Nature and Science of Sleep

Elevate Series

Open Access Full Text Article

ORIGINAL RESEARCH

Prevalence and Factors Associated with Rapid Eye Movement-Related Obstructive Sleep Apnea in Patients with Narcolepsy

Hamza O Dhafar[1], Ali A Awadh[2], Salih A Aleissi[1], Galal Eldin Abbas Eltayeb[3], Samar Z Nashwan[1], Ahmed S BaHammam[1,4]

[1]The University Sleep Disorders Center, Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [2]Seha Virtual Hospital, Ministry of Health, Riyadh, Saudi Arabia; [3]Department of Management Information Systems, College of Business and Economics, Qassim University, Buraydah, Saudi Arabia; [4]The Strategic Technologies Program of the National Plan for Sciences and Technology and Innovation in the Kingdom of Saudi Arabia, Riyadh, Saudi Arabia

Correspondence: Ahmed S BaHammam, University Sleep Disorders Center, Department of Medicine, College of Medicine, King Saud University, Box 225503, Riyadh, 11324, Saudi Arabia, Email ashammam2@gmail.com

Purpose: Data on the prevalence and correlates of rapid eye movement (REM)–related obstructive sleep apnea (REM-OSA) in narcolepsy remains limited. This study aimed to assess the prevalence and independent associated factors with OSA and REM-OSA in patients with narcolepsy, and to compare the distribution of REM-OSA between patients with narcolepsy and matched controls without narcolepsy.

Patients and Methods: This retrospective study of a prospectively collected cohort included 190 adult patients with narcolepsy (narcolepsy type 1 [NT1] = 119, narcolepsy type 2 [NT2] = 71) who underwent polysomnography and multiple sleep latency test at the University Sleep Disorders Center, King Saud University Medical City, between January 2007 and February 2022. REM-OSA was defined as an apnea–hypopnea index (AHI) ≥5, AHI-REM/AHI–non–rapid eye movement (NREM) ≥2, AHI-NREM <8, and REM sleep duration >10.5 minutes. A total of 106 patients with narcolepsy were diagnosed with OSA. A control group of 122 patients with OSA but without narcolepsy, matched by age, sex, AHI, and BMI, was used for comparison. Logistic regression identified independent associated factors with OSA and REM-OSA.

Results: OSA was diagnosed in 106 patients with narcolepsy (55.8%). REM-OSA was present in 26.4% of these cases, with a slightly higher prevalence in NT2 (30%) than in NT1 (24%). REM-OSA showed a trend toward higher prevalence in the narcolepsy group compared to controls (26.4% vs 17.2%, OR: 1.73, 95% CI: 0.91–3.27, p = 0.09). Male sex, BMI, and arousal index were independent correlates of OSA among patients with narcolepsy. REM-OSA was independently associated with arousal index and REM sleep duration.

Conclusion: OSA and REM-OSA are common in patients with narcolepsy. REM-OSA was more prevalent in the narcolepsy group than in matched controls, suggesting a potential association between narcolepsy and REM-OSA that warrants investigation in larger cohorts.

Plain Language Summary: People with narcolepsy often struggle with excessive daytime sleepiness and disrupted nighttime sleep. When another sleep disorder, such as obstructive sleep apnea (OSA), occurs alongside narcolepsy, it can make symptoms worse. A specific form of OSA, known as REM-OSA (which primarily occurs during rapid eye movement sleep), has been associated with an increased risk of heart and metabolic conditions. However, studies examining REM-OSA in people with narcolepsy remain limited.

In this study, we evaluated 190 adults with narcolepsy and found that more than half had OSA. Among those with OSA, over one in four also had REM-OSA. We compared these patients to a group of individuals who had OSA but not narcolepsy. The two groups were matched by age, sex, apnea severity, and body mass index (BMI). We found that REM-OSA was more common in people with narcolepsy than in the matched controls. Although the difference was not statistically significant, the trend suggests a possible link worth further investigation.

Understanding the relationship between narcolepsy and REM-OSA is important for improving diagnosis and treatment. A better understanding of this overlap may help improve patient outcomes. More research in larger groups is needed to confirm this connection.

Keywords: sleep-disordered breathing, REM sleep, arousal index, sleep fragmentation, polysomnography, multiple sleep latency test

Received: 18 July 2025
Accepted: 19 August 2025
Published: 25 August 2025

Introduction

Narcolepsy is a chronic neurological disorder with an autoimmune basis, affecting 25–50 per 100,000 individuals worldwide.[1] It is primarily characterized by excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, fragmented nighttime sleep, and hypnagogic hallucinations.[2] Narcolepsy is classified into two types: Type 1 (NT1), which includes cataplexy (the sudden loss of muscle tone in response to strong emotions), and Type 2 (NT2), which does not.[2] EDS, the hallmark symptom of narcolepsy, can also occur in other, more common sleep disorders, such as obstructive sleep apnea (OSA).[3] This overlap can complicate the diagnosis and management of narcolepsy.[4]

OSA is a prevalent sleep disorder characterized by repeated episodes of upper airway obstruction during sleep, leading to intermittent hypoxia and sleep fragmentation.[5,6] Its prevalence ranges from 9% to 38%, with a higher predominance in men.[5] While OSA events can occur during any sleep stage, they are typically more severe and prolonged during rapid eye movement (REM) sleep, resulting in significant oxygen desaturation and increased frequency of arousals.[7] This REM-specific vulnerability is associated with increased sympathetic stimulation, cardiovascular instability, and diminished vagal tone, potentially leading to adverse cardiovascular events such as hypertension, left ventricular hypertrophy, angina, and myocardial infarction.[8–11]

Narcolepsy and OSA may coexist, and both conditions share overlapping features such as EDS and elevated body mass index (BMI). These similarities can delay the diagnosis and complicate the management of narcolepsy, which is less common than OSA.[12–15] Therefore, clinicians are advised to assess for the unique symptoms of narcolepsy, particularly cataplexy, in patients presenting with OSA symptoms. Importantly, continuous positive airway pressure (CPAP) therapy, the standard treatment for OSA, does not necessarily resolve EDS in patients with comorbid narcolepsy and OSA.[3,4] Thus, proper diagnosis and management of narcolepsy are critical for controlling EDS, the most disabling symptom associated with poor outcomes.

Although the relationship between narcolepsy and OSA has been studied,[4,16] data on the specific association between narcolepsy and REM-related OSA remain limited. For clarity and brevity, we use the term REM-OSA throughout this manuscript to refer to patients who meet our study definition of REM-related OSA. REM-OSA represents a distinct phenotype of sleep-disordered breathing that predominantly affects younger women and involves respiratory events concentrated during REM sleep.[10,17]

Recent studies suggest that orexin deficiency in narcolepsy may predispose to REM-related respiratory instability through impaired upper airway regulation.[18] Orexin deficiency disrupts muscle tone control during REM sleep, particularly affecting upper airway stability, which may increase the risk of REM-OSA.[19,20] Studies have shown altered upper airway muscle activity during REM sleep in orexin-deficient models and in humans with narcolepsy.[19,20] Beyond muscle tone effects, fragmented sleep patterns common in narcolepsy create additional respiratory vulnerabilities. Sleep fragmentation disrupts normal ventilatory control mechanisms, while frequent sleep–wake transitions may compromise upper airway compensatory responses.[21,22] Moreover, autonomic dysfunction associated with orexin deficiency affects cardiovascular and respiratory regulation, potentially exacerbating sleep-disordered breathing episodes.[23] Exaggerated REM muscle atonia and fragmented sleep characteristic of narcolepsy may worsen respiratory events during this sleep stage.[24] However, the exact mechanisms linking orexin loss, changes in REM sleep, and airway collapse remain complex and under investigation.[10,25] Moreover, the temporal relationship between REM sleep and respiratory events in narcolepsy remains poorly understood, particularly given the altered REM sleep architecture characteristic of this disorder. Clarifying these relationships could guide treatments targeting sleep disordered breathing in narcolepsy.[18]

While Hoshino et al reported REM-OSA prevalence in Japanese patients with narcolepsy, their study was descriptive and lacked matched controls and was limited to a single population.[26] Our study addresses these gaps by including matched controls and representing the first investigation of REM-OSA in narcolepsy from the Middle East, expanding global understanding across diverse populations.

