Narcolepsy, Depression, and REM Suppressing Antidepressants: Comorbidity & Confound Impacts on Sleep Architecture and Diagnostic Sensitivity

Chris Fernandez, MSc*, Sam Rusk, BSc*, Yoav Nygate, MSc*, Nathaniel F. Watson, MD, MSc**, James Herdegen, MD***

* EnsoData Research, Ensodata, Madison, WI, USA, ** Department of Neurology, University of Washington School of Medicine, Seattle, WA, *** Rush University Medical Center
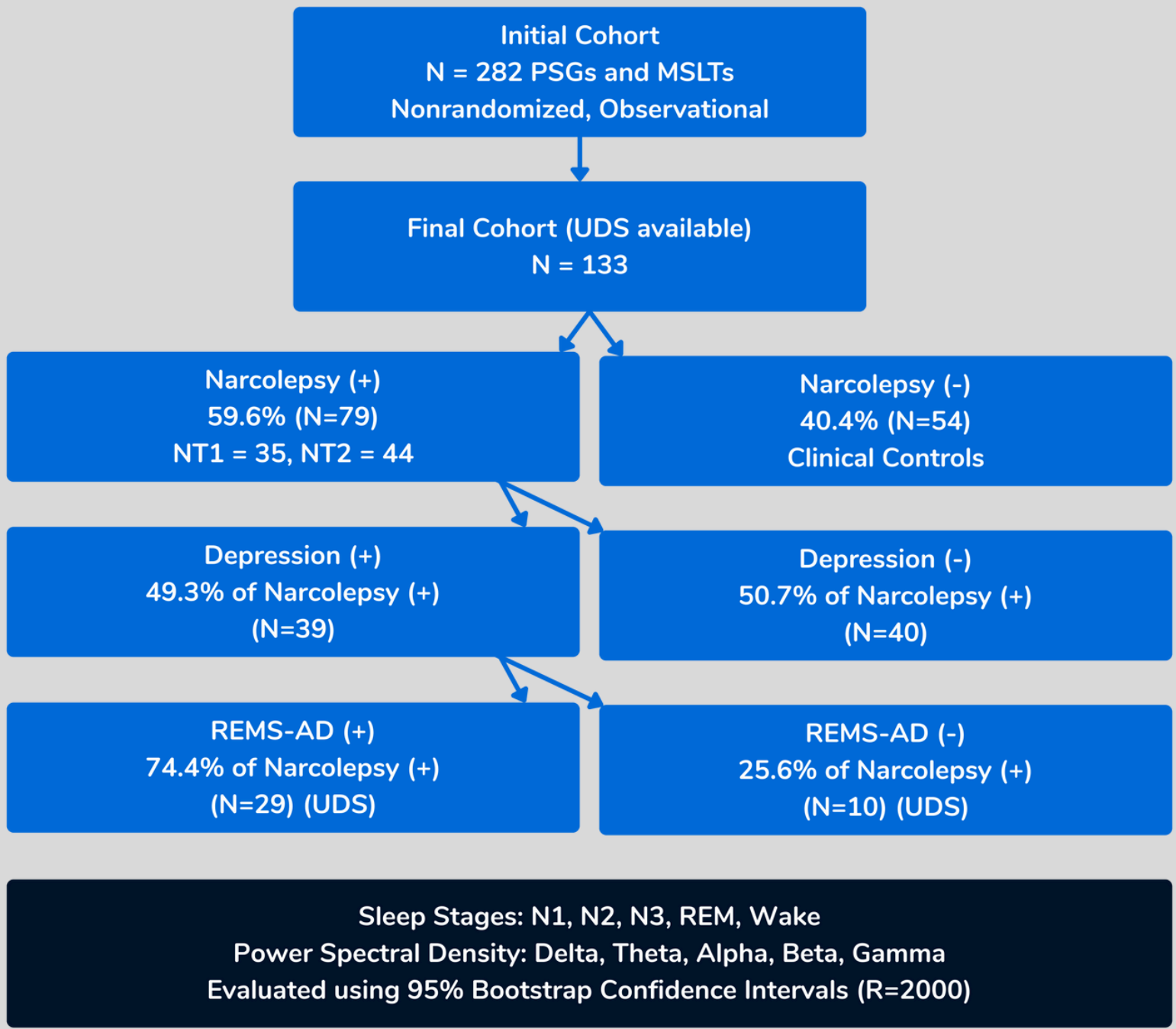
Introduction

