



OPEN The effect of sleep and its restriction on selected inflammatory parameters

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Insufficient sleep duration may lead to a series of immune dysfunctions. One of the factors influencing this effect could be physical activity (PA). The study aimed to assess the impact of deprivation of sleep (DS) on selected inflammatory parameters. Seventy-seven participants completed the protocol consisting of polysomnography (PSG) conducted in a sleep laboratory and DS, monitored with an actigraph. PA was assessed with actigraphy, which categorized participants as active or inactive. White blood cells (WBC) values negatively correlated with sleep efficiency based on sleep diaries and PSG parameters (total sleep time, sleep efficiency, and REM duration), but regression analysis showed that WBC depends only on the sleep diary parameter. Granulocytes (GRA) positively correlated with REM latency, and negatively with sleep efficiency. After DS, all participants exhibited an elevated GRA count. The number of WBC and GRA increased also in the active group; inactive participants showed no changes in inflammatory parameters. The overall number of WBC depends primarily on the quality of sleep over a period of several days. Under the influence of sleep deprivation, the number of GRA increases, but the number of leukocytes depends on the level of physical activity during DS.

Keywords Sleep deprivation, Inflammation, C-reactive protein

Sleep disorders are a common problem in the general population. It is estimated they affect about 30% of the population¹. Deprivation of sleep (DS) is defined as a forced lack of sleep, which might stem from a number of causes, including work, leisure or pain².

Insufficient sleep duration can lead to several systemic complications, including impairment of immunity. In a murine DS model, elevated levels of autoantibodies were observed, which are characteristic of many autoimmune diseases, such as systemic lupus erythematosus³. Hsiao et al. in their study showed that individuals with sleep disorders have a higher risk of developing the following immune-mediated diseases: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, and Sjögren's syndrome, with hazard ratios between 1.45 and 1.81, compared to those without sleep issues⁴.

One study showed that long-term DS affects changes in the levels of C-reactive protein (CRP), tumor necrosis factor, and interleukin-6, but not in the number of white blood cells (WBC)⁵.

The pathophysiology of the described effects is not fully understood. Most of them are based on animal models. Up to date only a few studies compared inflammatory parameters after a night of sleep and DS in the same participants, and the study groups were often small^{6,7}. In one study, 9 participants were deprived of sleep, and their results were compared to those of 8 other participants who had a full night's sleep. The WBC count increased after sleep deprivation, but there was no change in the WBC count after a night's sleep⁷.

Many factors can affect inflammatory parameters, such as chronic diseases, body mass, sex, and physical activity (PA). It seems that additional factors, such as activity during DS, may underlie the differences in human model studies. One study showed that acute exercise can reduce the production of tumor necrosis factor. It seems that the reduced inflammatory response during intense exercise can protect against low-grade chronic inflammation⁸.

However, the effect of physical activity during DS on inflammatory parameters was not investigated.

Therefore, the aim of the study was to estimate the effect of sleep duration, quality as well as both acute and chronic sleep deprivation on selected inflammatory factors, while taking into account actigraphic data obtained during DS.

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Results

For the study, 113 participants were recruited, and 36 of them were excluded from further analysis (31 participants did not complete the entire study protocol, 5 participants had a sleep time of less than 5 h). In total, the results of 77 participants were analyzed. The participant characteristics are presented in Table 1.

Average sleep efficiency based on sleep diaries was negatively correlated with morning WBC and lymphocytes (LYM) values, but not with granulocytes (GRA), monocytes (MON) values, or CRP concentration (Table 2). Additionally, sleep time and sleep latency did not correlate with any of the inflammatory parameters ($P > 0.05$, Table 2).

After a night of sleep (PSG examination), morning WBC values negatively correlated with total sleep time (TST), sleep efficiency, REM duration, but not with NREM duration. LYM and MON values did not correlate with PSG parameters ($P > 0.05$, Table 2). GRA positively correlated with REM latency, negatively with sleep efficiency and REM duration. CRP concentrations negatively correlated only with sleep latency, but not with other PSG parameters (Table 2). Regression analysis showed that WBC values were affected by sleep efficiency calculated on the basis of sleep diaries ($B = -0.04$, $t = -2.92$, $P = 0.005$), but not by PSG parameters (REM durations, number of REM events, sleep efficiency; $R^2 = 0.10$, $F = 8.55$, $P = 0.005$).

