Official Study Title:

Circadian Light Exposure Adjustment for Restfulness (CLEAR)

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Basic Information	
Title of Study:	Circadian Light Exposure Adjustment for Restfulness
Short Title:	CLEAR
Principal Investigator Name:	Lauren Hartstein
Principal Investigator's Department/Unit:	Psychiatry

1.0 Background (Limit 1,000 words):

Provide the scientific or scholarly background for the proposed Human Research. Discuss relevant prior experience or preliminary data (e.g., existing literature).

Insufficient sleep is prevalent in early childhood and a risk factor for poor health outcomes. Evening sleep problems are common in preschoolers, with approximately 30% of young children experiencing behavioral sleep disturbances (e.g., bedtime resistance, difficulty falling asleep, night awakenings).[1-5] Insufficient sleep in young children is associated with *concurrent* attentional, emotional, and behavioral problems,[6-8] and an increase in cardiometabolic risk.[9, 10] Additionally, sleep problems in early childhood *predict* later emotional/behavioral problems,[11-13] obesity,[14, 15] and alcohol and drug use, [16] highlighting the necessity of early intervention.

Circadian misalignment is present in young children and contributes to behavioral sleep problems. Sleep timing is regulated in part by the timing of the circadian clock. Circadian misalignment, a mismatch between sleep behaviors and the timing of the endogenous circadian rhythm, is associated with a variety of poor health outcomes. For preschoolers, parent-selected bedtime occurs an average of only 40 min after dim-light melatonin onset (DLMO),[17-19] compared with 2h in adults. As the phase angle between bedtime and children's DLMO decreases, children have greater bedtime resistance and longer sleep onset latencies, likely because the circadian clock is paradoxically signaling for wake at this time.[20]

Light exposure shifts the timing of the circadian clock. Light is the primary time cue of the circadian clock, and even small amounts of evening light can suppress production of melatonin and delay circadian timing.[21-23] Light exposure influences circadian timing largely through stimulation of the intrinsically photosensitive retinal ganglion cells (ipRGC), ocular photoreceptors maximally sensitive to short-wavelength blue light at ~480nm that express the photopigment melanopsin.[24-27] When stimulated, information is transmitted from the ipRGCs to the suprachiasmatic nucleus, the central circadian clock, which modulates melatonin production in the pineal gland.[28] The influence of light on the ipRGCs can be quantified via melanopic equivalent daylight illuminance (mEDI), an SI unit that strongly predicts the circadian response to light exposure in adults.[25] Extensive research with adults, adolescents, and older children indicates that evening exposure to short-wavelength blue light (or blue-enriched white light) leads to greater melatonin suppression, greater delays in melatonin onset, and decreased sleepiness than long-wavelength light.[29-39]

Young children's circadian clocks are highly sensitive to evening light exposure. Children are more sensitive to evening light exposure than adults.[40] This high photosensitivity may be due in part to differences in eye anatomy, including larger pupils and clearer lenses that increase light transmittance.[41] I previously demonstrated that young children's circadian clocks are exquisitely sensitive to light in the hour before bedtime, even at low intensities.[17, 42] These studies point to the importance of evening light exposure as a modifiable factor in children's environments that

could advance sleep and circadian timing. To date, however, research is lacking on light-based circadian health interventions in early childhood to improve sleep timing and behaviors. This is the primary objective of this research. In a first step towards developing a pediatric circadian health intervention, we propose to test the feasibility, acceptability, and preliminary efficacy of two evening light mitigation strategies (adjustment to home lighting, amber-tinted glasses) to advance sleep and circadian timing in young children with sleep-onset difficulties.

Heightened photosensitivity may contribute to sleep and circadian timing. Large individual differences in sensitivity of the circadian system to light are found in both adults[22] and children.[17] Individual differences in photosensitivity can be quantified through the post-illumination pupil response (PIPR), a marker of the strength of ipRGC activation and the melanopsin-mediated response.[43, 44] Individuals with greater sensitivity to blue light, as measured by the PIPR, have more delayed sleep timing.[45] Additionally, heightened photosensitivity has been observed in individuals with delayed sleep-wake phase disorder (DSWPD), as measured by both PIPR and circadian phase shift.[46] Individual light sensitivity has yet to be examined in young children and may contribute to delayed circadian timing and moderate the efficacy of a circadian light-based intervention.

Preliminary Studies

My preliminary data establish the rationale for targeting evening light exposure for intervention to advance sleep and circadian timing.

Preschoolers' circadian rhythms are highly sensitive to evening light. We examined preschoolers' sensitivity to evening light of various intensities. In a three-day dim-light protocol, children were exposed to a white light (randomly assigned 5-5,000 lux) for 1h before bedtime. Salivary melatonin was suppressed M=85.4 ± 7.2% during the light exposure, compared to the same period on the previous evening (baseline).[42] DLMO was delayed an average of 56 min the evening after the light exposure, compared with baseline.[17] Although evening light affects the adult circadian system in a non-linear, dose-dependent manner with intensity,[21] preschoolers displayed robust melatonin suppression and phase delay across the full range of light intensities, even in response to very dim light.

The early circadian clock is sensitive to differences in evening light spectrum. I examined melatonin suppression and phase delay in response to evening light of two different spectra in preschoolers utilizing a repeated measures crossover design (N=10). Exposure to 1h of light at a higher CCT (more blue light) resulted in greater melatonin suppression compared to a lower CCT light (less blue light). Both light conditions resulted in a significant delay in DLMO timing compared to baseline. These data provide preliminary evidence that the maturing circadian system is sensitive to differences in evening light spectrum and further highlight the high sensitivity of the circadian system to evening light exposure in early childhood.