Systematic reviews and meta-analyses showed a 32%-57% prevalence of Depression or depression symptoms in patients with Narcolepsy disorders. MSLT protocols recommend a drug washout period of ≥14-days for antidepressants and other medications known to confound sleep architecture and REM sleep. Patient noncompliance with washout protocols for REM-suppressing antidepressants (REMS-AD) was found to reduce the incidence of SOREMP observations in MSLTs by ≥89% compared to washout-compliant patients. Prior studies demonstrated potential for improvements in Narcolepsy diagnostic sensitivity and reproducibility by exploiting more comprehensive analysis of full-night polysomnography (PSG) signals, through deep learning-based AI models (ROC-AUC 0.96) and algorithmic approaches. Prior research characterized Narcolepsy-specific microarchitectural sleep EEG abnormalities that manifest in Sleep Latency (SL), REM (Latency (REML), median/minimum duration, density, prevalence), N3 (time/prevalence), hypnodensity characteristics, and separately, Depression-specific state and trait EEG markers including low Delta Sleep Ratio (DSR), high/oscillatory Gamma, and high/asymmetric Alpha. Few works examine the extent of confounds to Narcolepsy diagnostic parameters from Depression comorbidity with and without the specific influence of REMS-ADs.

Materials & Methodology

A nonrandomized, observational, de-identified cohort of N=282 PSGs were collected from subjects that underwent MSLT immediately following the PSG. Excluding subjects without UDS results, the final cohort (N=133) was composed of 59.6% Narcolepsy(+) subjects (N=35 NT1, N=44 NT2), and 40.4% Narcolepsy(-) Clinical Controls subjects. 47.9% of subjects had a documented Depression diagnosis, 52.1% with verified absence of Depression diagnostic history, and a 49.3% rate of comorbid Depression in Narcolepsy. The sample included N=39 subjects that were Narcolepsy(+)/Depression(+) for comparison to N=40 Narcolepsy(+)/Depression(-) subjects.
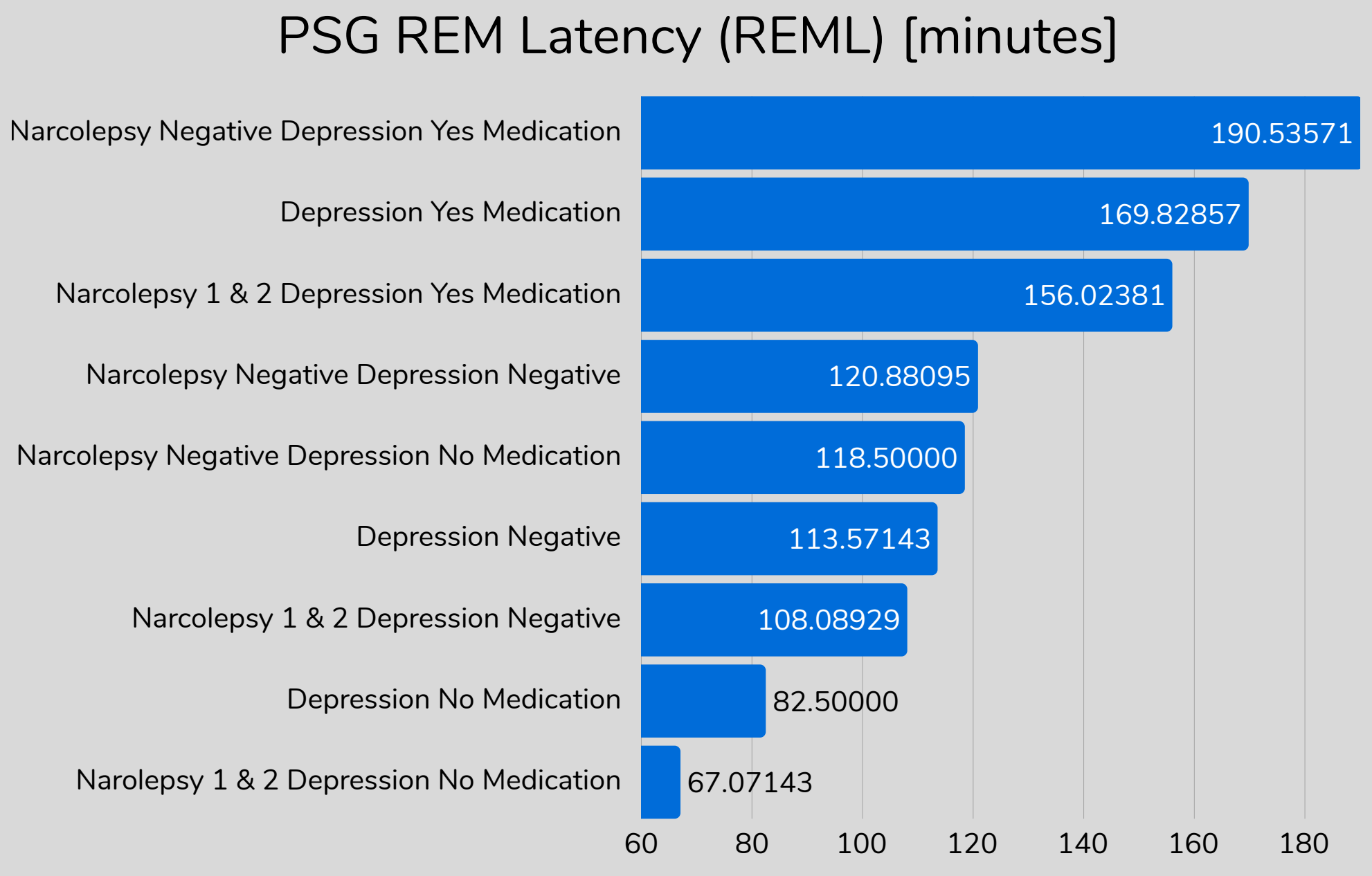
Materials & Methodology Continued

