Diurnal Preference Contributes to Maximal UVB Sensitivity by the Hour of the Day in Human Skin In Vivo

Raita, Annina

2022-08

Raita , A , Häggqvist , I-M , Joronen , H , Nikkola , V , Huotari-Orava , R , Ylianttila , L , Kautiainen , H , Snellman , E , Pasternack , R & Partonen , T 2022 , ' Diurnal Preference Contributes to Maximal UVB Sensitivity by the Hour of the Day in Human Skin In Vivo ' , Journal of Investigative Dermatology , vol. 142 , no. 8 . https://doi.org/10.1016/j.jid.2022.01.021

http://hdl.handle.net/10138/354507
https://doi.org/10.1016/j.jid.2022.01.021

Diurnal Preference Contributes to Maximal UVB Sensitivity by the Hour of the Day in Human Skin In Vivo

JID Open

Journal of Investigative Dermatology (2022) **142,** 2289–2291; doi:10.1016/j.jid.2022.01.021

TO THE EDITOR

There is a functional circadian clock in most of the skin's cell types (Plikus et al., 2015). In hairless mouse skin studies, it has been shown that the time of day of UVR exposure influences erythemal response, sunburn-induced apoptosis, p53 formation, and repair of DNA photoproducts, suggesting that the circadian clock plays a role in these UVR-induced responses (Gaddameedhi et al., 2015). In humans, we showed earlier that after exposure to narrow-band UVB, the summarized evening erythema index (EI) scores were higher than the morning scores, thus suggesting that human skin is more vulnerable to UVR in the evening in vivo (Nikkola et al., 2018). Diurnal preference (DP), the behavioral trait for timing daily activities, correlates with the intrinsic period of the human circadian clock (Duffy et al., 2001), and it might thereby influence the timing of being exposed to UVR.

Our current study reports the outcome of narrow-band UVB minimal erythema dose (MED) phototesting in the morning versus evening, being performed 12 hours apart, and defines erythema response of the skin in 36 volunteers (aged 22–65 years) with Fitzpatrick's skin phototype II to III (Fitzpatrick, 1988). The Regional Ethics Committee of Tampere University Hospital District (Tampere, Finland) approved the study protocol. All volunteers gave their written informed consent. We assessed their DP and analyzed whether the DP was associated with narrow-band UVB erythema 24 hours after irradiations.

By applying a single (sixth) item of the modified Morningness-Eveningness Questionnaire for the assessment of DP (Hätönen et al., 2008; Merikanto et al., 2021), 25 participants were of definitely or rather a morning type and 11 participants were of definitely or rather an evening type. Further details of the assessment are available in Supplementary Materials and Methods.

MED testing to define erythema sensitivity was performed twice, 12 hours apart, that is, between 7 and 9 AM and between 7 and 9 PM. The standard MED testing included five UVB doses, ranging from 1 standard erythemal dose increased stepwise by a factor $\sqrt{}$ to 4 standard erythemal dose. Twenty-four hours after exposure, a faint and just perceptible reddening without sharp borders or corners was defined as MED (Dornelles et al., 2004; Heckman et al., 2013; Taylor et al., 2002). MED was quantified by the naked eye (HJ and VN) using a five-point scale as −, (+), +, ++, or +++, where (+) was the MED. EI of the test squares, which represents the intensity of the reflected wavelengths of red and green (Ly et al., 2020), was measured using reflectance spectrometry (DermaSpectrometer; Cortex Technology, Hadsund, Denmark).

The human skin in vivo showed more redness in the evening than in the morning, and the results observed by the naked eye were consistent with the EI readings ($P < 0.001$, Wilcoxon signed-rank test with exact *P*-values; Supplementary Table S1). Furthermore, we found that morning larks appeared to be more prone to evening UVB exposure–induced skin burns than night owls. EI by morning or evening type is shown in Figure 1.

In the evening, the difference in EI between the two types of DPs was significant ($P < 0.001$, generalized estimating equations) (Figure 1). This may indicate that the individual circadian time of the morning types may compromise skin protection against UVR in the evening. In MED testing during morning sessions, no statistical difference between DPs was found in EIs. It is possible that the internal time in the evening type is delayed but not to an extent that could still affect the sensitivity of the skin to narrow-band UVB exposure at 7 to 9 AM. The results from the two alternative assignments to chronotype (morning vs. intermediate vs. evening and morning vs. intermediate + evening) were similar but not significant (Supplementary Figure S1).