This study aims to assess the prevalence and identify factors independently associated with OSA and REM-OSA in patients diagnosed with narcolepsy. In addition, we included a control group of individuals with OSA but without narcolepsy, matched for age, sex, AHI, and BMI, to compare the distribution of REM-OSA between the two groups. Specifically, we hypothesize that those diagnosed with narcolepsy have higher rates of REM-OSA compared to matched

controls. Given the known orexin deficiency in NT1, we further hypothesize that NT1 patients may demonstrate different REM-OSA patterns compared to NT2 patients. This investigation seeks to inform evidence-based screening protocols and treatment algorithms for sleep-disordered breathing in narcolepsy populations, ultimately improving patient outcomes through more targeted therapeutic interventions.

Materials and Methods

This retrospective analysis was conducted using prospectively collected cohort data from the University Sleep Disorders Center (USDC) research database at King Saud University Medical City, Riyadh, Saudi Arabia.[27] The USDC has maintained a comprehensive prospective research database, systematically capturing demographic, clinical, and polysomnographic data using predefined forms and standardized protocols. Trained personnel entered data prospectively at the time of clinical evaluation, with continuous quality control measures in place throughout the study period.[28,29]

The current analysis included all consecutive adult patients (≥18 years) diagnosed with narcolepsy between January 2007 and February 2022, identified through systematic database queries using International Classification of Sleep Disorders, 3rd edition (ICSD-3) diagnostic criteria. This approach ensured comprehensive case identification while minimizing selection bias inherent in retrospective analyses.[30]

The study received approval from the Institutional Review Board (IRB) at King Saud University Medical City (Approval Number: 19/0134IRB). Informed consent was obtained from all patients for clinical evaluation and data collection at the time of their initial assessment, with additional consent for research use of de-identified data when required by institutional policy.

Participants and Selection Criteria

The following criteria were applied to include patients with narcolepsy in the original recruitment protocol for the cohort: (1) age ≥18 years at the time of diagnosis; (2) confirmed diagnosis of NT1 or NT2 according to ICSD-3 criteria; (3) completion of overnight polysomnography and MSLT; and (4) availability of complete demographic and anthropometric data. Exclusion criteria included: (1) incomplete polysomnographic studies due to technical issues or insufficient sleep time (<6 hours total sleep time); (2) concurrent use of medications at the time of the sleep study or within 4 weeks of the study known to significantly affect REM sleep architecture (such as antidepressants or stimulants); and (3) significant medical comorbidities that could affect sleep architecture, including active psychiatric disorders requiring hospitalization or severe cardiopulmonary disease.

Sample Size Justification

The sample comprised 190 patients with narcolepsy, representing the entire population of diagnosed cases at our center during the 15-year study period, ensuring comprehensive case identification and minimizing selection bias. This approach is consistent with best practices for retrospective studies utilizing complete case ascertainment from defined clinical populations.[31] The inclusion of 122 matched controls with OSA but without narcolepsy provided reasonable comparison data for detecting potentially meaningful differences in REM-OSA distribution between groups.

Our study design improves upon previous narcolepsy-REM-OSA research by incorporating a matched control group, which was absent in the seminal work by Hoshino et al.[26] This methodological advancement enables direct comparative analysis and strengthens the inference of a potential association between narcolepsy and REM-OSA development.

Recent population-based data from Saudi Arabia show that REM-OSA affects 2.68% of adults overall and 30.64% of patients with OSA.[32] These benchmarks informed our power calculations and interpretation. Our tertiary-center narcolepsy cohort comprised 190 consecutive adults; 106 (55.8%) met the diagnostic criteria for OSA and thus entered the REM-OSA analysis set.

Although formal a priori power calculations were not feasible due to the retrospective design, we conducted a post-hoc power analysis for interpretive context. This analysis indicated approximately 83% power to detect the observed 9.2% difference in REM-OSA prevalence between narcolepsy patients and matched controls (Cohen's h = 0.22). We emphasize, however, that confidence intervals and effect sizes are more informative than significance testing in interpreting this finding.

The post-hoc power analysis is presented for interpretive context only. It does not alter the non-significant result, which should be interpreted primarily through confidence intervals and effect sizes.

Clinical Assessment and Data Collection

All patients completed a questionnaire assessing narcolepsy-related symptoms, including irresistible attacks of sleep as well as cataplexy, sleep paralysis, and sleep-related hallucinations. Additional information on comorbid conditions, including OSA symptoms, past medical history, and medication use, was also collected. The questionnaire was administered by trained sleep technologists and reviewed by sleep medicine physicians to ensure accuracy and completeness of symptom reporting.

Demographic and anthropometric measurements, such as age, sex, weight, height, neck circumference, waist and hip circumferences, blood pressure, pulse, and BMI, were recorded at the initial visit. All anthropometric measurements were performed using standardized techniques: height was measured to the nearest 0.1 cm using a wall-mounted stadiometer, weight was recorded to the nearest 0.1 kg using a calibrated digital scale, and neck circumference was measured at the level of the cricothyroid membrane.

Only data elements explicitly outlined in the approved protocol and relevant to the study's aims regarding REM-OSA prevalence and associated factors were extracted and made available for analysis.

Polysomnographic and MSLT Procedures

In-lab PSG and MSLT were performed based on clinical assessment. All polysomnographic studies were conducted using standardized equipment (Alice-4 and Alice-6 systems, Philips Respironics, Murrysville, PA, USA) and scored according to American Academy of Sleep Medicine (AASM) criteria.[33] Sleep stages were scored in 30-second epochs, and respiratory events were identified using standard AASM definitions. Hypopneas were defined as ≥30% reduction in airflow lasting ≥10 seconds associated with either ≥3% oxygen desaturation or arousal. Apneas were defined as ≥90% reduction in airflow for ≥10 seconds. The polysomnographic parameters analyzed included the apnea-hypopnea index (AHI), arousal index, mean oxygen saturation, minimum oxygen saturation, and sleep-onset REM periods (SOREMP). MSLT was performed the day following polysomnography according to the standard protocol, with five 20-minute nap opportunities at 2-hour intervals beginning 1.5–3 hours after morning awakening.[34]

Diagnostic Criteria

Narcolepsy and OSA were diagnosed according to the criteria outlined in the International Classification of Sleep Disorders, 3rd edition.[2] All patients met the requirement of having daily periods of irrepressible need to sleep or daytime sleep lapses for at least three months. NT1 was diagnosed if cataplexy was present along with a mean sleep latency ≤8 minutes and ≥2 sleep-onset REM periods (SOREMPs) on a standard MSLT, with a SOREMP on the preceding PSG allowed to substitute for one MSLT SOREMP. Alternatively, NT1 was also diagnosed if cerebrospinal fluid (CSF) hypocretin-1 concentration was ≤110 pg/mL or <1/3 of the mean normal values. NT2 was diagnosed when cataplexy was absent, the MSLT showed a mean sleep latency of ≤8 minutes and ≥2 SOREMPs, CSF hypocretin-1 was either not measured or >110 pg/mL (or >1/3 of the normal mean), and the findings could not be better explained by other causes of hypersomnolence. OSA was defined as AHI ≥5 events/hour of sleep accompanied by symptoms or comorbidities, or AHI ≥15 events/hour regardless of symptoms.

