous studies.

MATERIALS AND METHODS This meta-analysis protocol was developed following the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement. A search was performed in PubMed/ MEDLINE, EMBASE, Scopus, and Cochrane databases using the MeSH/key words: "light exposure" AND pre-term AND cycled AND (RCT OR trials OR "randomized controlled trial). The pooled Mean Difference with corresponding 95% CI was computed for weight gain, duration until start of enteral feeding, and duration of ICU stay using the Mantel–Haenszel random-effect model.

RESULTS: Nine studies were included. The pooled mean difference showed that among preterm infants who had cycled light exposure, average daily weight gain (MD=6.24 grams, 95%CI=1.36 to 11.13, p=0.01) was significantly higher than those with continuous light exposure. The average time to start enteral feeding (MD=-3.84 days, 95%CI=-7.56 to -0.13, p=0.04) and average ICU stay (MD=-8.43 days, 95%CI=-12.54 to -4.31, p<0.0001) among neonates who had cycled light exposure were significantly shorter.

CONCLUSION: Benefits were seen in preterm infants when exposed to cycled light as opposed to continuous light. CL exposed infants showed a daily weight gain that was 6.24 grams higher, on average, and began enteral feeding nearly 4 days sooner. It led to a decrease in the duration of ICU stay by around 8 to 9 days on average. Further trials to determine the impact of cycled light exposure on morbidity and mortality among preterm neonates is recommended.

KEYWORDS: *pre-term, cycled light (CL), continuous bright light*

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The authors affirm that this manuscript is original, has been read and approved by all contributing authors, that each author meets the established criteria for authorship, and that the content represents a truthful and accurate account of the work conducted.

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4. To compare the mortality rates between preterm neonates who underwent cycled light exposure versus constant light or control.

Materials and Methods

This meta-analysis protocol was developed following the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement. The selection criteria were as follows:

a.1. Type of intervention. Cycled light exposure (lighting that follows a day–night) of any duration or frequency was included. The comparator was continuous/constant light or standard care as control group.

a.2. Types of outcomes. The primary outcomes for the meta-analysis was daily weight gain, and duration of ICU stay. Secondary outcomes will be incidence of mortality and time to start enteral feeding.

a.3. Population of studies. Preterm neonates born <37 weeks of gestation who were admitted to the ICU for any indication. Neonates with congenital anomalies and those requiring a long period (more than 12 h) of continuous lighting for frequent treatment interventions, will be excluded from the study. No restrictions were applied in terms of sex, race/ethnicity or socioeconomic status.

a.4. Types of studies. Only randomized controlled trials were considered for inclusion. There were no limitations on language or date. The analysis excluded prospective cohort studies, observational studies, review papers, case reports, case series, letters to the editor, commentaries, proceedings, laboratory science investigations, poster or conference abstracts, and any other research that are not relevant.

a.5. Types of studies. Only published literature was included.

a.6. Publication date. Studies published until September 2024 were included

a.7. Language. Only studies written in the English language were included

a.8. Location. Studies published in any country were included.

A search was performed in PubMed/MEDLINE, EMBASE, Scopus, and Cochrane databases from inception to September 2024 databases using the MeSH and key words: "light exposure" AND pre-term AND cycled AND (RCT OR trials OR "randomized controlled trial). Two authors evaluated the titles and abstracts of the papers that have been found. The reference lists were imported into an Excel spreadsheet, and any duplicate articles were eliminated. Further pertinent articles were located by examining the reference lists of papers obtained from the initial search.

The number of preterm births has increased over the past 20 years, which is mostly attributed for the rise in premature neonates. The Philippines has a 3.0% preterm birth rate and ranks eighth in the world for preterm births, indicating a high burden. [1, 2] Admission in the neonatal intensive care units places the preterm infant in a significantly different environment. The NICU and intrauterine environments differ greatly from one another. One of the major concerns on neonates in the NICU is their early exposure to intense and variable lighting. A newborn baby's ability to develop normally can be impacted by the physical environment in the NICU, including the lighting.[3] With this, designing a NICU environment from a chronobiological standpoint might be beneficial in improving preterm outcomes.

Despite prior research examining the impact of cycled-light exposure on preterm newborn development, there is still a lack of consensus on the ideal NICU layout. In the local setting, the preterm neonates are exposed to varying light conditions, but the majority are constantly exposed to strong light at all times of the day. In the institution, patients in the NICU are often exposed to continuous bright light.