It was shown earlier that human proliferating epidermal cells from healthy skin biopsies exhibited circadian rhythms peaking at approximately 1 hour before midnight (the M-phase of the cell cycle) and troughs at noon (Mehling and Fluhr, 2006). In the keratinocyte cell line HaCaT, proliferation was influenced by melatonin, and interestingly, expression in circadian clock genes was modulated by low-dose UVB irradiation (Kawara et al., 2002). Accordingly, many skin functions exhibit circadian rhythms, and the skin seems to be more reactive toward the late afternoon and evening than in the morning and early afternoon (Le Fur et al., 2001).

To conclude, the mechanisms protecting human skin against UVR are proposed to be active in the morning and daytime. However, our current results show that night owls appear to have more active protective mechanisms in the evening hours than morning larks. This may be linked to differences in their circadian clock functions. UVR-induced erythema is an inflammatory response, and therefore, our findings may also reflect time-of-day influence on inflammation.

In addition, independent of DP, evening UVB exposures seem to be more dangerous considering the risk of skin burns. Our results suggest that it might

Abbreviations: DP, diurnal preference; EI, erythema index; MED, minimal erythemal dose

Accepted manuscript published online 8 February 2022

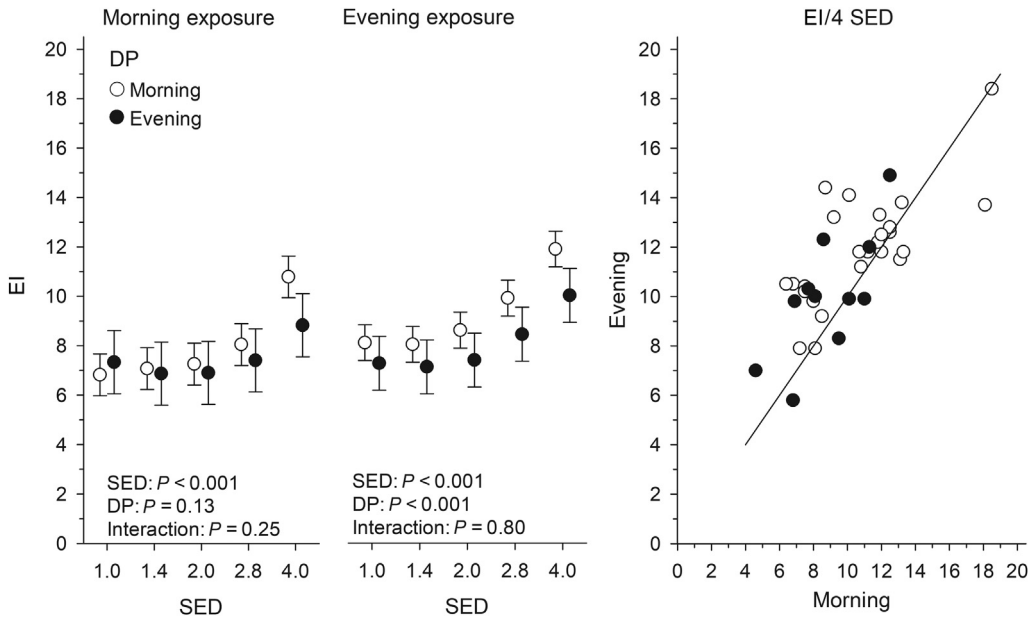


Figure 1. EI by morning and evening type. On the left, the graph shows EI as a function of SED of NB UVB after exposure in the morning and in the evening (n = 36). In the evening, the difference in EI between the morning and evening types as assessed by DP was significant ($P < 0.001$, generalized estimating equations), whereas no significant difference was found in the morning ($P = 0.13$, generalized estimating equations). On the right, the graph shows that 4 SED EIs are higher in the evening for both morning and evening types. DP, diurnal preference; EI, erythema index; NB, narrow band; SED, standard erythemal dose.

be beneficial to assess DP of each patient before testing the photosensitivity defining the MED. In this way, skin burns related to diurnal variation in photosensitivity could be avoided, especially if phototherapy were to be administered in the evening. Being aware of the impact of DP on sunburn sensitivity might be important in protecting the skin from sunlight when traveling across time zones to sunny destinations. Links between the circadian clock of skin cells and the time of UVR exposure may give a new insight into this puzzle.

Data availability statement

All data generated or analyzed during this study are included in this published article and its Supplementary Materials and Methods.