OSA was further categorized into REM-OSA and non-stage-specific (NSS-OSA). REM-OSA was defined by an AHI ≥5, an AHI-REM/AHI-NREM ratio ≥2, an AHI-NREM <8, and REM sleep duration exceeding 10.5 minutes.[26,35,36]

This definition was selected to ensure specificity and avoid misclassification of patients with minimal REM sleep, as shorter REM periods may not provide adequate time for reliable assessment of REM-specific respiratory events.[10]

Control Group Selection

To allow comparative analysis, a control group of 122 adult patients diagnosed with OSA but without narcolepsy was included. Controls were selected from the same sleep disorders center database and matched to the narcolepsy group based on age, sex, AHI, and BMI. Matching was performed using a 1:1 nearest neighbor approach with a caliper width of 0.2 standard deviations for continuous variables. When multiple potential matches were available, controls were selected

randomly to minimize selection bias. All control patients underwent overnight PSG during the same study period and met the diagnostic criteria for OSA according to AASM guidelines. Narcolepsy was excluded in the control group based on clinical assessment and the absence of MSLT. Standardized mean differences for age, sex, BMI, and AHI were all below 0.1 after matching, indicating successful balance between cases and controls. Additional exclusion criteria for controls included: (1) reported cataplexy-like episodes; and (2) documented sleep-onset REM periods during routine polysomnography. The control group was used to compare the prevalence and distribution of REM-OSA between patients with and without narcolepsy.

Control Group Rationale

We chose matched patients with OSA but without narcolepsy as the comparison group, rather than healthy sleepers, for three reasons. First, using disease controls allows us to isolate the incremental contribution of narcolepsy-related pathophysiology to REM-OSA while holding constant the baseline impact of upper-airway obstruction. Second, OSA is highly prevalent in narcolepsy; therefore, comparing narcolepsy + OSA with "OSA-only" patients addresses a question that clinicians face daily, namely, whether narcolepsy alters the OSA phenotype. Third, frequency-matching on AHI removes a major confounder; without this step, differing OSA severities would obscure any narcolepsy-specific effects.

While this design cannot establish absolute REM-OSA prevalence in narcolepsy, it provides a good, rigorous approach to isolate narcolepsy-specific contributions to REM-OSA.

Statistical Analysis

Descriptive statistics summarized demographic and clinical characteristics. Continuous variables are reported as mean ± SD and compared with independent *t*-tests (Welch *t*-test when variances were unequal); when Shapiro–Wilk or histogram inspection indicated non-normality, the Mann–Whitney *U*-test was applied. Normality assumptions for *t*-tested variables were verified statistically (Shapiro–Wilk test). Categorical variables were presented as frequencies (%) and compared with Pearson's χ^2-test; when any expected cell was < 5, Fisher's exact test was used. Associations between two binary variables (eg, narcolepsy subtype vs overall OSA status) were assessed with Pearson's χ^2-test; the φ coefficient was reported as the effect size. For the matched comparison of REM-OSA vs NSS-OSA, group differences were evaluated with conditional logistic regression (strata = age–sex–BMI triplets), and McNemar's exact test was used for the paired 2×2 counts. Multivariable logistic regression identified factors independently associated with OSA and REM-OSA; candidate variables entered the model if univariable $p < 0.10$ or strong clinical relevance was present. Models were restricted to ≥ 8 outcome events per variable (EPV) to limit over-fitting, following current methodological recommendations.[37,38] Model fit was assessed with the Hosmer–Lemeshow goodness-of-fit test, discrimination with the area under the ROC curve, explained variance with Nagelkerke R^2, and multicollinearity with variance-inflation factors (VIF < 5). Effect sizes were expressed for the primary comparisons using Cohen's conventions—*d* for continuous variables, *h* for proportions, and φ for binary associations. All descriptive and comparative analyses were executed in SPSS v25.0 (IBM Corp., Armonk, NY, USA). A post-hoc power analysis was performed for interpretive context only, showing ~83% power to detect the observed small-to-medium effect size (Cohen's h = 0.22). This analysis does not affect the interpretation of non-significant findings.[39,40] This yielded 83% power to detect a two-sided difference at $\alpha = 0.05$. Binomial 95% confidence intervals for single proportions were obtained with the Wilson score method.[41,42]

The original cohort was assembled prospectively, and every study variable was captured for each participant; the analytic dataset was therefore complete (with no missing data), and no imputation was required.

All statistical tests were considered exploratory; no correction for multiple comparisons was applied, and findings should be interpreted accordingly.

Results

This study investigated the prevalence and identified factors independently associated with OSA and its phenotype, REM-OSA, among patients with NT1 and NT2, and compared the distribution of REM-OSA with a matched control group of patients with OSA but without narcolepsy. A total of 190 patients were diagnosed with narcolepsy, including 152 males (80%) and 38 females (20%). Among them, 119 patients (62.6%) were diagnosed with NT1, and 71 patients

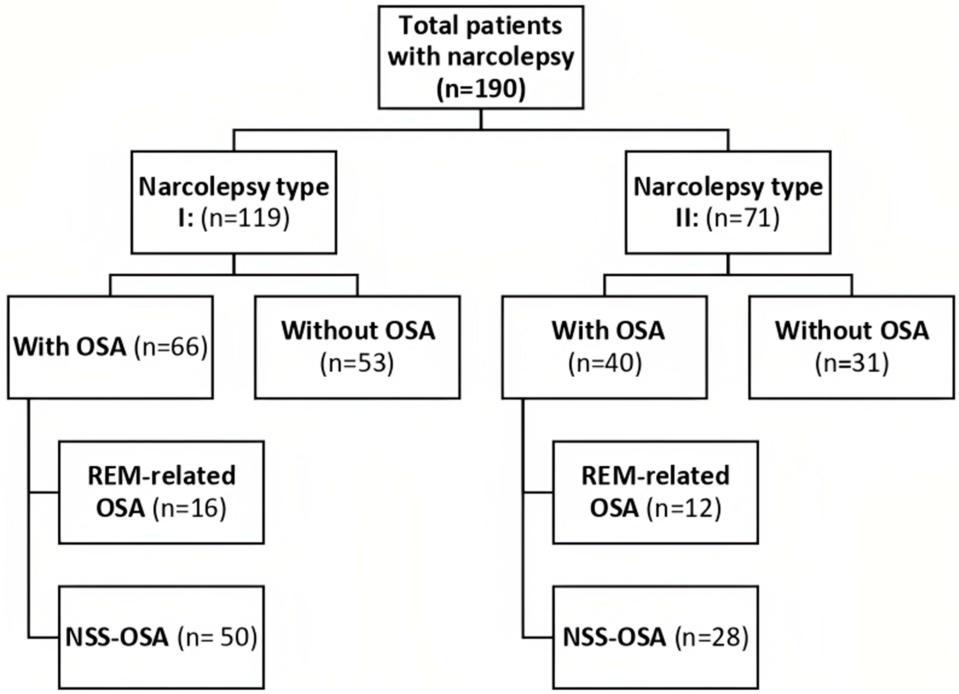

Figure 1 Flowchart of OSA, REM-Related OSA, and NSS-OSA Classification Among Patients with Narcolepsy.
Abbreviations: OSA, obstructive sleep apnea; REM-related OSA, rapid eye movement–related obstructive sleep apnea; NSS-OSA, non-stage-specific obstructive sleep apnea.

(37.4%) were diagnosed with NT2. The classification and distribution of OSA and its phenotypes among NT1 and NT2 are illustrated in Figure 1. Narcolepsy subtypes demonstrated remarkable similarity in both demographic characteristics and sleep-disordered breathing patterns. The sex distribution showed no significant difference between the NT1 and NT2 groups (OR: 0.62, 95% CI: 0.29–1.35, p = 0.31), although our tertiary care setting's male predominance may reflect referral patterns rather than the true population prevalence (Table 1).

