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Variation of circadian activity rhythm according to body mass index in children

Lorenzo Tonetti[a*], Monica Martoni[b], Marco Filardi[c], Marco Fabbri[d], Alicia Carissimi[e,f], Sara Giovagnoli[a], Vincenzo Natale[a]

[a] *Department of Psychology, University of Bologna, Viale Berti Pichat 5, 40127 Bologna, Italy*

[b] *Department of Experimental, Diagnostic and Specialty Medicine, DIMES, University of Bologna, Viale Berti Pichat 5, 40127 Bologna, Italy*

[c] *Department of Biomedical and Neuromotor Sciences, DIBINEM, University of Bologna, Via Altura 3, 40139 Bologna, Italy*

[d] *Department of Psychology, University of Campania "Luigi Vanvitelli", Viale Ellittico 31, 81100 Caserta, Italy*

[e] *Laboratório de Cronobiologia e Sono do Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul (UFRGS), Ramiro Barcelos 2350, CEP 90035-003 Porto Alegre, Rio Grande do Sul, Brazil*

[f] *Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento – Faculdade de Medicina, UFRGS, Ramiro Barcelos 2350, CEP 90035-003 Porto Alegre, Rio Grande do Sul, Brazil*

Authors' e-mail addresses. Monica Martoni: monica.martoni@unibo.it; Marco Filardi: marco.filardi@unibo.it; Marco Fabbri: marco.fabbri@unicampania.it; Alicia Carissimi: alicia.ufrgs@gmail.com; Sara Giovagnoli: sara.giovagnoli@unibo.it; Vincenzo Natale: vincenzo.natale@unibo.it

* Corresponding author
Lorenzo Tonetti MS PsyD PhD
University of Bologna
Department of Psychology
Viale Berti Pichat 5
40127 Bologna - Italy
Phone: +39-051-2091878
Fax: +39-051-243086
Email: lorenzo.tonetti2@unibo.it

ABSTRACT

Background/Objectives: This study aimed to examine the variations of circadian activity rhythm of children according to objective body mass index (BMI) values, using a novel statistical framework (i.e., Functional Linear Modeling, FLM), separately for school- and weekend days.

Methods: One hundred and seven participants (60 females; mean age: 10.25±.48 years) wore an actigraph for seven days during a regular school-week. While valid actigraphic data during school days were available for each of these children, this number decreased to 53 (31 females; mean age: 10.28±.51 years) during weekend days.

Results: Examining the school days, significantly higher motor activity in participants with higher BMI was observed from around 4:00 a.m. to 6:00 a.m., with a peak about 5:00 a.m. On the contrary, applying the FLM to the weekend days actigraphic data, no significantly different variation of circadian activity rhythm was observed, according to BMI.

Conclusions: In this specific sample of children, during school days, higher BMI is associated with higher activity level in a specific time window in the second half of nocturnal sleep. The lack of significant findings during weekend days could be explained because of higher variability of get-up time and/or the reduced sample size. Future longitudinal studies could explore if the higher motor activity in that specific time window qualifies as a predictive marker of the development of overweight and obesity. If so, early preventive strategies directed towards those at higher risk could be effectively implemented.

Keywords: actigraphy; body mass index; childhood; circadian rhythms; functional linear modeling; motor activity.

1. Introduction

In the last forty years a trend towards the increasing of body mass index (BMI) in children and adolescents has been observed, that seems to have reached a plateau in several high-income countries while has become faster in some parts of Asia [1]. It is known that childhood obesity is associated with several negative outcomes [2], that often track into adulthood. For this reason, it is extremely important to early detect those who are at higher risk of developing overweight and obesity, aiming to implement effective preventive strategies [3].

In recent years it has become more evident that the timing of food intake plays a key role in the regulation of body weight [4], a finding explained on the basis of the desynchronization of circadian system which leads to a less efficient regulation of the metabolism and increases the risk of developing obesity and metabolic syndrome [5]. To this regard, an interesting study [6] has shown that nocturnal mice, forced to eat during the light phase, increased significantly more in weight compared to nocturnal mice allowed to eat during the dark phase. With reference to humans, some evidence on the timing of food intake [7] indicated that those who have lunch later during the day (i.e., after 3:00 p.m.) are less able to lose weight in comparison to those who have lunch earlier (i.e., before 3:00 p.m.), despite the caloric intake was almost the same among those individuals. Moreover, recent data in humans confirm that later circadian timing of food intake was related to an increasing in body fat [8]. The strong interplay between a desynchronized circadian system and an altered regulation of the metabolism increases the risk of developing obesity or the so called *chronobesity* [9].