ORCIDs

Annina Raita: http://orcid.org/0000-0003-4811-6961
Iina-Maria Häggqvist: http://orcid.org/0000-0002-3588-0584
Heli Joronen: http://orcid.org/0000-0003-2880-0264
Veera Nikkola: http://orcid.org/0000-0002-0450-2871
Riitta Huotari-Orava: http://orcid.org/0000-0003-2014-2949
Lasse Ylianttila: http://orcid.org/0000-0002-9787-127X
Hannu Kautiainen: http://orcid.org/0000-0003-0786-0858
Erna Snellman: http://orcid.org/0000-0002-2093-9088
Rafael Pasternack: http://orcid.org/0000-0003-4899-1504
Timo Partonen: http://orcid.org/0000-0003-1951-2455

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

This study was financially supported (or partly supported) by the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital and Åke, Sara and Christer Lönnqvist's Foundation. We warmly thank research nurse Ulla Oesch-Lääveri for her dedication to the study.

AUTHOR CONTRIBUTIONS

Conceptualization: HJ, VN, RHO, LY, ES, RP, TP; Data Curation: AR, IMH, HJ, HK, ES, RP, TP; Formal Analysis: HK; Funding Acquisition: RHO, LY, ES, TP; Investigation: HJ, VN, RHO, ES, RP, TP; Methodology: VN, RHO, LY, HK, ES, TP; Project Administration: AR, IMH, HJ, VN, RHO, LY, ES, RP, TP; Resources: HJ, LY, HK, ES, TP; Supervision: VN, RHO, LY, ES, RP, TP; Validation: AR, IMH, HJ, RHO, LY, ES, RP, TP; Visualization: LY, HK; Writing - Original Draft Preparation: AR, IMH, RHO, LY, HK, ES, TP; Writing - Review and Editing: AR, IMH, HK, ES, TP.

***Annina Raita*[1,2,10,*], *Iina-Maria Häggqvist*[1,3,10], *Heli Joronen*[1,2,3], *Veera Nikkola*[1,2], *Riitta Huotari-Orava*[4], *Lasse Ylianttila*[5], *Hannu Kautiainen*[6,7], *Erna Snellman*[1,2,8], *Rafael Pasternack*[1,2] and *Timo Partonen*[9]**

[1]*Department of Dermatology, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland;* [2]*Department of Allergology and Dermatology, Tampere University Hospital, Tampere, Finland;* [3]*Department of Dermatology and Allergology, Päijät-Häme Social and Health Care Group, Lahti, Finland;* [4]*Department of Pathology, Fimlab Laboratories PLC, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland;* [5]*STUK Radiation and Nuclear Safety Authority, Helsinki, Finland;* [6]*Primary Health Care Unit, Kuopio University Hospital, Kuopio, Finland;* [7]*Folkhälsan Research Center, Helsinki, Finland;* [8]*Department of Dermatology and Venereology, University of Turku, Turku, Finland; and* [9]*Department of Public Health and Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland*
[10]*These authors contributed equally to this work.*
[*]*Corresponding author e-mail: annina.raita@tuni.fi*

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2022.01.021.

REFERENCES

Dornelles S, Goldim J, Cestari T. Determination of the minimal erythema dose and colorimetric measurements as indicators of skin sensitivity to UV-B radiation. Photochem Photobiol 2004;79:540–4.

Duffy JF, Rimmer DW, Czeisler CA. Association of intrinsic circadian period with morningness-eveningness, usual wake time, and circadian phase. Behav Neurosci 2001;115:895–9.

Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988;124:869–71.

Gaddameedhi S, Selby CP, Kemp MG, Ye R, Sancar A. The circadian clock controls sunburn apoptosis and erythema in mouse skin. J Invest Dermatol 2015;135:1119–27.

Hätönen T, Forsblom S, Kieseppä T, Lönnqvist J, Partonen T. Circadian phenotype in patients with the co-morbid alcohol use and bipolar disorders. Alcohol Alcohol 2008;43:564–8.

Heckman CJ, Chandler R, Kloss JD, Benson A, Rooney D, Munshi T, et al. Minimal erythema dose (MED) testing. J Vis Exp 2013;75:e50175.

Kawara S, Mydlarski R, Mamelak AJ, Freed I, Wang B, Watanabe H, et al. Low-dose ultraviolet B rays alter the mRNA expression of the circadian clock genes in cultured human keratinocytes. J Invest Dermatol 2002;119:1220–3.

Le Fur I, Reinberg A, Lopez S, Morizot F, Mechkouri M, Tschachler E. Analysis of circadian and ultradian rhythms of skin surface properties of face and forearm of healthy women. J Invest Dermatol 2001;117:718–24.

Ly BCK, Dyer EB, Feig JL, Chien AL, Del Bino S. Research techniques made simple: cutaneous colorimetry: a reliable technique for objective skin color measurement. J Invest Dermatol 2020;140:3–12.e1.

Mehling A, Fluhr JW. Chronobiology: biological clocks and rhythms of the skin. Skin Pharmacol Physiol 2006;19:182–9.