Most importantly, OSA prevalence was virtually identical between narcolepsy subtypes (55.5% vs 56.3%, OR: 0.97, 95% CI: 0.54–1.74, p = 1.00), suggesting that OSA risk in narcolepsy operates independently of cataplexy presence and orexin deficiency status. Among the 106 narcolepsy patients who had OSA, 28 fulfilled REM-OSA criteria (26.4%; 95% CI 18.9–35.5%, Wilson) (Figure 2). REM-OSA showed a non-significant trend toward higher prevalence in NT2 (30.0% vs 24.2%, OR: 0.75, 95% CI: 0.31–1.80, p = 0.67), though the wide confidence interval reflects limited statistical power for this subgroup analysis (Table 1).

Table 1 Prevalence and Distribution of OSA, REM-OSA, and NSS-OSA Among Patients with Narcolepsy (NT1 Vs NT2)

Characteristic	**Total Patients (N = 190)**	**NT1 (n = 119)**	**NT2 (n = 71)**	**NT1 vs NT2: OR (95% CI), *p-value***
Male Sex	152 (80%)	92 (77.3%)	60 (84.5%)	0.62 (0.29–1.35), *p* = 0.31
Diagnosed with OSA	106 (55.8%)	66 (55.5%)	40 (56.3%)	0.97 (0.54–1.74), *p* = 1.00
Within patients who have OSA (n = 106)				
Characteristic	**Total Patients (n = 106)**	**NT1 (n = 66)**	**NT2 (n = 40)**	**NT1 vs NT2: OR (95% CI), p-value**
REM-OSA	28 (26.4% of OSA)	16 (24.2%)	12 (30%)	0.75 (0.31–1.80), *p* = 0.67
NSS-OSA	78 (73.6% of OSA)	50 (75.8%)	28 (70%)	Reference

Note: P < 0.05 was considered statistically significant.
Abbreviations: NT1, Narcolepsy Type 1; NT2, Narcolepsy Type 2; OSA, Obstructive Sleep Apnea; REM-OSA, Rapid Eye Movement–related Obstructive Sleep Apnea; NSS-OSA, Non-Stage Specific Obstructive Sleep Apnea; CI, Confidence Interval.

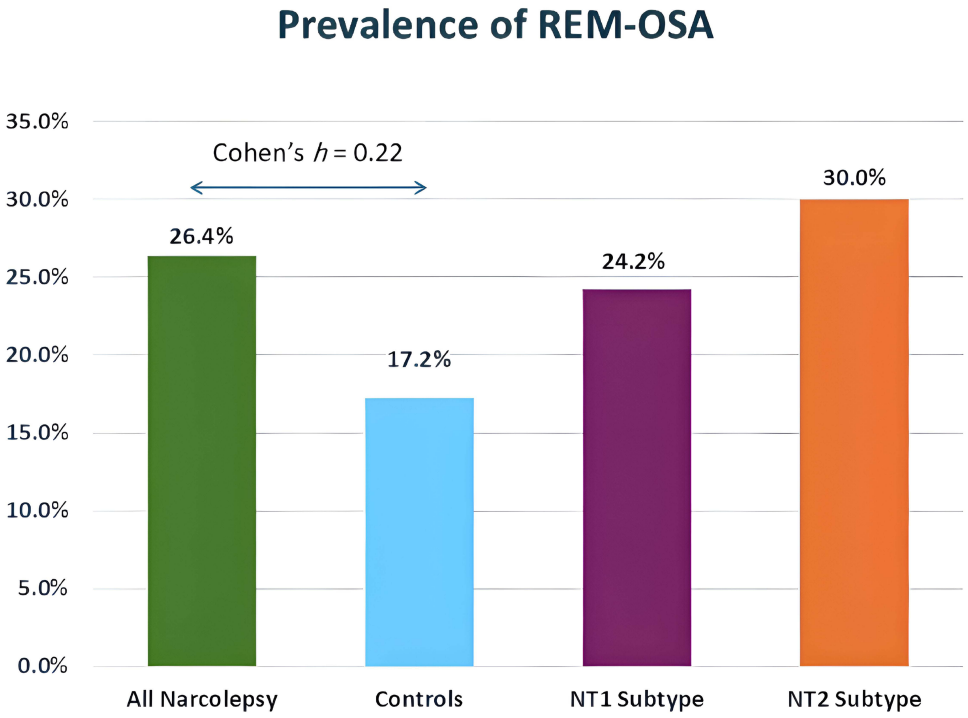

Figure 2 Prevalence of REM-OSA. Bars show the proportion of patients with REM-OSA among the pooled narcolepsy cohort (green), controls (blue), narcolepsy type 1 subtype (purple) and narcolepsy type 2 subtype (Orange). The double-headed arrow depicts the standardized difference between the pooled narcolepsy cohort and controls (Cohen's h = 0.22, small–to-medium effect).

Table 2 summarizes the demographic and polysomnographic characteristics of patients with narcolepsy with versus without OSA. Patients with OSA had a higher BMI (31.5 ± 7.2 vs 28.3 ± 5.9 kg m², $p = 0.001$, Mann–Whitney U), and an elevated arousal index (29.3 ± 20.1 vs 13.8 ± 7.7 events/hour, $p < 0.001$). As expected, respiratory event indices and oxygen-desaturation metrics were also markedly higher in the OSA subgroup during both REM and NREM sleep (all $p <$ 0.001). To interpret the clinical importance of observed group differences, effect sizes were calculated. Effect-size

Table 2 Clinical and Polysomnographic Characteristics of Patients with Narcolepsy with and Without Obstructive Sleep Apnea (N = 190)

Variable	OSA (n = 106)	Non-OSA (n=84)	P-value	Effect Size †
Demographics				
Age (Years)	27.8 ± 9.3	25.9 ± 9.5	0.17	d = 0.20 (small)
Body Mass Index (kg/m^2)	31.5 ± 7.2	28.3 ± 5.9	0.001	d = 0.48 (moderate)
Neck Circumference (Inches)	15.0 ± 1.4	14.5 ± 2.9	0.15	d = 0.22 (small)
Polysomnographic Features				
Arousal Index (events/hour)	29.3 ± 20.1	13.8 ± 7.7	<0.001	d = 1.02 (large)
Apnea-Hypopnea Index (AHI, events/hour)	18.3±12.0	1.9±1.3	<0.001	d = 1.91 (very large)
AHI-REM (events/hour)	32.2±22.2	11.0±10.8	<0.001	d = 1.21 (large)
AHI-NREM (events/hour	17.5±16.8	1.3±1.1	<0.001	d = 1.37 (large)
Desaturation Index (events/hour)	11.0±10.8	3.97±3.95	<0.001	d = 0.86 (large)

(*Continued*)

https://doi.org/10.2147/NSS.S554593

Table 2 (Continued).

Variable	OSA (n = 106)	Non-OSA (n=84)	P-value	Effect Size †
Symptoms				
Cataplexy	62 (58.5%)	50 (59.5%)	0.89	φ = 0.05 (negligible)
Hypnagogic Hallucinations	68 (64.2%)	44 (52.4%)	0.10	φ = 0.01 (negligible)
Hypnopompic Hallucinations	21 (19.8%)	11 (13.1%)	0.22	φ = 0.12 (small)
Sleep Paralysis	63 (58.9%)	44 (41.1%)	0.33	φ = 0.09 (small)
Comorbidities				
Hypertension	4 (3.8%)	0	0.13	φ = 0.15 (small)
Diabetes Mellitus	7 (6.6%)	2 (2.4%)	0.30	φ = 0.10 (small)
Bronchial Asthma	9 (8.5%)	2 (2.4%)	0.12	φ = 0.13 (small)

Note: Values are mean ± SD or n (%). Categorical variables with small expected frequencies (eg, Hypertension, Diabetes Mellitus) were compared using Fisher's exact test, explaining the reported P-values. † Effect size: Cohen's d for continuous variables, φ for categorical variables (small: 0.2, moderate: 0.5, large: 0.8+).
Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; NT, narcolepsy type.

estimates revealed moderate to very large differences between patients with narcolepsy with and without OSA, including a moderate difference in BMI (Cohen's d = 0.48) and a large difference in arousal index (d = 1.02). These findings underscore the clinical relevance of variables such as BMI, arousal index, and respiratory-event indices (Table 2).