Young children may be less sensitive to the circadian effects of morning light. We assessed the sensitivity of preschoolers' phase-advancing response to 1 h of *morning* light starting at habitual wake time across a wide range of intensities (1.5-2,000 lux, N=11). Across light intensities, the average circadian phase shift was a 13-min *delay* in DLMO timing, compared to baseline. After exposure to bright light at 2,000 lux, a phase advance of only 12 min was observed. These initial data suggest that the early circadian clock may be less sensitive to the phase-shifting effects of light in the morning and further emphasize evening light as a modifiable target in children's environments that could improve sleep and circadian health.

2.0 Lay Summary:

Provide a brief description of the proposed research using terms that someone who is not familiar with the science or discipline can understand.

With children's ever-growing use of light-emitting devices and evening exposure to artificial lighting, there is a crucial need to develop novel environmental and behavioral strategies to enhance sleep health in early childhood, a time when behavioral sleep problems commonly first emerge, increasing the risk for poor health outcomes. Informed by accumulating evidence indicating high sensitivity of the early circadian system to evening light exposure, this research project will examine the feasibility, acceptability, and preliminary efficacy of two strategies to reduce evening light exposure in order to advance sleep and circadian timing in children with sleep onset difficulties.

3.0 Purpose:

Describe the purpose, specific aims, objectives, questions to be answered, hypotheses, and/or primary and secondary study endpoints of this Human Research protocol.

The overall goal of this research is to test the feasibility and preliminary effectiveness of two proposed light-related intervention components to advance sleep and circadian timing in order to improve sleep quality in early childhood. After baseline assessments of circadian timing (salivary DLMO), sleep timing (actigraphy), and parent-reported sleep quality and behaviors, children (5.0-6.9 years) will be randomly assigned to one of three 2-week interventions: (1) adjustment of home lighting environment (implementation of smart lightbulbs to reduce intensity and blue-light 1 h before bedtime); (2) reduction in evening light exposure (amber-tinted glasses 1 h before bedtime[47, 48]); or (3) a sham intervention (clear glasses 1 h before bedtime). Post-intervention, a secondary assessment of all outcomes will be performed, as well as qualitative interviews with parents. With these data, we will address the following specific aims:

Aim 1: To determine <u>feasibility and acceptability</u> of two different potential components of a circadian health intervention in young children. We hypothesize that adjustment to home lighting environment and reduction in evening light exposure will both be perceived by parents and children as feasible and acceptable intervention strategies, as measured through compliance rates and qualitative post-intervention interviews with parents.

Aim 2: To examine the <u>preliminary effectiveness</u> of two different potential components of a circadian health intervention on sleep and circadian timing, sleep quality, and parent-reported sleep behaviors in young children. We hypothesize that adjustment to home lighting environment and reduction in evening light exposure will both result in an earlier DLMO and earlier sleep onset, compared to sham intervention.

Exploratory Aim 3: To examine individual differences in photosensitivity in young children. We hypothesize that individual differences in photosensitivity assessed through pupillometry will moderate the effects of the interventions on DLMO and sleep onset.

4.0 Funding Information:

Indicate all sources of funding for the project, including gift funds, departmental funds, or other internal funding. For each funder, list the name of the funder, and the institutional proposal number or award number you received from Sponsored Projects. eIRB tip: For externally funded projects, the institutional proposal or award number provided must be linked in the "Study Funding Sources" section in eIRB.

☐ **No Funding**	
☒ **Federal Funding**, including flow-through federal funding (i.e., NIH, NSF, DoD, etc.)	Name of funding source: NIH National Heart, Lung, and Blood Institute
	Institutional Proposal or Award Number: 024066-00001
	eDoc # (for multi-site projects):
☐ **Industry Funding**	Name of funding source:
	Institutional Proposal or Award Number:
	eDoc #:
☒ **Foundation Funding**	Name of funding source: American Academy of Sleep Medicine
	Institutional Proposal or Award Number: 25010270
☐ **Department Funding**	Name of funding source:
☐ **Gift Funding**	Name of funding source:
☐ **Other**	Name of funding source:

5.0 Resources Available to Conduct the Human Research:

Describe the resources (facilities, time, emergency resources, etc.) available to recruit, consent, conduct study procedures, and analyze data.

The Department of Psychiatry provides Dr. Hartstein with office space in the Arizona Health Sciences Center, as well as additional office space for study staff, and designated space to complete trainings, pupillometry, and cognitive testing. The in-lab circadian assessments will take place in the UAHS Center for Sleep, Circadian, and Neurosciences Research.

6.0 Study Population:

6.1 Select all the categories of participants included in the research:

☒ Healthy adults	☐ Non-English-speaking subjects
☐ Non-healthy adults	☐ UA staff/faculty
☒ Children (under 18 years old) *	☐ UA students
☐ Pregnant women, neonates, and/or fetuses*	☐ Banner employees
☐ Prisoners*	☐ Refugees
☐ Native Americans, Alaskan Native, and Indigenous Populations*	☐ Other – please explain: Click or tap here to enter text.
☐ Adults unable to consent (i.e., cognitively impaired adults) *	

6.2 For each of the above selected categories, describe the inclusion and exclusion criteria. Indicate age range, gender, and ethnicity.

Inclusion requires that children are aged 5.0-6.9 years at the time of enrollment with a parent-reported sleep onset of ≥ 60 min after parents' desired bedtime at least three nights per week. Equal numbers of boys and girls will be enrolled. Children are *excluded* for the following reasons:

- All sleep disorders as indicated on the telephone screener or by clinical cut-off scores on the Children's Sleep Habits Questionnaire (CSHQ), [49, 50] except for insomnia or DSWPD[51] as features of these disorders are directly targeted by the intervention. Secondary analyses will explore if outcomes differ among participants with or without parent-reported symptoms consistent with these diagnoses.
- Physical abilities that interfere with assessments (e.g., visual impairment), developmental disabilities (e.g., autism, attention-deficit/hyperactivity disorder (ADHD), pervasive developmental disorder), epilepsy or other neurological disorders, metabolic disorders, medical conditions that commonly require treatments or assessments during the night (e.g., cancer, diabetes, active asthma), current infection or lead poisoning; a head injury involving loss of consciousness in the past 6 months.
- Current use of medications affecting daytime sleepiness, the circadian system, or light sensitivity.
- Eye disorders or color blindness (determined with Ishihara Color Vision Test); corrected vision with eyeglasses is permitted.