Merikanto I, Kantojärvi K, Partonen T, Pesonen AK, Paunio T. Genetic variants for morningness in relation to habitual sleep-wake behavior and diurnal preference in a population-based sample of 17,243 adults. Sleep Med 2021;80:322–32.

Nikkola V, Grönroos M, Huotari-Orava R, Kautiainen H, Ylianttila L, Karppinen T, et al. Circadian time effects on NB-UVB-induced erythema in human skin in vivo. J Invest Dermatol 2018;138:464–7.

Plikus MV, Van Spyk EN, Pham K, Geyfman M, Kumar V, Takahashi JS, et al. The circadian clock in skin: implications for adult stem cells, tissue regeneration, cancer, aging, and immunity. J Biol Rhythms 2015;30:163–82.

Taylor DK, Anstey AV, Coleman AJ, Diffey BL, Farr PM, Ferguson J, et al. Guidelines for dosimetry and calibration in ultraviolet radiation therapy: a report of a British photodermatology group workshop. Br J Dermatol 2002;146:755–63.

CD14 Is Induced by Retinoic Acid and Is Required for Double Stranded Noncoding RNA–Induced Regeneration

Journal of Investigative Dermatology (2022) **142,** 2291–2294; doi:10.1016/j.jid.2021.12.023

TO THE EDITOR

How tissues recognize damage signals and initiate the rearrangement of epidermal stem cells and their niche is a fundamental question in regeneration. We previously showed that toll-like receptor 3 (TLR3) signaling is activated by endogenous double stranded noncoding RNAs (dsRNAs) released from damaged tissues (Nelson et al., 2015) and stimulates intrinsic retinoic acid (RA) synthesis to synergistically promote tissue regeneration (Kim et al., 2019). These combined effects are essential to understanding the mechanisms that underlie regeneration. However, the pathways that underlie the synergistic effect between RA and dsRNA are not known.

To investigate the molecular pathways that drive TLR3-mediated regeneration, we inquired how dsRNAs released by damaged tissues activate TLR3 to induce intracellular signaling. We first examined proteins known to participate in TLR3 signaling. In particular, we identified MSR1, RFTN1, RFTN2, ITGAM, and CD14 as potential targets. Previous studies have shown that these cell surface receptors are able to bind to dsRNA or its synthetic analog polyinosine:polycytidylic acid (poly I:C) and thereby facilitate TLR3 activation (Dansako et al., 2013; Lee et al., 2006; Nguyen et al., 2017; Watanabe et al., 2011; Zhou et al., 2013). Expression of CD14, a pattern-recognition receptor in the innate immune system, enhances TLR3-mediated dsRNA sensing. Specifically, when bone marrow–derived macrophages were treated with poly I:C, CD14 was found to bind directly to small fragments of dsRNA and promote cellular uptake and delivery to TLR3 (Lee et al., 2006).

To begin to understand the nature of the synergy between RA and poly I:C (Kim et al., 2019), we first tested whether the sequence of treatment with either agent was superior for activating *IL6* and *TLR3*, transcripts known to be activated by dsRNA. We compared between a pretreatment with RA (1 μM) followed by continued exposure to RA (48 hours) after the delayed addition of poly I:C (0.5 μg/ml, 48 hours) and pretreatment with poly I:C followed by continued exposure to poly I:C after the delayed addition of RA. Fascinatingly, in both mRNA (Figure 1a) and protein (Figure 1b) expressions, only pretreatment with RA but not delayed addition led to much higher levels of *IL6* and *TLR3*. We hypothesized that RA might somehow enhance subsequent dsRNA cellular internalization and signaling. To test this, we applied fluorescein-tagged poly I:C to keratinocytes (KCs) and discovered that pretreatment with RA dramatically enhanced dsRNA cellular internalization (Supplementary Figure S1). These results are consistent

Abbreviations: dsRNA, double-stranded noncoding RNA; K, keratin; KC, keratinocyte; poly I:C, polyinosine:polycytidylic acid; RA, retinoic acid; siRNA, small interfering RNA; TLR3, toll-like receptor 3; WIHN, wound-induced hair neogenesis

Accepted manuscript published online 7 January 2022; corrected proof published online 1 February 2022

SUPPLEMENTARY MATERIALS AND METHODS

Ethical consideration

The Regional Ethics Committee of Tampere University Hospital District (Tampere, Finland) approved the study protocols (R16001). All volunteers gave their written informed consent. The study was conducted in accordance with the Declaration of Helsinki and its amendments.