This has significance in the field of neonatology because it could result in new approaches to the management of preterm infants and the advancement of better health outcomes for this vulnerable group. Furthermore, knowing how cyclic light exposure affects treatment outcomes will help create evidence-based standards for infant care and provide as a foundation for more research in a comparable environment. Findings of this study can help establish the standard recommendation for light-dark environment in the Neonatal Intensive Care Unit of this institution and shed light to the significance of environmental factors in neonatal care. The study may serve as a guide to future initiatives meant to enhance outcomes for this population.

The general objective was to determine the effect of cycled light exposure on clinical outcomes among preterm neonates admitted in Neonatal Intensive Care Units. Specific objectives are as follows:

1. To compare weight gain (from pre-intervention to discharge) between preterm neonates who underwent cycled light exposure versus constant light or control

2. To compare the length of ICU admission and length of hospitalization between preterm neonates who underwent cycled light exposure versus constant light or control

3. To compare the time to enteral feeding between preterm neonates who underwent cycled light exposure versus constant light or control

To compare the mortality rates between preterm neonates who underwent cycled light exposure

The titles and abstracts obtained from the search approach were examined separately by two authors. To reduce data redundancy caused by several reports, articles authored by the same individual were compared. If the title or abstract of a report is found to meet the inclusion criteria, the full paper was obtained. Studies deemed potentially relevant by at least one author were obtained and assessed in their entirety. Articles that match the specified requirements were evaluated independently by two authors, and any differences were handled through agreement. A search and selection process flow diagram were created in accordance with PRISMA standards. Using a standardized extraction form, the following data were extracted independently by 2 authors: study name (along with the name of the first author and year of publication), country where the study was conducted, patient characteristics (AOG, sex, birthweight, APGAR scores), source from which patients or study participants were selected, study design, exposure definition, outcome definition, reported outcomes, methods for controlling covariates and confounding variables controlled for, number of neonates per study group, and total number of participants. Data extraction forms were cross-checked to verify accuracy and consistency of extracted data.

The quality of the studies was independently assessed by 2 investigators using the risk of bias tool according to the Review Manager (version 5.4, The Cochrane Collaboration, Oxford, UK). The quality was evaluated using the following potential sources of bias: sequence generation, allocation concealment, blinding of participants or outcome assessor, incomplete data, and selective reporting. The methodology for each study was graded as “high”, “low”, or “unclear”, to reflect the risk of bias. Any discrepancies were resolved through discussion. If agreement cannot be reached, the dispute will be resolved with the help of a third investigator. Authors of each study were contacted in case there is missing data. Ad-hoc tables and forest plots were designed to summarize data from the included studies and show their key characteristics and any important questions related to the objectives of this meta-analysis. The pooled Mean Difference with corresponding 95% CI was computed for weight gain, duration until start of enteral feeding, and duration of ICU stay. If a study only reported the median and range of the samples or the first and third quartiles, the sample mean and standard deviation were computed using the method by Wan et al 2014.[18] A two-sided p-value of 0.05 was considered statistically significant for mean difference. Between-study heterogeneity was assessed using Cochran’s Q and Higgins’s I^2 statistics. An I^2 greater than 50% was considered as showing considerable heterogeneity, and data were analyzed using the Mantel–Haenszel random-effect model.

Publication bias was assessed by using Begg's funnel plot. Begg's funnel plots are scatter plots of the log ORs of individual studies on the x-axis against 1/standard error (SE) of each study on the y-axis. An asymmetrical funnel plot was considered to indicate the presence of publication bias. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system was used to determine the evidence grade. This system employs a sequential evaluation process that starts with an assessment of the quality of the evidence, continues with an evaluation of the risk-benefit balance, and ends with a determination of the strength of the recommendations.

Results

A total of 835 studies were identified using the previously mentioned search terms and from backward research of references from previously cited journals, of which 817 were eliminated from title and abstract screening because of duplicates and non-relevant study population or treatment groups. From the remaining 18 studies, 9 were excluded because they have no comparator group or were non-RCTs. Overall, 9 studies were included in the meta-analysis (Fig. 1).

