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

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70 ABSTRACT

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

75 *Methods:* One hundred and seven participants (60 females; mean age: 10.25 \pm .48 years) wore an
76 actigraph for seven days during a regular school-week. While valid actigraphic data during school
77 days were available for each of these children, this number decreased to 53 (31 females; mean age:
78 10.28 \pm .51 years) during weekend days.

79 *Results:* Examining the school days, significantly higher motor activity in participants with higher
80 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,
81 applying the FLM to the weekend days actigraphic data, no significantly different variation of
82 circadian activity rhythm was observed, according to BMI.

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

90

91 *Keywords:* actigraphy; body mass index; childhood; circadian rhythms; functional linear modeling;
92 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

118 [10]. Evaluating a sample of adolescents aged between 12.5 and 17.5 years, high intradaily variability,
119 pointing towards high fragmented rhythm, was associated with obesity [11].

120 With reference to a children population, in a previous study [12] our research group examined
121 the circadian activity rhythm of 115 children (mean age of $10.21 \pm .48$ years) belonging to different
122 weight groups: underweight (2.60%), normal weight (61.70%), overweight (29.60%) and obese
123 (6.10%). Separately for schooldays and weekend days, we have compared the average raw motor
124 activity counts, hour-by-hour across the 24 hours, of children included in different weight groups.
125 We did not find any significant differences in circadian activity rhythm of children belonging to
126 different weight groups, neither during school- nor weekend days.

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

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

143 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.

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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.

196 2.4. *Circadian activity rhythm*

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

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203 2.5. *Anthropometric measurements*

204 Anthropometric measurements were conducted in the morning on day 1, with participants
205 dressed light clothing, without shoes and socks. Weight and height were measured through a digital
206 scale (accuracy of 0.1 Kg) and a portable stadiometer (accuracy of 0.1 cm), respectively. BMI was
207 then computed as the ratio between weight in Kg and height in m².

208

209 2.6. *Procedure*

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

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

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222 2.7. Statistical analyses

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

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

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236 3. Results

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238 With reference to school days, the examined sample was composed of 60 females (56.07%)
239 and 47 males (43.93%). Overall, the mean age of the sample was $10.25 \pm .48$; mean age of females
240 ($10.18 \pm .50$) and males ($10.34 \pm .44$) was similar ($t_{105} = -1.76$; $p = .08$; Cohen’s $d = .34$).

241 The mean BMI in such sample was 19.50 ± 3.72 (range: 13.79-32.32). Males’ BMI
242 (20.21 ± 4.01) was not significantly different from females’ BMI (18.94 ± 3.41) ($t_{105} = 1.77$; $p = .08$;
243 Cohen’s $d = .34$).

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

247 As regards the weekend days, the sample was composed of 53 children with valid actigraphic
248 data: 58.49% (n=31) females and 41.51% (n=22) males. The mean age in the whole sample was
249 $10.28 \pm .51$; females ($10.18 \pm .53$) did significantly differ in age from males ($10.41 \pm .46$) ($t_{51} = -1.62$;
250 $p = .11$; Cohen's $d = .46$).

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

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

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

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

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

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Please insert Figure 1 and Figure 2 about here

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,

301 the assessment of the activity of the HPA axis can be challenging; one possible way to successfully
302 measure its activity is based on the assessment of the awakening cortisol response (ACR), the marked
303 increase of cortisol levels 15-30 minutes after awakening which is advanced by the growth in the
304 release of this hormone in the last part of the night during sleep [27]. It is interesting that ACR was
305 reported to be twice in male patients with obesity than participants belonging to lean group [28],
306 providing a potential explanation of the results observed in our work. However, we wish to underline
307 that this explanation, based on the hyperactivity of the HPA axis and the resulting increase of the
308 release of cortisol in patients with obesity, should be merely treated as a working hypothesis because
309 no measurement of such hormone was taken in the present study. We could also put forward an
310 alternative explanation of this higher motor activity related to higher BMI, which is present during a
311 specific time window of school days and absent during the weekend days. We could suppose that the
312 higher motor activity, observed in the last part of the night of school days, could be due to a sort of
313 social stress because children with higher BMI are aware to have to go to school, facing for example
314 social stigma. The absence of this pattern during the weekend days could reinforce the hypothesis of
315 the social stress, opening a psychosocial field of obesity prevention. Clearly, this is simply a working
316 hypothesis that should be examined in depth by future studies.

317 The present study, based on the implementation of FLM to the analysis of the variations of
318 circadian activity rhythm according to BMI continuous values, allowed to detect significant
319 associations between motor activity and BMI during school days that our previous work [12], based
320 on a different categorical (i.e., weight groups) and analytical (i.e., analysis of average measures)
321 approach, failed to point out. These results highlight the potential usefulness of FLM to the
322 breakdown of circadian activity rhythm, previously documented in neurological [14] and psychiatric
323 [15,16] disorders, also according to BMI. In particular, the use of FLM has allowed to open new and
324 interesting questions.

325 Some limitations of the present study are the narrow age range of children, which limits the
326 generalizability of findings, and the relatively small size of the sample. More investigations on larger

327 sample size, aimed to apply the FLM method to the analysis of actigraphic data of participants
328 belonging to different age groups, are needed. Moreover, longitudinal studies examining participants
329 since early childhood are specifically requested to assess if the higher motor activity in a specific time
330 window qualifies as a predictive marker of the development of overweight and obesity. If so, early
331 preventive strategies directed towards those at higher risk could be effectively implemented [3].

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333

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335

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339 to submit the article for publication.

340

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342

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344 original study.