Among Narcolepsy(+)/Depression(+), N=29 were REMS-AD(+) and N=10 REMS-AD (-) confirmed by UDS. Mean latency, density, and prevalence were calculated for sleep stages (N1, N2, N3, REM, Wake, All-Stages), mean power spectral densities and ratios were calculated (Delta, Theta, Alpha, Beta, Gamma), then evaluated for differences and statistical significance in mean diagnostic parameter values based on two-sided 95% bootstrap median-percentile method Confidence Intervals (R=2,000).

Initial Cohort
N = 282 PSGs and MSLTs
Nonrandomized, Observational

Final Cohort (UDS available)
N = 133

| Narcolepsy (+) 59.6% (N=79) NT1 = 35, NT2 = 44 | Narcolepsy (-) 40.4% (N=54) Clinical Controls |

| Depression (+) 49.3% of Narcolepsy (+) (N=39) | Depression (-) 50.7% of Narcolepsy (+) (N=40) |

| REMS-AD (+) 74.4% of Narcolepsy (+) (N=29) (UDS) | REMS-AD (-) 25.6% of Narcolepsy (+) (N=10) (UDS) |

Sleep Stages: N1, N2, N3, REM, Wake
Power Spectral Density: Delta, Theta, Alpha, Beta, Gamma
Evaluated using 95% Bootstrap Confidence Intervals (R=2000)
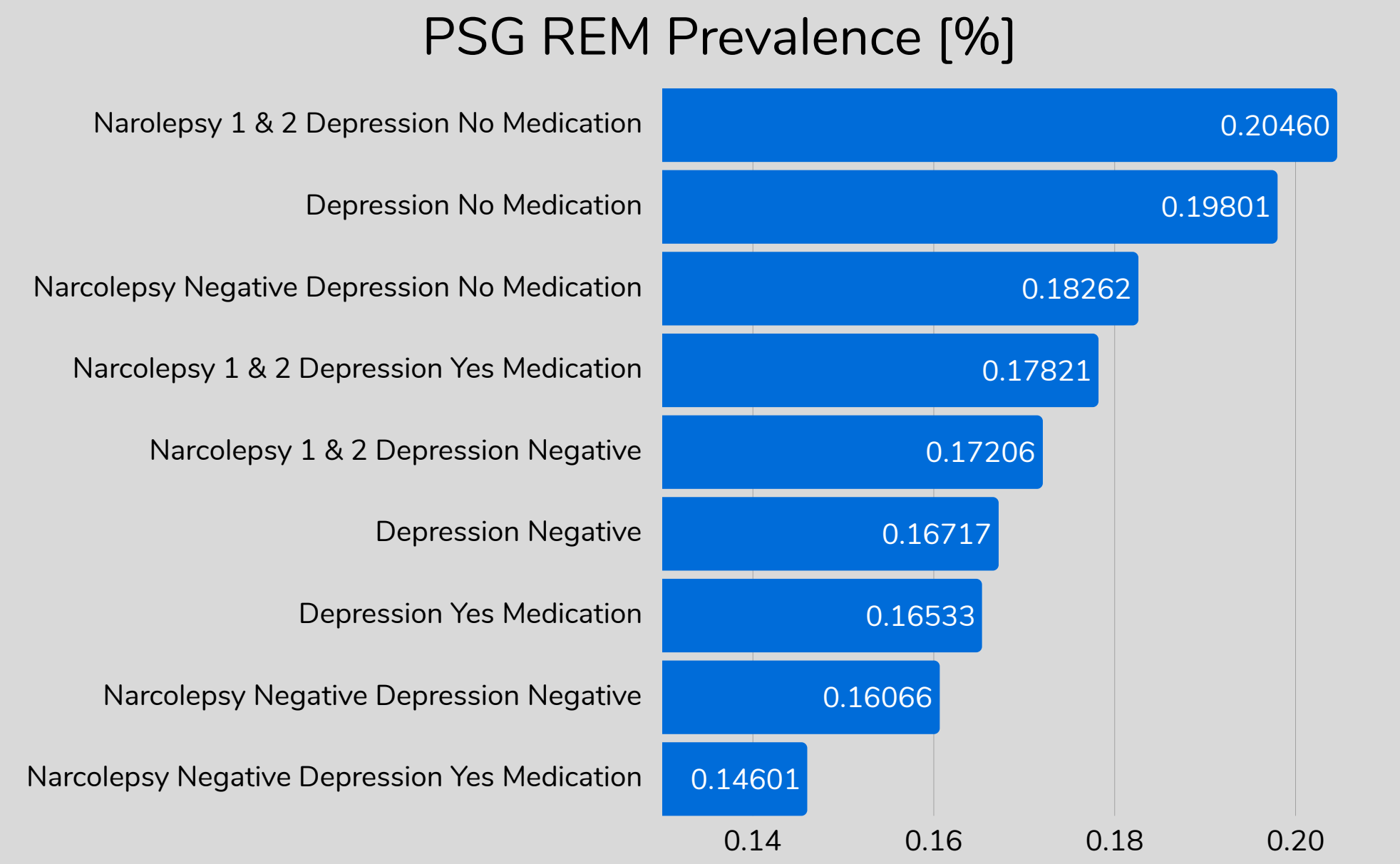
Results

