

Analysis of nocturnal actigraphic sleep measures in patients with COPD and their association with daytime physical activity

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What is the key question?

Are actigraphic sleep measures associated with disease severity, exertional dyspnea, gender, and parts of the week (i.e. weekdays vs. weekends); and is there an association between assessed sleep measures and next day physical activity?

What is the bottom line?

Actigraphic sleep measures in patients with COPD were found i) to be worse in patients with severe airway obstruction and dyspnea; ii) to be associated with the amount of physical activity the subjects undertake during the following waking day.

Why read on?

With poor sleep and physical inactivity each recognized as key public health priorities, this research has shown that poor sleep, assessed under free living conditions, may hamper efforts of patients with COPD to be physically active, emphasizing a relationship between sleep and daily physical activity.

Abstract

Background Sleep disturbances are common in patients with chronic obstructive pulmonary disease (COPD) with a considerable negative impact on their quality of life. However, factors associated with measures of sleep in daily life have not been investigated before nor has the association between sleep and the ability to engage in physical activity on a day-to-day basis been studied.

Aims To provide insight into the relationship between actigraphic sleep measures and disease severity, exertional dyspnea, gender, and parts of the week; and to investigate the association between sleep measures and next day physical activity.

Methods Data were analyzed from 932 patients with COPD (66% male, 66.4 ± 8.3 years, FEV_1 % predicted = 50.8 ± 20.5). Participants had sleep and physical activity continuously monitored using a multi-sensor activity monitor for a median of six days. Linear mixed effects models were applied to investigate the factors associated with sleep impairment and the association between nocturnal sleep and patients' subsequent daytime physical activity.

Results Actigraphic estimates of sleep impairment were greater in patients with worse airflow limitation and worse exertional dyspnea. Patients with better sleep measures (i.e. non-fragmented sleep, sleeping bouts ≥ 225 minutes, sleep efficiency $\geq 91\%$ and time spent awake after sleep onset < 57 minutes) spent significantly more time in light ($p < 0.01$) and moderate-to-vigorous physical activity ($p < 0.01$).

Conclusions There is a relationship between measures of sleep in patients with COPD and the amount of activity they undertake during the waking day. Identifying groups with specific sleep characteristics may be useful information when designing physical activity enhancing interventions.

Introduction

In addition to progressive chronic airflow limitation, patients with chronic obstructive pulmonary disease (COPD) commonly have multiple extrapulmonary effects and comorbidities, which are associated with physical inactivity.[1] Although there is general agreement about the need to assess and improve physical activity in people with COPD, the factors associated with patient's capability to engage in physical activity are not well established, which may limit the impact of physical activity enhancement interventions.[2]

Sleep disturbance, such as sleep fragmentation during the night, is common in patients with COPD,[3] and is a major complaint after dyspnea and fatigue.[4] Despite the high prevalence of disturbed sleep in COPD, nighttime symptoms are often underestimated and are not a focus of current disease management.[3]

Activity-based or actigraphy sleep-wake monitoring is a cost-effective method to assess sleep that has gained a central role in clinical sleep research, and sleep medicine [5] by providing invaluable insights for the improvements of individualized treatment decisions.[6] Although actigraphy should not be viewed as a substitute for sleep diaries or overnight polysomnography, it can provide useful information about sleep in the natural sleep environment if used for extended period of time with minimal participant burden.[7]

Nocturnal sleep, studied by actigraphy, has been shown to be markedly impaired in patients with COPD compared to controls.[8] However, there is scant and discordant information on whether actigraphic measures of sleep worsen as the severity of dyspnea and airflow limitation increases.[8, 9] Therefore, more data are needed for a better understanding of the factors associated with sleep impairment in patients with COPD. Moreover, although sleep disturbance likely contributes to daytime symptoms like chronic fatigue, lethargy and overall impairment in quality of life described by these patients,[10] no published study has objectively investigated the association between nighttime sleep measures and measures of spontaneous physical activity the following day.

In this study, data were pooled from different studies resulting in a large sample of patients with mild to very severe COPD who had extended objective measures of sleep and physical activity during daily life assessed using a multi-sensor activity monitor. These data were used to: (1) provide insight into the relationship between objectively determined sleep measures and disease severity, exertional dyspnea, gender, and parts of the week (i.e. weekdays vs. weekends); and (2) investigate whether there was an association between objectively assessed sleep measures and next day physical activity. Our hypotheses were that patients with more severe COPD defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [11] criteria and higher Modified Medical Research Council (MMRC) [12] dyspnea score would have more objectively measured sleep disturbances, and that nights of impaired sleep would be followed by days characterized by lower levels of physical activity.

