psychiatry international

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Supplement Table S1: Overnight PSG's compared (n=43): sleep movement parameters

	Night 1	Variability (%)	Night 2	Variability (%)	t-test dependent samples(12)	p-value
PLMS index, n/hr	17.8 ± 32.5	182.1	26.1 ± 39.9	153.0	-3.0	0.005
PLMS, n	111.7 ± 258.0	231.0	171.3 ± 305.6	178.4	-3.3	0.002
PLMS micro-arousal index, n/hr	2.3 ± 3.2	139.8	3.2 ± 4.4	140.0	-1.5	0.135
PLMS average interval, s	31.6 ± 15.1	47.7	30.1 ± 16.2	53.9	0.6	0.576
PLMW index, n/hr	2.5 ± 8.4	334.4	2.2 ± 4.9	222.4	0.2	0.830
PLMW, n	2.8 ± 10.8	386.8	2.0 ± 3.4	172.2	0.5	0.651
PLMW average interval, s	8.1 ± 19.1	235.3	11.3 ± 23.7	210.3	-0.7	0.482
PLMS series TST,%	10.9 ± 14.7	134.8	16.6 ± 19.6	118.2	-2.7	0.011
PLMS series N1,%	10.5 ± 13.8	131.7	15.9 ± 17.5	110.2	-2.8	0.007
PLMS series N2,%	11.9 ± 16.6	139.4	18.6 ± 23.3	124.9	-2.6	0.014
PLMS series N3,%	3.4 ± 12.1	351.9	1.6 ± 6.1	377.3	0.9	0.353
PLMS series REM,%	3.6 ± 9.8	271.0	6.2 ± 13.5	219.4	-1.6	0.118

Based on the adjusted p-value of ≤0.001 in bold are the significant results. Data are presented as mean±SD unless otherwise indicated. The variability is expressing the dispersion of the measure (%). **PLMS** = periodic limb movements during sleep; **PLMS series:** percentage of the different sleep stages associated with PLM; **PLMW**= periodic leg movements during wakefulness; **TST**=total sleep time; **N1-N3**: sleep stage; **REM**: rapid eye movement sleep

Supplement Table S2: Standard sleep study parameters of the clusters

	Total (n=33)	**Cluster 1** (n=17)	**Cluster 2** (n=16)	**Mann-Whitney U test**	**p-value**
Age, years	57.9±15.8	62.3±16.1	53.3±14.5	1.6	0.101
Male/female, n	22/11	13/4	9/7	$\chi^2(1)= 1.5$	0.218
Total sleep time, min.	379.6±107.4	410.6±121.8	346.7±81.0	1.7	0.087
Sleep efficiency, %	75.8±15.2	79.0±15.6	72.4±14.6	1.5	0.145
Sleep quality, %	16.8±8.7	13.7 ± 8.1	20.1±8.3	-2.0	0.042
Sleep latency, min.	24.4±24.7	22.7 ±26.5	26.1±23.4	-0.8	0.428
REM sleep latency, min.	125.9±94.1	117.7±100.7	141.0±87.2	-1.4	0.177
Wake after sleep onset, min.	75.4±59.2	59.0±55.6	92.9±59.6	-2.3	0.024
Arousals, n	92.2±69.6	110.1±89.0	73.1±33.7	0.8	0.449
Stage N1, %	22.6±13.9	23.0±12.5	22.1±15.6	0.4	0.679
Stage N2, %	60.7±12.8	63.3±13.5	57.9±11.8	1.3	0.189
Stage N3, %	3.4±4.9	2.0±3.6	5.0±5.7	-1.9	0.051
REM, %	13.3±5.7	11.6±5.8	15.1±5.3	-1.8	0.075
Total AHI, n/hr	17.9±17.4	19.0±16.7	16.8±18.5	0.4	0.679‡
Snore index, /hr	11.8±26.8	16.5±30.4	6.8±22.2	1.4	0.165
O_2 saturation nadir, %	93.3±1.6	93.5±1.5	93.1±1.7	0.3	0.787
PLMS index, n/hr	13.1±14.0	20.1±16.0	5.6±5.4	2.9	0.004‡
PLMS, n	71.2±78.4	113.4±88.3	26.4±25.4	2.8	0.005‡
PLMS micro-arousal index, n/hr	1.8±2.6	2.9±3.2	0.7±1.2	2.5	0.014‡
PLMS average interval, s	31.8±15.4	32.6±14.3	30.9±16.9	0.2	0.815
PLMW index, n/hr	1.6±4.4	2.6±5.9	0.6±1.8	1.0	0.341
PLMW, n	1.4±2.8	1.8±3.1	1.0±2.5	0.7	0.465
PLMW average interval, s	7.4±16.3	9.1±17.2	5.6±15.7	0.7	0.503
PLMS series TST,%	9.2±16.3	14.4±11.5	3.7±3.5	2.9	0.004‡
PLMS series N1,%	8.1±8.1	13.0±8.3	2.8±3.3	3.5	**0.0000**‡
PLMS series N2,%	10.3±12.3	15.7±14.7	4.5±5.0	2.3	0.021
PLMS series N3,%	4.5±13.7	6.0±17.7	2.9±7.9	0.4	0.665
PLMS series REM,%	2.1±5.0	2.9±4.7	1.3±5.3	2.1	0.037