Following DS, the GRA value increased compared to the value observed after a night of sleep (3.1 IQR: 2.6–3.9 vs. 3.5 IQR: 2.7–4.2 $\times 10^3/\mu\text{l}$, $P = 0.002$). Other inflammatory parameters remained unchanged (Table 3). Among participants classified as inactive, inflammatory parameters did not change ($P > 0.05$, Table 3). In the active group, both WBC and GRA counts increased (WBC: 5.3 IQR: 4.9–5.7 vs. 5.6 IQR: 5.1–7.5 $\times 10^3/\mu\text{l}$, $P = 0.015$; GRA: 2.9 IQR: 2.6–3.2 vs. 3.5 IQR: 2.7–4.6 $\times 10^3/\mu\text{l}$, $P = 0.003$), whereas MON values and CRP concentrations remained unchanged (Table 3).

After DS, inflammatory parameters did not correlate with the physical activity index during the entire night, apart from a negative correlation with the change in CRP concentration. The intensity of physical activity during the last two hours also did not correlate with inflammatory parameters. However, the activity during the last hour of DS positively correlated with WBC and GRA. The change in WBC values between a night of sleep and after DS negatively correlated with physical activity during the last hour of DS (Table 2).

Correlations between AHI and WBC, LYM, GRA, MON, LYM and CRP were statistically insignificant (all $P > 0.05$).

	All	Non-active	Active	<i>p</i>
N, %	77	50, 64.9	27, 35.1	–
Age (years, median, IQR)	24 (22–26)	24 (22–26)	23 (22–25)	0.441
BMI (kg/m ² , mean, SD)	22.8 \pm 2.7	22.8 \pm 2.5	22.9 \pm 2.9	0.863
Women (n, %)	40, 51.9	25, 50.0	15, 55.6	0.642
Smoking (n, %)	9, 11.7	6, 12.0	3, 11.1	1.000
Surgical operations (n, %)	27, 38.6	18, 36.0	9, 33.3	0.815
Higher education (n, %)	36, 46.8	21, 42.0	15, 55.6	0.432
sleep time before PSG (h, median, IQR)	7.0 (6.0–7.5)	7.0 (6.0–7.0)	7.0 (6.5–7.5)	0.662
sleep efficiency before PSG (% , median, IQR)	87.3 (80.0–94.1)	86.0 (77.8–90.9)	89.7 (82.5–95.7)	0.099
Sleep latencies time before PSG (min, median, IQR)	10.0 (5.0–20.0)	15.0 (7.5–20.0)	7.8 (5.0–15.0)	0.027
TST in PSG (min, median, IQR)	407.0 (358.0–471.5)	410.5 (360.0–471.5)	395.0 (337.0–476.0)	0.539
Sleep latencies in PSG (min, median, IQR)	35.5 (22.0–60.0)	37.5 (23.0–61.5)	33.5 (19.5–59.0)	0.575
Sleep efficiency in PSG (% , mean, SD)	77.8 \pm 11	78.1 \pm 10.4	77.2 \pm 12.2	0.727
REM duration in PSG as TST % (% , mean, SD)	23.1 \pm 8.0	25.2 \pm 8.2	22.0 \pm 7.8	0.320
NREM duration in PSG as TST % (% , mean, SD)	78.0 \pm 8.3	76.0 \pm 8.3	79.1 \pm 8.2	0.070
AHI (apnea–hypopnea/h, median, IQR)	0.9 (0.5–1.7)	0.86 (0.43–1.6)	1.1 (0.5–1.9)	0.408
Average saturation (% , median, IQR)	96.0 (96.0–97.0)	96.0 (96.0–97.0)	96.0 (96.0–97.0)	0.160
Oxygen desaturation index (episodes/h, median, IQR)	0.4 (0.2–0.9)	0.3 (0.2–0.8)	0.5 (0.1–1.1)	0.540
Desaturation < 90% as TST % (% , median, IQR)	0.0 (0.0–12.3)	0.0 (0.0–10.1)	0.0 (0.0–12.7)	0.898
PLM index (episodes/h, median, IQR)	0.5 (0.2–1.0)	0.4 (0.2–0.8)	0.7 (0.2–1.3)	0.175
Arousal index (episodes/h, median, IQR)	6.2 (4.5–8.7)	5.5 (4.2–7.4)	6.7 (4.5–8.8)	0.247
Movement in deprivation (median, IQR)	334.9 (259.5–424.9)	281.0 (244.5–324.8)	443.8 (403.0–481.8)	< 0.001
Time in the dark in deprivation (min, median, IQR)	344.0 (244.0–544.0)	464.5 (251.0–587.0)	312.0 (221.0–432.0)	0.020
Movement in deprivation, last hour (median, IQR)	394.1 (282.6–543.5)	378.7 (276.5–523.5)	422.5 (325.1–588.0)	0.356
Movement in deprivation, last two hours (median, IQR)	388.7 (297.9–522.1)	361.6 (286.0–522.1)	423.3 (367.1–540.2)	0.108