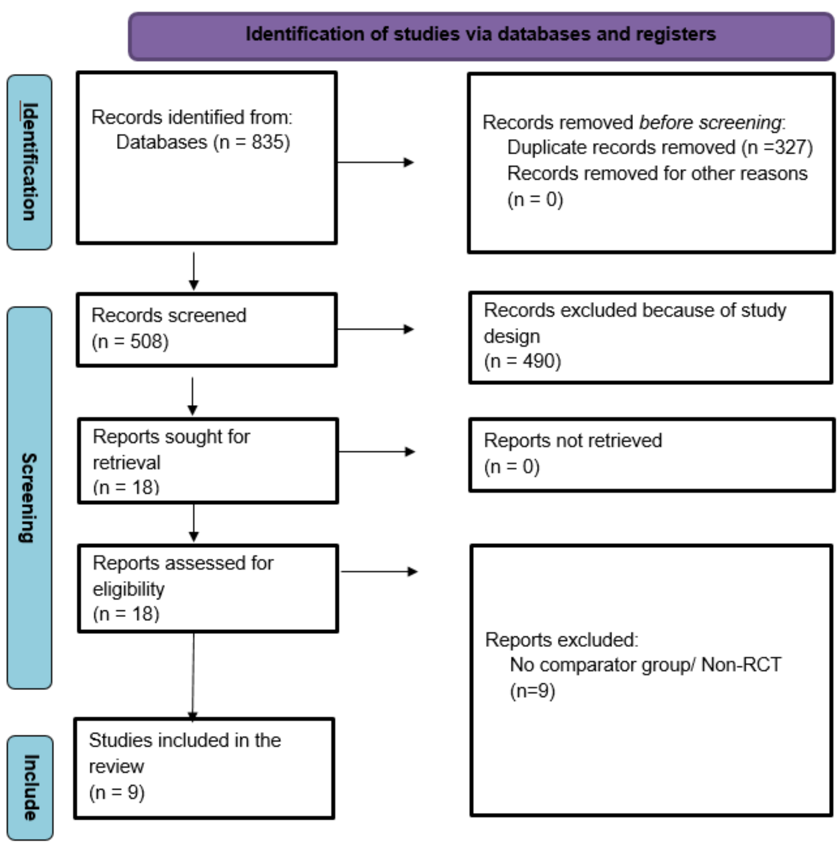


Figure 1. PRISMA Flowchart for the literature search.

As seen in Table 1, the studies were published between 1986 to 2022 from a variety of countries. The sample size varied between 30 to 294, with majority of patients being male. The timing of CL interventions also varied across studies including how it was implemented. In all studies, the control group was continuous lighting.

Table 1. Characteristics of studies included

Author, year, country	No. of patients	Male: Female ratio	Description of light cycle intervention	Control	Outcomes reported
Boo 2007 Malaysia	N=96	53:43	The cycled light exposure was performed by switching the lights in the cubicles on between 07:00 and 19:00 hours and switching them off between 19:00 and 07:00 hours.	Continuous light	Weight gain Time to initiate enteral feeding ICU stay
Esmaeilizadeh 2016 Iran	N=60	Not reported	During cycling, the levels of lighting and sound were kept respectively at 3 - 7 lux and 45 decibels. Specific timing of CL was not described	Continuous light	Weight gain
Farahani 2018 Iran	N=66	42:24	Cycled lighting (CL) exposure consisted of 12 hours of normal NICU lighting from 07:00 to 19:00 and 12 hours of reduced lighting from 19:00 to 07:00.	Continuous light	Weight gain ICU stay
Mann 1986 UK	N=41	Not reported	The study involved a night and day nursery where the intensity of light and noise was reduced between 7 pm and 7 am.	Continuous light	Time to initiate enteral feeding
Marzouk 2019 Egypt	N=40	31:9	In the study, CL consisted of 12 hours of normal NICU lighting and 12 hours of reduced lighting, achieved by using a sheet of acrylic glass covered by a dimming cotton cover.	Continuous light	ICU stay
Miller 1995 USA	N=41	Not reported	The lighting manipulation occurred in three stages: from 7 a.m. until dusk, both rooms had the same amount of illumination; from 6 p.m. until 11 p.m., an extra bank of lights was turned on in the noncycled room to approximate daytime illumination levels; and at 11 p.m., one of the banks of indirect fluorescent lights was turned off in the cycled lighting room	Continuous light	Time to initiate enteral feeding ICU stay
Olgun 2024 Turkey	N=30	Not reported	The cycled light exposure was performed by covering the infants' eyes with an eye patch (phototherapy patch) between 8 PM and 9 PM to create darkness until 8 AM, constituting the study group.	Continuous light	Weight gain Time to initiate enteral feeding ICU stay
Sánchez□ Sánchez 2022 Mexico	N=294	Not reported	The cycled light exposure was performed by implementing a light/darkness cycle (LDC) in which infants were exposed to normal room light conditions from 07:00 to 19:00 and to reduced light conditions (25 lx) from 19:00 to 07:00 the following day.	Continuous light	ICU stay
Vásquez-Ruiz 2014 Mexico	N=38	Not reported	The cycled light exposure was performed by placing individual removable helmets over the infants' heads to create a light/dark (LD) environment. This setup was used from 19:00 to 07:00, reducing illumination to a light intensity of 27 lux at the level of the eyes.	Continuous light	ICU stay

