TITLE

Assessment of time window for sleep onset on the basis of continuous wrist temperature measurement

AUTHORS

Timo Partonen[1], Jari Haukka[2,3], Liisa Kuula[4], Anu-Katriina Pesonen[4]

AFFILIATIONS

[1] National Institute for Health and Welfare (THL), Department of Public Health Solutions, Helsinki, Finland

[2] University of Helsinki, Department of Public Health, Helsinki, Finland

[3] Tampere University, Faculty of Medicine and Health Technology, Tampere, Finland

[4] University of Helsinki, SleepWell Research Program, Faculty of Medicine, Helsinki, Finland

CORRESPONDING AUTHOR: Timo Partonen, E-mail: timo.partonen@thl.fi

ACKNOWLEDGMENTS

The authors are indebted to and thank the research nurse Ms. Helena Alfthan for her help in carrying out the polysomnographic recordings. This study was based on the agreement between the University of Helsinki and Night Train Oy (Oulu, Finland) and supported in part by a grant from the latter party which was not involved in the design, interpretation, or writing of the manuscript.

WORD COUNT: 2892 (main text).

ABSTRACT

The interactions of the principal circadian clock with the homeostatic sleep process create the time-sensitive window for easy falling asleep in the evening, which is affected by a thermoregulatory process. It has been hypothesized that the changes in skin and core body temperatures before the sleep onset might play a direct role in sleep regulation. To determine this time window, we recorded from 20 healthy participants (11 women and 9 men), aged 26–58 years, one overnight own-home ambulatory polysomnography and measured continuously wrist skin temperature with a wrist-worn accelerometer containing a skin temperature thermometer. Wrist skin temperatures which were read out from the thermometer of the accelerometers were modeled using linear mixed models, and the linear effect of time before the sleep onset on wrist temperature was analyzed using a mixed model with the sex and age as the covariates. We found that wrist skin temperatures increased on average by 0.6° (of Celcius) in 10 minutes prior to the sleep onset and could be tracked robustly along a slope of time ($p=0.004$). Our current findings may be useful in further characterizing the window of time and its boundaries for easy falling asleep.

KEYWORDS

ambulatory monitoring, peripheral temperature, sleep stage, timing of sleep

INTRODUCTION

To understand sleep and its problems, sleep must be considered as part of the circadian rhythm (Hofstra and de Weerd 2008). The natural timing and structure (quantity and quality) of sleep are determined by both the intrinsic circadian rhythm of the nervous system and the need for sleep during wakefulness. These two interacting processes give rise to the sleep behavior of a person which can be observed, even by the naked eye, or recorded with polysomnography (PSG) for example. The circadian process is the dominant of these two (Kawato et al. 1982) and results from the functions of the cells located in the suprachiasmatic nucleus of the anterior hypothalamus, or the body's central internal clock, the outputs of whose contribute to the generation and maintenance of circadian rhythms. This clock also controls the emergence of a specific sleep stage after sleep onset, i.e., rapid eye movement (REM) sleep, but not that of non-REM (NREM) sleep. Moreover, the interactions of this clock with the homeostatic sleep process create the time-sensitive windows for easy falling asleep as well as refreshed waking-up after the night-time sleep, if the time slept fulfilled the individual sleep need in terms of quantity as well as quality (Wehr et al. 2001). Moreover, it has been hypothesized that the changes in skin and core body temperatures before the sleep onset might play a direct role in sleep regulation (Gilbert et al. 2004). Changes in body temperature, whether measured as core body temperature or peripheral (such as wrist skin) temperature, are highly correlated with the likelihood of falling asleep, but the degree of heat loss from the skin and the subsequent change in peripheral body temperature was a stronger predictor for the sleep onset than the change in core body temperature, irrespective of the circadian phase (Kräuchi et al. 2000).

During sleep, the sleep stages alternate in a healthy person according to a particular pattern or formula of the cycle of NREM-to-REM sleep stages (Kleitman and Ramsaroop 1948; Kleitman et al. 1948; Kleitman 1949, 1960). After falling asleep, healthy adults follow in

their night-time sleep the same cycling pattern, if not disturbed. During their natural night-time sleep, a person usually sleeps for 4 or 5 sleep cycles, short sleepers for fewer cycles and long sleepers for more cycles, and the average length of the NREM-to-REM sleep stages cycle in an adult is approximately 90 minutes on average, ranging from 80 to 110 minutes (Merica and Gaillard 1986; Le Bon et al. 2002). The opening of the sleep-friendly time window allows a person to have a sufficiently long night-time sleep during which the NREM-to-REM sleep stages cycle according to the formula. Finally, the need for sleep becomes fulfilled and the night-time sleep comes to its end, when another time window for a refreshed wake-up opens.