Age and AHI were approximately normally distributed (Shapiro–Wilk $p > 0.10$) and were compared with independent *t*-tests, whereas BMI showed mild right skew and was analyzed with the Mann–Whitney *U*-test. No significant differences emerged between NT1 and NT2 (Age: 31.2 ± 10.8 vs 32.0 ± 11.1 years, $p = 0.55$; BMI: 28.9 ± 4.6 vs 29.3 ± 4.2 kg m², $p = 0.62$; AHI: 23.8 ± 14.7 vs 24.4 ± 15.1 events/hours, $p = 0.80$). Cohen's *d* values for age (0.07) and AHI (0.05) were also ≤ 0.10, confirming that the observed differences are clinically negligible.

Regarding narcolepsy symptoms, the OSA group reported higher frequencies of hypnagogic and hypnopompic hallucinations, fragmented sleep, and sleep paralysis; however, these differences were not statistically significant. Comorbid conditions such as hypertension, diabetes mellitus, and bronchial asthma were more prevalent among patients with narcolepsy and OSA compared to those without, though these differences did not reach statistical significance (Table 2).

Logistic Regression Analysis

Logistic regression analysis revealed several factors independently associated with OSA and its phenotype, REM-OSA in narcolepsy (Table 3). For overall OSA, male sex conferred a more than fourfold increase in risk (OR = 4.45, 95% CI 1.44–13.73, $p < 0.01$), while each additional kilogram per square-meter of BMI raised the odds by 7% (OR = 1.07, 95% CI 1.00–1.15, $p = 0.05$). A higher arousal index was likewise associated with greater OSA probability (OR = 1.12, 95% CI 1.07–1.17, $p < 0.01$). Within the OSA subgroup, REM-OSA was independently associated with the arousal index (OR = 1.13, 95% CI 1.06–1.19, $p < 0.01$), whereas longer REM-sleep duration exerted a modest protective effect (OR = 0.98, 95% CI 0.97–0.99, $p < 0.01$). Pearson's χ^2-tests found no association between narcolepsy subtype (NT1 vs NT2) and either overall OSA status ($\chi^2 = 0.66$, df = 1, $p = 0.42$; φ = 0.06) or the distribution of REM-OSA versus non-stage-specific OSA ($\chi^2 = 0.01$, df = 1, $p = 0.91$; φ = 0.01). Model diagnostics supported the robustness of these findings: the OSA model showed good calibration (Hosmer–Lemeshow $\chi^2 = 7.2$, df = 8, $p = 0.51$) and strong discrimination (AUC = 0.84, 95% CI 0.78–0.90), while the REM-OSA model also fit adequately (Hosmer–Lemeshow $\chi^2 = 5.4$, df = 8, $p = 0.71$) with moderate discrimination (AUC = 0.73, 95% CI 0.63–0.82). Variance-inflation factors for all correlates were below 1.8, indicating that multicollinearity was not a concern.

Table 3 Factors Associated with OSA and REM-OSA Among Patients with Narcolepsy (Logistic Regression Analysis)

Factors	Univariable Odds Ratio	95% Confidence Interval (CI)	P-value	Multivariable Odds ratio	95% Confidence Interval (CI)	P-value
Factors Associated with OSA						
Male Gender	3.79	1.51–9.55	<0.01	4.45	1.44–13.73	<0.01
Body Mass Index (BMI)	1.07	1.01–1.13	0.02	1.07	1.00–1.15	0.05
Arousal Index	1.25	1.14–1.37	<0.01	1.12	1.07–1.17	<0.01
Factors Associated with REM-OSA						
Male Gender	4.76	0.89–25.39	0.07	1.99	0.59–6.72	0.27
Arousal Index	1.11	1.06–1.15	<0.01	1.13	1.06–1.19	<0.01
REM Sleep Duration	0.99	0.98–1.00	0.08	0.98	0.97–0.99	<0.01

Notes: The final multivariable OSA model showed good calibration (Hosmer–Lemeshow χ^2 = 7.1, *df* = 8, p = 0.53) and acceptable discrimination (area under the ROC curve = 0.84, 95% CI 0.77–0.90). Similarly, the REM-OSA model demonstrated adequate fit (Hosmer–Lemeshow χ^2 = 5.3, p = 0.72) and moderate discrimination (AUC = 0.72, 95% CI 0.62–0.82).

Comparison with Control Group

To characterize REM-OSA in narcolepsy, we compared 106 narcolepsy patients with OSA to 122 age-, sex-, AHI-, and BMI-matched OSA controls without narcolepsy (Tables 4 and 5). Among controls, 21/122 had REM-OSA (17.2%; 95% CI 11.0–25.1%), whereas in the narcolepsy group 28/106 had REM-OSA (26.4%; 95% CI 18.9–35.5%). The unadjusted odds ratio (OR) was 1.73 (95% CI 0.91–3.27, p = 0.09; see Table 4), with Cohen's h = 0.22 (small–medium effect). A conditional logistic model that preserved the matching yielded a similar estimate (OR = 1.69, 95% CI 0.89–3.18, p = 0.11); for comparison with earlier unmatched studies, the unmatched Pearson χ^2 (2.85, p = 0.09) is also shown in Table 4.

Table 4 Comparison of REM-OSA and Non-Stage Specific OSA Between Patients with Narcolepsy and the Control Group (Unadjusted Comparison)

Group	NSS-OSA (n, %)	REM-OSA (n, %)	Total	REM-OSA Prevalence	Odds Ratio (95% CI)	*p*-value (Pearson χ^2, *df* = 1)	Effect Size †
Control	101 (82.8%)	21 (17.2%)	122	17.2%	Reference	Reference	Reference
Narcolepsy	78 (73.6%)	28 (26.4%)	106	26.4%	1.73 (0.91–3.27)	0.09	h = 0.22 (small-medium

Notes: p-value from Pearson's χ^2-test; continuity correction not applied. Continuity correction was omitted because the primary matched analysis was performed with conditional logistic regression. Conditional logistic regression (matched analysis): OR = 1.69 (95% CI 0.89–3.18), p = 0.11. †Effect size (Cohen's h): small 0.20, medium 0.50, large 0.80.

Abbreviations: REM-OSA, rapid-eye-movement-related obstructive sleep apnea; NSS-OSA, non-stage-specific OSA.

Table 5 Sex Distribution and REM-OSA Phenotype Characteristics in Cases with Narcolepsy and Controls

Characteristic	Control Group (N = 122)	Cases Group (N = 106)	P-value† (Odds Ratio, 95% CI	Effect Size††
Comparison between cases and controls				
Male	98 (80.0%)	92 (86.8%)	0.22 (OR = 1.61, 0.78–3.30)	φ = 0.09 (small)
Age (y)	29.1 ± 9.1	27.8 ± 9.3	0.29 (Δ = –1.3, –3.7–1.1)	d = 0.14 (small)
BMI (kg/m²)	32.3 ± 7.4	31.5 ± 7.2	0.41 (Δ = –0.8, –2.7–1.1)	d = 0.11 (small)
AHI (events/hours)	19.0 ± 13.0	18.3 ± 12.0	0.67 (Δ = –0.7, –4.0–2.6)	d = 0.06 (negligible)

(*Continued*)

Table 5 (Continued).