As seen in Figure 2, all nine studies have concerns on performance bias while eight studies have concerns on detection bias due to the non-blinded study design. Given the nature of study interventions, clinicians conducting the study are impossible to be blinded on the treatment groups. However, Esmaeilizadeh et al. 2016 was able to perform blinding among data collectors to avoid detection bias. No other concerns were reported for attrition bias, reporting bias, and other biases.

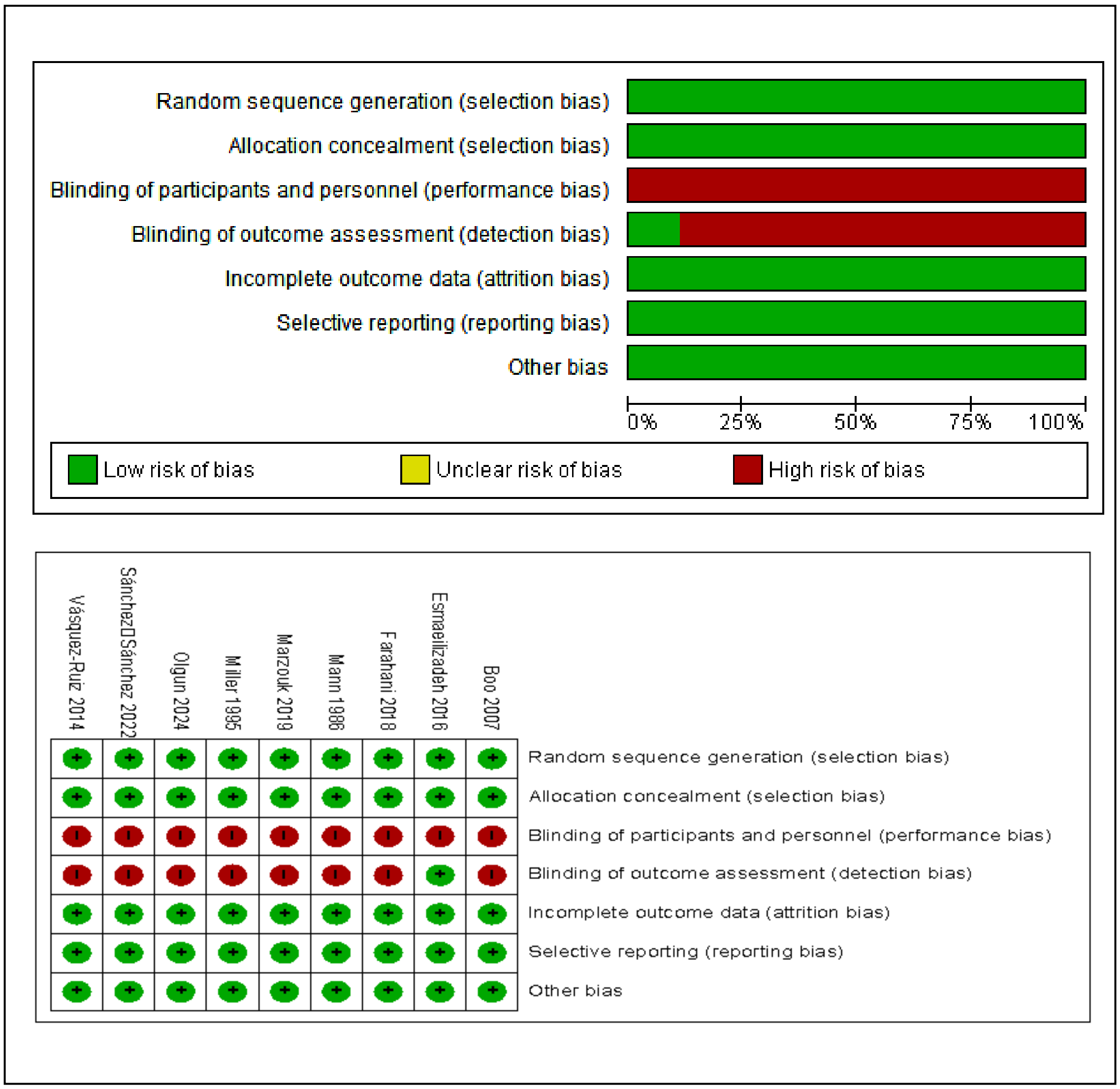


Figure 2. Risk of bias assessment of all included studies.

As seen in Figure 3, three of four studies showed significantly higher average daily weight gain in those who underwent cycled light exposure. Overall, the pooled mean difference showed that