Participants

The study was carried out in the Department of Dermatology and Allergology, Päijät-Häme Central Hospital (Lahti, Finland). Narrow-band (NB) UVB irradiations of minimum erythema dose (MED) testing were performed from January to April in 2016 and in midwinter in 2018–2019. The study was open equally to men and women, but more women than men volunteered. Altogether 36 participants, 33 women and 3 men, aged 22–65 years (mean age 42 years) participated in the study, and 16 of them had anamnestic skin phototype II and 20 had skin phototype III (Fitzpatrick, 1988) as described in Supplementary Table S1. Their mean body mass index was 24.7 kg/m^2 (ranging from 18.8 to 41.6 kg/m^2). None of them reported a history of skin cancer. No exposure to UVR in the 3 preceding months was allowed. Pregnant or lactating women were not included in the study. During the study, p-pills; thyroxin, proton pump inhibitors; and medication for asthma, hypercholesterolemia, and hypertension were allowed.

Assessment of the chronotype

Morningness-Eveningness Questionnaire (MEQ) is among the most commonly applied scales for measuring chronotype (Horne and Östberg, 1976). A number of large studies have reported MEQ to be a reliable measure across several countries. MEQ has received some criticism for the scale containing 19 items and has been considered lengthy. These criticisms underpinned the development of three shorter versions with either six (modified Morningness-Eveningness Questionnaire [mMEQ]), five (reduced MEQ), or four (shortened MEQ) items. The correlation between the original MEQ and short versions ranges from satisfactory to excellent (Kanagarajan et al., 2018). In this study, each participant filled in mMEQ once right in the beginning of the study. mMEQ is based on the original MEQ and contains items 4, 7, 9, 15, 17, and 19 of the original MEQ, which explain about 83% of the variance in full MEQ scale (Hätönen et al., 2008). We used a single item, the (6th) item of the 6-item mMEQ, which is equal to the 19th item of the original MEQ for assessment of diurnal preference. The item asks the question, "Which one of these types do you consider yourself to be?" The morning types were composed of those who answered to be "definitely a morning type, or rather a morning type," and the evening types were composed of those who answered to be "definitely an evening type, or rather an evening type." This single item has been widely used for the assessment of diurnal preference (Cheng et al., 2021; Cook et al., 2021; Jones et al., 2019; Kalmbach et al., 2017; Koskenvuo et al., 2007; Merikanto and Partonen, 2020; Merikanto et al., 2021; Simpkin et al., 2014).

For sensitivity analysis, we assigned the participants to their chronotype by dividing them into two (morning and intermediate + evening chronotypes) and three (morning, intermediate, and evening) groups on the basis of the sum score on the six-item mMEQ (Supplementary Figure S1). The rationale for combining intermediate and evening chronotypes was that the intermediate chronotypes are much more similar to the evening chronotypes than the morning chronotypes in terms of health hazards they have (Knutson and von Schantz, 2018; Partonen, 2015).

Definition of MED

Skin erythema from sunlight is predominantly a consequence of UVB rays. For MED testing, we used an NB UVB phototherapy device (Waldmann UV 801KL; Herbert Waldmann, Villingen-Schwenningen, Germany), which was equipped with four TL20W/01 tubes. The device and NB UVB radiation (311 nm) are commonly used for light therapy and so forth for psoriasis and eczemas in the Departments of Dermatology in Finland. Before the study, the Nuclear Safety Authority of Finland (LY) measured spectral irradiance using Ocean Optics S2000 spectroradiometer (Ocean Optics, Dunedin, FL), and the time to irradiate MED test squares was determined on the basis of these measurements. Uncertainty (2σ) of the measurement of Ocean Optics S2000 was estimated to be approximately 14% (Ylianttila et al., 2005). The measurements are traceable to the National Institute of Standards and Technology (Gaithersburg, MD). A majority of the rays from the NB UVB lamp have an emission peak at 311-nm as shown in Supplementary Figure S2. According to the measurements, in this NB UVB phototherapy device, 1 standard erythemal dose is equal to erythemal effective radiant exposure of 10 mJ/cm^2 or nonweighted physical UV dose of 172 mJ/cm^2. Before use, the device was always preheated for a total of 4 minutes.

According to spectral UV irradiance of the NB UVB device, the skin had to be kept at a distance of 21 cm from the UVB tubes. The skin of the buttocks was exposed to the desired dose of UVB radiation trough 1 cm^2 holes which had been precut in a black plastic impermeable material (Taylor et al., 2002). A timer was used to determine the correct irradiation time, and when the desirable UVB dose was reached, the square was covered with a piece of black plastic. During irradiations, the surrounding skin was protected against any UVR.