One adult parent of each participating child will also take part in the study. Parents must be able to provide consent and to complete the interview at the end of the study.

6.3 Describe the total number of subjects to be enrolled locally under this IRB approval. If obtaining specimens, specify the maximum number of specimens needed for this project.

We expect to enroll 60 children and 60 parents. We will aim to enroll 30 girls and 30 boys. Each child will provide a total of 24 saliva samples across the research protocol, for a total number of 1,440 samples expected to be collected as part of this project.

7.0 Recruitment Methods:

7.1 Select the methods used to recruit individuals.

☒ Email	☐ Screening of the Electronic Medical Record (EMR)
☒ Face to face	☒ Social media
☒ Flyers	☐ SONA System
☐ In person presentations	☐ TV, Radio, Print
☒ Online advertisements	☐ Other – please explain: Click or tap here to enter text.
☒ Phone calls	

7.2 Explain the recruitment process. Describe how potential subjects will be identified, where recruitment will take place, when recruitment will occur, and the methods that will be used to recruit individuals.

To recruit subjects from the general Tucson community, we will place advertisements and post informational flyers in the community (e.g., pediatricians' offices, museums, libraries, early childcare groups) and on university-affiliated websites (Department of Psychiatry, Sleep and Development Lab, Sleep Health Research Program). Participants will also be recruited from social media (Instagram, Twitter, Facebook, Reddit) using accounts created specifically for the research lab and university listservs. Permission will be obtained from owner/moderators of social media groups/pages and listservs prior to sharing any recruitment materials. Additionally, we will set up a booth at local community festivals and events in order to provide information to interested families. Families with children in the target age range who are part of our lab database, the Sleep and Development Lab Recruitment Database, (indicating they are interested in being contacted for research studies) will be contacted by phone or email regarding their interest in participating in this study. This database is a recruitment database maintaining contact information solely for recruiting efforts. Potential subjects will be screened through an online questionnaire and a more in-depth phone interview to confirm eligibility. Screening data for ineligible subjects will not be kept, except a log documenting the screening and outcome, to avoid re-contacting any potential subjects. The consent form will be used to guide face to face recruitment.

8.0 Diversity, Equity, and Inclusion

8.1 Explain how the research plan (recruitment, study population, data collection, etc.) is equitable and represents the demographic makeup for the location in which the research will be conducted.

Subjects will be recruited through flyers from within a 60-mile radius around The University of Arizona, as well as outreach at local community events and festivals. We will enroll an even number of male and female child participants. No child will be excluded from the study based on sex, race, ethnicity, or any other demographic characteristic.

8.2 Describe whether non-English speaking subjects will be included in the study. If yes, please explain how your research team is prepared to meet the needs of the population. If not, please explain why non-English speakers will be excluded from the study population.

As an early career PI, Dr. Hartstein will be the one consenting all participants and overseeing data collection and is not fluent in any other language. Non-English speaking subjects will not be included in the study because Dr. Hartstein would have no way of ensuring that they understood all aspects of the protocol and all of their questions were answered satisfactorily.

8.3 What methods will you use to collect demographic information from participants? If you will not collect demographic information, please explain why not.

Demographic information will be collected from participants via a Redcap questionnaire.

9.0 Consenting Process:

9.1 Indicate the informed consent process(es) and/or document(s) for the study. Check all that apply.

Written Consent
☒ Informed Consent (ICF) – written or electronically signed form
☒ Parental Permission – written or electronically signed form
☐ Assent (participants under 18) – written or electronically signed form

☐ Combined ICF/PHI Authorization – written or electronically signed form
☐ Standalone Protected Health Information (PHI) HIPAA Authorization – written or electronically signed
☐ Translated Consent/Assent – written or electronically signed form(s)
☐ Short Consent Form – written or electronically signed form (see guidance on **Short Form process**)
☐ Debriefing Script or Form – document used to properly inform subjects of the study's purpose when intentionally deceived

Oral/Online/Unsigned Consent
☐ Informed Consent – oral script/online/unsigned
☐ Parental Permission – oral script/online/unsigned
☐ Assent – oral script/online/unsigned
☐ Translated Consent/Assent – oral script/online/unsigned

Waivers of Informed Consent and/or PHI Authorization
☐ Waiver of Consent
☐ Full Waiver of PHI Authorization
☐ Partial Waiver of PHI for Screening Purposes

9.2 Describe in detail the consent processes checked above, including any waiting period for subjects to sign the consent, steps to minimize the possibility of coercion or undue influence, and the language used by those obtaining consent.

The parent and child will come to the sleep research center to meet with the PI. The PI will email the consent form to the parent prior to this visit so they have ample opportunity to read the document beforehand (but not required because the PI will review in detail with them at the visit) and come with any questions. The purpose of this project and study procedures will be explained to parents by the PI and parents will be given the opportunity to ask any questions before signing the paper consent form. Steps will be taken to minimize coercion, including highlighting that participation is entirely voluntary, and that they may withdraw from the study at any time. Parents will be given a copy of the informed consent document. Because the child participants are under the age of 7 years, we will not be collecting child assent (See Appendix for Children/Wards).

9.3 Where will the original signed consent and PHI authorization documents be stored?

The original signed consent forms will be stored in PI Dr. Hartstein's locked office. Consent forms will be kept separate from any data collection forms and study ID numbers.