the average daily weight gain was significantly higher among preterm infants who had cycled light exposure (MD=6.24 grams, 95%CI=1.36 to 11.13, p=0.01). The studies showed moderate heterogeneity (I^2=54%).

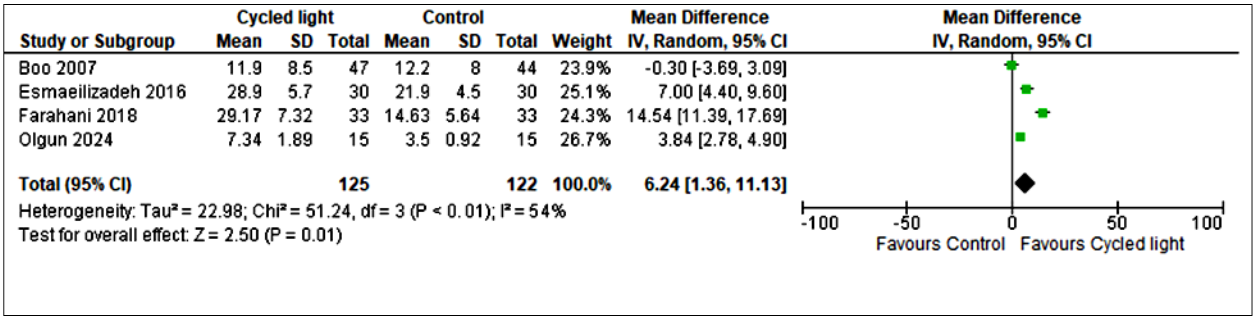


Figure 3. Effect of cycled light exposure vs continuous bright light exposure on average daily weight gain.

As seen in Figure 4, three of four studies showed significantly shorter time to start enteral feeding in those who underwent cycled light exposure. Overall, the pooled mean difference showed that the average time to start enteral feeding was significantly shorter among preterm infants who had cycled light exposure (MD=-3.84 days, 95%CI=-7.56 to -0.13, p=0.04). The studies showed moderate heterogeneity (I^2=59%).