Previous studies have examined the association between circadian activity rhythm, recorded through actigraphy, and BMI/obesity in adults and adolescents, using nonparametric rhythm and cosinor analysis. In a sample of community-dwelling adults (mean age of 52±15 years), lower relative amplitude, that implies high nighttime activity and low daytime activity, was related to higher BMI

[10]. Evaluating a sample of adolescents aged between 12.5 and 17.5 years, high intradaily variability, pointing towards high fragmented rhythm, was associated with obesity [11].

With reference to a children population, in a previous study [12] our research group examined the circadian activity rhythm of 115 children (mean age of 10.21±.48 years) belonging to different weight groups: underweight (2.60%), normal weight (61.70%), overweight (29.60%) and obese (6.10%). Separately for schooldays and weekend days, we have compared the average raw motor activity counts, hour-by-hour across the 24 hours, of children included in different weight groups. We did not find any significant differences in circadian activity rhythm of children belonging to different weight groups, neither during school- nor weekend days.

In 2011, a novel statistical framework to analyse actigraphic data has been proposed (Functional Linear Modeling – FLM) [13]. The FLM has the advantage to examine actigraphy data in their natural form, i.e., time series of raw motor activity values, being able to provide more information than the classically used analysis of average measures. The FLM has been successfully applied to characterize the circadian activity rhythm of healthy children and of patients with neurological [14] and psychiatric disorders [15,16]. Moreover, overcoming the inherent limitations of the categorical approach previously used [12], the FLM framework offers an unique opportunity as it allows to stratify the circadian activity rhythm across BMI continuous values.

The aim of this study was to analyse, separately for school days and weekend days, the minute-by-minute variation of the circadian activity rhythm in children according to BMI, through the FLM. Given the association between BMI on one hand and actigraphic sleep quality/quantity/timing [17] and social jetlag [18] on the other, we decided to run a set of correlation analyses between these parameters. To this end, a secondary analysis of data previously collected by our research group [12] was carried out. FLM could potentially highlight significant variations of the circadian activity rhythm in function of BMI continuous values that were not previously detected adopting the categorical approach based on the analysis of average measures [12].

To sum up, the main differences between the current and the previous study [12] are:

1. Analysis of the functional forms of circadian activity rhythm minute-by-minute instead of the analysis of row-hourly circadian activity rhythm.
2. Advanced statistical analyses through the FLM framework instead of more classical analytical approach based on the analysis of average measures.
3. Analysis of the variation of circadian activity rhythm according to the covariate BMI instead of using a BMI grouping approach.

The main expectation was to find lower motor activity to the increasing in BMI. Furthermore, if obesity is prevalently a genetic-driven disease, we would not expect to find differences between school days and weekend days, both in circadian activity rhythm and actigraphic sleep parameters. On the contrary, if modulations by social rhythms would have an effect, we could expect to find some differences between school- and weekend days at the level of both circadian activity rhythm and actigraphic sleep indexes.

2. Materials and methods

2.1. Participants

Actigraphic recordings of 107 children [12] were examined extracting the motor activity counts minute-by minute over the 24 h for each recording day. While for the school days valid actigraphic data were retrieved for each of the 107 children, such number decreased to 53 for the weekend days due to a lesser use of the actigraph. Children were originally enrolled in a study on the association between sleep-wake cycle, circadian motor activity and the timing of food intake in different weight groups [12]. They were attending primary schools in the city of Bologna (Italy) or in some municipalities of its province, as well as in the town of Castelfranco Emilia (province of Modena, Italy) and some of its hamlets. As regards the school hours [19], classes were scheduled from Monday to Friday, from 8:30 a.m. to 4:30 p.m.

2.2. Actigraphy

The Actiwatch AW64 (Cambridge Neurotechnology Ltd, UK) was used to directly quantify motor activity levels and to indirectly assess sleep, according to the algorithm proposed by Oakley [20].