Because the purpose was to ascertain whether the time of day made a difference to erythema reaction, the MED test series had to be performed twice, once in the morning (between 7 and 9 AM) and once in the evening (between 7 and 9 PM). In each MED series, the erythemal responses in each square were assessed 24 hours after irradiation. The MED test series were performed in duplicate 12 hours apart from each other. The NB UVB dose series was composed of five standard erythemal doses as follows: 1, 1.4, 2, 2.8, and 4 standard erythemal dose. The reading was taken 24 hours after irradiation and separately for the two MED test series 12 hours apart. MED was defined as just-perceptible erythema without definite sharp borders or corners (Taylor et al., 2002). Erythema detected by the naked eye by the two authors (HJ and VN) was scored using a five-point scale as follows: −,

(+), +, ++, or +++. In this study, a MED value of (+) indicated the lowest UVB dose needed to produce minimal or just perceptible erythema 24 hours after exposure (Supplementary Table S1).

Quantification of erythema (erythema index) was assessed with reflectance spectrometry (Diffey et al., 1984; Farr and Diffey, 1984; Jemec and Johansen, 1995; Qian et al., 2015; Tejasvi et al., 2007; Wengström et al., 2004) using a calibrated DermaSpectrometer (Cortex Technology, Hadsund, Denmark). Each time, the device was calibrated according to manufacturer's instructions. Each MED test square was read out a total of three times, and the mean value of the three readings was used in calculations.

Statistical methods

Changes within the participants were analyzed by applying permutation type (10,000 replications) generalized estimating equations and Wilcoxon signed-rank test with exact *P*-values. Generalized estimating equations were developed as an extension of the general linear model (e.g., ordinary least squares regression analysis) to analyze longitudinal and other correlated data. Generalized estimating equation models take into account the correlation between repeated measurements in the same individual. A permutation type test was used because the sample size was small (Manly, 2007). Adjustment for multiple comparisons was considered unnecessary. Statistical package Stata version 16.1 (StataCorp, College Station, TX) was used for analysis of the dataset.

SUPPLEMENTARY REFERENCES

Cheng WJ, Puttonen S, Vanttola P, Koskinen A, Kivimäki M, Härmä M. Association of shift work with mood disorders and sleep problems according to chronotype: a 17-year cohort study. Chronobiol Int 2021;38:518–25.

Cook JD, Peppard PE, Blair EE, Tran KM, Hertting MC, Plante DT. Associations of school night sleep duration and circadian preference with middle school-aged student attendance, tardiness, and suspension. Sleep Health 2021;7:708–15.

Diffey BL, Oliver RJ, Farr PM. A portable instrument for quantifying erythema induced by ultraviolet radiation. Br J Dermatol 1984;111:663–72.

Farr PM, Diffey BL. Quantitative studies on cutaneous erythema induced by ultraviolet radiation. Br J Dermatol 1984;111:673–82.

Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988;124:869–71.

Hätönen T, Forsblom S, Kieseppä T, Lönnqvist J, Partonen T. Circadian phenotype in patients with the co-morbid alcohol use and bipolar disorders. Alcohol Alcohol 2008;43:564–8.

Horne JA, Östberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976;4:97–110.

Jemec GBE, Johansen JD. Erythema-index of clinical patch test reactions. Skin Res Technol 1995;1:26–9.

Jones SE, van Hees VT, Mazzotti DR, Marques-Vidal P, Sabia S, van der Spek A, et al. Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. Nat Commun 2019;10:1585.

Kalmbach DA, Schneider LD, Cheung J, Bertrand SJ, Kariharan T, Pack AI, et al. Genetic basis of chronotype in humans: insights from three landmark GWAS. Sleep 2017;40:zsw048.

Kanagarajan K, Gou K, Antinora C, Buyukkurt A, Crescenzi O, Beaulieu S, et al. Morningness-Eveningness Questionnaire in bipolar disorder. Psychiatry Res 2018;262:102–7.

Knutson KL, von Schantz M. Associations between chronotype, morbidity and mortality in the UK Biobank cohort. Chronobiol Int 2018;35:1045–53.

Koskenvuo M, Hublin C, Partinen M, Heikkilä K, Kaprio J. Heritability of diurnal type: a nationwide study of 8753 adult twin pairs. J Sleep Res 2007;16:156–62.

Manly BFJ. Randomization, bootstrap and Monte Carlo methods in biology. 3rd ed. Boca Raton, FL: Chapman and Hall/CRC; 2007.

Merikanto I, Kantojärvi K, Partonen T, Pesonen AK, Paunio T. Genetic variants for morningness in relation to habitual sleep-wake behavior and diurnal preference in a population-based sample of 17,243 adults. Sleep Med 2021;80:322–32.

Merikanto I, Partonen T. Increase in eveningness and insufficient sleep among adults in population-based cross-sections from 2007 to 2017. Sleep Med 2020;75:368–79.

