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Obstructive sleep apnea (OSA) and narcolepsy cause excessive daytime sleepiness (EDS) and hypersomnia. Daytime sleepiness can be measured by the maintenance of wakefulness test (MWT). OSA and upper airway resistence syndrome (UARS) patients frequently have abnormal MWTs. Co-morbidities and medication of patients are likely to influence the results of MWT. We set out to study the association between MWT sleep latencies and patients' background characteristics and co-morbidity.

We studied retrospectively 506 MWTs in 361 patients. MWT testing was performed between January 2006 and November 2014. We gathered also information about age, gender, BMI, smoking, snoring, waist circumference, disease burden, diagnostic cardiovascular polygraphy, medication, CPAP-treatment, ESS, GHQ-12 and DEPS scores and subjective sleep quality. Then we examined how sleep latiencies in the MWT were influenced by these factors.

We found that professional drivers, sleep apnea patients and men were more alert than non-professional drivers, patients without sleep apnea or women, respectively. Patients suffering from long-term snoring and using almost all types of medication had worse results in MWT compared to others. Higher scores in ESS, GHQ-12 and DEPS questionnaires associated with shorter sleep latencies. We conclude that gender, sleep disorder type, co-morbidity and medication influence the results of MWT.

Asiasanat: Uniapnea, Hereilläpysymistesti (MWT), Liitännäissairaudet, Vireystila,

The Association between the Results of Maintenance of Wakefulness Test and Co-morbidity of Patients suffering from Excessive daytime sleepiness

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Abstract

Objectives: Obstructive sleep apnea (OSA) and narcolepsy cause excessive daytime sleepiness (EDS) and hypersomnia. Daytime sleepiness can be measured by the maintenance of wakefulness test (MWT). OSA and upper airway resistence syndrome (UARS) patients frequently have abnormal MWTs. Co-morbidities and medication of patients are likely to influence the results of MWT. We set out to study the association between MWT sleep latencies and patients′ background characteristics and co-morbidity.

Methods: We studied retrospectively 506 MWTs in 361 patients. MWT testing was performed between January 2006 and November 2014. We gathered also information about age, gender, BMI, smoking, snoring, waist circumference, disease burden, apnea-hypopnea index (AHI), oxygen desaturation index of 4 percentage points (ODI4) and mean oxygen saturation during a diagnostic cardiovascular polygraphy, medication, CPAP-treatment, ESS, GHQ-12 and DEPS scores and subjective sleep quality. Then we examined how sleep latiencies in the MWT were influenced by these factors.

Results: We found that professional drivers, sleep apnea patients and men were more alert than non-professional drivers, patients without sleep apnea or women, respectively. Patients suffering from long-term snoring and using almost all types of medication had worse results in MWT compared to others. Higher scores in ESS, GHQ-12 and DEPS questionnaires associated with shorter sleep latencies.

Conclusions: Gender, sleep disorder type, co-morbidity and medication influence the results of MWT.

Keywords

Maintenance of Wakefulness Test (MWT), Obstructive sleep apnea (OSA), Excessive daytime sleepiness (EDS), co-morbidity, professional drivers

Introduction

Obstructive sleep apnea (OSA) and narcolepsy are two main sleep disorders to cause excessive daytime sleepiness (EDS) and hypersomnia (1). OSA increases the risk of cardiovascular diseases, such as hypertension and coronary artery disease (2) and it is also associated with diabetes (3, 4, 5), asthma (6,7) and psychiatric diseases such as depression (8). It also increases accident likelihood (9).

Daytime sleepiness can be measured in several ways. The Epworth Sleepiness Scale (ESS) is a brief and simple questionnaire-based scale which measures the propensity to fall asleep at daytime (10). ESS, however, is a subjective test and good objective measures of vigilance are needed.