2.3. Actigraphic parameters

The following actigraphic sleep measures, separately for school- and weekend days, were computed using the low sensitivity threshold activity value [21,22] implemented within the Actiwatch Activity & Sleep Analysis version 5.32 software (Cambridge Neurotechnology Ltd, UK):

1. Bedtime (BT), the clock time at which participants went to bed trying to sleep.
2. Get-up time (GUT), the clock time at which children woke-up after a night's sleep.
3. Time in bed (TIB), the time in minutes between BT and GUT.
4. Midpoint of sleep (MID), the clock time that splits the TIB in half.
5. Total sleep time (TST), the sum in minutes of all sleep epochs between sleep onset (SO) and GUT.
6. Wake after sleep onset (WASO), the sum in minutes of all wake epochs between SO and GUT.
7. Sleep efficiency (SE), the ratio between TST and TIB multiplied for 100.
8. Sleep onset latency (SOL), the interval in minutes between BT and SO.
9. Wake bouts (WB), the number of sleep interruptions.
10. Mean activity score (MAS), the mean value of activity counts per epoch over the assumed sleep period.

Furthermore, the social jetlag (SJL), as the difference between weekend days MID and school days MID, was computed.

2.4. Circadian activity rhythm

We used the Actiwatch Activity & Sleep Analysis version 5.32 software (Cambridge Neurotechnology Ltd, UK) to extract from the actigraphic files the raw motor activity counts minute-by-minute over the 24-h of the school and weekend days. Actigraphic recordings were visually inspected to identify periods of device removal (reported in the sleep log) that were excluded from analyses.

2.5. Anthropometric measurements

Anthropometric measurements were conducted in the morning on day 1, with participants dressed light clothing, without shoes and socks. Weight and height were measured through a digital scale (accuracy of 0.1 Kg) and a portable stadiometer (accuracy of 0.1 cm), respectively. BMI was then computed as the ratio between weight in Kg and height in m^2.

2.6. Procedure

Each participant originally wore the actigraph 24-h per day around the non-dominant wrist for seven consecutive days [23] during a regular school week and pushed the event-marker button on the top of the actigraph to signal BT and GUT. If they missed to press the event-marker button, the replies to the questions on BT and GUT reported in a sleep log were used to set the TIB for the actigraphic analyses on sleep of both school- and weekend-nights [12].

The Bioethics Committee of the University of Bologna (Bologna, Italy) and the involved schools originally approved the research protocol. Parents provided written informed consent prior to the participation of their child into the original study.

2.7. Statistical analyses

We computed some descriptive statistics (i.e., mean, standard deviation and range) of the actigraphic sleep parameters, separately for school and weekend days, as well as SJL. Moreover, we also carried out some Pearson correlation analyses between actigraphic sleep parameters (separately for school and weekend days) as well as SJL on one hand and BMI on the other.

The mean of the raw motor activity counts minute-by-minute over the 24-h, separately for school and weekend days, was computed and processed through the "Actigraphy" package implemented in R software [24]. FLM replaced raw 24-h profile with a function through a Fourier expansion model fitted at a periodicity of 24 hours and, afterwards, used non-parametric permutation F-test to assess if and when the circadian activity rhythm significantly differed according to continuous BMI values.

3. Results

With reference to school days, the examined sample was composed of 60 females (56.07%) and 47 males (43.93%). Overall, the mean age of the sample was 10.25±.48; mean age of females (10.18±.50) and males (10.34±.44) was similar (t_{105}=-1.76; p=.08; Cohen's d=.34).

The mean BMI in such sample was 19.50±3.72 (range: 13.79-32.32). Males' BMI (20.21±4.01) was not significantly different from females' BMI (18.94±3.41) (t_{105}=1.77; p=.08; Cohen's d=.34).

We observed the following distribution of children, with valid actigraphic data during school days, within the different weight groups: 1) normal weight=60.75% (n=65); 2) overweight=27.10% (n=29); 3) obese=9.35% (n=10); 4) underweight=2.80% (n=3).

As regards the weekend days, the sample was composed of 53 children with valid actigraphic data: 58.49% (n=31) females and 41.51% (n=22) males. The mean age in the whole sample was 10.28$\pm$.51; females (10.18$\pm$.53) did significantly differ in age from males (10.41$\pm$.46) (t_{51}=-1.62; p=.11; Cohen's d=.46).

In this sample, the mean BMI was 19.37$\pm$3.70, ranging between 13.79 and 31.39. The BMI of males (21.22$\pm$4.31) was significantly higher than BMI of females (18.06$\pm$2.54) (t_{51}=-3.35; p<.005; Cohen's d=.89).