Partonen T. Chronotype and health outcomes. Curr Sleep Med Rep 2015;1:205–11.

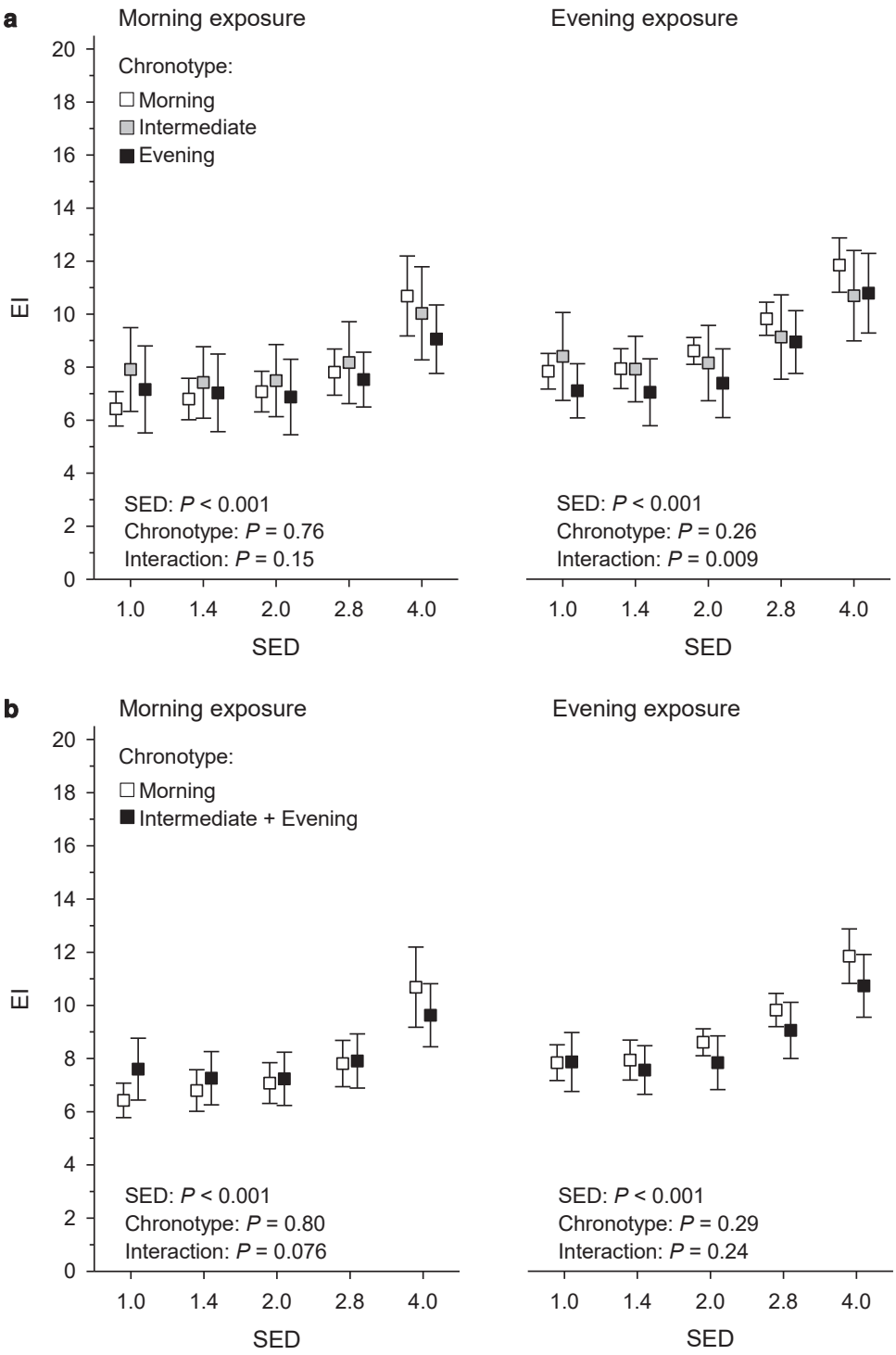
Qian CY, Yuan C, Tan YM, Liu XP, Dong YQ, Yang LJ, et al. Comparing performance of Chromameter®, Mexameter® and full-field laser perfusion imaging for measurement of ultraviolet B light-induced erythema. Clin Exp Dermatol 2015;40:438–40.

Simpkin CT, Jenni OG, Carskadon MA, Wright KP Jr, Akacem LD, Garlo KG, et al. Chronotype is associated with the timing of the circadian clock and sleep in toddlers. J Sleep Res 2014;23:397–405.