Impaired daytime alertness can be identified with the maintenance of wakefulness test (MWT) in a sleep laboratory. The response to treatment of excessive sleepiness can also be assessed with MWT. (11) MWT is a costly in-laboratory test where the patient is requested to stay awake for 40 minutes while sitting comfortably in a non-stimulating room with dim light and electroencephalography (EEG) is recorded to observe sleep onset. There are four MWT trials with two hours in between. (12)

Obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) patients frequently have abnormal MWTs (13), but it has been shown that patients treated with continuous positive airway pressure (CPAP) have better MWT results as compared to patients without treatment (14). Narcolepsy patients also seem to fall asleep faster in MWT compared to those without narcolepsy (15).

Co-morbidities and medication of patients are likely to influence the results of the MWT. Therefore, we set out to study the association between MWT sleep latencies and patients' background characteristics and co-morbidity. We wanted to know if higher co-morbidity of patients with EDS associates with worse results in the MWT.

Methods

We made a retrospective patient chart review of all patients who had undergone MWT testing in the Department of clinical neurophysiology at Turku university hospital, Turku, Finland, between January 2006 and November 2014. Clinical and diagnostic data was assessed and MWT data re-evaluated for the study.

For the MWT, a MWT40 protocol with four 40-minute recordings at 8 am, 10 am, 12 noon and 2 pm was used with the international 10-20-system EEG electrodes F3, F4, C3, C4, O1 and O2 in combination with left and right electro-oculogram and submental electromyogram, according to the AASM recommendations (11).

The patient was observed *via* digital video and a technician marked eye opening and closing on the recording online. The patients reported subjective total sleep time from the previous night before the MWT. For the evaluation of daytime somnolence, ESS, with scores over ten points out of a maximum of 24 considered abnormal, was used. The patients also filled in the General Health Questionnaire-12 (GHQ-12) (in which at least three points out of a maximum score of 12 was considered abnormal) for the evaluation of possible psychiatric disorders. Further, the patients filled in the depression questionnaire (DEPS) in which at least nine points out of the maximum score of 30 points was considered as suggestive of depression. (16)

Original MWT data were reanalyzed by an experienced clinical neurophysiologist (I.V.) defining N1 sleep latency from lights off to the appearance of theta of drowsiness of at least ten consecutive seconds' duration OR at least fifteen seconds' duration during a thirty second epoch for each recording as originally defined by Doghramji et al (12).

All in all 518 MWTs in 370 patients were found but after all 506 MWTs in 361 patients were included in the fina data set. Nine MWTs and one recording session from 3 MWTs was missing and these were rejected from the final analyses. (16) From the patient charts, we gathered all available information about age, gender, BMI, smoking, snoring, waist circumference, disease burden such as sleep apnea, hypertension, hypothyroidism, and mood disorders, apnea-hypopnea index (AHI), oxygen desaturation index of 4 percentage points (ODI4) and mean oxygen saturation during a diagnostic cardiovascular polygraphy, medication defined by ATC codes, CPAP-treatment compliance in actual hours used, ESS, GHQ-12 and DEPS scores and the best and worst subjective sleep quality in a previous sleep diary on a scale of 0-10 where 10 marks best possible quality. We then examined how the mean and minimum sleep latencies in the MWT were influenced by these factors.

Statistics

Statistical analyses were made using SPSS ver. 22 software. We used the Mann-Whitney U test to evaluate group differences in dichotomous variables such as gender, sleep apnea, basic diseases, CPAP treatment use and the use of different types of medications. We also used Spearman correlation coefficients to evaluate correlation between MWT results and the continuous variables such as age, BMI, waist circumference, snoring, cardiovascular polygraphy results, ESS, GHQ-12, and DEPS scores, and sleep quality. A p-value of <0.05 was considered statistically significant.

Ethics

The Advisory board of the Hospital District of Southwest Finland accepted this study. Database sample size was large so informed consent from the patients was not required.