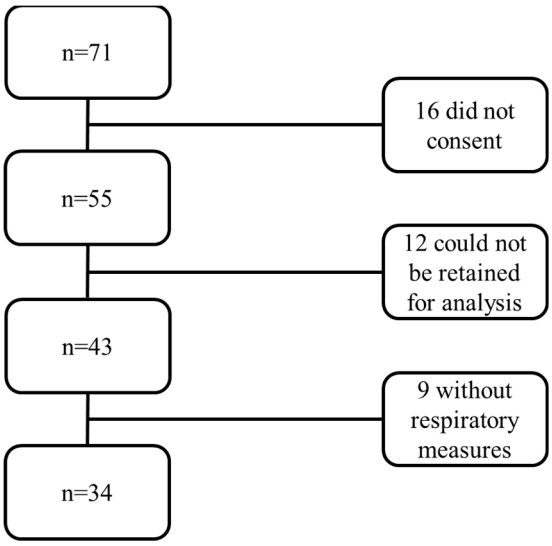
In bold the significant results based on the adjusted p-value of ≤0.001. ‡ per Mann-Whitney U test, in contrast to the previous Cluster analysis, same result. Data are presented as mean ± SD unless otherwise indicated. **AHI** = apnea-hypopnea index; **N1-N3**: sleep stage % of total sleep time; **PLMS** = periodic limb movements during sleep; **PLMS series:** percentage of the different sleep stages associated with PLM; **PLMW**= periodic leg movements during wakefulness; **REM**: rapid eye movement sleep; **TST**= total sleep time; **WASO** = wake after sleep onset.

Supplement Table S3: Overview of the samples investigated

Sample size	**n = 43** (all G25.81/333.94)		
Sample size in cluster analysis	**n = 33** (excluding F41.2/309.28 as outlier)		**Not in cluster analysis (n = 9)**
Groups	**Cluster 1**	**Cluster 2**	
ICD-10 diagnoses	F20+F33 (n=1); F31.2 (n=1); F33 (n=9); F33+F60.9 (n=1); F41.1 (n=3); F41.2 (n=2)	F31.2+F41.1+F60.9 (n=1); F33+F41.1 (n=2); F41.1 (n=4); F41.2 (n=8); F60.9 (n=1)	F31.2 (n=1); F31.2+F60.9 (n=1); F33 (n=1); F33+F60.9 (n=1); F41.1 (n=2); F41.1+F60.9 (n=1); F41.2 (n=2)
DSM-5 diagnosis	295.9; 296.31; 296.44; 300.02; 301.9; 309.28 and combinations	300.02; 301.9; 309.28 and combinations	296.31; 296.44; 300.02; 309.28 and combinations
Medication*	Alprazolam; Clomipramine; L-Dopa; Levothyroxine; Parkinane; Pramipexol; Risperidone; Sertraline; Silodosine; Solian; Telmisartan; Trazodone; Zopiclone	Effexor; Lexomil; Loxapine; Mirtazapine	Clomipramine; Clozapine; Cyamemazine; Effexor; Lamotrigine; Pramipexol;Quetiapine; Zopiclone

(+) = dual diagnosis, primary + secondary ; *several patients are on multidrug treatments