In NT1, NT2, and CC, Mean REML was shortest in MDD(+)/REM-AD(-) subjects (NT1/NT2: 67mins (54mins, 77mins), CC: 118mins (97mins, 125mins)), the longest in MDD(+)/REM-AD(+) subjects (NT1/NT2: 156mins (115mins, 203mins), CC: 190mins (133mins, 247mins)), with MDD(-) subjects falling between (NT1/NT2: 108mins (93mins, 125mins), CC: 120mins (94mins, 152mins)).

PSG REM Latency (REML) [minutes]

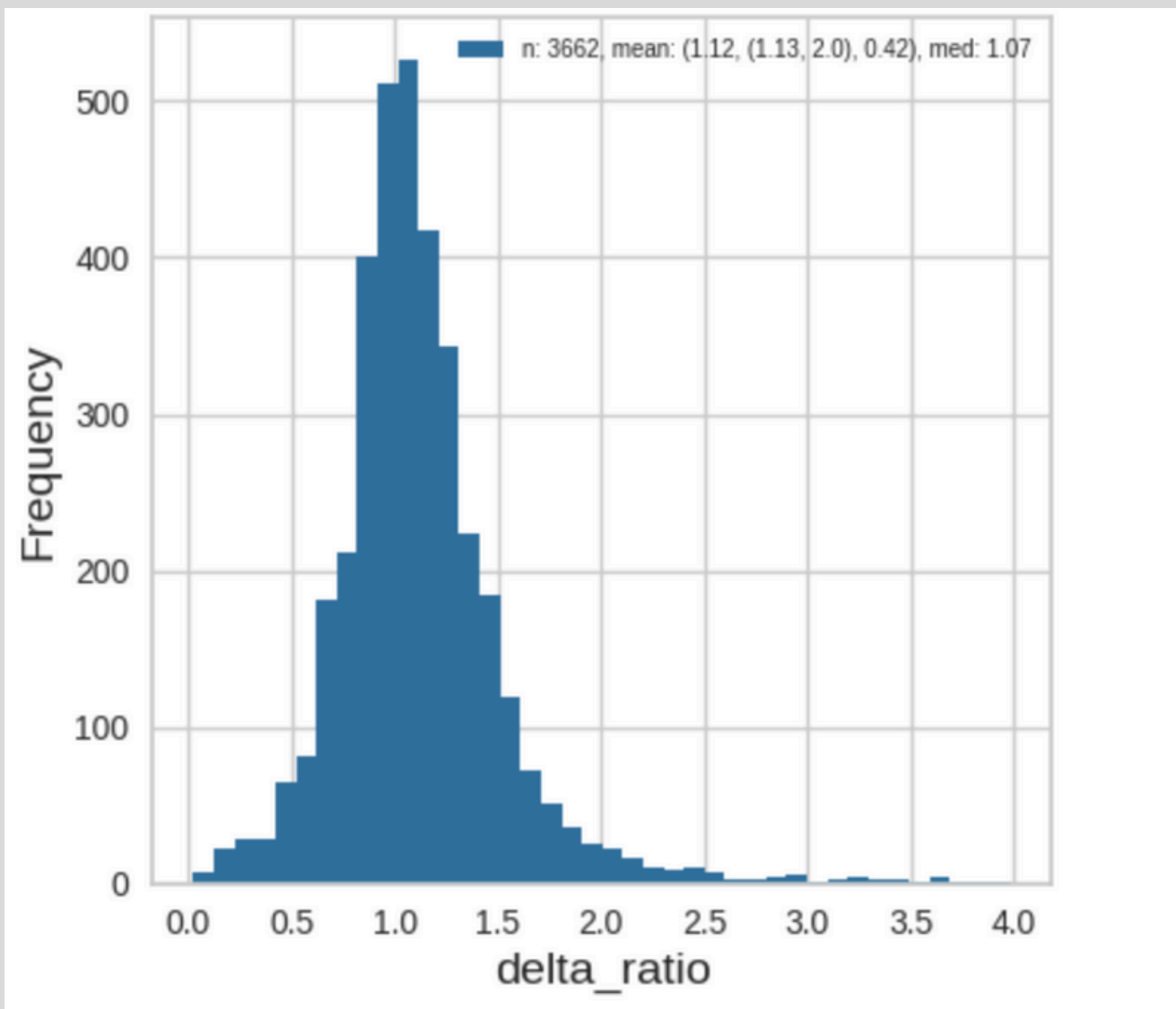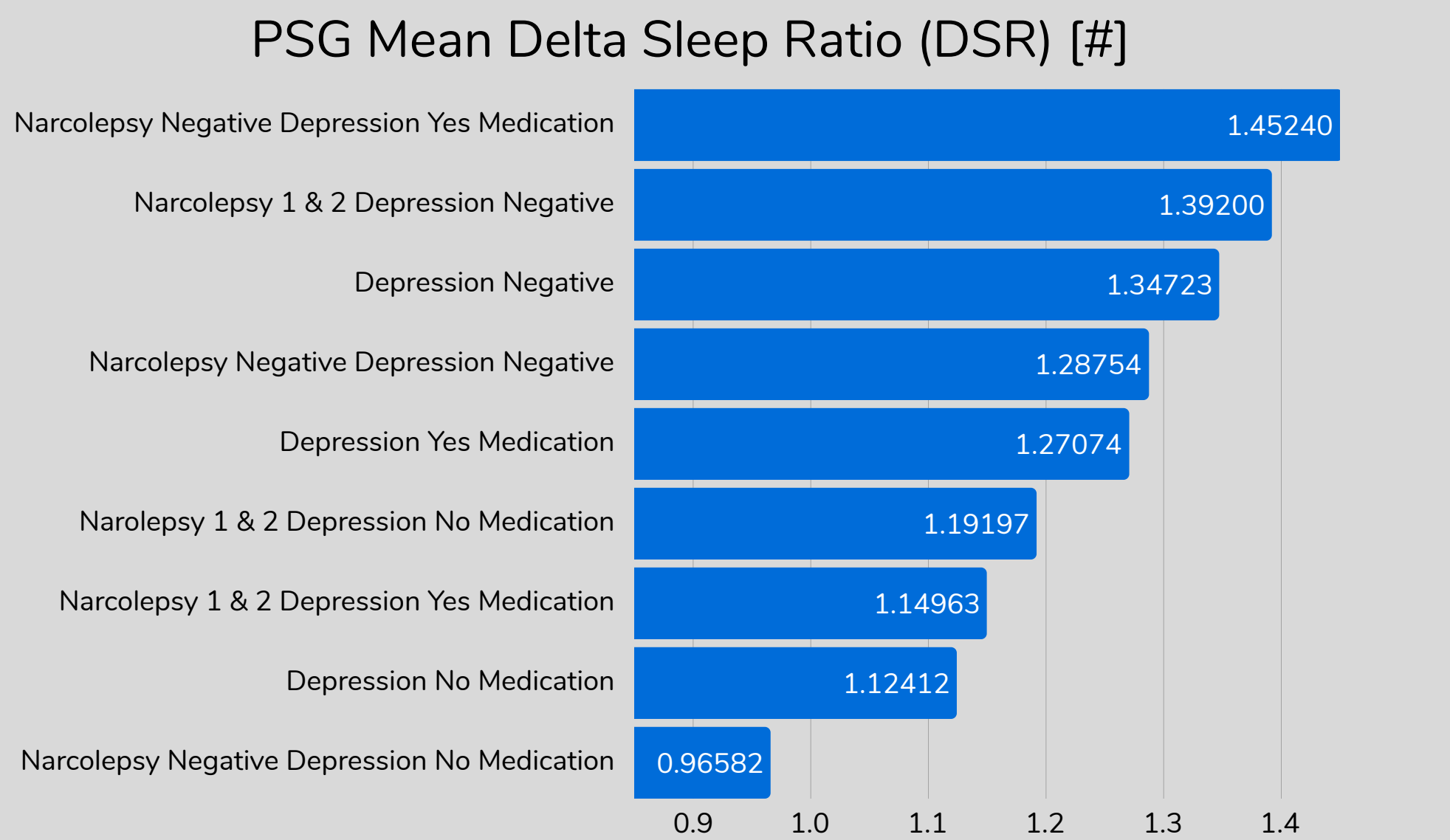| Category	Value
Narcolepsy Negative Depression Yes Medication	190.53571
Depression Yes Medication	169.82857
Narcolepsy 1 & 2 Depression Yes Medication	156.02381
Narcolepsy Negative Depression Negative	120.88095
Narcolepsy Negative Depression No Medication	118.50000
Depression Negative	113.57143
Narcolepsy 1 & 2 Depression Negative	108.08929
Depression No Medication	82.50000
Narcolepsy 1 & 2 Depression No Medication	67.07143