Results

Most of the 361 patients were men (91,4%), professional drivers (85,3%) and sleep apnea patients (91,7%). Many of the patients had other diseases (hypertension, hypothyroidism and mood disorders) and the medication load was heavy. (Table 1)

Professional drivers had longer mean and minimum sleep latencies compared to other drivers, and men had longer mean and minimum sleep latencies compared to women. Patients who suffered from sleep apnea had longer mean and minimum sleep latencies than those suffering from other types of hypersomnia, while patients on narcolepsy medication had shorter mean and minimum sleep latencies compared to other patients. Consequently, this indicates that professional drivers, men and sleep apnea patients stayed awake better than non-professional drivers, women or other hypersomnia patients, respectively. (Table 2)

Patients with hypertension had longer mean and minimum sleep latencies as compared to patients without hypertension. The use of cardiovascular medication was also associated with longer mean sleep latencies and the use of statins was associated with longer mean and minimum sleep latencies. Patients with hypothyroidism had shorter mean and minimum sleep latencies as compared to others. Shorter mean sleep latencies were also associated with mood disorders and the use of antidepressants. Patients who used neuropsychiatric medication had shorter minimum sleep latencies as compared to the others. This indicates that patients having cardiovascular diseases seem to be more alert compared to others. Instead other co-morbidities and almost all other medication use seem to cause increased tiredness. (Table 2)

No correlation was found between MWT results and age, BMI or waist circumference. Nor were any correlations observed between MWT results and AHI, AHI in supine position, ODI4, mean or minimum oxygen saturation during a diagnostic cardiovascular polygraphy, smoking load in packet years, CPAP pressure, maximum or minimum duration of sleep or best sleep quality in the preceding sleep diary and the duration of sleep during the preceding night. (Table 3)

There was a significant correlation between shorter minimum and mean sleep latencies and duration of snoring, indicating that long term snorers are less alert. Logically longer CPAP using hours, as well as lower ESS, GHQ-12, and DEPS scores correlated with longer minimum and mean sleep latencies. In addition, there was a correlation between a better score of worst sleep quality in the sleep diary and longer minimum and mean sleep latencies. This indicates patients who slept worse before testing performed also worse in the MWT. (Table 3)

Discussion

In this large retrospective study of patients suffering from excessive daytime sleepiness undergoing MWT vigilance test, we found that professional drivers, sleep apnea patients and men were more alert than non-professional drivers, patients without sleep apnea or women, respectively. Long-term snoring and almost all types of medication for comorbidities worsened the MWT results. Also, higher scores in ESS, GHQ-12 and DEPS questionnaires were associated with shorter sleep latencies.

We found that non-professional drivers fell asleep faster in MWT compared to professional drivers, when patients had EDS. Previously Anund et al. found that professional drivers had longer blink durations and more line crossings while driving in a simulator compared to non-professional drivers, indicating that professional drivers were sleepier than others in the driving simulator test (17). MWT and driving simulator are two completely different tests which probably explain the difference.

In our study sleep apnea patients had longer sleep latencies than other hypersomnia patients. We also found that patients using narcolepsy medication had shorter sleep latencies compared to those who did not. Previous research has also found that untreated narcolepsy patients performed significantly worse in a driving simulator test than untreated sleep apnea patients (18). Our data included 331 sleep apnea patients and 29 patients had some other form of hypersomnia (including narcolepsy). In the sleep apnea patient group, we found a significant correlation between CPAP using hours and longer sleep latencies indicating a good treatment effect. Indeed, previous data shows that CPAP treatment lengthens MWT sleep latencies by 2.1 minutes. (19)

Women had shorter sleep latencies than men according to our results. Mitler et al studied 530 narcolepsy patients (239 men and 291 women) and found no difference in MWT sleep latencies between men and women (15). Our gender distribution, however, was not equal, which could have resulted in a sample bias.

Self-reported snoring has been shown to be a symptom of sleep apnea (20). In our data the longer snoring time in years correlates with shorter sleep latencies. So it seems that patients who have suffered from snoring, with or without sleep apnea, for a longer time also have a more severe sleep apnea syndrome as measured with daytime sleepiness. We also found that if a patient reported better "worst sleep quality" in sleep diary it correlated with longer sleep latencies. It indicates that patients who had slept better before testing could stay awake significantly better in MWT than those who had slept worse.