Characteristic	Control Group (N = 122)	Cases Group (N = 106)	P-value† (Odds Ratio, 95% CI	Effect Size††
OSA Phenotype in both sexes in cases and controls				
REM-OSA (Male)	16 (76.2% of REM-OSA)	23 (82.1% of REM-OSA)	0.7 (OR = 1.44, 0.36–5.80)	φ = 0.07 (small)
REM-OSA (Female)	5 (23.8% of REM-OSA)	5 (17.9% of REM-OSA)	0.7 (OR = 0.69, 0.17–2.80)	φ = 0.07 (small)

Notes:†Statistics. Continuous variables are presented as mean ± SD and compared with an independent-samples Welch *t*-test (unequal variances). The effect size reported is the mean difference (Δ) with its 95% confidence interval. Categorical variables are shown as n (%); comparisons use a two-sided Fisher exact test. Effect size is the odds ratio (OR) for being a case versus a control, with exact 95% CIs (log method). ††Effect size: Cohen's d (continuous), φ (binary), h (proportion difference); small (0.2), medium (0.5), large (0.8). All P-values are two-tailed; values < 0.05 indicate statistical significance.

McNemar's exact test was concordant ($p = 0.12$). Because none of these tests crossed the 0.05 threshold, the higher REM-OSA prevalence in narcolepsy should be viewed as a non-significant trend; with only 28 events, the study may be underpowered to detect a modest effect.

Sex distribution within the REM-OSA subgroup showed a similar male predominance in both groups, with males representing 76.2% in the control group and 82.1% in the narcolepsy group (Table 5).

Discussion

This is the first controlled investigation of REM-OSA in patients with narcolepsy, representing a significant methodological advancement over previous descriptive studies through the inclusion of age-, sex-, AHI-, and BMI-matched controls. In the present study, OSA was found to be prevalent in both types of narcolepsy, with more than half of the patients (55.8%) diagnosed with OSA. These results are consistent with previous reports that suggest an increased prevalence of OSA among patients with narcolepsy.[4,43–45] The coexistence of narcolepsy and OSA may further worsen fragmented sleep and negatively impact the quality of life for these patients.[46,47]

Several factors may explain the high prevalence of OSA observed in our study. Notably, BMI, a well-established risk factor for OSA, was elevated in our cohort. The average BMI of 31.5 ± 7.2 classifies the majority of patients as overweight or obese, which likely contributed to the increased occurrence of OSA. Other factors may also elevate OSA risk in patients with narcolepsy. For example, low orexin levels in patients with NT1 could attenuate the ventilatory response to hypercapnia and intermittent hypoxia.[18,48] A poor response to these conditions may result in inadequate activation of the muscles that maintain upper airway patency, increasing the risk of airway collapse during sleep. Experimental studies have shown that orexin A and B enhance the activity of the genioglossus muscle, a major upper airway dilator muscle.[49,50] Consequently, orexin deficiency may impair genioglossus muscle function, especially in REM sleep when muscle tone is naturally reduced, thereby increasing the risk of REM-OSA.[10]

The comparative analysis between NT1 and NT2 revealed several unexpected findings that challenge the conventional understanding of narcolepsy pathophysiology. The virtually identical OSA prevalence between subtypes (55.5% vs 56.3%, p = 1.00) suggests that sleep-disordered breathing risk in narcolepsy may be independent of orexin deficiency status. This finding contradicts the previously discussed hypothesis linking orexin deficiency to greater respiratory instability during sleep.[49]

There is a lack of unified criteria for diagnosing REM-OSA, and significant heterogeneity exists in its definition; therefore, varying prevalence rates, natural history, and clinical significance have been reported in the literature.[10] We used a strict definition of REM-OSA that includes REM duration (defined as an AHI ≥5, AHI-REM/AHI-NREM ≥2, AHI-NREM <8, and REM sleep duration >10.5 minutes) to avoid misclassification bias and ensure that our findings accurately represent the true prevalence of REM-OSA in our sample. Despite using this precise definition, REM-OSA was observed in 26.4% of patients with narcolepsy and OSA. Recent population-based studies have reported REM-OSA prevalence ranging from 2.7% in the general population to 30.6% among patients with OSA, providing important context for interpreting our findings.[32] The 26.4% REM-OSA prevalence in our narcolepsy cohort falls within the upper range of these estimates, supporting the hypothesis that narcolepsy may predispose to REM-related respiratory events.

Moreover, our findings align with and significantly extend the work of Hoshino et al,[26] who reported REM-OSA prevalence of 25.6–47.1% in Japanese patients with narcolepsy, depending on the diagnostic criteria used. However, our study provides several methodological advances that strengthen the evidence base: (1) inclusion of matched controls enabling direct comparative analysis, (2) larger sample size with 190 patients with narcolepsy versus 141 in the Japanese study, (3) representation of a previously unstudied Middle Eastern population, and (4) rigorous statistical methodology including conditional logistic regression and comprehensive effect size reporting.

REM-OSA prevalence did not differ significantly between narcolepsy subtypes (30.0% in NT2 vs 24.2% in NT1, $\chi^2 = 0.01$, $p = 0.67$), a finding that challenges the expectation of greater REM-related respiratory instability in orexin-deficient NT1. If orexin deficiency were the primary driver of REM-related respiratory events, one would expect higher REM-OSA rates in NT1 patients. However, our findings suggest alternative mechanisms may be responsible for REM-OSA development in narcolepsy. Recent research has identified multiple pathways through which REM sleep and narcolepsy may influence respiratory control, including altered sleep architecture and modified arousal thresholds, which predispose to respiratory instability.[10,51] These mechanisms may operate independently of orexin status, potentially explaining the similar OSA risk across narcolepsy subtypes. Clinicians should maintain equal vigilance for OSA symptoms in both NT1 and NT2, as the presence or absence of cataplexy does not appear to influence the burden of respiratory comorbidity. Given that EDS is universal in narcolepsy, it is important to consider that coexisting OSA may contribute to or worsen this symptom, underscoring the need for polysomnographic evaluation regardless of narcolepsy subtype.

Beyond orexin pathways, emerging research suggests that sleep fragmentation itself may play a role in REM-OSA development in narcolepsy. The characteristic sleep instability in narcolepsy, evidenced by frequent sleep-onset REM periods and disrupted sleep architecture, may create conditions that favor REM-specific respiratory events.[52] Additionally, the altered arousal threshold in patients with REM-OSA might influence the termination of respiratory events, potentially prolonging apneas during REM sleep when arousal mechanisms are naturally suppressed.[53] These findings suggest that therapeutic interventions targeting sleep consolidation, in addition to traditional OSA treatments, may be particularly beneficial in this population.

While REM-OSA is often reported to be prevalent among middle-aged female patients, the majority of our study population was male (80%), yet REM-OSA remained prevalent. This demographic pattern may reflect referral bias in our tertiary care setting, where males with narcolepsy symptoms might be more likely to seek medical attention or be referred for sleep evaluation. However, the persistent high REM-OSA prevalence despite male predominance suggests that narcolepsy-related mechanisms may override typical gender-based risk patterns observed in general OSA populations, strengthening the hypothesis for an intrinsic pathophysiological link.