Methods

Study design and participants

In this retrospective, cross-sectional study data from previous studies (details can be found in the appendix pp. 3-5) were obtained from research groups in ten countries: Europe (The Netherlands, UK, Switzerland, Germany, Italy, Ireland, Spain); North America (USA); South America (Brazil); and Oceania (Australia). Criteria to include participants in the current analyses were: clinically stable COPD (i.e., stable shortness of breath and sputum production) with a post-bronchodilator ratio of forced expiratory volume in the first second (FEV₁) to forced vital capacity (FVC) < 0.70; no COPD exacerbations within the last 30 days; and availability of sleep and daytime physical activity baseline data recorded in daily life using the SenseWear Armband or SenseWear Mini Armband activity monitors (BodyMedia Inc., Pittsburgh, PA, USA) before any specific interventions were undertaken. The SenseWear Armband (SWA) has been previously used to study the circadian pattern of sleep and skin temperature,[13] to assess sleep pattern in patients with acute coronary disease,[14] and to monitor sleep in COPD.[15, 16, 17] Data from 1384 patients were available for the present study. The data collection was conducted in accordance with the declaration of Helsinki and approved by ethics committees at each of the participating centers, according to local regulations. Written informed consent was provided by all participants.

Data recordings

Study participants wore the SWA on the upper arm both during daytime and nighttime so that continuous data related to sleep and real-life activities were recorded.

While worn, the SWA recorded continuously longitudinal and transverse acceleration, skin temperature, near body temperature, heat flux, and galvanic skin response. Collected data sent to a PC were used to calculate the metabolic equivalent of task (MET), number of steps, posture (lying down vs. not lying down) and sleeping status (sleep vs. wakefulness) on a minute-by-minute basis.[18] The use of multisensory data in combination with pattern recognition algorithms ensured that the MET estimation was insensitive to noise and random motion artefacts [19] and allowed the objective assessment of sleep [20] and daytime activity levels.[21] METs data were divided into activity intensity levels using the thresholds proposed by the American College of Sports Medicine: very light intensity, < 2.0 METs; light intensity, 2.0 to 2.9 METs; and moderate-to-vigorous intensity, ≥ 3.0 METs.[22]

Time in bed and time out of bed were derived from the minutes coded by the activity monitor as “sleeping” and “lying down” using a custom-made algorithm (appendix pp. 6-9). Based on these data the following nighttime and daytime sleep measures were derived: total night sleeping time, number of nocturnal sleeping bouts, duration of nocturnal sleeping bouts, sleep efficiency, wake after sleep onset, total day sleeping time, number of daytime sleeping bouts, and average duration of daytime sleeping bouts. Sleeping bouts were defined as consecutive minutes marked by the sensor as sleeping. In this study, “sleep quality” is used to refer to the collection of these sleep measures with definitions presented in Table 1.

Table 1 Nocturnal and daytime sleep measures derived from actigraphy data.

Variable name	Abbreviation	Description
Total Night Sleeping Time	TNST	Total night sleeping time is calculated as the sum of all minutes scored as sleep during time in bed.
Number of Nocturnal Sleeping Bouts	NNSB	Number of nocturnal sleeping bouts during time in bed. A higher NNSB indicates more fragmented sleep.
Duration of Nocturnal Sleeping Bouts	DNSB	Average duration of nocturnal sleeping bouts during time in bed. A higher DNSB indicates longer sleeping bouts, and, in turn less nocturnal sleeping disturbances.
Sleep efficiency	Seff	Sleep efficiency defined as the ratio of TNST and time in bed.
Wake After Sleep Onset	WASO	Time spent awake during time in bed after the first nocturnal sleep onset.
Total Day Sleeping Time	TDST	Total day sleeping time defined as the total time spent asleep during the out of bed period.
Number of Daytime Sleeping Bouts	NDSB	Number of daytime sleeping bouts indicates how many naps a patient takes during the day.
Duration of Daytime Sleeping Bouts	DDSB	Average duration of daytime sleeping bouts during the day. A higher DDSB indicates longer naps.