To determine these two time windows, a person's daily rest-activity or sleep-wakefulness rhythm must be measured. It can be reliably determined by measuring body temperature under controlled conditions (Gilbert et al. 2004). The circadian rhythm of body temperature can be measured, for example, from the skin using a measuring device placed over the radial artery (Sarabia et al. 2008; Martinez-Nicolas et al. 2013; Bonmati-Carrion et al. 2014). In such case, the measuring device for use is compact, taped to the skin and worn by the person for several days. The wrist temperature increase onset calculated from these measurements reliably reports the phase of the circadian rhythm of skin temperature and correlates, e.g., with the phase of the circadian rhythm of melatonin as calculated on the basis of the dim light melatonin onset (Lewy et al. 2007).

Circadian rhythm sleep-wake disorders due to disturbances of the body's central internal clock often result in insomnia, tiredness or hyperactivity (Abbott et al. 2015). Of these, insomnia and tiredness are very common symptoms in the general population among adults as well as adolescents (Chattu et al. 2018). Partly because of this, they are also big diagnostic and therapeutic challenges. A key therapeutic goal is to regularize the sleep-wakefulness

schedule, which favors the opening of the window of time suitable for falling asleep in the evening hours (van Straten et al. 2018).

Delayed sleep (delayed sleep phase syndrome) is the most common one of the circadian rhythm sleep disorders, especially in younger age groups, but it also affects 1.5% to 9% of adults (Nesbitt 2018). Concomitant or comorbid substance abuse disorders, mood disorders or anxiety disorders are common as well (Abbott et al. 2018), thus the circadian rhythm sleep disorders are relevant and important in terms of public health. Finding new ways to determine and regularize the sleep-wakefulness patterns is therefore justified.

Aims

The purpose of this study is to determine, whether the continuous measurement of wrist skin temperature can determine the time window for falling asleep. Earlier, there is a view on that the increase in heat loss prior to sleep increases sleep propensity, thereby facilitating the sleep onset (for review, see Gilbert et al. 2004). To make it clear, we do not claim that the idea of thermoregulatory responses in relation to falling asleep is new, but herein, we wanted to answer the following two research questions. First, is there a characteristic, rapid and relatively large variation in wrist skin temperature in the evening? If it were, it would be due to changes in thermoregulation (such as an increase in wrist skin temperature) which are irrespective of the circadian phase able to trigger directly sleep and wakefulness promoting areas of the brain to initiate sleep, and then the second question would be, whether the moment of falling asleep is trackable and reliably predictable from this characteristic variation?

MATERIALS AND METHODS

Participants

We recruited 20 participants (11 women and 9 men), aged 26–58 years (mean = 39 years, standard deviation = 11.01 years), through word of mouth. They were interviewed in person and assessed as psychologically healthy. Any potential individuals who had current health problems or were taking medication known to affect thermoregulation or sleep were excluded from participating. For the 24 hours prior to each session the participants abstained from alcohol and caffeine.

All participated voluntarily with no monetary compensation. Potential participants were fully informed of the procedure before they agreed to participate: they were given a detailed written procedure description and an overall verbal explanation of the measurements. All participants gave their written consent and were aware that interrupting their participation was possible at any phase of the study. The study was conducted in accordance with the Declaration of Helsinki and its amendments. The detailed research protocol was approved by the Helsinki University Hospital Coordinating Ethics Committee (#HUS/652/2017).

Assessments

All of the participants scheduled an overnight, own-home ambulatory PSG with the research nurse according to their own timetables. In addition to the PSG, the participants also filled in a short background questionnaire, and used wrist-worn accelerometers (for actigraphy) and skin temperature loggers for three days starting from the PSG night. Details regarding these measurements are described in the following paragraphs.

Polysomnography

All recordings were done using SOMNOscreen plus (SOMNOmedics GmbH, Germany). A trained research nurse attached gold cup electrodes at 6 EEG locations (frontal (F) hemispheres: F3, F4; central (C) hemispheres: C3, C4; occipital (O) hemispheres: O1, O2) and two for the mastoids (A1, A2) accordingly. The electro-oculogram (EOG) and the

electromyogram (EMG) were measured by using disposable adhesive electrodes (Ambu Neuroline 715, Ambu A/S, Denmark), two locations for EOG and three locations for EMG. In addition, an online reference Cz and a ground electrode in the middle of forehead were used. PSG data were scored manually using the DOMINO program (v2.7; SOMNOmedics GmbH, Germany) in 30-second epochs into Stage 1, Stage 2, SWS and REM sleep according to AASM guidelines.