OSA increases the risk of having cardiovascular diseases (21). Previous research has found an association between hypertension and objective daytime sleepiness in patients with OSA (22). Ren et al. also concluded that OSA patients who reported shorter sleep duration were more likely to have hypertension that others (23). In addition, previous research has found some synergistic adverse effects on the cardiovascular system if a patient suffers from both hypertension and OSA (24). Surprisingly, we found that cardiovascular medication, statins and hypertension were associated with longer sleep latencies. This could be explained by the previous finding that OSA patients having insomnia-like symptoms and suffering from nocturnal hypoxemia also seem to have more cardiovascular comorbidity (25). One could hypothesize that OSA patients with cardiovascular diseases have insomnia-like symptoms more often than expected.

In our data, 57 patients reported using antidepressants but only 48 patients had mood disorders. This could be explained by the various indications of antidepressants (for example patients using antidepressant as a hypnotic.) We found that patients using antidepressants and neuropsychiatric medication had shorter sleep latencies. A study performed in the United States compared MWT results between patients with depression and patients with sleep apnea. They found that if depressed patients slept more poorly their level of alertness rose during daytime. On the other hand, the more the sleep of sleep apnea patients was disturbed the more they had difficulties in maintaining daytime alertness. (26) Many of our patients had both sleep apnea and depression and it seems that combination of these two diseases impairs their daytime alertness.

Hypothyroidism is very uncommon in OSA patients (27) but hypothyroid patients often seem to have disordered breathing (28). Our results showed that hypothyroidism and the use of thyroxin are associated with shorter sleep latencies.

Previous studies have found no high correlation between ESS and MWT (29, 30, 31). Sforza et al tested sixty patients who suffered from snoring or OSA with HAD (the Hospital Anxiety and Depression Scale), TCI (the Temperament and Character Inventory), MWT and ESS. They found that higher depression scores were associated with impaired daytime alertness as measured with MWT. (32) Our results indicate a statistically significant correlation coefficient between lower ESS, GHQ-12, and DEPS scores and longer sleep latencies. However, scatterplots (appendix) show that ESS, GHQ-12, and DEPS scores are widely scattered around the fitted linear regression line, giving no constant correlation.

The main advantage in our study is the large sample size. Our patients were aged between 18-81 years, so the age range was wide, increasing the generalizability of our results, especially in sleep apnea patients. Comorbidity was high and medication load as well in our group, which indicates that patients needing an MWT represent a group of patients who are heavy users of the health care system.

There are also some limitations in our study. Because of our retrospective study design, patient information was not evenly or consistently recorded in the patient information. Our study group included 330 men and 31 women, so the gender differences in our results should be estimated with caution.

Conclusions

We conclude that professional drivers seem to be more alert in the daytime as compared to other patients. Women performed worse in MWT compared to men. Sleep apnea patients were more alert than other hypersomnia patients and especially CPAP treatment seemed to improve their alertness. Patients who had snored longer were sleepier than others. Almost all medication, except for cardiovascular medication, statins and euphorizing analgesics, seemed to reduce daytime alertness. Statistically significant correlation was found between higher ESS, GHQ and DEPS scores and shorter MWT sleep latencies but the figures showed that relationship between these variables is not straightforward.

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Table 1. Descriptive statistics.

		N (%) /mean (SEM)
Demographics		
	Gender: male	330 (91,4 %)
	Age (yrs) (N=361)	49,4 (0,5)
	BMI (kg/m2) (N=353)	33,4 (0,4)
	Smokers	164 (45,4%)
	Waist circumference (cm) (N=203)	116,9 (1,2)
	Professional drivers	308 (85,3 %)
Comorbidity and medication		
	Snorers	44 (12,2%)
	Snored (yrs) (N=145)	14,5 (0,8)
	OSAS	331 (91,7%)
	Hypertension	138 (38,2%)
	Hypothyroidism	19 (5,3%)
	Mood disorder	48 (13,3%)
	Cardiovascular medication	158 (43,8%)
	Statins	82 (22,7%)
	Thyroxin	19 (5,3%)
	Stimulants / narcolepsy medication	12 (3,3%)
	Antidepressants	57 (15,8%)
	Euphorizing analgetics	11 (3,0%)
	Other neuropsychiatric medication	25 (6,9%)
OSA patient characteristics		
	AHI (events/h) (N=326)	28,4 (1,4)
	ODI4 (events/h) (N=295)	23,9 (1,5)
	CPAP use	261 (72,3% of all patients)
	CPAP use time (hh:mm) (N=240)	4:53 (0:09)
	CPAP pressure (cmH_2O) (N=256)	10,8 (0,2)
Pre-MWT evaluation of sleepiness		
	ESS (pts) (N=352)	6,5 (0,2)
	GHQ (pts) (N=343)	1,9 (0,2)
	DEPS (pts) (N=236)	5,2 (0,4)
	Sleep quality (min) (N=258)	5,7 (0,1)
	Sleep quality (max) (N=258)	8,2 (0,1)