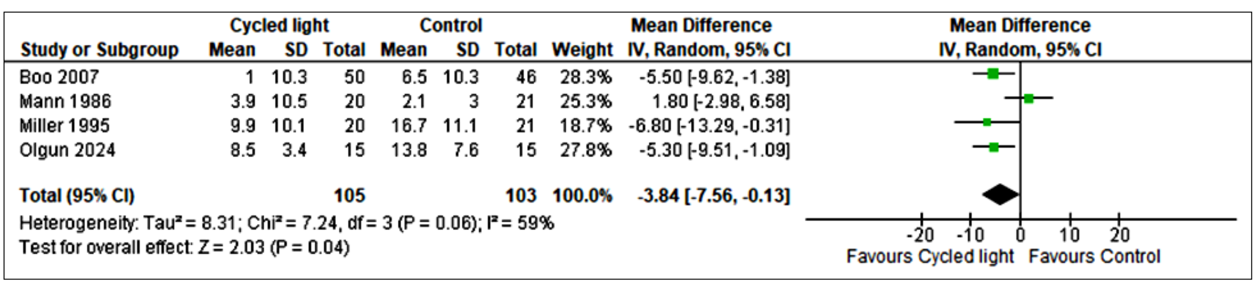
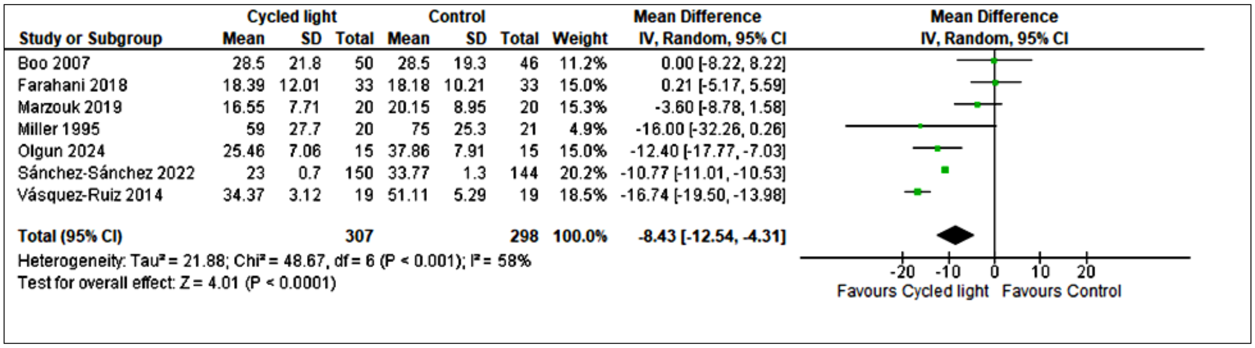


Figure 4. Effect of cycled light exposure vs continuous bright light exposure on time to enteral feeding

As seen in Figure 5, five of seven studies showed significantly shorter ICU length of stay among those who underwent cycled light exposure. Overall, the pooled mean difference showed that the average ICU length of stay was significantly shorter among preterm infants who had cycled light exposure (MD=-8.43 days, 95%CI=-12.54 to -4.31, p<0.0001). The studies showed moderate heterogeneity (I^2=58%).



Study or Subgroup	Cycled light Mean	Cycled light SD	Cycled light Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Boo 2007	28.5	21.8	50	28.5	19.3	46	11.2%	0.00 [-8.22, 8.22]
Farahani 2018	18.39	12.01	33	18.18	10.21	33	15.0%	0.21 [-5.17, 5.59]
Marzouk 2019	16.55	7.71	20	20.15	8.95	20	15.3%	-3.60 [-8.78, 1.58]
Miller 1995	59	27.7	20	75	25.3	21	4.9%	-16.00 [-32.26, 0.26]
Olgun 2024	25.46	7.06	15	37.86	7.91	15	15.0%	-12.40 [-17.77, -7.03]
Sánchez-Sánchez 2022	23	0.7	150	33.77	1.3	144	20.2%	-10.77 [-11.01, -10.53]
Vásquez-Ruiz 2014	34.37	3.12	19	51.11	5.29	19	18.5%	-16.74 [-19.50, -13.98]
Total (95% CI)			**307**			**298**	**100.0%**	**-8.43 [-12.54, -4.31]**

Heterogeneity: Tau² = 21.88; Chi² = 48.67, df = 6 (P < 0.001); I² = 58%
Test for overall effect: Z = 4.01 (P < 0.0001)

Figure 5. Effect of cycled light exposure vs continuous bright light exposure on length of ICU stay

In terms of morbidity and mortality, none of the studies included mortality as its outcome. This is because mortality is an exclusion criterion in all the studies included. Also, no studies reported on morbidity outcomes associated with cycled or non-cycled light therapy. The symmetry in funnel plot analysis indicates low likelihood of publication bias (Figure 6).