9.4 Acknowledgement of consent form storage.

☐ I will store original signed consent and/or PHI authorization documents for at least 6 years past the time the study is concluded.
☒ For studies involving minors, I will store original signed consent and/or PHI authorization documents for at least 6 years after the youngest participant turns 18.
☐ Not applicable – I am not collecting signed documents.

10.0 Research and Data Collection Procedures:

10.1 Select the methods of data collection that will be used in this study (select all that apply):

☐ Anthropometric measures (e.g., height, weight, waist circumference, etc.)	☐ Participant observation
☐ Audio/video recording	☒ Screening data
☒ Benign interventions	☒ Self-health monitoring (e.g., pedometers, food diaries, etc.)
☐ Biological specimens – blood draws	☐ Surveys – paper
☐ Biological specimens – clinically discarded blood or specimens	☒ Surveys – internet (including online and email-based data collection)
☒ Biological specimens (urine/feces, tissue, saliva, skin, hair, nails, nasal swab)	☐ Surveys – telephone
☐ Clinical Data Warehouse (CDW)	☒ Randomization with control and experimental groups
☒ Cognitive or behavioral measures, including daily diaries	☐ Records – billing
☐ Data collected using other communication/electronic devices (e.g., cell phones, pagers, and texting devices)	☐ Records – educational
☐ Data previously collected for research purposes	☐ Records – employee
☐ Deception	☐ Records – lab, pathology and/or radiology results
☐ Instrumentation, equipment, or software not approved by the FDA	☐ Records – mental health
☐ Interviews – focus groups	☐ Records – substance abuse
☒ Interviews – in person	☐ Research imaging protocols
☒ Interviews – virtual/online	☐ Recombinant DNA
☐ Medical records review	☐ Social networking sites
☐ MRI/ultrasound with contrast	☐ Stem cells
☐ MRI/ultrasound without contrast	☐ Radiation Scans (X-Ray, CT Scans, etc.)
☒ Non-invasive instruments (e.g., external sensors applied to the body)	☐ Other activities or interventions – describe: Click or tap here to enter text.

10.2 Description of research procedures.

Data from the screening questionnaire and phone screening will be kept for use in the study for subjects who sign the consent. Screening data for ineligible subjects or other subjects who do not sign the consent will not be kept. After signing the informed consent, parents will also be asked to review the media authorization form and sign it if they are comfortable with their child being photographed during study procedures for use in academic presentations or lab materials (e.g., website, brochure). The photos/videos will never be published alongside study data or in any resulting manuscripts. Aside from publicity/marketing, they may be used in academic

presentations (such as a research conference) solely to illustrate the study methodology (e.g., a picture of a child chewing on a cotton swab to illustrate the methods for collecting saliva samples). Additionally, the researcher will ask parents to complete a form about their child's likes and dislikes to match games and rewards to the child's interests.

Data collection will take place solely during the academic school year (Sept – June). Using a randomized design, participants will complete a five-week protocol.

Pre-assessment: During the initial phase of the study (pre-assessment), participants will come to the lab for 3 training visits to familiarize the child with the researchers, measure photosensitivity (pupillometry), cognitive performance (NIH Toolbox), and to introduce them to the saliva collection technique.

Baseline assessment: After the first pre-assessment visit, there will be a two-week at-home baseline assessment. Pre-intervention data will be collected on sleep timing (actigraphy), parent-reported sleep timing and behavioral sleep quality, light exposure (actigraph), and a baseline assessment of circadian timing (salivary DLMO). During 7 of the days (chosen by the subjects), parents will be asked to complete a daily diary of their child's screen media use. The second and third pre-assessment visits will occur during the baseline assessment period.

Randomization: Children will be randomly assigned to one of three two-week interventions (adjustment to home lighting, amber-tinted glasses, or clear glasses). Children will be randomized to the three conditions in a 2:2:1 ratio, stratified by sex. For each participant enrolled, a random number generator will provide a number from 1-30, which corresponds to an intervention condition for each sex.

Intervention Period: Changes in sleep timing and light exposure will be assessed throughout the intervention period via actigraphy, light sensing, and sleep diaries. Parents in the amber-tinted or clear glasses arms will also complete a daily diary detailing when the glasses are worn.

Post-intervention: After the intervention is complete, a secondary assessment of sleep timing via actigraphy (one week), light exposure, parent-reported questionnaires, cognitive performance, media diaries, and DLMO will be performed, as well as qualitative interviews with parents to assess child and family experiences. Interviews will not be audio- or video-recorded.

Throughout the duration of the study, the child will wear a wrist actigraph to record sleep timing and light history. Parents will complete a daily sleep diary, which documents children's sleep schedules and nocturnal awakenings.

5.A. Interventions

Adjustment to Home Lighting. The presence of more blue light in the home is associated with later circadian timing in both school-aged children and adults.[52] This intervention will adjust the evening home lighting environment to be less stimulating to children's circadian clocks. Researchers will visit the participant's home to install smart light bulbs. Smart light bulbs (WYZE, dimmable and color tunable LED bulbs with CCT range of 2700K – 6500K) will be installed in participants' homes light fixtures (in the child's bedroom, bathroom, as well as areas the child is likely to spend time in after dinner (i.e., living room, playroom)). The researchers will program the lights to transition to a lower CCT and dimmer intensity to achieve the recommended evening mEDI of 10 lux[53] starting 1 h before the child's parent-selected bedtime.