The distribution of children with valid actigraphic data during weekend days among the different weight groups was: 1) normal weight=67.92% (n=36); 2) overweight=22.64% (n=12); 3) obese=7.55% (n=4); underweight=1.89% (n=1).

The descriptive statistics of actigraphic sleep parameters, separately for school- and weekend days, and SJL as well as the Pearson correlation values between each of them and BMI are presented in Table 1. During school days, BMI was negatively related to GUT and TST while during weekend days no significant correlations were observed.

Please insert Table 1 about here

Results of the FLM analyses during school days are reported in Figure 1. Considering the meaning of data reported in panel A and B, explained in figure legend, higher BMI is associated with significantly higher motor activity levels from around 4:00 a.m. to 6:00 a.m., with a peak about 5:00 a.m.

Performing the FLM analyses on weekend days, we did not observe a significantly different variation of circadian activity rhythm according to BMI (Figure 2).

Please insert Figure 1 and Figure 2 about here

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4. Discussion

During school days, participants with higher BMI moved significantly more in comparison to those with lower BMI just in one specific time window across the 24-h, i.e., from 4:00 a.m. to 6:00 a.m., with a peak around 5:00 a.m. Furthermore, during school days, an advanced get-up time and lesser total sleep time were significantly related with higher BMI. On the contrary, during weekend days, no significant variation of circadian activity rhythm, according to BMI, was observed as well as no significant correlations between actigraphic sleep parameters and BMI were detected. Such pattern of results, i.e., significant differences observed during the school days and not during the weekend days, seem to point out that the modulations by social rhythms could have an effect on the motor- and the sleep-related manifestations of obesity. However, when interpreting this pattern of results, we should be cautious because alternative explanations of the lack of significant differences during the weekend could be put forward. For example, it is possible to suggest that higher variability of get-up time, the reduced sample size and/or the higher percentage of normal weight children, that characterize the weekend days compared to school days, could at least partially explain the lack of significant variations of circadian activity rhythm and actigraphic sleep parameters according to BMI.

As regards the findings on school days, we suggest that the higher activity levels in children with higher BMI at that specific time window could be due to higher levels of restlessness. Such restlessness may be interpreted within the framework of a hyperresponsivity of the hypothalamic-pituitary-adrenal (HPA) axis in patients with obesity [25], which leads to a condition of higher release of cortisol called “functional hypercortisolism” [26]. Such condition could provide a potential explanation of our findings because cortisol is known to be an activating hormone. More in details, the assessment of the activity of the HPA axis can be challenging; one possible way to successfully measure its activity is based on the assessment of the awakening cortisol response (ACR), the marked increase of cortisol levels 15-30 minutes after awakening which is advanced by the growth in the release of this hormone in the last part of the night during sleep [27]. It is interesting that ACR was reported to be twice in male patients with obesity than participants belonging to lean group [28], providing a potential explanation of the results observed in our work. However, we wish to underline that this explanation, based on the hyperactivity of the HPA axis and the resulting increase of the release of cortisol in patients with obesity, should be merely treated as a working hypothesis because no measurement of such hormone was taken in the present study. We could also put forward an alternative explanation of this higher motor activity related to higher BMI, which is present during a specific time window of school days and absent during the weekend days. We could suppose that the higher motor activity, observed in the last part of the night of school days, could be due to a sort of social stress because children with higher BMI are aware to have to go to school, facing for example social stigma. The absence of this pattern during the weekend days could reinforce the hypothesis of the social stress, opening a psychosocial field of obesity prevention. Clearly, this is simply a working hypothesis that should be examined in depth by future studies.

The present study, based on the implementation of FLM to the analysis of the variations of circadian activity rhythm according to BMI continuous values, allowed to detect significant associations between motor activity and BMI during school days that our previous work [12], based on a different categorical (i.e., weight groups) and analytical (i.e., analysis of average measures) approach, failed to point out. These results highlight the potential usefulness of FLM to the breakdown of circadian activity rhythm, previously documented in neurological [14] and psychiatric [15,16] disorders, also according to BMI. In particular, the use of FLM has allowed to open new and interesting questions.

Some limitations of the present study are the narrow age range of children, which limits the generalizability of findings, and the relatively small size of the sample. More investigations on larger sample size, aimed to apply the FLM method to the analysis of actigraphic data of participants belonging to different age groups, are needed. Moreover, longitudinal studies examining participants since early childhood are specifically requested to assess if the higher motor activity in a specific time window qualifies as a predictive marker of the development of overweight and obesity. If so, early preventive strategies directed towards those at higher risk could be effectively implemented [3].