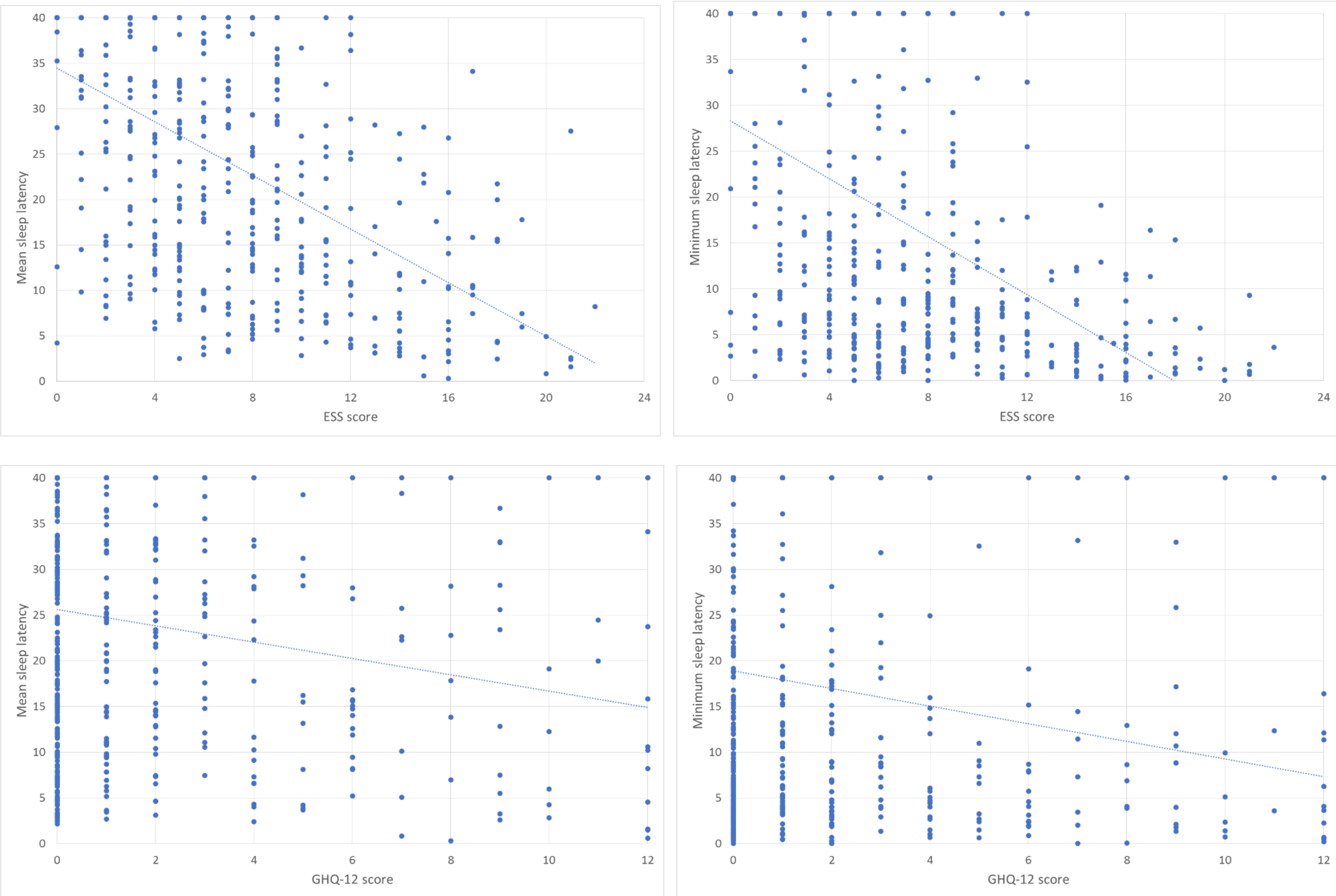
Table 2 Effects of demographics, comorbidity and medication on sleep latencies. (Mean (SEM))