Amber-Tinted Glasses. Wearing "blue-blocker" glasses (lenses that filter out the blue portion of the visible spectrum) can reduce the melatonin suppression and alertness effects of evening light exposure in both adults[48] and adolescents,[54] as well as advance the timing of the circadian clock and sleep onset,[55] compared with participants wearing placebo lenses. This intervention will examine their efficacy in advancing young children's sleep and circadian timing. Children will be given a pair of glasses (Block Blue Light), with amber-tinted lenses (advertised as blocking

100% of light from 380-550 nm;[56] reduction in mEDI measured as 96.5%. The glasses being used in this study are specifically designed and marketed for children to block blue light. They are commercially available devices that will be used how they are supposed to be used. Link: https://www.blockbluelight.co.nz/collections/kids-blue-light-glasses/products/kids-blue-blocking-glasses-pink. Children will wear the glasses starting 1 h before parent's selected bedtime. A small temperature sensor is placed on the inside of the glasses to objectively determine when children are wearing them. Parents will also complete a daily diary detailing when the glasses are worn.

Sham Intervention (clear glasses). The sham intervention consists of the same protocols for the amber-tinted glasses, except that children will be asked to wear a pair of glasses with clear lenses (advertised as blocking 50% of light from 400-500 nm; reduction in mEDI measured as only 16.7%, which are significantly less effective at blocking short-wavelength light.

5.B. Measures

Parent-Report (Aim 2). Parents will be given a link to a series of secure online questionnaires (REDCap) to assess sleep timing and behaviors, which take ~30 min to complete. These include the following:

1. Children's Sleep-Wake Scale (CSWS): assesses behavioral sleep quality of children and has strong reliability and validity for research studies. [57] These data will be used to determine changes in bedtime resistance, difficulty falling asleep, and night awakenings.
2. Children's Sleep Habits Questionnaire (CSHQ): measures sleep behaviors and screens for common pediatric sleep disorders. The CSHQ has adequate reliability and validity for preschool- and school-aged children. [49, 50] These data will be used to determine changes in bedtime and sleep behaviors, including sleep onset delay, sleep anxiety, and daytime sleepiness, as well as for exclusionary criteria.
3. Children's Chronotype Questionnaire (CCTQ): assesses morningness/eveningness preference in children. The CCTQ has excellent reliability and validity (concordance with DLMO) [58, 59] and provides three measures of chronotype (midsleep on free days, morningness/eveningness scale, chronotype score). These data will be used to determine changes in children's circadian phase preference.
4. Children's Behavior Questionnaire: Widely used in developmental research, the CBQ assesses children's temperament and provides measures of Negative Affect, Surgency, and Effortful Control.[60]

Sleep Timing (Aim 2). The actigraph is a watch-size monitor worn on the non-dominant wrist, providing continuous imputation of sleep-wake states via arm activity (ActLumus, Condor Instruments). Children will wear the actiwatch for the duration of the study, removing it ony when swimming/bathing, during which time the device is placed face up in the same room as the child. We will employ standard procedures for obtaining and analyzing actigraphy data for young children.[18, 19] These data will be used to examine changes in habitual sleep timing, sleep onset latency, and for computing phase angle of entrainment. We will follow published guidelines for all device parameters, data management, and scoring procedures.[61] These devices have been specifically validated for use in pediatric populations,[62] including young children.[63]

Light Exposure (Aims 1 and 2). The actiwatch (ActLumus, Condor Instruments) is equipped with a high quality light sensor that assess light exposure in both photopic and melanopic lux. These data provide an objective measure of the child's light exposure throughout the protocol

(including compliance with the home lighting intervention) and will be used to examine changes in habitual light exposure.

Dim Light Melatonin Onset (DLMO) (Aim 2). At the end of the baseline and intervention periods, the child will come to the laboratory for a circadian assessment. The child will enter the dim-light (< 10 lux) laboratory suite 4.5 h before their habitual bedtime (average parent-reported bedtime across previous five days). Throughout the assessment, researchers will play with the child, providing toys and games specific to their interests. Starting 3.5 h before habitual bedtime, saliva samples will be collected in 30 min intervals, then 20 min intervals in the hour before habitual bedtime, continuing until 2 h past bedtime for a total of 12 saliva samples. Saliva samples will be obtained and stored using our standard published methods.[64] The child mouths/chews on one end of a braided cotton roll for 1-2 min. Children will remain in a sitting posture for 5 min before and during each saliva sample.[65] Lux levels will be obtained during each saliva sample using a research photometer (ILT2400; International Light Technologies, Inc.) held approximately 5 cm adjacent to the child's eye and directed in the angle of gaze. Samples will be immediately centrifuged and stored in a minus 80° C freezer. Following the completion of data collection, samples will be assayed by technicians blind to the study conditions. Saliva samples will be stored in the UA Biorepository and then sent to SolidPhase Inc. (Portland, ME) for assays. DLMO will be computed as the linear interpolated clock time at which melatonin levels cross (and remain above) 4 pg/mL.[66] The data will be used to examine changes in DLMO, a marker of circadian timing.

Cognitive Performance (Aim 2). During one of the training visits to the laboratory, children will complete the NIH Toolbox Early Childhood Cognition Battery, which consists of a series of tasks on an iPad that assess dimensions of executive function (e.g., inhibitory control, working memory). The battery will be repeated during the post-intervention phase to examine changes in cognitive performance and the association with sleep outcomes. These tasks are validated for children ages 3-15 years[67] and the early childhood battery is recommended for children ages 4-6.

Qualitative Interviews (Aim 1). Following the completion of the post-intervention assessments, researchers will conduct short interviews with parents to assess the feasibility and acceptability of each intervention component. Parents will be asked a series of questions (see Appendix) to ascertain how satisfied they were with the intervention, how effective they believed the intervention to be in improving their child's sleep timing and behavior, how easy/difficult it was to implement the intervention with their child, and what challenges they faced in implementing the intervention.

