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Research Article

Environmental lighting conditions in neonatal intensive care units and their potential relevance for circadian entrainment: A multicenter observational study

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ABSTRACT

Background: Light is the primary environmental cue synchronizing circadian rhythms, yet the lighting conditions in neonatal intensive care units (NICUs) often deviate from natural light–dark cycles. This study aimed to quantify circadian-relevant light exposure in NICUs and examine its potential association with neonatal melatonin production.

Methods: In this prospective multicenter study, ambient and procedural illuminance were measured at patient and caregiver eye level using a portable light meter across eight NICUs in four tertiary hospitals. In a single-center substudy, a dosimeter continuously recorded illuminance and correlated color temperature (CCT). Urinary 6-sulfatoxymelatonin (aMT6s) was collected every four hours on days 1, 2, 3, 5, and 7 from 37 preterm and term neonates.

Results: Among 1022 measurements, 82.3% (neonates) and 81.8% (caregivers) were exposed to <100 lx at eye-level. Examination lamps displayed significant variability, with maximum intensities ranging from 3747 to 25,720 lx. Across 314 patient-days, median daytime illuminations never exceeded 100 lx, whereas nighttime exposure exceeding 100 lx for more than 10 min occurred on 24.4% of days. CCT values remained near 4000 K throughout the 24-h cycle, showing minimal spectral variation. Urinary aMT6s showed no diurnal rhythm and did not differ between term and preterm infants.

Conclusion: NICU lighting conditions were characterized by low daytime illuminance, limited day–night spectral variation, and recurrent nocturnal exposure to artificial light with higher correlated color temperatures. These environmental lighting patterns may be potentially unfavorable for circadian entrainment in neonates and warrant further investigation regarding their biological relevance for hospitalized infants and healthcare staff within the same environmental setting.

Implications for clinical practice: Integrating circadian-aware lighting concepts into daily nursing workflows, including optimized daytime illumination and reduced nocturnal light exposure during care activities, may represent a practical strategy to support neonatal adaptation and improve NICU lighting environments.

Introduction

Life on earth has evolved under cyclic environmental conditions shaped by the 24-h light–dark cycle, temperature fluctuations, and feeding rhythms [1]. Among environmental time cues, light is the most potent synchronizer of the circadian system, acting primarily on the

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central circadian pacemaker in the suprachiasmatic nucleus, whereas additional zeitgebers, such as feeding rhythms, may contribute more strongly to peripheral circadian entrainment. Through a network of photoreceptors, each sensitive to specific wavelengths, light signals are transduced into neuronal and hormonal outputs that modulate rhythmic gene expression and systemic physiology [2].

Natural day–night light variation is a major regulator of circadian timing [3]. The circadian effects of light depend not only on illuminance intensity, but also on spectral composition, timing, duration of exposure, and retinal light exposure characteristics [4]. However, since the Industrial Revolution, humans have spent most of their daytime hours indoors under artificial lighting while becoming increasingly exposed to light at night. This imbalance has given rise to a modern phenomenon known as light pollution, defined as excessive or mistimed exposure to artificial light, with adverse biological and ecological consequences [3]. Moreover, recent evidence suggests that altered or circadian-unfavorable environmental lighting conditions may negatively affect human health. It is estimated that today, over 80% of the world's population is affected by circadian-unfavorable lighting conditions in various forms [3]. The health effects of circadian-unfavorable lighting conditions appear particularly detrimental in vulnerable populations, including pregnant women, developing fetuses, and preterm infants in Neonatal Intensive Care Units (NICUs) [5–8].