As physical activity measures, the number of steps performed during daytime and the time spent in very light, light and moderate-to-vigorous activities were computed for each assessed day.

Participants who wore the SWA for at least 22 hours per day, with a minimum of four assessed consecutive days (two weekdays + Saturday + Sunday) were included.[21] Participants who did not have their sleep regularly distributed during nighttime or who had less than four hours of time in bed were excluded in order to minimize possible errors due to methodological limitations. For these patients it was not possible to find a reliable estimation of the time in bed and time out of bed as explained in the appendix pp. 6-9.

Statistical analysis

Since physical activity can vary from day to day, complex effects and interactions are expected to occur, which creates the need for multiple days of measurements and proper statistical approaches to identify associations with sleep. Linear mixed-effect models (LMM) were used to study: (i) which factors influenced sleep quality measures, and (ii) whether and to what extent sleep quality measures were associated with subsequent daily physical activity levels and daytime sleep. This kind of multilevel analysis was chosen to account for repeated measurements and control for several confounding factors such as disease and dyspnea severity, current smoking status at the time of enrolment, country, gender, parts of the week (i.e. weekdays and weekends), age, and body mass index (BMI). To construct the models standard statistical packages were used (details can be found in the appendix p 12). Similar analyses were carried out in.[23, 24, 25] Least squares means (LS-means) and differences of LS-means of the fixed effects were calculated to present the results. Degrees of freedom and *p*-values for significant differences (significant if $p < 0.05$) were computed using Satterthwaite's approximation.[26] Comparisons of demographic and clinical characteristics between included and excluded patients were evaluated by Mann-Whitney U-test for continuous variables and Chi-square test for categorical variables. Analyses were carried out using MATLAB R2015a (The MathWorks, Inc., Natick, Massachusetts, United States) and R (R Core Team, 2012) software.

Results

In total 932 patients with COPD were eligible for analysis. Figure 1 shows the flow of participants through the study. Patients excluded due to irregular sleeping patterns and not enough time in bed had significantly lower FEV₁ % predicted compared with included patients (46.6±19.4 vs. 50.8±20.5, p<0.05). No significant differences between included and excluded patients were observed for age, gender, BMI, smoking status at enrollment and MMRC. The median number of days analyzed per patient was six (four weekdays + Saturday and Sunday), resulting in a total of 5646 valid assessed days, of which 3788 (67%) were weekdays. Demographic and clinical characteristics of the patients included in the study are presented in Table 2 (those of excluded patients can be found in Supplementary Materials Table 1, appendix p 11).

Table 2: Demographic and clinical characteristics.

	Included patients (n=932)
Male / female (%)	66 / 34
Smokers* / never or former smokers** (%)	33 / 67
Age (yr)	66.4±8.3
BMI (kg/m ²)	26.3±5.4
FEV ₁ % predicted	50.8±20.5
GOLD 1 - 2 - 3 - 4 (%)	10 - 40 - 32 - 18
MMRC*** 0 - 1 - 2 - 3 - 4 (%)	14 - 27 - 22 - 18 - 6

*Data in the table are expressed as percentages, or means ± standard deviation. BMI: Body Mass Index, FEV₁: forced expiratory volume in 1 s, GOLD: Global Initiative for Chronic Obstructive Lung Disease grade, MMRC: modified Medical Research Councils scale. *Current smokers at the time of enrollment. **Never or former smokers at the time of enrollment. ***MMRC data for 805 patients.*

Sleep measures evaluation in patients with COPD

Figure 2 shows the associations of nighttime and daytime sleep measures with disease severity, dyspnea, gender, and parts of the week. In particular, the total night sleeping time (Fig. 2A) was significantly higher in women (p<0.01) and during weekends (p<0.01). The number of nocturnal sleeping bouts (Fig. 2B) increased both with airflow limitation and exertional dyspnea. Patients with the most severe airflow limitation and exertional dyspnea had significantly more fragmented sleep than patients with the lowest GOLD grade (p<0.01) and MMRC score (p<0.05). The number of nocturnal sleeping bouts was significantly higher in men (p<0.001) and during weekends (p<0.05). Both short duration of nocturnal sleeping bouts and low sleep efficiency were associated with a higher GOLD grade and dyspnea score (Fig. 2C-D). Patients with the most severe airflow limitation had significantly shorter sleeping bouts (p<0.05) and lower sleep efficiency (p<0.01) than patients classified as GOLD 3. Patients reporting the highest MMRC score had significantly shorter sleeping bouts (p<0.05) and lower sleep efficiency

($p < 0.01$) compared to patients with lower MMRC scores. Duration of sleeping bouts and sleep efficiency were significantly higher for women ($p < 0.001$). The time spent awake after the first sleep onset (Fig. 2E) increased both with disease severity and dyspnea, being worst in patients with GOLD grade 4 ($p < 0.05$) and MMRC score 4 ($p < 0.01$).