Table 1. Baseline characteristics. AHI apnea/hypopnea index, BMI body mass index, IQR interquartile range, n: number of participants, NREM non-rapid eye movement, PLM periodic limb movement, PSG polysomnography, REM rapid eye movement, SD standard deviation, TST total sleep time. Significant values are in bold.

		R	P	R	P	R	P	R	P	R	P
		WBC-A		LYM-A		MON-A		GRA-A		CRP-A	
Before PSG	sleep efficiency	-0.28	0.02	-0.25	0.03	-0.18	0.14	-0.13	0.29	0.16	0.17
	sleep time	-0.03	0.78	-0.08	0.48	-0.02	0.84	0.12	0.33	0.09	0.47
	sleep latencies	0.13	0.26	0.07	0.57	-0.05	0.65	0.11	0.35	-0.08	0.48
		WBC-A		LYM-A		MON-A		GRA-A		CRP-A	
After PSG	TST	-0.24	0.04	-0.20	0.09	-0.01	0.95	-0.21	0.07	0.00	0.99
	REM duration	-0.29	0.01	-0.22	0.06	-0.04	0.76	-0.23	0.04	0.03	0.81
	NREM duration	-0.14	0.24	-0.1	0.37	-0.04	0.73	-0.13	0.28	-0.07	0.55
	REM latencies	0.22	0.06	0.22	0.06	-0.01	0.94	0.31	0.01	-0.05	0.69
	Sleep latencies	0.08	0.48	0.07	0.55	-0.2	0.08	0.08	0.49	-0.24	0.04
	Sleep efficiency	-0.26	0.02	-0.20	0.08	0.00	0.97	-0.3	0.01	-0.03	0.82
	Number of REM events	-0.23	0.04	-0.14	0.23	-0.18	0.12	-0.22	0.06	0.11	0.34
	Number of NREM events	-0.04	0.71	0.11	0.37	0.00	1.00	-0.13	0.26	-0.05	0.67
After DS		WBC-B		LYM-B		MON-B		GRA-B		CRP-B	
	mov. during DS. (all time)	0.12	0.28	0.00	1.00	0.14	0.24	0.11	0.35	0.12	0.29
	mov. during DS. (last two h)	0.06	0.58	-0.04	0.74	0.06	0.57	0.12	0.28	-0.07	0.54
	mov. during DS. (last one h)	0.28	0.02	0.19	0.09	0.16	0.17	0.27	0.02	-0.11	0.35
		Δ WBC		Δ LYM		Δ MON		Δ GRA		Δ CRP	
	mov. during DS. (all time)	-0.21	0.07	-0.10	0.40	-0.21	0.07	-0.20	0.08	-0.21	0.07
	mov. during DS. (last two h)	-0.08	0.47	-0.06	0.63	-0.03	0.81	0.04	0.72	-0.14	0.24
	mov. during DS. (last one h)	-0.23	0.04	-0.20	0.09	-0.09	0.45	-0.18	0.12	-0.02	0.88

Table 2. Correlations between immune and sleep parameters before and during polysomnographic examination, and movement during sleep deprivation. *A* after PSG, *B* after deprivation of sleep, *CRP* C-reactive protein, *DS* deprivation of sleep, *GRA* granulocytes, *LYM* lymphocytes, *MON* monocytes, *NREM* non-rapid eye movement, *REM* rapid eye movement, *TST* total sleep time. The last row depicts differences between two time points, morning after PSG and morning after DS. Significant values are in bold.