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Conflict of Interest

Monica Martoni reports a grant from Fondazione del Monte di Bologna e Ravenna (Bologna, Italy) to carry out the original study. Lorenzo Tonetti, Marco Filardi, Marco Fabbri, Alicia Carissimi, Sara Giovagnoli and Vincenzo Natale report no conflicts of interest.

Highlights

1) Variation of circadian activity rhythm in children according to BMI was examined.
2) Higher BMI children had higher motor activity from 4 am to 6 am of school days.
3) No significant variations were observed during weekend days.

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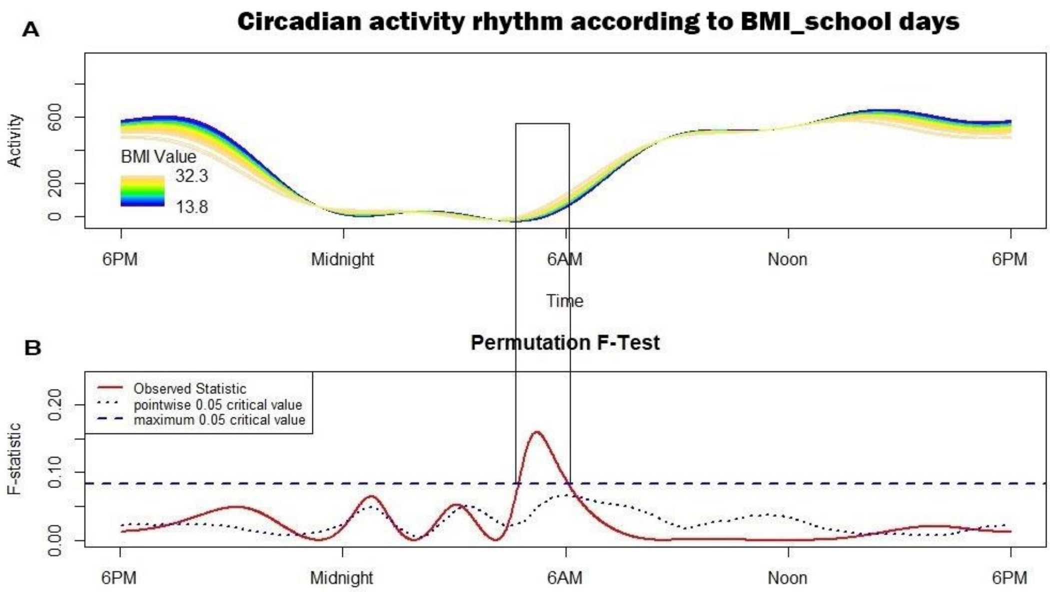

Fig. 1. Results of the Functional Linear Modeling, performed on school days, for body mass index (BMI) treated as a continuous variable.

The panel A shows the circadian activity rhythm plotted according to BMI treated as a continuous variable, with different colours depicting circadian activity rhythm of children with different BMI: blue colours point towards lowest BMI values, while pink colours towards highest BMI values. The wave showed in panel A (composed by as many lines as participants) in specific time-points tends to enlarge and to shrink in other time-points: the amplitude of the wave does not represent the effect (higher or lower) of the BMI. The points at which the wave is wider are the time-points in which the variability between participants in the circadian activity rhythm is greater.

The panel B displays the results of the non-parametric permutation F-test. More in details, the red solid line represents the permutation F value observed at each time point. The p value of the test is defined as the proportion of the permutation F values (red solid line) higher than the F statistics, computed as global or point-wise test of significance. The blue dashed line points to the global test of significance, which is a single number corresponding to the proportion of maximized F values resulting from each permutation. The blue dotted line corresponds to the point-wise test of significance, which is a curve representing the proportion of all permutation F values at each time point. Significant results are observed when the red solid line - representing the observed statistic - is above the blue dashed - the global test of significance with alpha set to .05 – or dotted - the point-wise test of significance - line. However, bearing in mind that the global test of significance is more conservative, it is preferable to consider the differences in circadian activity rhythm as significant only when the red solid line is above the blue dashed line.

Lines connecting panel B with panel A highlight the time window characterized by significant differences in circadian activity rhythm according to BMI.