During daytime (Fig. 2F-H) the sleeping time, the number and duration of sleeping bouts increased significantly with dyspnea ($p < 0.05$). Sleeping time and duration of sleeping bouts were significantly shorter in patients with GOLD grade 4 compared to patients classified as GOLD 3 ($p < 0.05$).

Association between objective sleep measures and daytime physical activity

Nocturnal sleep measures were divided into quartiles (Q₁, shortest/lowest-Q₄, longest/highest) to assess the association with daytime physical activity measures (Supplementary Materials Table 2, appendix p 13).

As shown in Fig. 3A, the number of steps performed during the day was inversely related to the number of sleeping bouts and the minutes spent awake after the sleep onset. On the other hand, the number of steps increased as the duration of the sleeping bouts and the sleep efficiency increased. In particular, patients who had their sleep characterized by one sleeping bout, long sleeping bouts (≥ 225 minutes), high sleep efficiency ($\geq 91\%$), and low time spent awake after the sleep onset (< 57 minutes) performed, on average, 600 steps more on the following day with respect to patients who had more fragmented sleep (≥ 4 bouts), lower sleep efficiency ($< 71\%$), lower sleeping bout durations (< 86 min) and higher time spent awake after the sleep onset (≥ 165 minutes) ($p < 0.001$ for all). Patients who slept more than 480 minutes performed a smaller number of steps than the other patients, but no significant differences were found if the number of steps of each patient is divided by the time spent awake (data not shown). As presented in Fig. 3B, the percentage of daytime spent in very light activities was higher in patients who slept more than 480 minutes and it increased with sleep fragmentation, and time spent awake after the sleep onset. Furthermore, the time spent in very light activities decreased as sleep efficiency and duration of sleeping bouts increased. Patients with the worst nocturnal sleep measures (i.e. sleep characterized by sleeping bouts < 86 minutes, sleep efficiency $< 71\%$, and time spent awake after the sleep onset ≥ 165 minutes) spent on average the 74% of the time awake in very light intensity activities, 1% more than patients with sleep characterized by sleeping bouts ≥ 225 minutes ($p < 0.01$), sleep efficiency $\geq 91\%$ ($p < 0.001$), and time spent awake after the sleep onset < 57 minutes ($p < 0.01$).

Patients with the smallest number of sleeping bouts per night, longest sleeping bouts, highest sleep efficiency and shortest time spent awake during the night spent more time in light (Fig. 3C) and moderate-to-vigorous (Fig. 3D) physical activities on the following day ($p < 0.01$ for all). In particular, compared to patients with the worst sleep measures, these patients spent on average 9

minutes more in light intensity activities and 8 minutes more in moderate to vigorous activities that correspond to the 26% of the recommended daily amount.[27]

Daytime sleep was inversely related to the amount of nocturnal sleep, the duration of sleeping bouts and the sleep efficiency (Fig. 4). Patients who showed relatively short sleep duration during the night (<347 minutes), who had short sleeping bouts (<86 minutes) and low sleep efficiency (<71%) reported more daytime sleep compared to subjects who slept more than 480 minutes during the night ($p<0.001$), had sleeping bouts longer than 225 minutes ($p<0.05$) and a sleep efficiency higher than 91% ($p<0.05$).

Discussion

We describe, to our knowledge, the first study in a large sample of participants with COPD, targeting the association of objectively measured sleep impairment with airflow limitation, exertional dyspnea, gender, parts of the week and daytime activity levels.

We found that objective sleep quality measures are worse in patients with severe airway obstruction and dyspnea. This is in agreement with George et al.[28] who showed that subjective sleep disturbances tend to be more severe with advanced COPD and with Dodge et al.[29] who showed that patients with dyspnea are more likely to report persistent sleep disturbance. Conversely, Hartman et al.[9] failed to find a significant association between night's rest parameters assessed by an accelerometer and both airflow limitation and dyspnea. However, this latter study did not evaluate sleep quality measures, but rather quantitative parameters such as body movements and number of posture transitions that are not necessarily related to poor sleep quality.[9] Nunes et al.[8] reported that the MMRC score was an important predictor of objectively measured sleep quality in 26 patients with moderate to very severe COPD. However, the small sample size precluded any firm conclusions on the differences between patients with different dyspnea scores.