	All			Non-active			Active		
	B	D	p	B	D	p	B	D	p
WBC *103/ μ l	5.4 (4.7–6.4)	5.8 (4.9–6.8)	0.109	5.7 (4.6–6.7)	5.8 (4.8–6.6)	0.967	5.3 (4.9–5.7)	5.6 (5.1–7.5)	0.015
LYM *103/ μ l	2.0 (1.7–2.3)	1.9 (1.7–2.4)	0.625	2.1 (1.7–2.3)	1.9 (1.6–2.3)	0.538	2.0 (1.8–2.3)	2.0 (1.8–2.5)	0.054
MON *103/ μ l	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.249	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.052	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.496
GRA *103/ μ l	3.1 (2.6–3.9)	3.5 (2.7–4.2)	0.002	3.3 (2.7–4.0)	3.5 (2.9–4.1)	0.114	2.9 (2.6–3.2)	3.6 (2.7–4.6)	0.003
CRP mg/L	0.7 (0.4–1.2)	0.6 (0.3–1.1)	0.167	0.7 (0.4–1.2)	0.6 (0.3–1.0)	0.122	0.7 (0.5–1.8)	0.8 (0.4–1.4)	0.962

Table 3. Change in levels of immune parameters at two time points: after a night’s sleep and after sleep deprivation. *A*—after PSG, *B*—after DS. *CRP* C-reactive protein, *GRA* granulocytes, *LYM* lymphocytes, *MON* monocytes, *WBC* white blood cells. Significant values are in bold.

Discussion

The role of sleep as a modulator of inflammation has been described for many years. However, studies on this topic are often inconclusive because they involve different sleep disorders. The difficulties arise also due to the diversity of the adopted models of insomnia and DS. Other causes of insufficient or ineffective sleep are often not taken into account. In addition, comparisons are frequently made at different points in time, disregarding the circadian rhythm.

In the first stage of this study, the association of selected inflammatory parameters with sleep quality was assessed for 2 weeks using sleep diaries. It was observed that the concentration of WBC and LYM negatively correlated with sleep efficiency. No correlation of inflammatory parameters with sleep duration or sleep latency was observed. A Korean study of 136 participants found that poor sleep quality is associated with increased WBC count⁹. Another study found that shift workers with higher scores on the Athens Insomnia Scale also had a higher WBC count. The study also found that the association between insomnia symptoms and WBC was stronger in shift workers than in day workers¹⁰.

This study also showed a relationship between sleep efficiency and the level of granulocytes. Nie et al. did not observe any differences in their levels. Similarly, another study did not show any significant differences in the levels of neutrophils, lymphocytes, monocytes, and platelets, CD8 + T and CD56 + lymphocytes, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, complement C3, complement C4, IgM, IgA, and interleukin-6

between the experimental group with insomnia and the control group¹¹. However, the diagnosis of insomnia was based solely on clinical criteria, and PSG was not performed to rule out other causes of insufficient sleep.

In the following step, the relationship between inflammatory markers and sleep quality was examined, as determined by the outcomes of a one-night PSG study. To the best of our knowledge, there are currently no studies that have chosen more objective parameters for the assessment of the link between symptoms of insomnia and inflammation. Negative correlations were observed between WBC and total sleep time and sleep efficiency. However, regression analysis showed that WBC levels mainly depend on sleep efficiency, which is the average of 2-week measurements, and not on a single night. These results confirm the above-mentioned association of WBC with chronic insomnia⁹.

In this study, CRP was negatively correlated only with sleep latency. The results were unexpected, as the available literature showed no association between CRP and sleep quality parameters. For example, a negative correlation was shown between CRP concentration and sleep duration¹². In a large study, it was observed that men who slept 10 h or more per day had elevated levels of CRP¹³. In women, difficulty falling and staying asleep were associated with elevated CRP levels, however, sleep duration was self-reported thus prone to bias¹³. The average CRP level in women who woke up early in the morning was 72% higher than in women without such problems, while, contrary to this study, no association was observed between difficulty falling asleep and CRP levels¹⁴. The association between CRP and sleep restriction still requires further research.

After DS, a significant increase in GRA levels was observed compared to the morning after a night's sleep but other parameters did not change. In a similar study on 15 healthy participants, an increase in GRA levels was observed under the influence of DS¹⁵. Similarly, Heiser et al. observed an increase in GRA after DS, and no differences were observed in WBC or LYM count¹⁶. However, in contrast to our study, among 23 volunteers, an increase in CRP levels was observed after DS compared to levels after a night's sleep assessed by actigraphy¹⁷. The abovementioned studies and available literature confirm an increase in GRA levels, while studies on other inflammatory parameters are inconsistent.