Actigraphy

GENEActiv Sleep actigraphs (Activinsights Ltd., Kimbolton, UK) are wrist-worn, tri-axial accelerometers which can be initialized to collect raw 12-bit MEMS acceleration data at selected frequencies and contain linear active thermistor sensors which measure temperature with 0.25°C resolution and have the accuracy of ±1.0°C from 0°C to +60°C. They include memory for storing data on the temperature and time recordings, and measure temperature every 30 seconds. Participants were instructed to wear the actigraph device on their non-dominant wrist for three days and nights. They were given a sleep log booklet to fill in alongside the actigraphy measurement period, and were instructed to write down sleep onset and offset times, as well as all times when the device was not worn on the wrist. The devices were set to sample activity at a frequency of 50 Hz, and their data were downloaded onto a computer and aggregated into 30-second epochs.

Temperature logger

Thermochron iButtons (DS1922L, Maxim Integrated, San Jose, CA, USA) are small, light (about 3 g), round, stainless steel data loggers with thermometers. They contain digital thermistor sensors which measure temperature with 0.0625°C resolution and have the accuracy of ±0.5°C from –10°C to +65°C. They include memory for storing data on the temperature and time recordings, and can be initialized to the desired logging frequency. In

the current study, we selected the measurement rate to be one per minute. The research nurse attached the iButton onto the wrist (inner side, approximately upon the radial artery) using a comfortable adhesive medical tape, and instructed the participants to write down all times when the device was removed from the wrist. The data were read with the USB Port Adapter as connected to the PC 1-Wire Connectivity Reader, and extracted with the OneWireViewer software (Maxim Integrated, San Jose, CA, USA).

Background questionnaire

The participants were given a short questionnaire, which included questions regarding their current health (a self-rated Likert-like scale from 1 to 4, where 1=excellent, 2=good, 3=moderate, 4=poor), and an open field to describe their current health in more detail if desired. The questionnaire also included three further questions on height, weight, and handedness.

Statistical analysis

Sleep onset can be and has been defined in different ways in the literature. For this reason, in this study, we used the following three definitions for sleep onset. First (Definition 1), sleep onset was met after three consecutive epochs of N1 sleep. Second (Definition 2), sleep onset was met at after the first epoch of N2, N3 or REM sleep. Third (Definition 3), sleep onset was met after the first epoch of N1, N2, N3 or REM sleep. Of these, the Definitions 1 and 2 are classic, i.e., gold standards (Rechtschaffen et al. 1968), and the Definition 3 is the updated version of the classical definitions (Iber et al. 2007). This allowed us also to compare and analyze, whether the definition affected the outcome.

We derived the wrist temperature read-outs from both devices, and after the initial inspection and preliminary analyses, we decided to use the 1-second epoch data derived from the actigraphy (GENEActiv Sleep actigraphs) for analysis, because the data derived from the

temperature loggers (Thermochron iButtons), with the 60-second epochs, were not reactive nor sensitive enough to capture changes in temperature. For the analysis, the 1-second epoch data derived from actigraphy (GENEActiv Sleep actigraphs) were aggregated into 30-second epochs which matched with the epochs of polysomnography.

First, the curves of wrist skin temperature were visualized as a function of time, i.e., from 30 minutes before the onset of sleep to 5 minutes after the onset of sleep and calculated with linear mixed models using splines of time as the fixed effect, with the knots for 20, 10 and zero minutes before the sleep onset minute by minute, which covered the data well. We used the intercept of individuals as the random effect. Cubic splines with knots is a piece-wise cubic polynomial with continuous derivatives upto order 2 (the 1st and the 2nd derivatives) at each knot. Secondly, we modelled the fixed linear effect of time before the sleep onset on wrist temperature using a mixed model, with the sex and age as the fixed covariates, and including only data for10 minutes prior to the sleep onset. In this model, we also included the intercept of individuals as the random effect, and we tested whether the slope was different from zero using the Wald type test. For this analysis, the R software (R Core Team 2015) was used and we give the codes computed in the Appendix. The model was used to calculate the adjusted curves we present in the figures.

RESULTS

There were increases in wrist temperature on average were 0.62 (95% confidence interval of 0.52-0.72), 0.47 (0.33-0.61) and 0.60 (0.50-0.71) degrees (of Celsius) in 10 minutes as calculated from the slopes minute by minute prior to the sleep onset for definitions 1, 2 and 3, repectively (Figures 1-3).

Of the definitions for sleep onset, the Definitions 1 and 3 yielded very similar, almost equal, associations of wrist temperatures with the estimated slope of time prior to the sleep onset (Table 1). The Definition 2 was in contrast to the remaining.

DISCUSSION

Concerning our two research question we proposed a priori for this study, we are able to give the following answers. To the first question, whether there is a rather rapid and relatively large variation in skin temperature in the evening close to falling asleep, the answer was that there was such variation. The skin temperature increased on average by 0.6° (of Celcius) in 10 minutes prior to the sleep onset. Later during the night when the individual is asleep there are larger, but however slower, variations in temperature (Sarabia et al. 2008), but as we focused on the sleep onset we did not analyze these fluctuations in the current study.