The geographic and ethnic diversity represented by our Middle Eastern cohort addresses a critical gap in narcolepsy research, which has been predominantly conducted in Asian, European, and North American populations. Given the potential influence of genetic, environmental, and lifestyle factors on sleep-disordered breathing patterns, our findings provide essential validation of REM-OSA prevalence in narcolepsy across different populations.[54]

Our study found that male sex, higher BMI, and elevated arousal index were significantly associated with OSA, consistent with established risk factors such as male predominance and obesity. Arousal index, an indicator of sleep fragmentation, also emerged as a significant correlate of REM-OSA. Elevated arousal index reflects frequent sleep interruptions and non-restorative sleep, which may contribute to EDS, even when total sleep time appears normal, and may exacerbate irresistible sleep attacks in individuals with narcolepsy.[55] Moreover, previous studies have identified the arousal index as a predictor of carotid atherosclerosis in patients with OSA,[56] underscoring the importance of treating OSA effectively. In our study, longer REM sleep duration was associated with a decreased risk of REM-OSA, possibly suggesting that patients with more stable REM sleep are less likely to experience REM-related apneas.

Comparison with a control group of patients with OSA but without narcolepsy revealed a trend toward higher REM-OSA prevalence among those with narcolepsy (26.4% vs 17.2%, OR: 1.73, 95% CI: 0.91–3.27, p = 0.09). While this difference did not achieve conventional statistical significance, the effect size (Cohen's h = 0.22) suggests a small to medium effect that may have clinical relevance. This trend did not meet conventional significance thresholds and should be viewed as hypothesis-generating, warranting validation in larger studies. The wide confidence interval reflects the inherent challenges of studying rare sleep disorders. It indicates that larger, multicenter studies are needed to definitively

establish whether narcolepsy contributes to REM-OSA development independent of traditional risk factors such as age, sex, and BMI. The observed trend aligns with theoretical considerations regarding altered REM sleep architecture in narcolepsy, though the current sample size may be insufficient to detect this association with adequate statistical power.[10]

Narcolepsy, OSA, and its subtype REM-OSA have all been associated with increased cardiometabolic risks.[57–59] The simultaneous presence of these conditions may have a synergetic effect, leading to worse cardiometabolic outcomes. This mandates close monitoring of cardiometabolic comorbidities and the concurrent treatment of both narcolepsy and OSA to optimize patient outcomes.

Our identification of independent associations between narcolepsy and REM-OSA supports the notion that sleep-disordered breathing subtypes warrant distinct clinical consideration, as REM-OSA has been found to be associated with increased risk of hypertension and metabolic complications such as insulin resistance and metabolic syndrome.[10] Recognizing REM-OSA in patients with narcolepsy warrants tailored evaluation and management to mitigate sleep fragmentation and improve daytime functioning through targeted interventions. These may include optimizing positive airway pressure therapy to address REM-specific obstruction and exploring adjunctive pharmacologic strategies that stabilize REM sleep or enhance upper airway muscle tone.[60] The clinical implications of our findings therefore extend beyond diagnostic considerations to treatment strategies. Current evidence suggests that patients with narcolepsy may respond differently to CPAP therapy compared to those with OSA alone, potentially requiring modified treatment approaches or adjunctive therapies.[4] Furthermore, the presence of REM-OSA in patients with narcolepsy may necessitate careful titration of CPAP pressures, as REM-specific respiratory events often require higher therapeutic pressures than non-REM events.[10] The interaction between narcolepsy medications and OSA treatment also warrants consideration, as stimulants commonly used for EDS may affect sleep architecture and potentially influence OSA severity.[61] Current evidence suggests that adherence to positive airway pressure (PAP) therapy in patients with REM-OSA is suboptimal, and the currently accepted criteria for good adherence to PAP therapy, 4 hours per night, may not be suitable for REM-OSA, as they do not cover most of the REM sleep periods.[10] Clinical management should consider potential confounding effects of narcolepsy treatments, such as sodium oxybate, which may exacerbate sleep-disordered breathing, highlighting the need for close monitoring and multidisciplinary care, though treatment with CPAP has been shown to normalize AHI in patients while continuing therapy with sodium oxybate.[62] Although prospective trials are needed, emerging evidence suggests that combined therapeutic approaches may yield superior outcomes through phenotypic clustering approaches that leverage the heterogeneity of OSA by classifying it into smaller, more homogeneous disorder subtypes, with approximately half of patients with narcolepsy with comorbid OSA who are adherent to PAP therapy showing improvements in EDS and sleep quality, though responses vary widely.[62,63] These complexities underscore the importance of integrating polysomnographic phenotyping with personalized patient care in a multidisciplinary setting, as OSA is a complex and heterogeneous disorder where severity criteria based on AHI alone do not capture the diverse spectrum of the condition.[60] Our findings thus highlight the clinical promise of REM-OSA phenotyping as a tool to refine management and alleviate disease burden in patients with narcolepsy.

Future research should prioritize several key areas to advance our understanding of the narcolepsy-REM-OSA relationship. First, longitudinal studies are needed to determine whether REM-OSA development precedes or follows narcolepsy onset, which could inform screening protocols and early intervention strategies. Second, investigations examining the response to different OSA treatments in patients with narcolepsy could guide evidence-based therapeutic approaches. Third, genetic studies exploring shared susceptibility factors between narcolepsy and REM-OSA may reveal novel pathophysiological pathways. Finally, research examining the impact of narcolepsy-specific treatments on OSA severity and REM-OSA prevalence could inform integrated management approaches.

Several limitations warrant careful consideration. First, the subtype comparison between NT1 and NT2 was strictly exploratory; the present study was not powered to detect smaller inter-subtype differences, and larger multicenter cohorts will be required to definitively address this question. The limited number of REM-OSA events (n = 28) reduced statistical power for subgroup analyses and fell below recommended thresholds for stable logistic regression, potentially inflating variance around these estimates. Nevertheless, the confidence interval around the primary estimate (OR = 1.73, 95% CI: 0.91–3.27) excludes a trivial effect, supporting our interpretation of a small-to-medium association that merits replication in larger samples. Second, the observational, retrospective design inherently limits causal inference and introduces

selection bias, a common issue in tertiary sleep clinic populations.[31] Third, incomplete orexin measurements restricted exploration of potential mechanisms linking orexin deficiency to REM-OSA, especially given the theoretical role of orexin in upper airway tone regulation during REM sleep. Forth, our single-ethnicity cohort from the Middle East limits generalizability to populations with different genetic backgrounds and environmental exposures. Fifth, sampling controls from the same tertiary center introduces referral bias, as both groups reflect specialized care-seeking populations rather than community samples.[28] Residual confounding remains possible because variables like detailed sleep architecture metrics and subclinical narcolepsy features were not matched. Additionally, heterogeneity in REM-OSA definitions complicates direct comparisons despite our stringent criteria. Furthermore, detailed REM sleep parameters (such as REM density, REM latency, and total REM duration) and specific sleep fragmentation indices (including apnea arousal index and PLMI arousal index) were not systematically extracted as part of the originally approved protocol. Future prospective studies incorporating these comprehensive sleep architecture parameters would be valuable for elucidating the detailed mechanistic pathways linking narcolepsy to REM-OSA. Finally, we did not assess treatment response or long-term outcomes, limiting direct clinical applicability.

Our choice of OSA patients as controls rather than healthy sleepers enhances internal validity for characterizing REM-OSA phenotype in narcolepsy by addressing clinically relevant dual pathology and controlling for the baseline effects of sleep-disordered breathing. However, this design limits conclusions about absolute REM-OSA prevalence in narcolepsy. Future studies with healthy controls and population-based samples are needed to establish baseline REM-OSA rates, particularly given recent evidence of variability in sleep-disordered breathing patterns across clinical populations. Thus, while our findings suggest a potential link between narcolepsy and REM-OSA, they should be viewed as hypothesis-generating and require validation in larger, multicenter studies with adequate power for detecting smaller effect sizes.