An explanation for the observed differences may be physical activity during DS. After dividing the study participants into active and inactive during DS, the active group exhibited an increase in WBC, and GRA. On the other hand, in the inactive group none of the studied parameters changed. Notably, the greatest impact on WBC and GRA count in the morning was exerted by the activity in the last hour of actigraphy. According to our best knowledge, there are no similar studies. The available literature suggests an anti-inflammatory effect of physical activity, although this has only been studied during the daytime¹⁸. Therefore, any extrapolations should be made with caution. Additionally, a higher level of activity was observed in people whose mood did not change under the influence of DS¹⁹. It is difficult to definitively answer the question of the cause of the observed differences in the response of depressed participants to DS. Inflammation, one of the underlying causes of depression, could fulfill an important role also here²⁰. However, this issue requires further research.

Our study is one of the few that comprehensively examined the effects of sleep and a lack thereof on selected inflammatory parameters. However, this study has several limitations. Blood morphology as well as assessment of other inflammatory parameters was performed only in the morning after a night's sleep and DS, not in the evening, which limits the scope of the study. On the other hand, the number of leukocytes naturally changes throughout the day, so comparing morning and evening measurements would be biased¹⁵. Even though actigraphy is a reliable method for controlling participant activity, it carries the risk of missing short naps and mistaking periods of inactivity with sleep. Observing patients during DS in a sleep laboratory with electroencephalography would probably yield the most objective results. The "First night effect" of the PSG is another important limitation of the present study, as it significantly skews sleep structure.

In summary, we observed that the overall number of WBCs, including LYM, depends primarily on the quality of sleep over a period of several days. GRA correlates with objective sleep parameters, especially sleep latency and efficiency. Under the influence of sleep deprivation, the number of GRA increases, but the number of leukocytes depends on the level of physical activity during DS. Physical activity during DS may influence inflammatory parameters. This may explain the hitherto ambiguous literature on the impact of DS on inflammatory parameters. In further studies, it would also be advisable to investigate the impact of longer sleep deprivation, as acute DS may not be sufficient to change some blood morphological elements. It is also necessary to search for other factors that affect the body's response to sleep deprivation.

Methods

The study was conducted in the sleep laboratory at the Department of Sleep Medicine at the Medical University of Lodz, Poland. All research was performed in accordance with the Declaration of Helsinki. Participants were recruited through the scientific team's social media profiles and snowball sampling method. The study protocol was depicted in Fig. 1.

The Bioethical Committee of the Medical University of Lodz, Poland has approved of the study protocol (number: RNN/302/20/KE). Informed consent was obtained from all participants in written form.

Inclusion criteria were body mass index of 20–30 kg/m², and age range 18–35 years.

Exclusion criteria comprised the following: untreated or ineffectively treated mental disorders, a total sleep time below 5 h (in sleep diary and PSG examination; the lower quartile for the given age group among healthy volunteers, based on the study by Mitterling et al.²¹), obstructive sleep apnea (diagnosed during the PSG or in medical history), periodic limb movement sleep disorder, parasomnias, acute infections in the last month, surgery in the last 6 months, diagnosis of endocrine diseases, metabolic, chronic inflammatory disorders, actively treated psychiatric diseases, substance abuse, radio/chemotherapy in the medical history, pregnancy, breastfeeding, renal, respiratory or circulatory insufficiency, tumors (excluding basal-cell carcinoma), intercontinental flight during study or within 2 weeks preceding qualification.

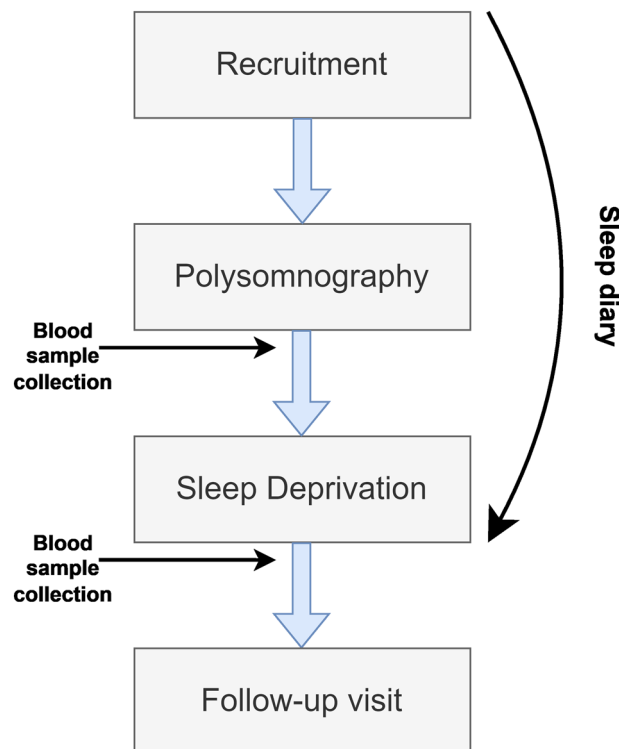


Figure 1. Study design flowchart.