Pregnancy, fetal development, and the neonatal period constitute a unique biological continuum characterized by profound, highly regulated physiological adaptations [9]. The circadian system plays a central role in this process. During late gestation and early postnatal life, the fetal clock progressively matures under the influence of maternal circadian signals—most notably melatonin-which cross the placenta and entrain fetal rhythms to external day–night cycles [10,11]. This maternal–fetal synchrony supports the coordination of endocrine, metabolic, and behavioral functions, preparing the neonate for extrauterine life. Disruption of this circadian coupling during the perinatal window-through shift work, hospitalization, or exposure to artificial light-can have immediate and long-term repercussions, including altered metabolic, cardiovascular, neurological, and psychiatric outcomes later in life [10,12]. High-risk pregnancies are especially vulnerable to chrononisruption, as inpatient care often involves prolonged stays under artificial light with reduced access to natural daylight [13]. Preterm birth, in turn, abruptly interrupts maternal–fetal circadian communication, exposing the neonate to environmental time cues that differ substantially from intrauterine conditions, while endogenous circadian rhythmicity may remain immature during early postnatal life. After birth, the lighting environment of the Neonatal Intensive Care Unit (NICU) becomes an important environmental cue that may contribute to the development and entrainment of the neonatal circadian system alongside other biological and behavioral zeitgebers. However, this environment is typically characterized by low daytime illuminance, limited day-night contrast, reduced spectral variation across the 24-h cycle, and recurrent nocturnal exposure to brighter artificial procedure lighting-conditions that differ substantially from natural light–dark variation patterns.

Despite the recognized importance of light for neonatal physiology, quantitative data on illumination and spectral characteristics in modern NICUs remain limited. Therefore, we conducted a prospective multicentre pilot study in four tertiary neonatal centres. Our study aimed to characterize environmental lighting conditions in NICUs and to explore whether these conditions differ substantially from physiologic day–-night light variation patterns that are generally considered relevant for circadian entrainment. In addition, we explored potential associations between NICU lighting exposure and neonatal melatonin rhythm development as reflected by urinary 6-sulfatoxymelatonin excretion.

Methods

Objective

This prospective observational pilot study aimed to evaluate light exposure and circadian rhythm characteristics of neonates hospitalized in the Neonatal Intensive Care Unit (NICU). Specifically, we sought to (1) quantify the illumination levels and spectral composition of the NICU environment during day and night, and (2) assess the potential influence of these lighting conditions on neonatal melatonin production, as reflected by urinary 6-sulfatoxymelatonin (aMT6s) excretion.

Assessment of lighting conditions in NICUs

Illuminance (lux) was measured at both patient and caregiver eye level using a portable light meter (Testo 540, Testo SE & Co. KGaA, Germany) across eight NICUs in four tertiary hospitals in Germany. Caregiver eye-level measurements were included to characterize NICU lighting conditions during routine caregiving activities. Measurements were performed in 86 bedside locations at three distinct daytime intervals-morning, afternoon, and evening. For each measurement, patient and nurse positioning, distance to the nearest window, and weather conditions were documented. In addition, the illuminance of bedside examination lamps was recorded at patient eye level from a standardized distance of 70 cm, using standardized positioning conditions designed to simulate typical procedural lighting exposure during routine clinical care. Measurements were obtained between 10:00 and 23:15 under varying ambient and procedural light conditions. To differentiate between indirect and direct lighting, bedside lamps were positioned at a standardized distance of 70 cm from the infant's eye level and directed either toward the ceiling (indirect mode) or toward the patient (direct mode). The caregiver's eye level was standardized at 165 cm. In accordance with European lighting standards for infant care units (DIN EN 12464-1), daytime ambient illumination exceeding 200 lx was considered adequate. For each measurement, the following parameters were documented: lamp type, time of day, weather conditions, window orientation, and caregiver's position relative to the window.

Continuous light monitoring and melatonin assessment

A subset of neonates admitted to the NICU at the University Children's Hospital Bonn underwent continuous monitoring of circadian-active light parameters and urinary melatonin excretion.

A total of 37 neonates (25 preterm-born [PT] and 12 term-born [TB]) were included in the study. Preterm-born infants had a median gestational age of 32.6 weeks (range 25.1–36.9 weeks) and a median birth weight of 1930 g (range 580–3005 g). Term-born infants had a median gestational age of 39.1 weeks (range 37.1–41.3 weeks) and a median birth weight of 3090 g (range 1980–3530 g). Infants with renal or hepatic failure or hydrocephalus were excluded. Retinal pathology and major neurological injury were not systematically assessed as exclusion criteria in this pilot study. To characterize the 24-h lighting environment, a portable light dosimeter (LDM) developed by the University of Lucerne (Switzerland) was placed at the patient's eye level. The LDM continuously recorded illuminance (lux), correlated color temperature (CCT, K), and circadian-effective radiation dose (Hec) at 10-s intervals throughout hospitalization. The dosimeter was positioned toward the infant's face and routinely adjusted during nursing care according to changes in head and body positioning in order to maintain alignment with the infant's direction of gaze whenever possible. While illuminance and CCT provide indirect information regarding environmental lighting characteristics, they do not directly quantify melanopic or circadian-effective retinal irradiance. Illuminance >200 lx during daytime was considered adequate; nighttime conditions (21:30–07:00), selected to approximate the expected biological night and routine nocturnal care period within participating NICUs, were considered potentially

unfavorable for circadian entrainment if illumination exceeded 100 lx or CCT exceeded 3500 K.