Photosensitivity (Exploratory Aim 3). During one of the training visits to the laboratory, a standard protocol[68] will be used to measure pupillary reactions to two light conditions (red light (627 nm) and blue light (459 nm) at 3.0×10^{13} photons/cm^2/s). The researcher will fit an eye-tracking device to the child (ETL-100H, ISCAN, Inc.), consisting of safety glasses with two infrared cameras and reflectors. After adapting to a dim-light room for 15 min (< 1 lux), the child's pupil diameter will be measured during a 30 s baseline, followed by a 10 s light exposure, and a 40 s recovery in darkness to assess pupillary re-dilation and the PIPR. After a 7 min dim-light re-adaptation, the procedure will be repeated for the remaining light condition. The ETL-100H device has been used to assess chromatic pupillometry across a variety of populations,[69-71] including my recent publication on healthy school-aged children and adolescents.[68] During my NIH F32 study, I collected pilot data confirming the device fits preschool-aged children and reliably tracks changes in their pupil diameter.

10.3 Specify the total estimated time commitment for subject participation, and the estimated time commitment for each activity.

Participants will be enrolled in the study for a total of 5 consecutive weeks in addition to the time taken for screening and enrollment itself. The estimated time for parents to complete the online questionnaires each time (twice) is 30 min. Each of the 3 initial training visits (including pupillometry and cognitive testing) are expected to last approximately 1h. The daily diaries (sleep diary, media diary) will take 10-15 min each day. Each of the 2 evening visits to the sleep lab (DLMO assessments) are expected to take approximately 7h. Children in the amber-tinted glasses intervention will be asked to wear them for 1h each night for 2 weeks. The qualitative interview is expected to last approximately 30 min.

10.4 If any biological specimens (blood, urine, tissue, etc.) are being collected for research, state the amount (ml/tsp/tbsp, etc.), method, frequency, and type of specimen to be collected and what the specimen will be used for.

Saliva will be collected during two one-evening visits to the University of Arizona Center for Sleep, Circadian & Neuroscience Research. Starting 3.5 h before habitual bedtime, saliva samples will be collected in 30 min intervals, then 20 min intervals in the hour before habitual bedtime, continuing until 2 h past bedtime for a total of 12 saliva samples per visit. The child mouths/chews on one end of a braided cotton roll for 1-2 min, which is then immediately placed in a tube and centrifuged, resulting in ~2 mL of saliva per sample. The specimen will be used for determining changes in the concentration of melatonin throughout the evening in order to calculate DLMO, a marker of circadian timing.

10.5 If the study is a clinical trial:

a) Confirm registration with https://clinicaltrials.gov/ has been completed:

This study is not a clinical trial: ☐
Registration complete: ☐
Registration pending: ☒

b) If the Principal Investigator (PI) does not possess a medical license, describe the scope and nature of the PI's previous clinical trial experience, including other studies they have led or participated in as Co-Investigator. If applicable, describe the previous clinical trial experience for the appointed Responsible Physician.

Dr. Hartstein has extensive experience with each facet of the research protocol. She has successfully completed > 75 assessments of salivary dim-light melatonin onset with young children using the techniques used in the present study. She has also completed assessments of the pupillary light response with children ages 3 through 16 using the same equipment and protocols as the present study. Additionally, co-investigator Dr. Grandner is a licensed Clinical Psychologist with extensive experience conducting clinical trials in behavioral sleep medicine.

11.0 Potential Benefits to Subjects:

11.1 Describe the anticipated benefits of this study to society, academic knowledge, or both.

This study will represent the first to experimentally assess the impacts of a light-based intervention on sleep and circadian rhythms in young children and will make a significant contribution to the fields of behavioral sleep medicine and chronobiology. Our findings will represent a first step in developing circadian interventions to support sleep health in early childhood.

11.2 Describe any benefits that individuals may reasonably expect from participation (not including compensation, which cannot be considered a benefit of participation).

There are no direct benefits to participants in this study. Parents will learn about their child's sleep patterns and melatonin profile. Children may enjoy participating in the study activities and receiving personalized attention from researchers.

12.0 Risks to Subjects:

12.1 Describe all physical, psychological, social, legal, and/or economic risks that could be associated with participation in this research.

The risks of this research are consistent with the risks that a normal child would experience as a part of their daily life. The risks associated with wearing the actigraph are no greater than those associated with wearing a wristwatch. However, there are three sources of potential risk in this study. First, there is the safety risk of the child coming to the laboratory for assessments. Second, there is a risk that parents may experience some distress while answering some of the survey questions related to parental or child behavior. It is also possible that children may express discomfort from the study activities. Third, there is a risk of potential loss of confidentiality. We are unaware of any risks associated with the collection of saliva using our published methods. I will use standard procedures, which I have refined during more than 75 circadian assessments with young children over the past six years.

12.2 Discuss what steps will be taken to minimize risks to subjects/data.

Although the risks involved in each of the study procedures are minimal, we will take necessary precautions to minimize the risks to the greatest extent possible.

Safety of child participants in the laboratory: Researchers will be with subjects at all times during in-lab data collection, and at least one parent/guardian must be present throughout all laboratory visits. All researchers and student research assistants must pass a comprehensive background check and obtain a fingerprint clearance card from the Arizona Department of Public Safety before interacting with subjects or families. There is also the risk that the parent may disclose, or study staff may observe, instances of child maltreatment that must be reported to child protective authorities. Parents will be informed of this and other potential risks during the informed consent process.

Comfort of child participants during study activities: It is up to the parent to determine whether they would like to keep trying to encourage their child to complete the activity, but we will never force a child to continue with a study activity against their will. If the child is expressing clear discomfort with a study activity, the study team will pause the activity and give the child a break and discuss with the parent. At the parent's request we will try to engage the child in the study activity again. If they continue to express discomfort, then the study team will stop the study activity. During the in-lab salivary assessment, this may mean skipping the currently scheduled saliva sample and coming back to the child in 20-30 minutes to see if they are willing to try the next sample. Because we are keeping kids up past their bedtime for the two salary melatonin assessments, they can sometimes get overtired and cranky. We find that a little break and encouragement from the parent or a snack often allows the child to reset and finish the assessment.