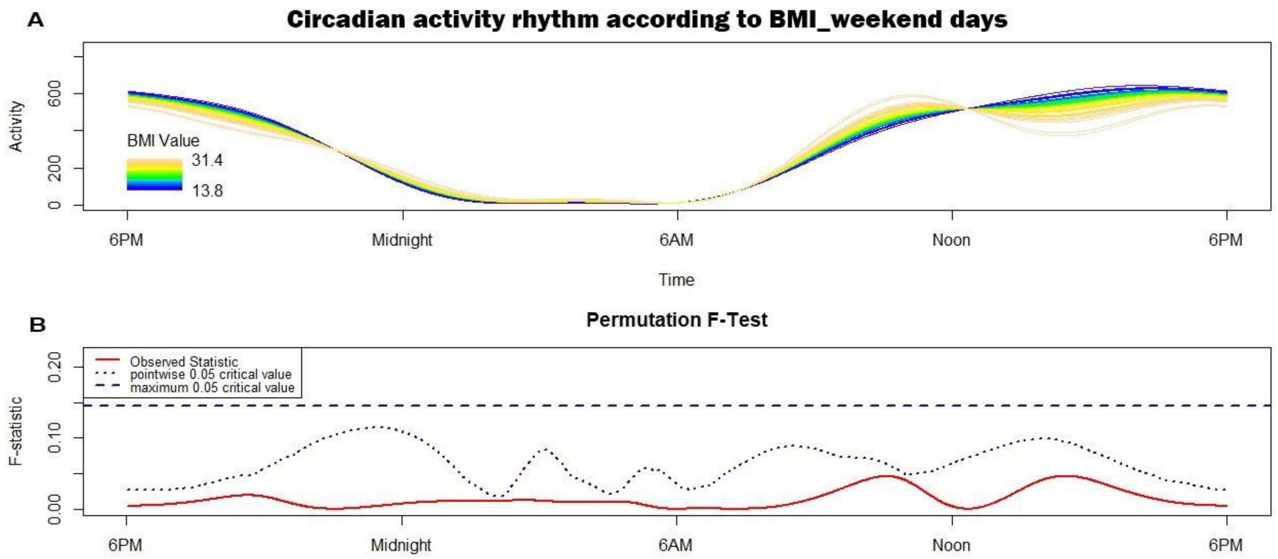

Fig. 2. Results of the Functional Linear Modeling, performed on weekend days, for body mass index (BMI) treated as a continuous variable.

Table 1

Descriptive statistics of the actigraphic sleep parameters (separately for school days and weekend days) and social jetlag as well as Pearson correlation values between them and BMI. Significant correlations are marked with an asterisk.

	Mean	Standard deviation	Range	BMI[a]
Actigraphic school days sleep parameters				
Bedtime (h:min)	22:21	0:41	20:35-24:54	-.03
Get-up time (h:min)	07:32	0:32	05:54-08:59	-.24*
Midpoint of sleep (h:min)	02:56	0:32	01:22-04:26	-.02
Time in bed (min.)	549.7	36.7	423-675	-.14
Total sleep time (min.)	488.7	33.9	365-597	-.22*
Wake after sleep onset (min.)	40.5	13.7	16-76	.02
Sleep efficiency (%)	88.7	3.4	79.2-95.4	-.10
Sleep onset latency (min.)	15.2	10.5	1-61	.05
Wake bouts (number)	24.3	6.1	12.8-41.6	-.04
Mean activity score (activity counts)	15.3	5.7	6.5-32.3	.10
Actigraphic weekend days sleep parameters				
Bedtime (h:min)	23:09	0:52	21:35-24:58	.12
Get-up time (h:min)	08:44	0:52	07:12-11:02	-.12
Midpoint of sleep (h:min)	03:56	0:42	02:34-05:33	.0004
Time in bed (min.)	575.6	60	444-733	-.21
Total sleep time (min.)	511.2	70.8	388-851	-.16
Wake after sleep onset (min.)	49.6	26.6	12.5-197	-.04
Sleep efficiency (%)	88.1	3.8	77.2-96.7	-.09
Sleep onset latency (min.)	14.5	14.7	0.3-88	-.005
Wake bouts (number)	26.5	6.8	10-39	.06
Mean activity score (activity counts)	16.8	6.4	4.9-33.8	.22
Social jetlag (min.)	52	37	-20-166	.24

Note. BMI=body mass index.

[a] Pearson correlation values between each parameter and BMI

* p<.05