345

346 **Conflict of Interest**

347

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

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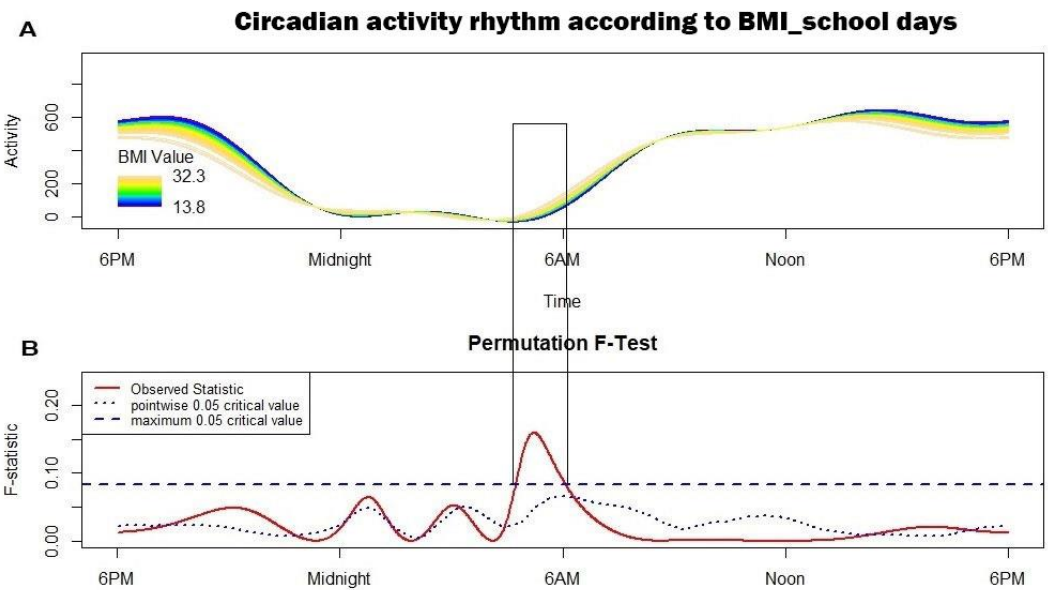
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489 **Fig. 1.** Results of the Functional Linear Modeling, performed on school days, for body mass
490 index (BMI) treated as a continuous variable.

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

498 The panel B displays the results of the non-parametric permutation F-test. More in details, the
499 red solid line represents the permutation F value observed at each time point. The p value of the test
500 is defined as the proportion of the permutation F values (red solid line) higher than the F statistics,

501 computed as global or point-wise test of significance. The blue dashed line points to the global test
502 of significance, which is a single number corresponding to the proportion of maximized F values
503 resulting from each permutation. The blue dotted line corresponds to the point-wise test of
504 significance, which is a curve representing the proportion of all permutation F values at each time
505 point. Significant results are observed when the red solid line - representing the observed statistic - is
506 above the blue dashed - the global test of significance with alpha set to .05 – or dotted - the point-
507 wise test of significance - line. However, bearing in mind that the global test of significance is more
508 conservative, it is preferable to consider the differences in circadian activity rhythm as significant
509 only when the red solid line is above the blue dashed line.

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

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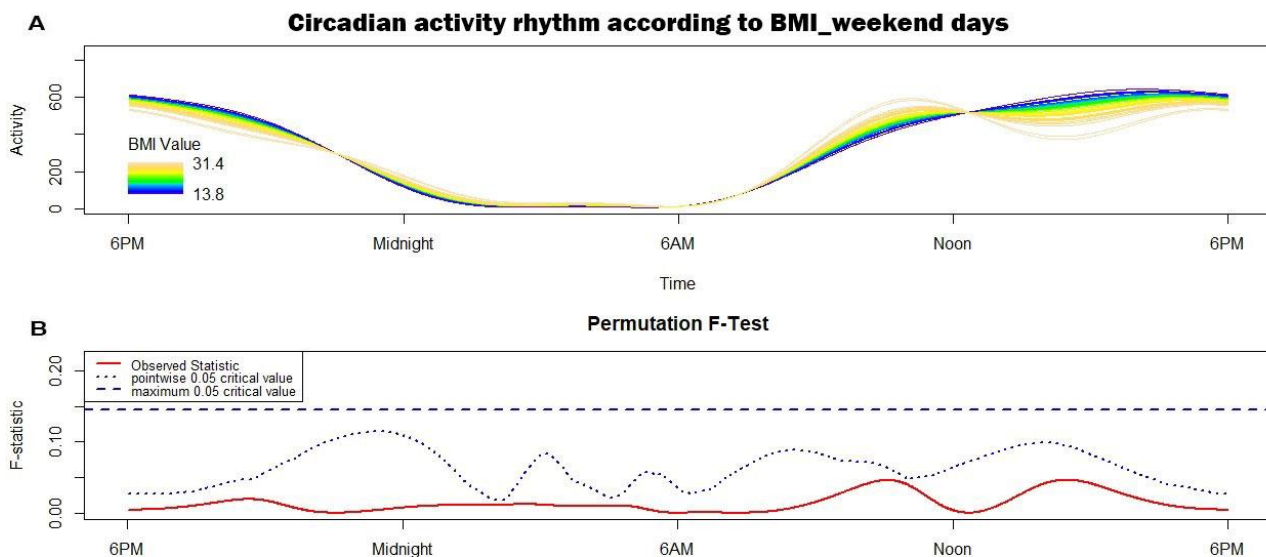


Fig. 2. Results of the Functional Linear Modeling, performed on weekend days, for body mass index (BMI) treated as a continuous variable.

544

545 **Table 1**

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

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	Mean	Standard deviation	Range	BMI ^a
<i>Actigraphic school days sleep parameters</i>				
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
<i>Actigraphic weekend days sleep parameters</i>				
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

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552 *Note.* BMI=body mass index.

553 ^a Pearson correlation values between each parameter and BMI

554 * p<.05

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