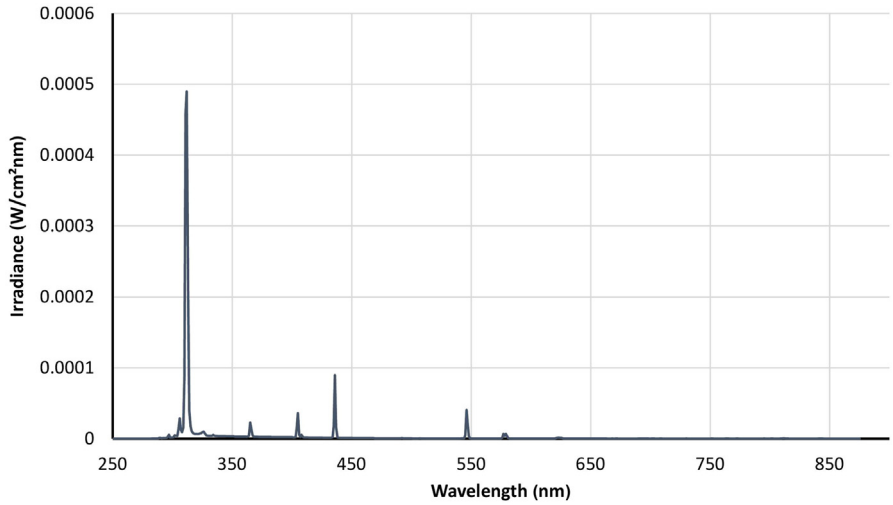
Taylor DK, Anstey AV, Coleman AJ, Diffey BL, Farr PM, Ferguson J, et al. Guidelines for dosimetry and calibration in ultraviolet radiation therapy: a report of a British photodermatology group workshop. Br J Dermatol 2002;146:755–63.

Tejasvi T, Sharma VK, Kaur J. Determination of minimal erythemal dose for narrow band ultraviolet B radiation in north Indian patients: comparison of visual and Dermaspectrometer readings. Indian J Dermatol Venereol Leprol 2007;73:97–9.

Wengström Y, Forsberg C, Näslund I, Bergh J. Quantitative assessment of skin erythema due to radiotherapy–evaluation of different measurements. Radiother Oncol 2004;72:191–7.



Supplementary Figure S1. EI as a function of SED of NB UVB after exposure in the morning and in the evening (n = 36). (**a**) Figure shows participants who were divided into three groups on the basis of the sum score on the six-item mMEQ. (**b**) Figure shows participants who were divided into two groups on the basis of the sum score on the six-item mMEQ. The results are similar to our primary results with division done on the basis of diurnal preference, but owing to a limited number of volunteers in the groups, the results are not statistically significant. EI, erythema index; mMEQ, modified Morningness-Eveningness Questionnaire; NB, narrow band; SED, standard erythemal dose.



Supplementary Figure S2. Calibration measurement. TL20W/01 tubes emit almost solely UVB around 311 nm as shown by the author's (LY) calibration measurement of the study device.

Supplementary Table S1. Fitzpatrick's Skin Phototypes and MED of the Volunteers

Volunteer ID Number	Fitzpatrick's Skin Phototypes (II–III)	MED (SED) Morning	MED (SED) Evening
1.	III	2.8	2.8
2.	III	1.4	1.4
3.	II	4.0	2.8
4.	III	4.0	2.8
5.	II	4.0	2.8
6.	II	2.8	2.0
7.	III	4.0	2.8
8.	III	4.0	2.8
9.	II	2.8	2.0
10.	III	2.8	2.8
11.	III	2.8	2.0
12.	III	4.0	2.8
13.	III	4.0	2.0
14.	III	2.8	2.0
15.	III	2.8	2.0
16.	III	>4.0	4.0
17.	II	2.8	2.0
18.	III	4.0	2.8
19.	II	4.0	2.0
20.	III	2.8	2.8
21.	III	2.8	2.0
22.	II	2.8	2.0
23.	III	2.8	2.0
24.	III	4.0	2.8
25.	II	1.4	1.4
26.	III	4.0	>4.0
27.	II	2.0	2.8
28.	III	4.0	2.0
29.	III	4.0	2.0
30.	II	2.0	2.0
31.	III	2.8	2.8
32.	III	2.0	2.0
33.	III	4.0	4.0
34.	II	2.0	2.8
35.	II	2.8	2.8
36.	II	2.0	2.0

Abbreviations: MED, minimal erythemal dose; SED, standard erythemal dose.

MED was observed by the naked eye as just perceptible faint erythema in the morning and in the evening. Wilcoxon signed-rank test with exact *P*-values: $P < 0.001$ (>4.0 SED = there were no erythema visible to the naked eye within the tested doses).