Parental distress when completing questionnaires: This distress would be expected to be only transient, and parents will be reminded that they can skip any question they do not feel comfortable answering.

Maintaining participant confidentiality: Children will be assigned ID numbers upon enrollment in the study and these numbers will be used in all data records. Parent contact information, signed consent forms, and the code to match ID numbers to participants will be kept separately in a secure location in the locked laboratory. All data records will be maintained on password protected computers in the Sleep and Development Laboratory, only accessible to the appropriate study researchers.

Participants will be informed that they can withdraw from the study at any time and will receive pro-rated compensation.

13.0 Costs, Compensation, and Injury:

13.1 Describe any costs, monetary and non-monetary, that subjects may incur. This includes time.

There are no costs to subjects except for their time.

13.2 Discuss the amount of compensation (monetary and/or non-monetary) subjects may receive. Describe if compensation will be prorated.

For completing the study protocol, families are compensated a total of $400. Children receive small non-monetary gifts for completing each circadian assessment. For any family who chooses to terminate study participation, compensation will be pro-rated as follows:

Baseline:
Completing online surveys: $20
Actigraphy: $40
In-lab phase assessment: $80

Intervention:
$50/week for 2 weeks

Post-Intervention:
Completing online surveys: $20
Actigraphy: $40
In-lab phase assessment: $80
Completing qualitative interview: $20

The breakdown of the pro-rated compensation will be discussed with parents during consent. This study requires a significant amount of work and time on the part of parents. Thus, we believe this compensation structure and amount are consistent with the effort of participating families, but not so high as to be coercive.

14.0 Privacy of Subjects and Confidentiality of Data:

14.1 Describe steps, if any, to protect the privacy of the subjects throughout their participation (e.g., during the recruitment process, consent process, and/or research procedures).

Consenting and all lab-based assessments (e.g., training visits, pupillometry, DLMO) will occur privately in designated lab space in UAHS or in the UAHS Center for Sleep, Circadian, and Neurosciences Research behind closed doors with no windows conveying into the room. All other research activities will occur at the subject's homes.

14.2 Will data/specimens be kept for future research, including unspecified future research and genetics? Yes ☒ No☐

14.3 If yes to the above question, describe future use plans here, including unspecified research, any storage in a repository (if applicable), and what data will be retained/reused.

No specimens or identifiable data will be kept. Only fully unidentified data will be kept indefinitely by the PI for future, unspecified research. De-identified data will also be deposited into the National Sleep Research Resource repository.

14.4 Discuss how study results will be shared with subjects, families, and/or the institution, both immediately and long-term.

Parents will have the opportunity to review their child's actigraphy and melatonin data with the researchers after completion of the study and melatonin assays.

14.5 Indicate if the research team will be accessing any of the following records.

☐ Substance abuse records (HIPAA and **42 CFR Part 2**)
☐ Medical records (HIPAA)
☐ Educational records (FERPA)*
☐ Employee records (**ABOR Policy 6-912**)*
☐ Other, specify: Click or tap here to enter text.

14.6 For each record source selected above, list the data elements to be accessed, who will access them, and how the information will be obtained.

N/A

14.7 Indicate where data will be stored:

☐ Box@UA	☒ OnCore
☒ Box@UA Health	☐ PACS medical imaging software
☐ Clinical Data Warehouse (CDW)	☐ Password Protected Drive
☐ Cloud Server	☒ REDCap
☐ Department Drive	☒ Transmitting/receiving subject data to/from an outside group
☒ Department Office	☐ UA Records Management & Archives
☐ Encrypted Drive	☐ Banner Server/Platform, specify:
☐ External Drive (hard drive, USB, disk)	☐Soteria
☐ Google Suite for Education	
☐HIPAA Research Computing Service	☐Other, specify: Click or tap here to enter text.

14.8 For EACH of the storage locations checked above, discuss the type of data to be stored, including if the data will be identifiable, coded, or de-identified upon storage.

If data will be coded, specify who will maintain the code, where it will be stored, and when it will be destroyed. If data will be de-identified, explain if there is any possibility that the data could be re-identified.

All signed paper consent forms and media authorization forms will be stored in separate binders in Dr. Hartstein's locked office.

All electronic data will be stored on an encrypted server only accessible to authorized personnel. The data will be stored indefinitely. Information about the data may be shared with the University of Arizona Institutional Review Board, the Office for Human Research Protections and other federal or state regulatory agencies. No external third parties will have access to the data.

- REDCap: All questionnaire data will be obtained and initially stored using REDCAP. This will include identifiable and coded data.

-Box Health: Will be used to store identifiable and coded information collected. Copies of raw data from the REDCap questionnaires will be later downloaded and stored in Box Health. Only the Principal Investigator, Co-Investigator, and relevant research assistants may access records stored in the Box Health drive. Photographs taken of participants will be stored in Box Health by coded number. The study code will be stored on a password-protected excel file in Box Health, maintained by the PI, and will be destroyed upon completion of data analysis. We will also keep a separate list of ineligible subject's names to avoid recontact, which will be deleted upon completion of data collection.

De-identified or coded data will also be stored in OnCore per UAHS policy.

De-identified data will also be deposited into the National Sleep Research Resource repository.

14.9 If collecting biological specimens, please describe the storage location for the specimens, including if they will be identifiable, coded, or de-identified upon storage.

Saliva samples will be stored in a minus 80-degree freezer in a locked laboratory in the UAHS Center for Sleep, Circadian, and Neurosciences Research (UAHS 0418) immediately after data collection. They will then be transferred to the University of Arizona Biorepository for long-term storage before being shipped out for assaying. Saliva samples will be labeled with participant's ID number, the date collected, and sample number. Samples will not be labeled with any identifiable information.