To the second question, whether the moment of falling asleep is reliably predictable from this variation, the answer was that it may be able to be predicted, since we applied the usage of splines of time for our data analysis and of the inter-individual variation we were able identify a significant slope of time prior to the sleep onset. However, we did not conduct a further study to test the predictive values, but such tests remain to be done and the second research question of ours awaits an answer.

Our analysis showed that on average the wrist skin temperatures tended to increase before falling asleep, and this finding was robust and independent of the definition for sleep onset. It supports, but does not confirm, the hypothesis that changes in thermoregulation including a co-occurring change in body temperature, a characteristic increase in wrist skin temperature and a characteristic decrease in core body temperature, being irrespective of the circadian phase, triggers directly sleep and wakefulness promoting areas of the brain to initiate sleep. This is recorded and assessed as the sleep onset with polysomnography. However, the

criterion chosen for the PSG-defined sleep onset revealed diversity in wrist temperature dynamics at cross-sections, as visualized at 5 minutes before the sleep onset pending on definition. The Definition 2 was in contrast to the remaining, so it appears that if the sleep onset was defined to be met only at after the first epoch of N2 sleep stage, not paying attention to epochs of N1 sleep stage the peripheral skin temperature fluctuated more during the period of time from the first N1 epoch(s) to the first N2 epoch.

In addition to the circadian and homeostatic processes which underlie and contribute to the sleep-wakefulness cycle, it is known that sleep propensity is affected by a thermoregulatory process, and thus it is plausible that the changes in skin and core body temperatures before the sleep onset might play a direct role in sleep regulation (Gilbert et al. 2004). Earlier, among men who were aged 19 to 27 years and healthy good sleepers, a significant increase in hand skin temperature contributed to the concomitant decrease in rectal core temperature which occurred at 20 minutes prior to sleep initiation (van den Heuvel et al. 1998). However, while changes in these body temperatures were evident before the sleep onset, the amplitude of pre-sleep effects was less than the evoked effects of sleep on the body temperatures. Mechanistically, it appears that selective vasodilation of distal skin regions and their heat loss facilitates the onset of sleep (Kräuchi et al. 2000).

As our study was based on recordings for one night only, however, our study was not free of limitations. On the other hand, we included both women and men in our study sample and provided data on both genders, whereas earlier studies on this subject (van den Heuvel et al. 1998; Kräuchi et al. 2000) were on men only. Allowing the subjects to sleep according to their preferred schedule at their homes is an additional strength of the current study.

As we see these findings of ours from the current study, they may be useful in further characterizing the window of time and its boundaries for easy falling asleep. Continuous recording of wrist skin temperature before the bedtime may be useful to discover such

window of time. This information might thus be used as a source of input for machine learning procedures to identify the opening of window of time favoring sleep onset and to provide feedback to the individual about this. It may be seen as an automated component for a guided self-care intervention as part of the formal cognitive behavioral treatment for insomnia or anyone who is interested in identifying and thereby becoming more aware of an opportune moment for bedtime and starting night sleep.

ACKNOWLEDGMENTS

The authors are indebted to and thank the research nurse Ms. Helena Alfthan for her help in carrying out the polysomnographic recordings. This study was based on the agreement between the University of Helsinki and Night Train Oy (Oulu, Finland) and supported in part by a grant from the latter party which was not involved in the design, interpretation, or writing of the manuscript.

DISCLOSURE OF INTEREST

Timo Partonen, Liisa Kuula and Anu-Katriina Pesonen declare as co-inventors for a patent (EPO No. 17761107.6-1115, priority FI/25.08.16/FIA20165631, and PCT/FI2017/050582) as a spin-off from the first Helsinki Challenge, a science-based idea competition organised by the University of Helsinki, Finland, in 2014 to 2015.

REFERENCES

Abbott SM, Malkani RG, Zee PC. 2018. Circadian disruption and human health: a bidirectional relationship. Eur J Neurosci. [accessed 2020 Jan 3]:[17 p.]. https://doi.org/10.1111/ejn.14298.

Abbott SM, Reid KJ, Zee PC. 2015. Circadian rhythm sleep-wake disorders. Psychiatr Clin North Am. 38:805–823.

Bonmati-Carrion MA, Middleton B, Revell V, Skene DJ, Rol MA, Madrid JA. 2014. Circadian phase assessment by ambulatory monitoring in humans: correlation with dim light melatonin onset. Chronobiol Int. 31:37–51.

Chattu VK, Manzar MD, Kumary S, Burman D, Spence DW, Pandi-Perumal SR. 2018. The global problem of insufficient sleep and its serious public health implications. Healthcare (Basel). 7:E1.

Gilbert SS, van den Heuvel CJ, Ferguson SA, Dawson D. 2004. Thermoregulation as a sleep signalling system. Sleep Med Rev. 8:81–93.