Results Continued

In both Narcolepsy and CC, Mean REM density was highest in MDD(+)/REM-AD(-) subjects (NT1/NT2: 111mins (88mins, 128mins), CC: 97mins (91mins, 105mins)), and substantially reduced in MDD(+)/REM-AD(+) subjects (NT1/NT2: 101mins (87mins, 113mins), CC: 82mins (62mins, 104mins)).

PSG REM Prevalence [%]

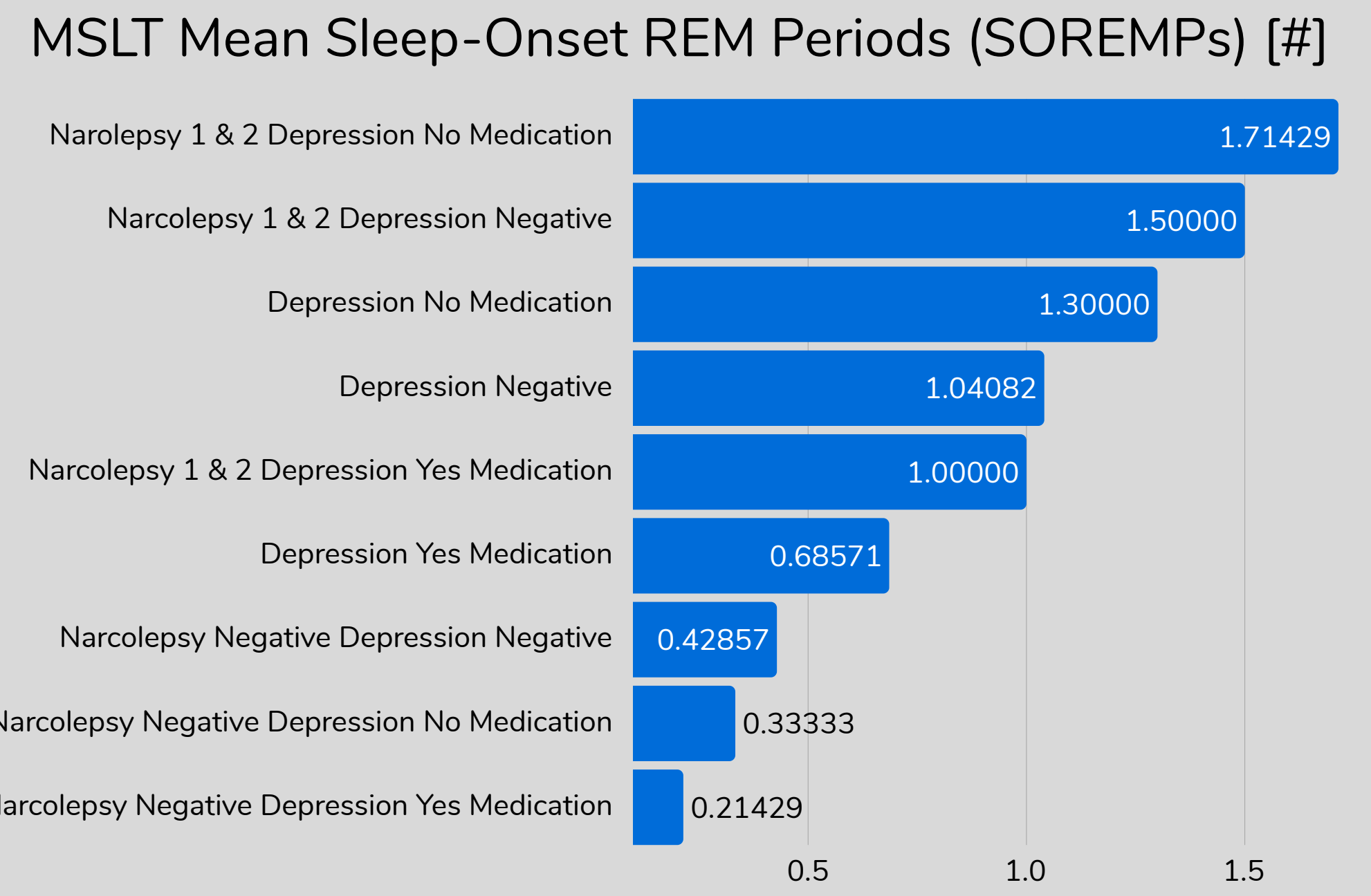| Category	Value
Narolepsy 1 & 2 Depression No Medication	0.20460
Depression No Medication	0.19801
Narcolepsy Negative Depression No Medication	0.18262
Narcolepsy 1 & 2 Depression Yes Medication	0.17821
Narcolepsy 1 & 2 Depression Negative	0.17206
Depression Negative	0.16717
Depression Yes Medication	0.16533
Narcolepsy Negative Depression Negative	0.16066
Narcolepsy Negative Depression Yes Medication	0.14601