14.10 Storage of research records (research records should be maintained for whichever of the following time periods is the longest, select one):

☐ I will store research records for at least 6 years past the time the study is concluded.
☒ For studies involving minors, I will store research records for at least 6 years after the youngest participant turns 18.
☐ I will store research records for the length of time required by law or study sponsor, please specify: Click or tap here to enter text.

14.11 Describe what security controls (e.g., administrative, physical, technical) are in place to make sure data/specimens are secure.

Names, contact information, and any identifiable information from the subject will be kept separately from the subject's data records. All electronic data is stored on password protected computers that are only accessible by authorized study personnel. Saliva samples will be labeled only with the participant ID number and data collected and stored in a locked laboratory.

REDCap is a secure, web-based application designed to support data capture and storage for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. REDCap has been designed to allow for compliance with such standards as HIPAA, 21 CFR Part 11, FISMA (low, moderate, high), and international standards. Also included are a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields. The University of Arizona is an institutional member with a Bioinformatics Manager in the CaTS Research Center responsible for development and maintenance. This application will be used in the development of electronic forms for data collection to be used by study staff.

14.12 Indicate how data/specimens will be shared with collaborating entities:

☐ Data and/or specimens will not be shared between UA and any outside group or collaborating entity.
☒ Data/or specimens will be transmitted and/or disclosed to an outside group or a collaborating entity.
☒ Data and/or specimens will be received from an outside group or a collaborating entity.
☐ PHI will be transmitted to or received from an outside group or a collaborating entity. *
☐ A Limited Data Set will be transmitted or received from an outside group or a collaborating entity. *
☐ Data/specimens will be sold to pharmaceutical companies.

14.13 Describe what information will be shared, who it will be shared with, and how it will be shared (e.g., secure file transfer, REDCap, etc.). Also include information about future use sharing and repositories. Specify if the shared data will be identifiable, coded, a limited data set, or de-identified.

De-identified data will be deposited into the National Sleep Research Resource repository.

Coded samples will be sent to Solid Phase Inc. for assaying. Solid Phase Inc will provide the assay results back to the UA study team.

15.0 Additional Questions (complete as applicable):

15.1 Subject Injury: If the research involves more than minimal risk to subjects, describe the provisions for medical care and available compensation in the event of research related injury. If the Human Research has a clinical trial agreement, this language should reflect what is stated in the agreement.

N/A

15.2 <u>Withdrawal of Subjects</u>: Discuss how, when, and why subjects may be removed from the study. If abrupt withdrawal is necessary, discuss how subjects will be withdrawn so that they are not put at increased risk. Discuss what happens if a subject is withdrawn from one part of the study but asked to continue with other parts, such as ongoing follow-up.

Because salivary melatonin is a main measure of the study, participants may be removed if it becomes evident during the training visits that they are not able to provide adequate saliva for samples. Subjects may also be removed from the study for consistently failing to complete study activities (e.g., not wearing the actiwatch or completing the sleep diaries). Any subject withdrawn from the study will receive pro-rated compensation commensurate with the sections of the study already completed.

15.3 <u>Monitoring for Subject Safety</u>: Provide a brief lay discussion of your plan to monitor for subject safety. Describe what safety information will be collected, including serious adverse events, how safety information will be collected, and the frequency of collection including a timeline of when the data and review(s) will occur, who will review the information, and the plan for reporting findings.

If there will not be a way to monitor for subject safety, please explain.

All adverse events will be recorded and reported to the IRB. Participants will have access to a phone number and email address through which to contact study personnel and in the case of any emergencies.

15.4 Data Management Plan: Please discuss the data management plan, if required by your funder. For additional resources, reference the HSPP Data Management webpage. If your sponsor/funding agency requires a Data Management Plan, please upload the approved copy in eIRB. This section and the informed consent form should contain all pertinent information including:

- **What data/metadata will be shared (imaging, survey; raw data or derived; protocol, data form; etc.)**
- **What repository will be used (if known)**
- **How will data be stored (in a de-identified or identifiable format)**

De-identified data will also be deposited into the National Sleep Research Resource repository. Appropriate measures such as assigning each participant a unique code will be used for data de-identification and sharing. The final dataset will consist of demographics, sleep behavior collected through parent-report questionnaires (Children's Sleep-Wake Scale, Children's Sleep Habits Questionnaire, and Children's Chronotype Questionnaire), sleep timing and light history assessed through wrist actigraphy, salivary melatonin, and pupillometry from 60 children ages 5.0-6.9 years with parent-reported sleep-onset difficulties.

The University of Arizona will assure the timely release and sharing of appropriate data no later than the acceptance for publication of the main findings from the final dataset. The duration of preservation and sharing of the data will be a minimum of 10 years after the funding period.

15.5 International Research: Describe site-specific regulations or customs affecting the research, local scientific and/or ethical review structures that differ, and if community advisory boards are involved. If so, describe their composition and involvement. For research being conducted outside of the US, please explain any local laws, regulations, or customs the IRB needs to be aware of.

N/A

Additional items needed for review:

- Word versions of applicable subject materials: Consent Forms, Recruitment Materials, Data Collection Materials, Participant Materials
- Current PI CV or biosketch
- Advisor approval (if the PI is a student or medical resident)
- Department/Center/Section Review approval
- Scientific/Scholarly review approval
- Responsible physician approval and CV (if the PI is conducting medical procedures for which he/she is not clinically certified to perform)
- Additional approvals, as needed (e.g., RAP/Banner feasibility, Export Control, Radiation, COI, CATS, SRC, school district approval, tribal approval, etc.)

Other items as applicable:

- HSPP Appendices
- Data Monitoring Plan or Data Management Plan
- Drug/Device information
    - Applicable Drug or Device Appendix

    - Investigator's Brochure, drug product sheet, device manual, user's manual, instructions for use, package insert, IND/IDE documentation, FDA 1572 form, 510k indication, FDA exemption, sponsor determination of device risk, etc.
- Sponsor Protocol and MOPs that are used in the study

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