Hofstra WA, de Weerd AW. 2008. How to assess circadian rhythm in humans: a review of literature. Epilepsy Behav. 13:438–444.

Iber C, Ancoli-Israel S, Chesson A, Quan SF, editors. 2007. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification. Westchester (IL): American Academy of Sleep Medicine.

Kawato M, Fujita K, Suzuki R, Winfree AT. 1982. A three-oscillator model of the human circadian system controlling the core temperature rhythm and the sleep-wake cycle. J Theor Biol. 98:369–392.

Kleitman N. 1949. Biological rhythms and cycles. Physiol Rev. 29:1–30.

296 Kleitman N. 1960. The sleep cycle. Am J Nurs. 60:677–679.

297 Kleitman N, Ramsaroop A. 1948. Periodicity in body temperature and heart rate.
298 Endocrinology. 43:1–20.

299 Kleitman N, Ramsaroop A, Englmann T. 1948. Variations in skin temperatures of the feet
300 and hands and the onset of sleep. Fed Proc. 7:66.

301 Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. 2000. Functional link between distal
302 vasodilation and sleep-onset latency? Am J Physiol Regul Integr Comp Physiol. 278:R741–
303 R748.

304 Le Bon O, Staner L, Rivelli SK, Hoffmann G, Pelc I, Linkowski P. 2002. Correlations using
305 the NREM-REM sleep cycle frequency support distinct regulation mechanisms for REM and
306 NREM sleep. J Appl Physiol. 93:141–146.

307 Lewy AJ, Rough JN, Songer JB, Mishra N, Yuhas K, Emens JS. 2007. The phase shift
308 hypothesis for the circadian component of winter depression. Dialogues Clin Neurosci.
309 9:291–300.

310 Martinez-Nicolas A, Ortiz-Tudela E, Rol MA, Madrid JA. 2013. Uncovering different
311 masking factors on wrist skin temperature rhythm in free-living subjects. PLoS One.
312 8:e61142.

313 Merica H, Gaillard J-M. 1986. Internal structure of sleep cycles in a healthy population.
314 Sleep. 9:502–513.

315 Nesbitt AD. 2018. Delayed sleep-wake phase disorder. J Thorac Dis. 10 Suppl 1:S103–S111.

316 R Core Team. 2015. R: a language and environment for statistical computing. Vienna: R
317 Foundation for Statistical Computing.

318 Rechtschaffen A, Kales A, editors, Berger RJ, Dement WC, Jacobson A, Johnson LC, Jouvet
319 M, Monroe LJ, Oswald I, Roffwarg HP, Roth B, Walter RD. 1968. A manual of standardized
320 terminology, techniques and scoring system for sleep stages of human subjects. National
321 Institutes of Health Publication No. 204. Washington (DC): Public Health Service, U.S.
322 Government Printing Office.

323 Sarabia JA, Rol MA, Mendiola P, Madrid JA. 2008. Circadian rhythm of wrist temperature in
324 normal-living subjects: a candidate of new index of the circadian system. Physiol Behav.
325 95:570–580.

326 van den Heuvel CJ, Noone JT, Lushington K, Dawson D. 1998. Changes in sleepiness and
327 body temperature precede nocturnal sleep onset: evidence from a polysomnographic study in
328 young men. J Sleep Res. 7:159–166.

329 van Straten A, van der Zweerde T, Kleiboer A, Cuijpers P, Morin CM, Lancee J. 2018.
330 Cognitive and behavioral therapies in the treatment of insomnia: a meta-analysis. Sleep Med
331 Rev. 38:3–16.

332 Wehr TA, Aeschbach D, Duncan WC Jr. 2001. Evidence for a biological dawn and dusk in
333 the human circadian timing system. J Physiol. 535:937–951.

334

APPENDIX

We modelled the linear effect of time before the sleep onset on wrist temperature using a mixed model, with the sex and age as the covariates, and including only data less 10 minutes before the sleep onset. For this analysis, the R software (R Core Team 2015) was used and the codes were computed as follows.

(1) uni.m0 <- lmer(ga.temp ~ I(24×60×ga.aika) + (1 | PID), data=apu.data.1.B)

(2) uni.m1 <- lmer(ga.temp ~ I(24×60×ga.aika) + sex+age+(1 | PID), data=apu.data.1.B)

(3) uni.m1.sp <- lmer(ga.temp ~ ga.aika.1 + I(ga.aika.1^2) + I(ga.aika.1^3) + pmax(0,(ga.aika.1-(-20))^3) + pmax(0,(ga.aika.1-(-10))^3) + pmax(0,(ga.aika.1-(0))^3) + (1 | PID), data=tmp.data)

The first one was without the background variables (sex and age), whereas the second one included the two background variables. Time (*ga.aika*) was transformed into minutes (24×60), and the dependent variable was wrist temperature (*ga.temp*). The individual was used as a random effect in these models [(1 | PID)]. The third model is with the splines of time. The model was used to calculate the adjusted curves which we present in the figures.