Mean DSR was lowest in REM-AD(-) Clinical Controls (CC: 0.96), and normalized in REM-AD(+) (CC: 1.45) relative to MDD(-) subjects (CC: 1.28). DSR was lower in REM-AD(+) and MDD(-) in Narcolepsy than Clinical Controls (NT1/NT1: REM-AD(+): 1.14, REM-AD(-): 1.19, MDD(-): 1.39).

PSG Mean Delta Sleep Ratio (DSR) [#]

Category	Value
Narcolepsy Negative Depression Yes Medication	1.45240
Narcolepsy 1 & 2 Depression Negative	1.39200
Depression Negative	1.34723
Narcolepsy Negative Depression Negative	1.28754
Depression Yes Medication	1.27074
Narcolepsy 1 & 2 Depression No Medication	1.19197
Narcolepsy 1 & 2 Depression Yes Medication	1.14963
Depression No Medication	1.12412
Narcolepsy Negative Depression No Medication	0.96582

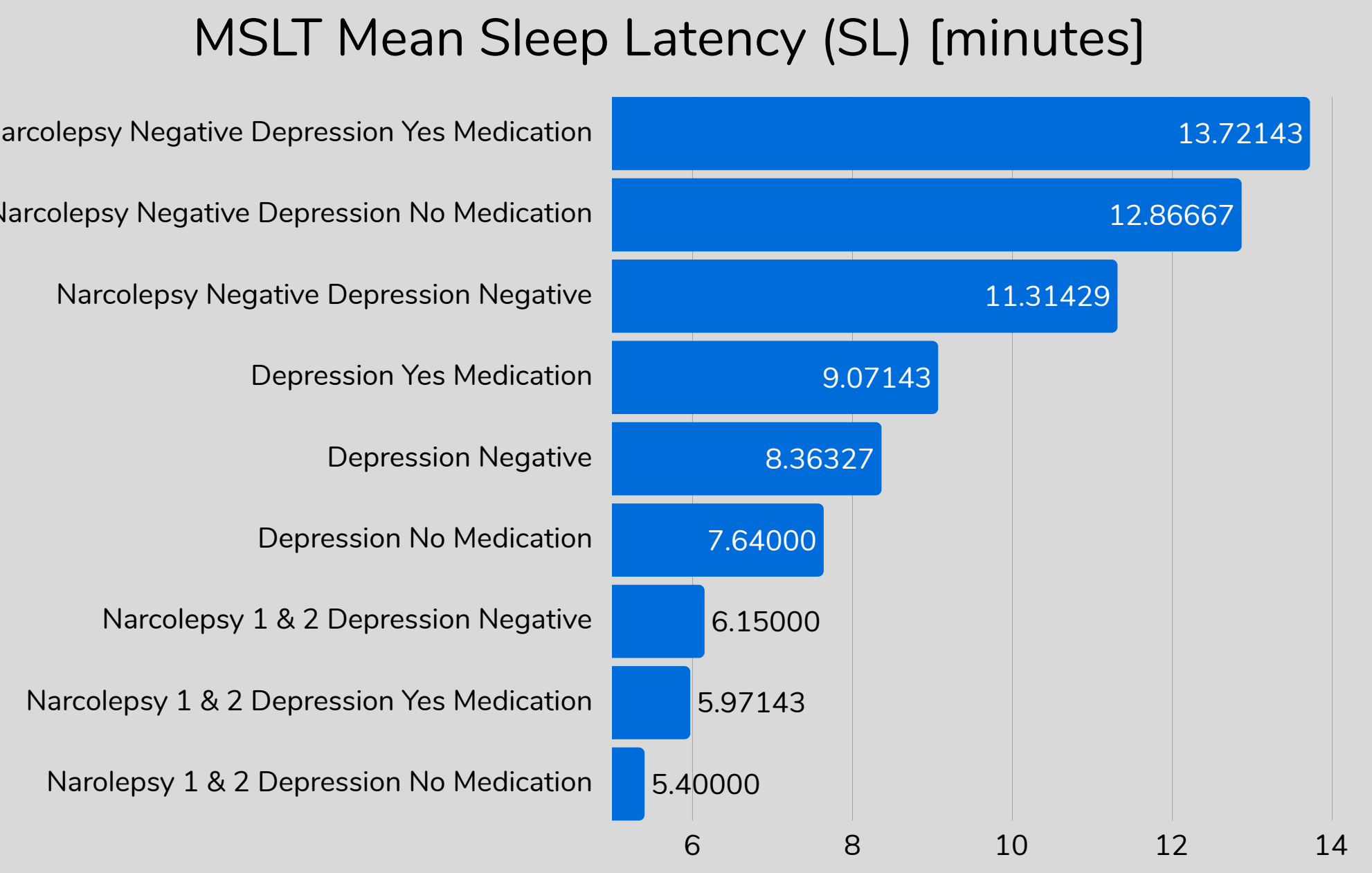n: 3662, mean: (1.12, (1.13, 2.0), 0.42), med: 1.07

Results Continued

Mean SOREMPs were lowest in REM-AD(+) both in Narcolepsy (NT1/NT2: REM-AD(+): 1.00, REM-AD(-) 1.71, MDD(-): 1.50) and clinical controls (CC: REM-AD(+): 0.21, REM-AD(-) 0.33, MDD(-): 0.42).

MSLT Mean Sleep-Onset REM Periods (SOREMPs) [#]

Category	Value
Narcolepsy 1 & 2 Depression No Medication	1.71429
Narcolepsy 1 & 2 Depression Negative	1.50000
Depression No Medication	1.30000
Depression Negative	1.04082