The strong evidence provided by our findings regarding the association of sleep impairment with the most severe stage of the disease and dyspnea could be explained by several potential mechanisms. First, it is intuitively apparent that because severe COPD patients have a lower oxygen saturation during wakefulness, the normal ventilation changes that occur with sleep exacerbate this preexisting state to the point of severity impairing sleep.[30] Second, the lying sleeping position assumed by the participants in the study and the reduction in muscle tone causes increased upper airway resistance.[30, 10] This might have more impact in patients who are least able to tolerate any further challenge to their ventilatory capability. Moreover, patients with severe COPD frequently experience episodes of worsening symptoms that may also preclude from adequate sleep.

Participants with the most severe disease had worse sleep but they did not seem to compensate it during the day by adding naps. Most dyspneic patients, in turn, seemed to do so. Other

investigators have also found that daytime sleepiness was related more strongly to the presence of respiratory symptoms than to a diagnosis of lung disease or the degree of airway obstruction.[31]

We saw significant gender differences after correction for age, BMI, smoking status at enrollment, country of origin, GOLD and MMRC. Men had worse sleep quality measures and spent more time sleeping during the day than women. There is currently only limited information regarding the influence of gender on sleep in COPD. In a previous study using actigraphy no significant gender-related differences in sleep quality were found.[8] Other studies have documented that women appear to report more sleep-related complaints.[32] However, objective and subjective assessments of sleep seem to reflect different aspects and need therefore not be necessarily in agreement.[33]

During weekends patients had significant more fragmented sleep and spent significantly more time awake after the first sleep onset than during weekdays. Our results showed that impaired sleep during weekends was compensated by sleeping longer.

This study showed that nights of lower sleep quality were followed by days of lower levels of physical activity in people with COPD. It is important to note that potential influence of airflow limitation, severity of dyspnea smoking status at enrollment, country, gender, parts of the week (i.e. weekdays and weekends), age, and BMI was taken into account since these variables were included in the multilevel models used.

The association of impaired sleep with worse daytime performance is consistent with findings showing that it plays a substantial role in reduced quality of life in patients with COPD.[34, 35] Moreover these findings are consistent with other correlational evidence drawn from older adults suggesting that objectively measured poor sleep was associated with worse daytime physical function evaluated in clinical settings,[36, 37] yet none of these studies demonstrates a direct effect of sleep on subsequent physical activity during daily life. Although inferring a causal relationship was out of the scope of this study, our finding provided a good illustration of the sequential association as it incorporated a clear chronological order of the predictor (sleep quality measure) and the predicted variable (physical activity). However, the possibility that poor daytime performance may be a causative factor for poor sleep quality should be considered. In this regard, it has been previously shown that patients who are most hypoxaemic when awake are most severely hypoxaemic when asleep with the consequence of having both reduced physical activity during the day and sleep disturbance during the night. On the contrary, in patients with mild (or absent) daytime hypoxaemia, this nocturnal desaturation is, in most cases, slight to moderate.[30]

The deficit in good sleep, in association with changes of sleep architecture, may make sleep not as restorative as needed and may cause a significant sleep deficit.[38] Accordingly, our study

provides evidence to suggest that poor sleep efficiency and short sleeping bouts during the night are possibly compensated by additional daytime naps.

The fact that poor sleep quality was associated with reduced physical activity levels may have important consequences with regard to current clinical practice. First, our findings suggest the possibility of increasing spontaneous engagement in physical activity through improving sleep since, in the absence of any intervention, patients having had a better night of sleep spontaneously engaged in more physical activity the following day. Second, existing strategies for promoting physical activity tend to focus on actions during the day. Additional efforts in promoting quality sleep among physically inactive subgroups may increase the overall impact of these interventions. Finally, sleep should be assessed and taken into account when analyzing physical activity in COPD, although recent literature is often overlooking the continuity between nighttime sleep and daytime physical activity.[39]

This study has some limitations which should be considered when interpreting the results. First, data regarding exacerbations, hospitalizations frequency and smoking history prior to enrolment was not available which prevented to investigate their potential impact on daytime physical activity and sleep disruption. Our participants were not screened for sleep-related disorders, such as obstructive sleep apnea (OSA). However, because COPD and OSA are both common chronic conditions, these should be expected to occur together, particularly among overweight individuals with COPD.[40] Moreover, no significant differences were previously found in measures of dyspnea, sleep quality, sleep efficiency, and sleepiness during the day between patients with COPD only and patients with COPD-OSA overlap.[40] Although we cannot know whether the patients included had OSA, we can rule out that specific interventions influenced quality or quantity of sleep since only baseline data were analyzed.