The dosimeter was shielded whenever the patient's eyes were covered (e.g., during phototherapy). For infection control reasons, monitoring was omitted in patients with multi-resistant organisms. Of 17 available NICU beds, 15 yielded analyzable recordings.

Analysis of urinary 6-sulfatoxymelatonin (aMT6s) excretion

Urine samples were collected from 26 catheterized neonates on days 1, 2, 3, 5, and 7 following study inclusion. Samples were obtained every four hours at 04:00, 08:00, 12:00, 16:00, 20:00, and 24:00 h to align with routine clinical care. Urine volume was documented for each 4-h collection to calculate the total aMT6s excretion per interval (ng/4 h). Samples were centrifuged at 3000*g* for 5 min within one hour of collection and stored at −80 °C until analysis. aMT6s concentrations were quantified by a competitive ELISA (IBL-International, Hamburg, Germany). The assay procedure followed the basic principle of a competitive ELISA. The results were expressed as ng/mL. The mean recovery of aMT6s was 105.8%, and the assay's sensitivity was 1.0 ng/mL. The intra-assay variation was 5.2% at 5.8 ng/mL and 12.2% at 204 ng/mL. The inter-assay variation was 5.1% at 12.4 ng/mL and 14.9% at 220 ng/mL. All samples were analyzed in duplicate. The aMT6s excretions were calculated by multiplying the measured aMT6s concentrations by the 4-h urine volumes and expressed as ng/4 h.

Statistical analysis

Statistical analyses were conducted via SPSS 29.0 (SPSS Inc., Chicago, IL, USA). The variables were tested for normality using the Kolmogorov-Smirnov test. Documented values were not normally distributed, so the two-tailed non-parametric Mann-Whitney *U* test was used for group comparison. The non-parametric Friedman and Wilcoxon signed-rank tests were used for the inferential statistics on paired samples. To further analyze associations between parameters, Spearman's rank correlation coefficient test was used. To account for diurnal light variation, the 24-h period was divided into five intervals representing characteristic lighting phases. Median and maximum illuminance (lx), exposure duration within specific illuminance bands (<100 lx, 100–300 lx, >300 lx), and median CCT (K) were calculated per interval. Urinary aMT6s excretion was analyzed across the corresponding 4-h time bins. All data are presented as the median (interquartile range (IQR)). In our analysis, *p*-values of <0.05 were considered statistically significant.

Results

Ambient lighting conditions

A total of 1022 individual illuminance measurements were obtained across participating centers (Table 1). In 82.3% of neonatal and 81.8% of caregiver measurements, the recorded illuminance at eye level was below the European Union-recommended 100 lx for infant care environments.

Table 1
Indoor lighting conditions in the 8 NICUs.

	Morning	Afternoon	Evening/ Night
Eye level of newborns	46 lx (18–75)	35 lx (18–78)	13 lx (2–48)
Eye level of the healthcare professional	47 lx (25–87)	47 lx (25–75)	14 lx (3–45)
Indirect lighting by examination light	61 (35–80)	47 (31–86)	15 (7–29)
Direct lighting by examination light	582 (221–1051)	475 (221–985)	678 (243–3511)

All data is presented as the median (interquartile range (IQR)).

Illuminance levels showed a significant inverse correlation with the distance between the patient bed and the nearest window (Spearman's $\rho = -0.344$, $p < 0.001$). Furthermore, illumination was strongly influenced by outdoor weather conditions: under sunny conditions, median (IQR) illuminance reached 47 lx (18–85) for newborns and 65 lx (37–147) for caregivers, whereas under cloudy conditions, values dropped to 25 lx (10–64) and 35 lx (14–60), respectively ($p = 0.048$ for neonates; $p < 0.001$ for caregivers).