TABLES

Table 1. Associations of wrist skin temperatures on average (standard deviation) with the sleep onset. Slopes from mixed effect models with fixed effect linear time (minutes), sex and age, and individual intercept as random effect.

Sleep onset definition[a]	Wrist temperature 5 minutes before the sleep onset, mean (s.d.)	Wrist temperature at the sleep onset, mean (s.d.)	Wrist temperature 5 minutes after the sleep onset, mean (s.d.)	Slope of time before the sleep onset (per 1 minute)	Standard error of the slope	t-value	p-value
#1	32.13 (2.33)	32.47 (2.35)	32.78 (2.28)	0.0622937	0.0007921	78.641	0.0040
#2	32.53 (2.41)	32.37 (2.52)	32.82 (2.20)	0.047087	0.001087	43.303	0.0073
#3	32.15 (2.31)	32.47 (2.35)	32.76 (2.29)	0.0603308	0.0008039	75.049	0.0042

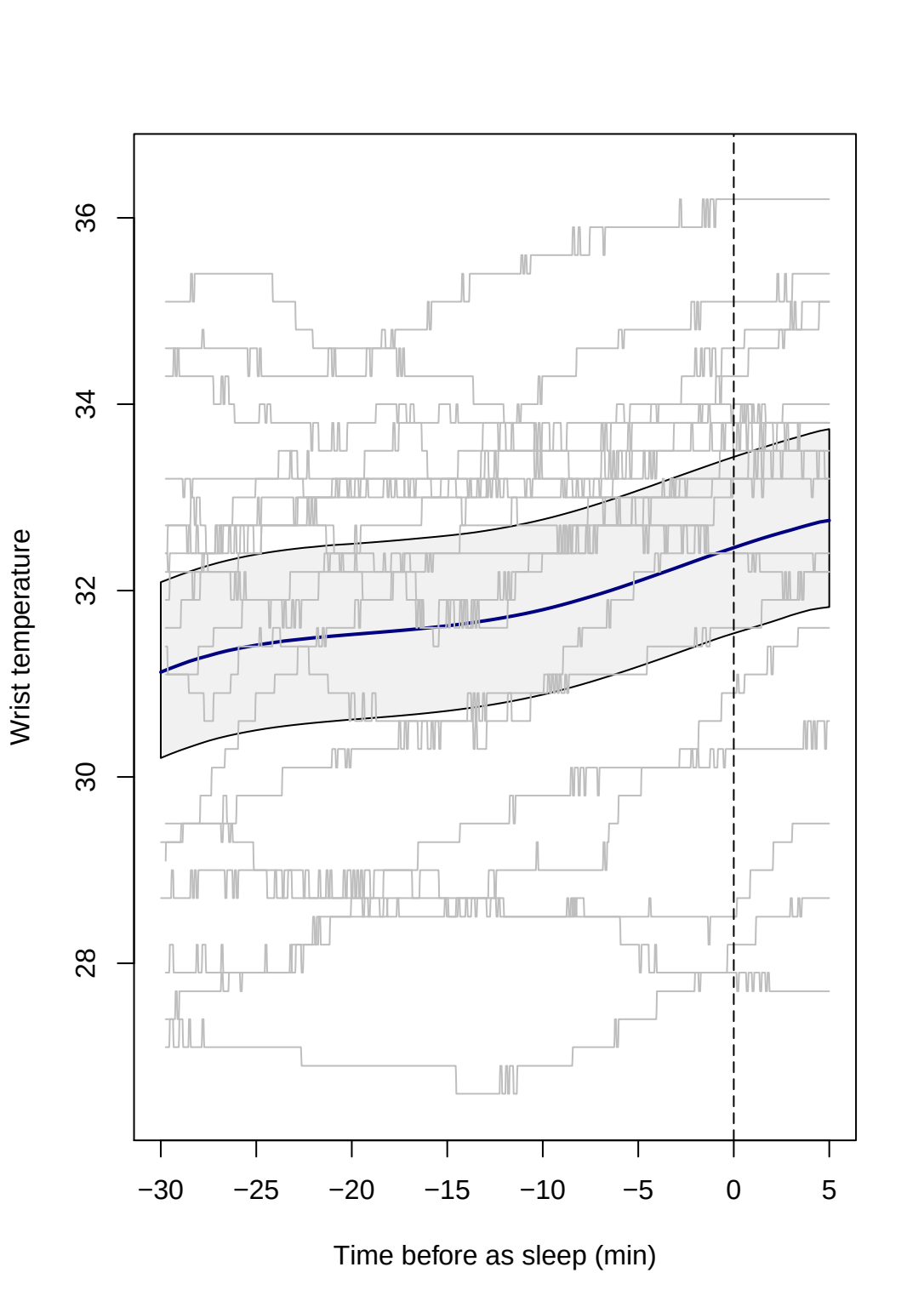
[a] Definition 1 = sleep onset was met after three consecutive epochs of N1 sleep; Definition 2 = sleep onset was met at after the first epoch of N2, N3 or REM sleep; Definition 3 = sleep onset was met after the first epoch of N1, N2, N3 or REM sleep.