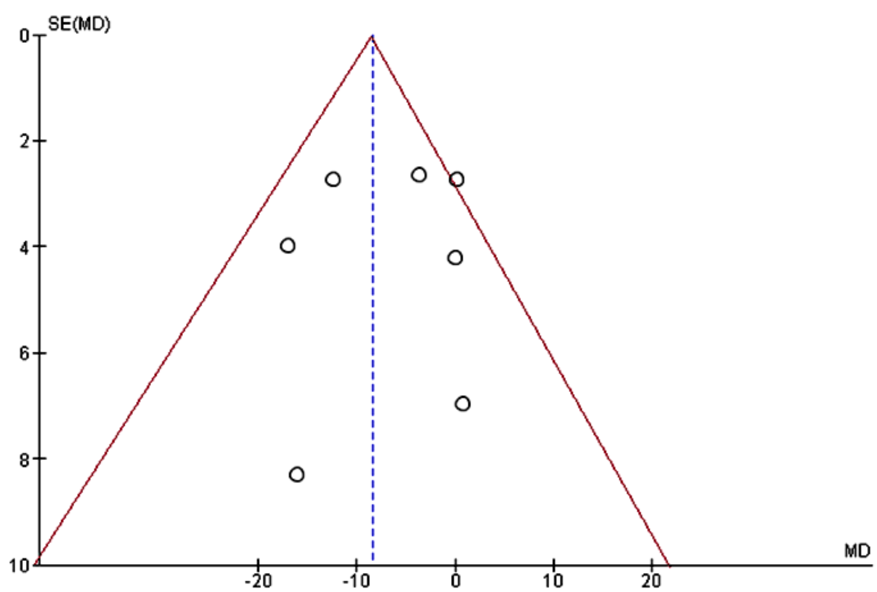


Figure 6. Funnel plot analysis on included studies

As seen in Table 2, the GRADE level of evidence generated by this meta-analysis was high. All outcomes started with a high grading since they included RCTs. The quality of evidence is maintained to be high despite the risk for performance and detection bias due to moderate heterogeneity only, consistency in observed effect, and large effect size.

Table 2. SUMMARY EFFECT ON PATIENT OUTCOMES

Outcomes	Pooled Mean Difference	p-value	Heterogeneity	GRADE level of evidence
Daily weight gain	MD=6.24 grams, 95%CI=1.36 to 11.13	p=0.01	54%	+++ High
Time to enteral feeding	MD=-3.84 days, 95%CI=-7.56 to -0.13	p=0.04	59%	+++ High
Length of ICU stay	MD=-8.43 days, 95%CI=-12.54 to -4.31	p<0.0001	58%	+++ High

Discussion

There were 9 studies included in this meta-analysis. All the studies concluded, as well as the analysis showed that cycled light (CL) promotes weight gain among premature infants. All the studies highlight the significance of CL for the health, growth, and development of premature newborns. Cyclical lighting, which refers to natural day/night-based illumination, aligns with the body's circadian rhythm and hence enhances conditions for deep sleep. [14] Implementing the light-dark cycle can mitigate environmental stress and difficulties in NICU preterm newborns, leading to improved weight gain. The enhancement of the synthesis of growth-related components, promote weight gain, and improve the health status of neonates.[14] In elaboration, the full-term newborn sleeps approximately 16 to 17 hours within a 24-hour period, evenly distributed between night and day.[16] By 3 to 6 weeks of age, overall sleep duration has diminished to 14 to 15 hours, and a typical circadian rhythm characterized by increased nocturnal and reduced daytime sleep has emerged. This sequence is thus delayed in preterm newborns.

Consequently, disparities in sleep habits between infants from the two groups would not be anticipated at birth but would manifest after the projected delivery date. The hypothalamus regulates sleep, hunger, and weight growth, which may be influenced by exposure to light and darkness. Conversely, if alone sleep were affected by the cyclical environment, weight gain might occur as a secondary consequence of sleep's anabolic action. [16]

Some studies contradict the findings that continuous 24-hour near darkness, facilitated by light-reducing goggles, can significantly improve weight gain in very low-birth-weight preterm newborns. This is because persistent darkness doesn't promote the proper development of circadian rhythms and can be distressing for preterm infants. [19] Another study found no significant difference in the effects of continuous light and low lighting both in the hospital and the home settings on weight gain in premature newborns. The difference may be due to their similar influences on weight gain or because CL at home was executed by parents without direct oversight, potentially not following the protocol. [20] In another study on 38 preterm neonates, it found no significant difference in weight gain pattern before or after a cyclical or continuous lighting intervention for five days. This is because day-night synchronized cyclical lighting does not significantly affect weight gain during the first days of the intervention. [21]