Examination light used in NICUs

Across the four participating NICUs, seven different models of examination lamps were identified. Three models featured adjustable color settings (warm white (~3000 K), neutral white (~4100 K), and cold white (~5000 K)) in addition to a dimmer function. Among these, minimum light intensities ranged from 720 lx to 6093 lx, while maximum direct illuminance values varied between 3747 lx and 25,720 lx. The remaining four lamp models offered only two fixed intensity settings and lacked spectrum (color temperature) adjustment. Their output intensities ranged from 50 lx to 904 lx, with median values of approximately 145 lx, 395 lx, 625 lx, and 945 lx, respectively.

Exposed illuminance in newborn infants in the NICU

Over a total of 314 patient-days, illuminance exposure was documented for 37 neonatal patients (Table 2). At no time of day did the median exposed illuminance reach the recommended minimum indoor standard of 100 lx as specified by DIN EN 12464–1. Illuminance levels exceeding 300 lx for longer than 30 min were observed on only 8.3% of patient-days before noon and 3.4% in the afternoon, indicating limited daytime light exposure that may be less favorable for circadian entrainment. Conversely, nighttime illuminance levels exceeding 100 lx for more than 10 min occurred on 24.4% of patient-days, reflecting frequent episodes of bright light during the nocturnal period. Although color temperature (CCT) values were significantly lower at night—3987 K (IQR 3324–4680)—compared with pre- and post-noon periods (4362 K [3920–4738] and 4299 K [3902–4662], respectively; $p < 0.001$), the nocturnal CCT remained within a neutral-white spectrum (~4000 K). Such relatively stable exposure to mid-range CCT values during late afternoon and night hours differs from natural day–night spectral variation patterns and may be less favorable for circadian entrainment.

Urinary aMT6s excretion in newborn infants

The median (IQR) aMT6s excretion did not differ significantly between afternoon, evening, and night ($p > 0.05$). aMT6s excretion was not significantly different in preterm-born infants and term-born infants (See Table 3).

Discussion

Our study provides quantitative evidence that contemporary NICU lighting environments differ substantially from natural day–night light-variation patterns and exhibit limited temporal and spectral dynamics throughout the 24-h cycle. Across all units, daytime illuminance at both newborn infants' and healthcare professionals' eye levels remained well below the recommended European indoor standard of 200 lx (DIN EN 12464–1), with median levels of <50 lx. For context: even on a cloudy day, natural daylight reaches approximately 10,000 lx, while it can reach 100,000 lx or more on sunny days around noon. [14]. In contrast, nocturnal measurements frequently exceeded 100 lx during procedure lighting. Moreover, color temperature remained essentially constant around 4000 K, showing minimal diurnal variation and reflecting a persistent “neutral-white” spectrum during both day and night. Urinary aMT6s concentrations did not show a significant diurnal pattern and did not differ between term and preterm infants. Together, these findings

Table 2
The exposed illuminance (Lux) and color temperatures (Kelvin, K) of newborn infants in the neonatal intensive care unit.

Time interval	0700–1200 (300 min)	*1200–1700 (300 min)*	p Value [*]	*1700–2130 (270 min)*	p Value[†]	*2130–0000 (150 min)*	*p* Value[‡]	*0000–0700 (420 min)*	p Value[§]
Median exposed illuminance	11 (0–2091)	14 (0–502)	0.032	3 (0–12,385)	<0.001	0 (0–16,040)	<0.001	0 (0–1557)	a, b, c vs. e < 0.001; d vs. e = 0.002
Maximum exposed illuminance (Range)	79 (0–10,335)	79 (0–15,066)	0.087	74 (0–17,220)	ns	8 (0–17,596)	<0.001	33 (0–4094)	a, c, d vs. e < 0.001; b vs.e = 0.012
Duration of exposed illuminance, <100 lx, min	300 (265–300)	300 (233−300)	0.031	270 (253–270)	<0.001	150 (150–150)	<0.001	420 (410–420)	<0.001
Duration of exposed illuminance, 100–300 lx, min	0 (0−10)	0 (0–10)	0.710	0 (0–5)	a vs. c < 0.001; b vs. c = 0.002	0 (0–0)	<0.001	0 (0–2)	a,b,d vs. e < 0.001; c vs e;0.003
Duration of exposed illuminance, > 300 lx, min	0 (0–2)	0 (0–0)	<0.001	0 (0–1)	b vs. c 0.002	0 (0–0)	<0.001 b vs. c = 0.012	0 (0–2)	a,b,c vs. e = ns; d vs. e < 0.001
Median exposed color temperature, Kelvin	4362 (3920–4738)	4299 (3902–4662)	0.059	4216 (3716–4651)	<0.001	3693 (3302–4480)	<0.001	3987 (3324–4680)	a, b vs. e < 0.001; c vs. e = 0.004 d vs. e = 0.121