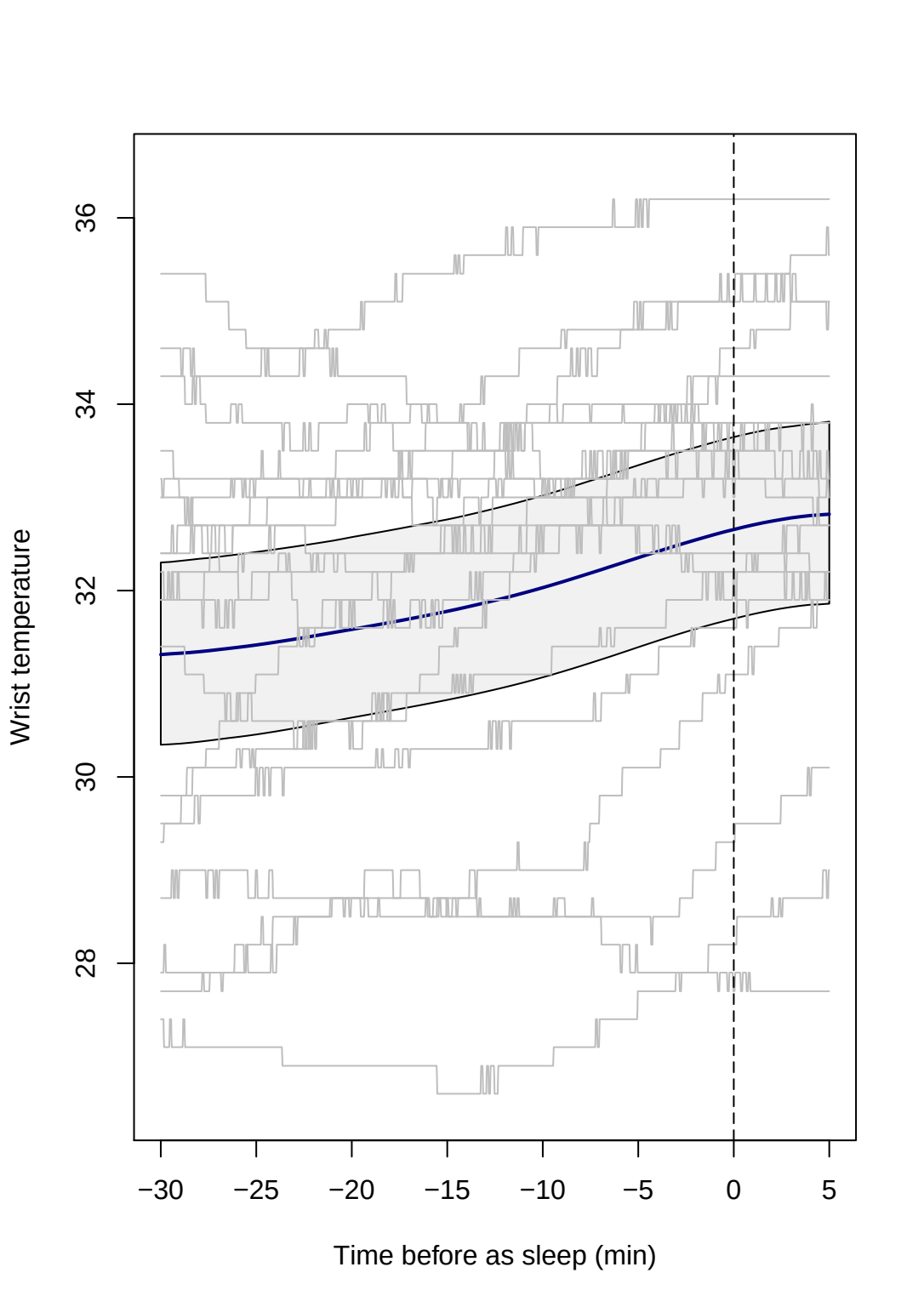
FIGURE LEGENDS

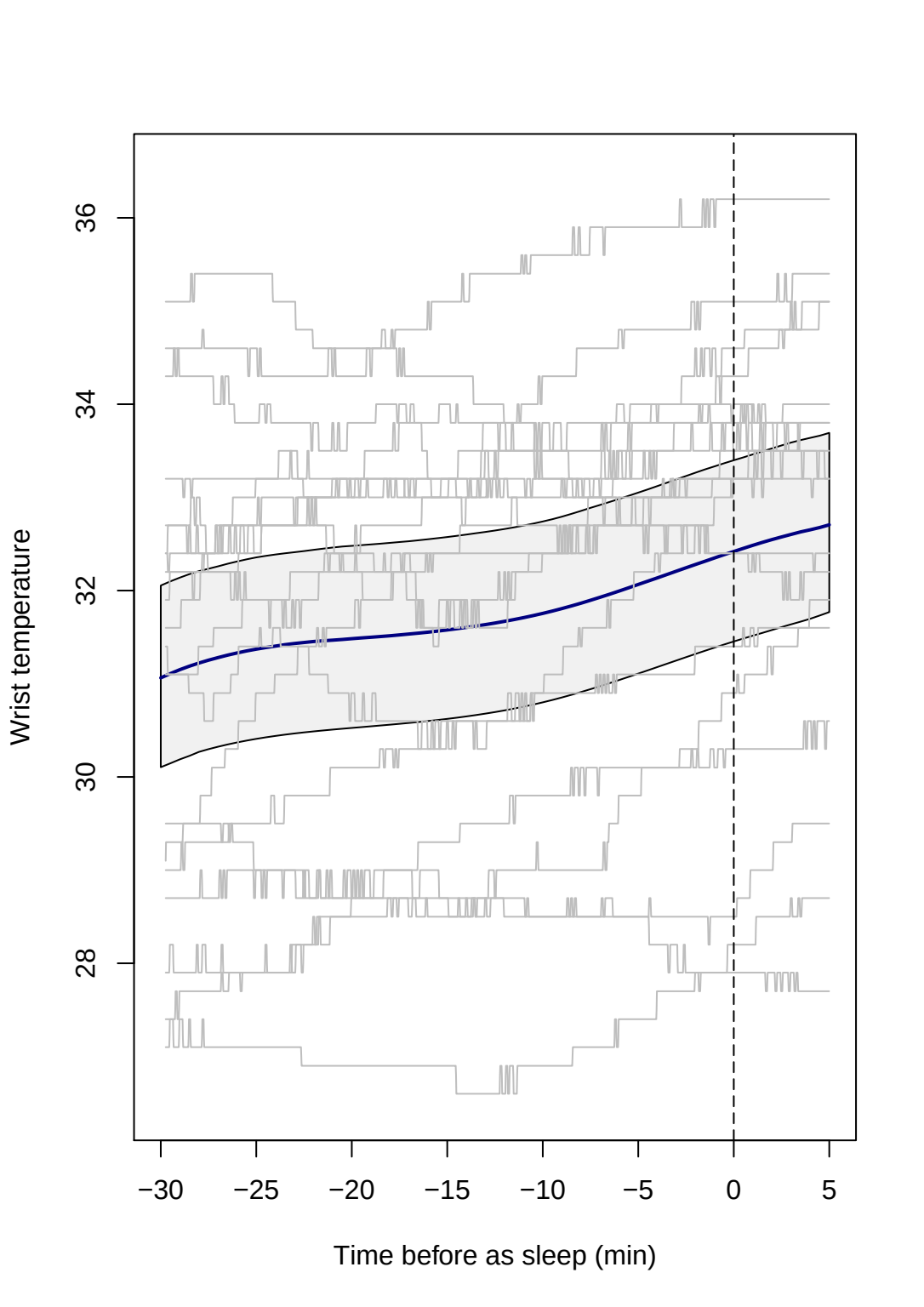
Figure 1. Wrist skin temperature (in degrees of Celsius) as a function of time, i.e., from 30 minutes before the onset of sleep, as assessed with the Definition 1 and indicated with the vertical dashed line, to 5 minutes after the onset of sleep. The predicted values based on random effects model with splines together with their 95% confidence limits are given. In the background, the read-outs for each individual are presented.

Figure 2. Wrist skin temperature (in degrees of Celsius) as a function of time, i.e., from 30 minutes before the onset of sleep, as assessed with the Definition 2 and indicated with the vertical dashed line, to 5 minutes after the onset of sleep. The predicted values based on random effects model with splines together with their 95% confidence limits are given. In the background, the read-outs for each individual are presented.

Figure 3. Wrist skin temperature (in degrees of Celsius) as a function of time, i.e., from 30 minutes before the onset of sleep, as assessed with the Definition 3 and indicated with the vertical dashed line, to 5 minutes after the onset of sleep. The predicted values based on random effects model with splines together with their 95% confidence limits are given. In the background, the read-outs for each individual are presented.


Wrist temperature
36
34
32
30
28
−30
−25
−20
−15
−10
−5
0
5
Time before as sleep (min)


Wrist temperature
36
34
32
30
28
−30
−25
−20
−15
−10
−5
0
5
Time before as sleep (min)


Wrist temperature
36
34
32
30
28
−30
−25
−20
−15
−10
−5
0
5
Time before as sleep (min)