The study protocol consisted of two parts: PSG and DS. Recruitment took place from February 2021 to April 2022, data collection was conducted between March 2021 and June 2022. Follow-up visits summarizing results were performed from December 2022 to December 2023.

At least two weeks prior to the planned nocturnal PSG, participants were obliged to keep a structured sleep diary (information about naps, total time spent in bed, estimated sleep time, sleep quality, number and duration of awakenings); a diary template was provided by the researchers for the sake of standardization. The data mentioned above was obtained using the arithmetic mean. The first two and the last two days of the sleep diary were excluded from the calculations to enhance the accuracy of this sleep assessment method.

In the study, a single-night PSG was conducted, which began around 10 PM and lasted until 7 AM (± 15 min) the next day. Routine PSG parameters were assessed: chin and limb electromyography, electroencephalography (leads F3, F4, C3, C4, O1 and O2), electrooculography, electrocardiography (leads V1 and V2), body position, airflow signals (oronasal flow; thermistor gauge), oxygen saturation, respiratory effort signals from chest and abdomen (piezoelectric gauges) (Alice 4, Phillips-Respironics, USA). Video-PSG was not performed.

The interpretation and scoring of the recordings were carried out by the same researcher, adhering to the American Academy of Sleep Medicine (AASM) guidelines (The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.3), utilizing a 30-s epoch standard to identify sleep-disordered breathing, arousals, periodic limb movements, or any other abnormalities²².

DS was conducted at least two weeks after the PSG; DS duration was set at ca.24 h, from one morning to the next. Enrolled subjects were permitted to spend the DS night in their place of residence.

Physical activity was evaluated using actigraphy. Participants were provided with an actigraph (actigraph GENEActive Original, ActivInsights Ltd.) during their visit in the Department on the DS day.

Actigraphy data were scored based on AASM guidelines²³. Sedentary time was defined as a gravity-subtracted sum of vector magnitudes $< 386^{\circ}$ ²⁴. Based on this calculation, subjects were divided into two groups: inactive (at least 70% of DS duration spent sedentary) and active (less than 30% of DS duration spent sedentary).

Blood cell count was performed on venous blood collected in the morning after PSG as well as DS (10 PM and 7 AM (± 15 min)) in an EDTA tube using a Hematology Analyzer (Horiba ABX SAS, Montpellier, France). Assessment of serum CRP concentration was performed using a standardized procedure by the medical laboratory of the Central Clinical Hospital of the Medical University of Lodz.

Statistica 13.1 PL (StatSoft, Tulsa, OK, USA) was used for data analysis. The significance level was set at $p < 0.05$. Assessment of distribution (normal/non-normal) for continuous variables was performed with the Shapiro–Wilk test. Data were presented as median with interquartile range or mean with standard deviation in case of non-normal and normal distribution, correspondingly. Parametric independent variables were assessed with a student t-test. Mann–Whitney U test or Wilcoxon signed-rank test was applied for nonparametric independent or dependent variables, respectively. Spearman's correlation test was applied for correlations. Linear regression models were created by means of stepwise elimination—parameters were taken into account based on a sleep diary (sleep efficiency) and PSG examination (sleep efficiency, TST, NREM duration, REM duration).

Ethics approval

The Bioethical Committee of the Medical University of Lodz, Poland has approved of the study protocol (number: RNN/302/20/KE). Informed consent was obtained from all participants in written form.

Data availability

Data available on request from the authors, contact: Marcin Sochal, MD, PhD, Department of Sleep Medicine and Metabolic Disorders, Medical University of Lodz, ul. Mazowiecka 6/8, 92-215 Łódź, Poland, phone: + 48,422,725,660, email: sochalmar@gmail.com.

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Conceptualization, M.S.; Methodology, M.S., and A.G.; Formal analysis, M.S.; Investigation, M.S., A.G., M.D., S.T., F.F.K., P.B.; Writing—original draft, M.S.; Writing—review & editing, A.G., P.B. All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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