The data are expressed as the median (IQR).
a:0700–1200; b:1200–1700; c:1700–2130; d:2130–0000; e:0000–0700.
[*] a vs. b.
[†] a vs. c; b vs. c.
[‡] a vs. d; b vs. d; c vs. d.
[§] a vs. e; b vs. e; c vs. e; d vs. e.

Table 3
Urinary 6-Sulfatoxymelatonin (aMT6s) excretion (ng/4 h) across time intervals in preterm and term neonates.

Time Interval (h)	aMT6s- Excretion (ng/4 h)			p Value[*]
	Total	Preterm	Term	
1200–1600	77.2 (33.4–141.6)	95.7 (33.7–141.6)	48.2 (32.7–124.6)	0.384
2000–0000	64.9 (28.0–145.0)	76.5 (39.5–141.7)	43.4 (26.1–163.7)	0.655
0400–0800	65.8 (25.6–129.2)	65.8 (28.0–101.2)	67.6 (23.7–129.2)	0.897

All data are presented as the median (interquartile range (IQR)).
[*] *p* Value is for preterm vs. term.

depict an environment characterized by constant dim light during the day and intermittent bright artificial light at night, which may represent environmental conditions less favorable for circadian entrainment. Importantly, the absence of detectable rhythmicity in urinary aMT6s in our cohort does not permit direct conclusions about circadian disruption and may also reflect developmental immaturity, clinical heterogeneity, or environmental masking effects.

These findings are consistent with previous reports showing that NICUs operate within their own chronobiological ecosystem, characterized by constant dim light and devoid of environmental cues necessary for circadian entrainment [15–17]. However, light represents only one component of the neonatal circadian environment. Additional zeitgebers including feeding schedules, handling, noise exposure, temperature regulation, and kangaroo care may also contribute to sleep–wake organization and circadian development in hospitalized neonates. The typical NICU setting may therefore represent an environment with altered temporal organization compared with natural external day–night cycles. The use of incubator covers, drawn blinds, and artificial darkening further exacerbates the deficiency of diurnal light variation [18]. Although such dimming aims to mimic the intrauterine milieu, it disregards the essential materno-fetal circadian coupling that occurs typically in relation to environmental lighting conditions, either via the melatonin signal and/or by other means (dopamine, glucocorticoids, prolactin, etc.) [11,19,20]. Conversely, the lighting procedure frequently used during nighttime care represents an intense, spectrally inappropriate stimulus for both the developing and mature circadian systems. In our analysis, bedside lamps demonstrated extreme inter-model variability, with minimum intensities ranging from 720 to 6093 lx and maximum direct intensities exceeding 25,000 lx. Such illuminance levels correspond to outdoor daylight conditions and far exceed the physiological nighttime threshold at which melatonin suppression and circadian phase shifts can occur in adults (≥30–50 lx melanopic equivalent daylight illuminance) [21]. Our data, showing nocturnal illuminance greater than 100 lx on 24.4% of patient-days, confirm that bright-light episodes are frequent, not exceptional. While brief light exposure is often necessary for patient safety and clinical procedures, its magnitude and spectral content make it biologically potent. These high-intensity, short-duration light pulses may acutely suppress pineal melatonin synthesis and alter the phase of the master circadian pacemaker in the suprachiasmatic nucleus (SCN), as shown in both adult and neonatal models [22,23]. For neonates, whose endogenous rhythmicity is still immature, recurrent nocturnal exposure to bright artificial light may influence the maturation and entrainment of developing circadian rhythms. Particularly in term-born infants approaching discharge, altered nocturnal light exposure may additionally affect the early organization of sleep–wake patterns and behavioral day–night adaptation after transition to the home environment.