In addition to the benefits of CL to weight gain, it also showed shortened NICU stay. The duration of premature neonates' hospitalization in the NICU serves as a reliable metric for evaluating the intervention impact on clinical outcomes. [22] A possible explanation for this observed effect is the significant shorter time to start enteral feeding infants exposed to cycled light. Time to start enteral feeding is an indicator of gastrointestinal maturity and overall health in premature neonates. [23] This finding suggests that cycled light therapy may have a positive impact on the development and functioning of the gastrointestinal system in preterm infants, potentially leading to improved health outcomes and reducing their NICU stay. Yet, it should be kept in mind that different outside factors can either shorten and lengthen the stay of the pre-termed infant inside of NICU and cannot solely attribute to their weight gain. A prolonged NICU stay may put not only significant financial burdens but also higher risk for infections. Thus, the clinical significance of this study's findings emphasizes that a simple and cost-efficient intervention may help reduce financial burden and reduce exposure to hospital infections. Therefore, it is important to consider the potential benefits of implementing such interventions in NICU settings to improve outcomes for pre-term infants. Additionally, further research is needed to explore the long-term effects of these interventions on both financial and health outcomes for this vulnerable population.

The previous study of Morag and Ohlsson, including the updated version, also examined the potential advantages of a light/ dark cycle, revealing its beneficial effects for infants, which included a reduction in the duration of supplemental oxygen requirement, as well as improved food tolerance resulting in enhanced average weight gain.[6,23] These results support the findings of this meta-analysis, demonstrating that the necessity for a light/dark cycle in the NICU has remained consistent over the years. The study implies that a standardized lighting scheme tailored to various developmental stages of infants is essential, capable of delivering varying light intensities at different times throughout the day. This can help optimize the benefits of CL on weight gain while also addressing other factors that contribute to the growth and health of the neonates, such as feeding practices and developmental care.

Most studies in the meta-analysis include investigation with limited number of sample size which limited the generalizability of their results. Nevertheless, the findings on the weight gain of the preterm neonates remain consistent, enhancing the accuracy of the results. Majority of the studies included adjustment in the intensity of the lighting in the room to facilitate the shifting in the light-dark cycle. Two studies however used a different method, one using eye patches (Olgun 2024) while the other placed removable helmets to create the light/dark environment (Vásquez-Ruiz 2014). Light-triggering signals sent from the retina to the suprachiasmatic nucleus of the brain set the timing of the circadian clock, hence variation in the light-dark environment would especially entail the reduction of the light exposure of the retina through the eyes [24]. There was however no study that described how the light intensity is affected by changing the ambient light, putting on an eye patch or placing a removable helmet. Also, there were 2 studies that included noise reduction together with the manipulation of the light as form of intervention (Esmaeilizadeh 2016; Mann 1986). Some studies have shown that noise levels have effects on the physiological processes and stress levels of newborns in the NICU, which may affect their growth and development [25]. An analysis exploring the effect of noise in the outcomes measured in this study as an independent factor and in combination with light exposure may be one area which can be explored further. To further explore the benefits of adapting cycled lighting in NICUs, it is recommended that the relationship between the NICU lighting environment, infant biological rhythms, and behavioral development in preterm infants needs to be explored. Exploring the effects of varying methods of light intensity adjustments and noise manipulation are also areas of interest further future research. Hopefully a local clinical trial here in this institution can be done once the on-going expansion of the

NICU is completed. In combination, these research findings should provide helpful information to clinicians as they make decisions concerning the use of different lighting arrangements in infant nurseries.

Conclusion

This meta-analysis provides a high-quality evidence supporting the benefit of using cycled light exposure compared to continuous light among preterm infants. The average daily weight gain of CL exposed infants was higher by as much as 6.24 grams per day while the time to start enteral feeding was shorter by an average of almost 4 days. These positive outcomes also resulted in shorter length of ICU stay by an average of 8 to 9 days. These findings suggest that cycled light exposure may have a significant impact on the overall health and development of preterm infants. Implementing this intervention in neonatal intensive care units could potentially lead to improved outcomes and reduced healthcare costs for this vulnerable population. Further trials with cycled light exposure protocols is recommended to determine the impact of CL on morbidity and mortality.

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