	Mean sleep latency (mm:ss)			Minimum sleep latency (mm:ss)		
	Yes	No	P	Yes	No	P
Gender /male	27:43 ± 0:40	20:44 ± 0:51	***0.000***	20:44 ± 0:51	11:23 ± 2:14	***0.001***
Professional driver	28:26 ± 0:40	18:09 ± 1:44	***0.000***	21:16 ± 0:52	12:13 ± 1:57	***0.000***
Sleep apnea as cause of hypersomnia	27:37 ± 0:40	19:07 ± 2:17	***0.001***	20:34 ± 0:50	12:50 ± 2:35	***0.004***
Comorbidity						
Hypertension	29:11 ± 0:58	25:32 ± 0:51	***0.006***	22:11± 1:19	18:33 ± 1:01	***0.014***
Coronary artery disease	27:20 ± 3:27	26:55 ± 0:39	***0.948***	20:26 ± 4:19	19:55 ± 0:50	***0.007***
Hypothyroidism	20:04 ± 2:42	27:19 ± 0:40	***0.014***	10:47 ± 2:43	20:27 ± 0:50	***0.007***
Mood disorder	23:29 ± 1:45	27:28 ± 0:41	***0.034***	16:26 ± 1:58	20:28 ± 0:53	0.189
Medications						
Thyroxin	21:45 ± 2:43	27:13 ± 0:40	0.053	12:05± 2:49	20:22 ± 0:50	***0.020***
Statins	29:19 ± 1:16	26:14 ± 0:44	***0.038***	22:31± 1:41	19:11± 0:55	***0.042***
Antidepressants	23:46 ± 1:38	27:31 ± 0:42	***0.021***	16:09 ± 1:48	20:39 ± 0:54	**0.068**
Stimulants /narcolepsy medication	17:47 ± 3:40	27:14 ± 0:39	***0.015***	10:48 ± 4:02	20:15± 0:49	***0.018***
Euphorizing analgesics	22:54 ± 3:42	27:04 ± 0:39	0.207	13:29 ± 3:17	20:08 ± 0:50	0.293
Other neuropsychiatric medication	22:05 ± 2:43	27:17 ± 1:16	0.059	14:50 ± 3:11	20:19 ± 1:36	***0.027***
Cardiovascular medication	28:34 ± 0:55	25:40 ± 0:53	***0.033***	21:13 ± 1:14	18:56 ± 1:04	0.137

Table 3. Correlations between continuous variables and sleep latencies.

	N	Mean sleep latency		Minimum sleep latency	
		r	P	r	P
Age (years)	361	0.059	0.267	0.022	0.677
BMI (kg/m^2)	353	0.010	0.852	-0.006	0.910
Waist circumference (cm)	203	-0.087	0.219	-0.110	0.119
Smoking (packet years)	164	-0.002	0.976	-0.038	0.630
Snoring (years)	145	-0.215	***0.009***	-0.220	***0.008***
AHI (events / h)	326	0.059	0.286	0.061	0.274
AHI supine (events / h)	260	0.036	0.563	0.026	0.681
ODI4 (events / h)	295	0.041	0.485	0.036	0.538
Mean SpO_2	332	-0.082	0.132	-0.066	0.228
Minimum SpO_2	309	0.006	0.922	0.017	0.763
CPAP daily time of use (h)	240	0.152	***0.019***	0.159	***0.014***
CPAP pressure (cmH_2O)	262	0.014	0.824	0.032	0.601
Sleep diary					
Best sleep quality (pts, 0-10)	258	0.072	0.248	0.081	0.197
Worst sleep quality (pts, 0-10)	258	0.157	***0.012***	0.159	***0.010***
Maximum sleep duration (h)	139	-0.020	0.815	-0.002	0.985
Minimum sleep duration (h)	138	-0.054	0.527	-0.034	0.693
Sleep time during preceding night (h)	302	0.016	0.781	-0.018	0.760
ESS	352	-0.453	***0.000***	-0.432	***0.000***
GHQ-12	343	-0.276	***0.000***	-0.274	***0.000***
DEPS	236	-0.215	***0.001***	-0.195	***0.003***