To the current authors' knowledge, the SenseWear armband has not been properly validated to study sleep in COPD. However, several days of assessment reduce the inherent measurement errors in actigraphy and further increase the reliability.[5] Moreover, although it has been shown to be a reliable method for determining sleep in patients with sleep-breathing disorders when compared against polysomnography,[20] the SenseWear armband might underestimate the time spent sleeping for those patients who sleep in a sitting position in order to facilitate their breathing.

In summary, sleep impairment in patients with COPD tends to be more pronounced in patients with severe airflow limitation and in those with worse exertional dyspnea. Moreover, nocturnal sleep impairment appears to be an important factor associated with the capability to engage in physical activity on a day-to-day basis. In particular, nights of better sleep quality measures were followed by days of higher levels of physical activity. Further research is needed to identify the causal association between nighttime sleep and the decline in daytime physical activity, as well as to assess whether the management of nighttime symptoms and the reduction of sleep impairment can facilitate the adoption of a physically more active lifestyle in patients with

COPD. Considering both our current understanding of the negative health consequences of sleep disturbance in COPD and the current limited efficacy of interventions in significantly improving and maintain physical activity enhancement, our data suggest that approaches to improve sleep need to be considered as additional targets for tailored interventions in patients with COPD since may have significant implications for facilitating greater adherence and a favorable impact on lifestyle.

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The authors declare that there are no conflicts of interest.

Contributors

G. S., M.A.S., A.C.d.B., conceived and designed the analysis. G.S. analyzed the data and drafted the first version of the manuscript. M.A.S. and A.C.d.B. provided advice at all stages of the analysis. A.C.d.B. provided statistical support.

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Figure legends

Figure 1 Flow of patients through the study.

Figure 2 Impact of disease severity according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades, daytime dyspnea according to the modified Medical Research Council (MMRC) scale, sex (f = female, m = male), and parts of the week (wd = weekdays, we = weekends) on sleep parameters (A: Total Night Sleeping Time; B: Number of Nocturnal Sleeping Bouts; C: average Duration of Nocturnal Sleeping Bouts; D: Sleep efficiency; E: time aWake After the first Sleep Onset ; F: Total Day Sleeping Time; G: Number of Daytime Sleeping Bouts; H: average Duration of Daytime Sleeping Bouts). Data are expressed as least-square means \pm standard error. Significance levels for pairwise comparisons are indicated as horizontal bars with $*=p<0.05$, $**=p<0.01$, and $***=p<0.001$.

Figure 3 Association between nocturnal sleep parameters (Total Night Sleeping Time; Number of Nocturnal Sleeping Bouts; average Duration of Nocturnal Sleep Bouts; Sleep efficiency; time aWake After the first Sleep Onset) and daytime physical activity measures (A: STEP = Steps performed; B: TIME VL = Time spent in Very Light activity, C: TIME L = Time spent in Light activity, D: TIME MV = Time spent in Moderate-to-Vigorous activity). Data are expressed as least-square means \pm standard error. Significance levels for pairwise comparisons are indicated as horizontal bars with $*=p<0.05$, $**=p<0.01$, and $***=p<0.001$. TIME VL, TIME L, TIME VM are presented in % of the out of bed time.

Figure 4 Association between nocturnal sleep parameters (Total Night Sleeping Time; Number of Nocturnal Sleeping Bouts; average Duration of Nocturnal Sleeping Bouts; Sleep efficiency; time aWake After the first Sleep Onset) and Total Day Sleeping Time. Data are expressed as least-square means \pm standard error. Significance levels for pairwise comparisons are indicated as horizontal bars with $*=p<0.05$, $**=p<0.01$, and $***=p<0.001$. Total Day Sleeping Time is presented in % of the out of bed time.