Narcolepsy 1 & 2 Depression Yes Medication	1.00000
Depression Yes Medication	0.68571
Narcolepsy Negative Depression Negative	0.42857
Narcolepsy Negative Depression No Medication	0.33333
Narcolepsy Negative Depression Yes Medication	0.21429

MSLT Mean Sleep Latency (MSL) was shorter in REM-AD(-) NT1/NT1 than REM-AD(+) NT1/NT2, shorter in REM-AD(-) Clinical Controls than MDD(-) or REM-AD(+).

MSLT Mean Sleep Latency (SL) [minutes]

Category	Value
Narcolepsy Negative Depression Yes Medication	13.72143
Narcolepsy Negative Depression No Medication	12.86667
Narcolepsy Negative Depression Negative	11.31429
Depression Yes Medication	9.07143
Depression Negative	8.36327
Depression No Medication	7.64000
Narcolepsy 1 & 2 Depression Negative	6.15000
Narcolepsy 1 & 2 Depression Yes Medication	5.97143
Narcolepsy 1 & 2 Depression No Medication	5.40000

Conclusions

Comorbid Depression patients with and without REM-ADs showed substantial alterations in key Narcolepsy disorder diagnostic and sleep architecture parameters. Given significant rates of comorbidity, these findings highlight needs to better understand the interactions and impact of Depression on Narcolepsy diagnosis. Future work involves further validation of AI-enabled identification and detection for NT1 and MDD respetively.