BMI = Body mass index, AHI = Apnea-hypopnea index, ODI4 = Oxygen desaturation index of > 4 percentage points, ESS = Epworth sleepiness scale, GHQ-12 = General Health Questioinnaire-12, DEPS = Depression Scale
Sleep quality assessed as 0 = worst possible sleep quality, 10 = best possible sleep quality


Mean sleep latency
ESS score
Minimum sleep latency
ESS score
Mean sleep latency
GHQ-12 score
Minimum sleep latency
GHQ-12 score

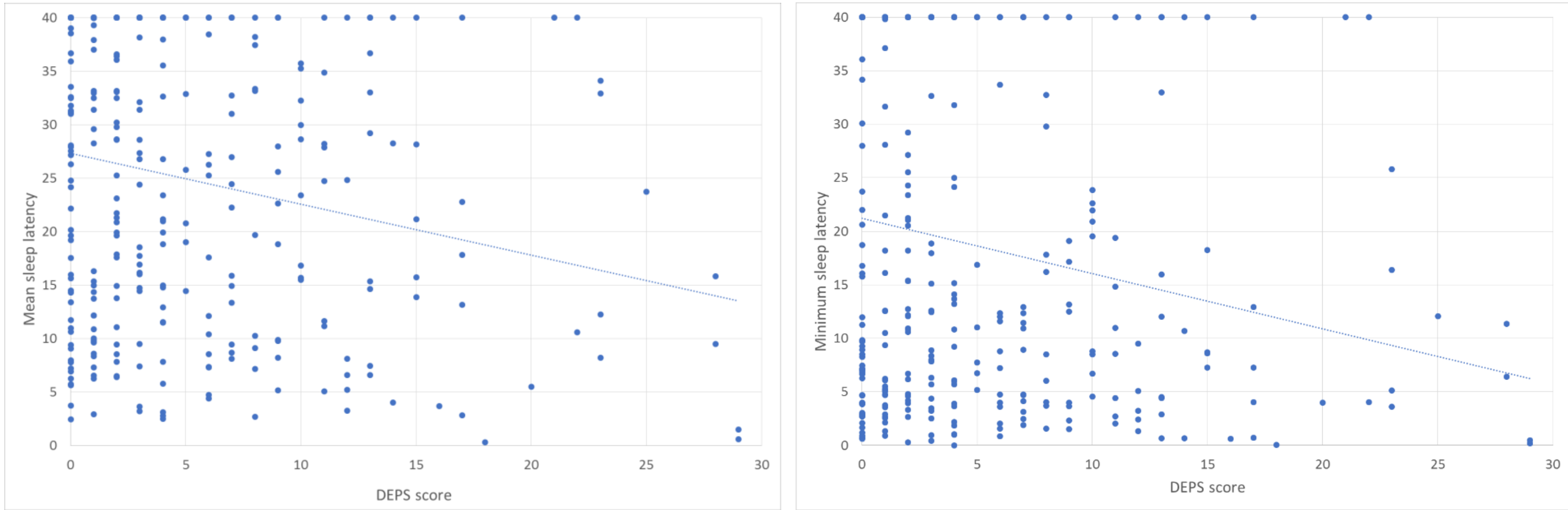


Figure. MWT sleep latencies vs. ESS, GHQ-12, and DEPS scores, scatterplots and correlation graphs.