The spectral properties of procedure lighting may further influence the circadian relevance of these environmental conditions. Although many LED-based medical lamps emit light with substantial short-wavelength components, detailed spectral characteristics were not directly measured in the present study. Therefore, melanopic or circadian-effective stimulation could not be directly quantified in the present study. The lack of standardized spectral specifications among NICU lighting systems further complicates this issue: two bedside lamps operating at identical photopic illuminance may differ several-fold in melanopic efficacy, creating unpredictable biological effects and challenging light hygiene protocols. In our study, the persistent spectral uniformity around 4000 K CCT across the 24-h cycle indicates that neonates were continually exposed to a spectral composition resembling midday daylight, without the physiologically necessary evening transition toward warmer, longer-wavelength light. This relative spectral

constancy, combined with recurrent nocturnal exposure to brighter artificial lighting, may contribute to circadian-unfavorable environmental conditions for both infants and caregivers.

Limitations

While these findings highlight critical shortcomings in current NICU lighting environments and underscore the need for integrative, circadian-informed design strategies, they should be interpreted with several methodological and contextual limitations. Architectural differences, including building structure, room geometry, window orientation, bedside distance from natural daylight exposure, and local lighting design, varied substantially across participating NICUs and were not systematically controlled for in this multicenter observational study. Because of this structural heterogeneity, detailed architectural stratification and bed-level daylight comparisons were beyond the scope of the present analysis. Spectral power distribution and melanopic irradiance were not directly measured. Therefore, circadian-effective retinal light exposure could only be estimated indirectly using proxy parameters such as illuminance and correlated color temperature. Similar CCT values may correspond to different spectral profiles and melanopic effects. Melatonin measurements were limited to critically ill, catheterized infants, who may have experienced physiological stress influencing melatonin metabolism. aMT6s values were not normalized to creatinine, which may have introduced additional variability. The wide gestational age range (25–41 weeks) also reflects heterogeneity in neurological maturity. Furthermore, as this was a pilot study, no control group exposed to cycled or biodynamic lighting was included, limiting causal inference. Long-term assessments of caregiver melatonin status and sleep quality were beyond the scope of this study but warrant further investigation.

Conclusion

In conclusion, this study documents NICU lighting environments characterized by low daytime illuminance, limited day–night spectral variation, and frequent nocturnal exposure to artificial light with higher correlated color temperatures. These lighting patterns may be potentially unfavorable for circadian entrainment and warrant further investigation regarding their influence on neonatal adaptation and caregiver well-being. Future controlled trials integrating continuous light dosimetry, hormonal markers, sleep–wake metrics, and clinical outcomes are needed to better understand whether circadian-adapted lighting strategies may support neonatal adaptation and caregiver well-being.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this manuscript, the authors used generative AI tools (ChatGPT and Grammarly) to support language editing, improve clarity, and enhance text organization. The authors developed all scientific content, data interpretation, and conclusions. After using these tools, the authors critically reviewed, edited, and validated the manuscript and took full responsibility for the integrity and accuracy of the published work.

CRediT authorship contribution statement

Benedikt Bonsau: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Ebru Aileen Alsat:** Visualization, Methodology, Investigation. **Angela Kribs:** Writing – review & editing, Supervision, Resources. **Ursula Felderhoff-Müser:** Writing – review & editing, Supervision, Resources. **Kathrin Schneider:** Supervision, Resources. **Gizem Izmir Tunahan:** Writing – review & editing. **Andreas Müller:** Supervision, Resources, Conceptualization. **Soyhan Bagci:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis, Conceptualization.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and relevant national regulations. Ethical approval was obtained from the Ethics Committee of the University of Bonn (approval number: 322/17).

Written informed consent was obtained from both parents and legal guardians prior to inclusion of all neonates. The study was observational and did not involve any interventions beyond routine clinical care.

Measurements of environmental lighting at the eye level of healthcare professionals were performed exclusively as non-invasive workplace environmental assessments. No personal, behavioral, or health-related data were collected from nursing or medical staff, and no individual consent was required for these measurements, in accordance with institutional and ethical guidelines.

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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.

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