Supplement Figure S1: Flowchart of patients included in our study

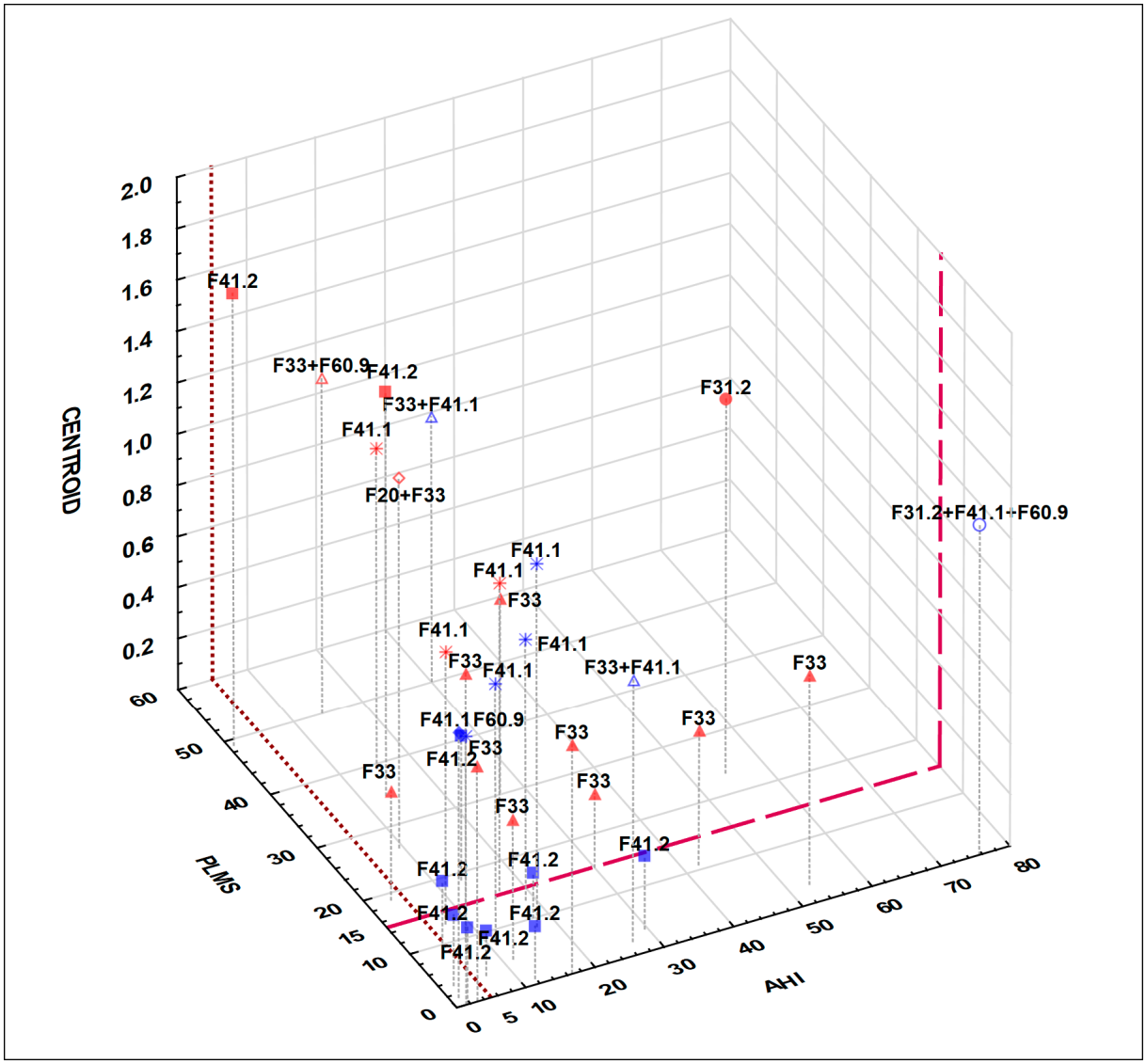


We started with the retrospective collection of sleep data that was consented by a population with newly diagnosed RLS at the time of their sleep recording. This sample is 55 subjects. Data of 12 subjects could not be used.

The sleep data (between 2016 to 2019) of newly diagnosed RLS subjects of whom the sleep study was performed at the time of diagnosis, was collected by the authors in a psychiatric setting, in contrast to data collected from a psychiatric patient attending a sleep clinic. We also extracted the psychiatric diagnosis, somatic condition and medication information available at the time of PSG. This was done for 55 consented records, of which 43 subjects remained for further analysis.

Next, we analyzed the available sleep data from a sleep perspective:
1. The standard clinical approach: Associative risk of sleep disordered breathing and RLS; PLM were scored in several ways per WASM guidelines. This was done for 43 subjects, except that respiratory assessment was only available in 34.
The impact of this missing data is analyzed separately. Because we had two nights of sleep recording available, we opted for the most complete dataset.
2. The datamining approach with cluster analysis: In the statistical analysis of step 1, the relationships between the psychiatric state, a comorbid somatic issue or medication is not considered. However in step 2, the data mining approach, these relationships are considered. Datamining was done on the 34 subjects, except here 1 subject was an outlier for which cluster analysis is sensitive and hence the subject was excluded. The significant sleep variables from approach 1 were used in step 2, showing significant differences between two 'datamined' subgroups.
Lastly, because this is a retrospective analysis of clinical data, we performed several post hoc analysis (i.e. the sensitivity analysis) to test the robustness of our statistical outcomes.

Supplement Figure S2: Distance from the individual cluster centroid, plotted against the PLMS and AHI



Red color = Cluster 1 and Blue color = Cluster 2. This scatterplot illustrates that for instance the F41.2 belonging to cluster 1 have not only higher PLMS (versus those in Cluster 2) but are further away from their Cluster 1 centroid. Remember, clustering aims at maximal homogeneity with in the cluster, so the closer to their centroid the more "similar" cases are.
Dashed line denotes the PLMS cut-off of 15, and the AHI cut-off of 5, as reference lines.