The borderline non-significant REM-OSA difference (χ^2=2.85, p=0.09; Cohen's h=0.22) had ~83% post-hoc power, suggesting a potentially meaningful effect (9.2% prevalence difference) warranting validation in larger studies. Subgroup analyses (NT1 vs NT2) were underpowered (only 28 REM-OSA events, ~9 EPV), falling below the recommended ≥10 EPV for stable logistic regression.[37,38] Thus, similar OSA prevalence between NT1 and NT2 should be interpreted cautiously. Multicenter collaborations recruiting larger, diverse cohorts with standardized REM-OSA definitions and comprehensive orexin measures are needed to clarify mechanisms and predictors of sleep-disordered breathing in narcolepsy across different ethnic and geographic populations. We also acknowledge that alternative definitions of REM-related OSA exist and were not tested in sensitivity analyses, which could influence prevalence estimates. Furthermore, given the limited number of REM-related OSA events (~28), small-sample bias remains possible. Future analyses may benefit from penalized regression methods such as Firth correction to address this.

Conclusion

This study represents the first controlled investigation of REM-OSA in patients with narcolepsy, advancing beyond previous descriptive reports through matched control design and comprehensive statistical analysis. Using stringent diagnostic criteria, we found a high prevalence of OSA (55.8%) and REM-OSA (26.4%) among patients with narcolepsy. A trend toward higher REM-OSA prevalence was observed compared to matched controls (26.4% vs 17.2%, p = 0.09), suggesting a potential association requiring validation in larger studies.

Importantly, OSA prevalence was virtually identical between NT1 and NT2 (55.5% vs 56.3%, p = 1.00), suggesting that sleep-disordered breathing risk may operate through mechanisms other than orexin deficiency status. These results emphasize the importance of comprehensive evaluation and tailored management strategies in patients with narcolepsy, while highlighting the need for adequately powered multicenter investigations to definitively establish the narcolepsy-REM-OSA relationship. Finally, observed differences that did not achieve statistical significance should be interpreted as hypothesis-generating and require validation in larger, multicenter cohorts.

Data Sharing Statement

Data can be obtained upon request from the corresponding author "ASB", but this requires institutional approval by the Institutional Review Board of the College of Medicine at King Saud University.

Ethics Approval and Informed Consent

The study received approval from the Institutional Review Board (IRB) at King Saud University Medical City (Approval Number: 19/0134IRB). Informed consent was obtained from all patients for clinical evaluation and data collection at the time of their initial assessment, with additional consent for research use of de-identified data when required by institutional policy. For this retrospective analysis, the requirement for additional informed consent was waived by the ethics committee because the study involved anonymized data and posed minimal risk to participants. All procedures involving human participants were conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its subsequent revisions.

Author Contributions

Hamza O. Dhafar: Conceptualization, Methodology, Writing – original draft preparation, Writing – review and editing, Project administration. Ali A. Awadh: Conceptualization, Writing – original draft preparation, Writing – review and editing. Salih A. Aleissi: Conceptualization, Writing – original draft preparation, Writing – review and editing. Galal Eldin Abbas Eltayeb: Formal analysis, Data curation, Writing – review and editing. Samar Nashwan: Formal analysis, Data curation, Writing – review and editing. Ahmed S. BaHammam: Conceptualization, Writing – original draft preparation, Writing – review and editing, Project administration, Supervision.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

The work was funded by the Strategic Technologies Program of the National Plan for Sciences and Technology and Innovation in the Kingdom of Saudi Arabia (08-MED511-02).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Longstreth WT, Koepsell TD, Ton TG, Hendrickson AF, van Belle G. The epidemiology of narcolepsy. *Sleep*. 2007;30(1):13–26. doi:10.1093/sleep/30.1.13
2. American Academy of Sleep M. *The International Classification of Sleep Disorders: (ICSD-3)*; 2014.
3. Bonsignore MR, Pepin JL, Cibella F, et al. Excessive daytime sleepiness in obstructive sleep apnea patients treated with continuous positive airway pressure: data from the European sleep apnea database. *Front Neurol*. 2021;12.
4. Sansa G, Iranzo A, Santamaria J. Obstructive sleep apnea in narcolepsy. *Sleep Med*. 2010;11(1):93–95. doi:10.1016/j.sleep.2009.02.009
5. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev*. 2017;34:70–81. doi:10.1016/j.smrv.2016.07.002
6. Lévy P, Kohler M, McNicholas WT, et al. Correction: obstructive sleep apnoea syndrome. *Nat Rev*. 2015;1(1). doi:10.1038/nrdp.2015.15
7. Almeneessier AS, Alshahrani M, Aleissi S, Hammad OS, Olaish AH, BaHammam AS. Comparison between blood pressure during obstructive respiratory events in REM and NREM sleep using pulse transit time. *Sci Rep*. 2020;10(1):3342. doi:10.1038/s41598-020-60281-2
8. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96(4):1897–1904. doi:10.1172/JCI118235
9. Lanfranchi PA, Somers VK. Cardiovascular physiology. *Principles Pract Sleep Med*. 2011;226–236.
10. Pirzada AR, BaHammam AS. Rapid eye movement predominant obstructive sleep apnoea: prognostic relevance and clinical approach. *Curr Opin Pulm Med*. 2021;27(6):514–522. doi:10.1097/MCP.0000000000000817
11. BaHammam AS, Alshahrani M, Aleissi SA, Olaish AH, Alhassoon MH, Shukr A. Blood pressure dipping during REM and non-REM sleep in patients with moderate to severe obstructive sleep apnea. *Sci Rep*. 2021;11(1):7990. doi:10.1038/s41598-021-87200-3
12. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328(17):1230–1235. doi:10.1056/NEJM199304293281704
13. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013;177(9):1006–1014. doi:10.1093/aje/kws342
14. Seneviratne U, Puvanendran K. Excessive daytime sleepiness in obstructive sleep apnea: prevalence, severity, and predictors. *Sleep Med*. 2004;5(4):339–343. doi:10.1016/j.sleep.2004.01.021
15. Dhafar HO, BaHammam AS. Body weight and metabolic rate changes in narcolepsy: current knowledge and future directions. *Metabolites*. 2022;12(11):1120. doi:10.3390/metabo12111120
16. Pataka AD, Frangulyan RR, Mackay TW, Douglas NJ, Riha RL. Narcolepsy and sleep-disordered breathing. *Eur J Neurol*. 2012;19(5):696–702. doi:10.1111/j.1468-1331.2011.03610.x

17. Koo BB, Patel SR, Strohl K, Hoffstein V. Rapid eye movement-related sleep-disordered breathing: influence of age and gender. *Chest*. 2008;134 (6):1156–1161. doi:10.1378/chest.08-1311
18. Wang Y, Deng T, Zhao X, et al. Control of breathing by orexinergic signaling in the nucleus tractus solitarii. *Sci Rep*. 2024;14(1):7473. doi:10.1038/s41598-024-58075-x
19. Tarasiuk A, Levi A, Berdugo-Boura N, Yahalom A, Segev Y. Role of orexin in respiratory and sleep homeostasis during upper airway obstruction in rats. *Sleep*. 2014;37(5):987–998. doi:10.5665/sleep.3676
20. Gestreau C, Bévengut M, Dutschmann M. The dual role of the orexin/hypocretin system in modulating wakefulness and respiratory drive. *Curr Opin Pulm Med*. 2008;14(6):512–518. doi:10.1097/MCP.0b013e32831311d3
21. Baumann CR, Mignot E, Lammers GJ, et al. Challenges in diagnosing narcolepsy without cataplexy: a consensus statement. *Sleep*. 2014;37 (6):1035–1042. doi:10.5665/sleep.3756
22. Kubin L. Neural control of the upper airway: respiratory and state-dependent mechanisms. *Compr Physiol*. 2016;6(4):1801–1850. doi:10.1002/j.2040-4603.2016.tb00729.x
23. Grimaldi D, Calandra-Buonaura G, Provini F, et al. Abnormal sleep-cardiovascular system interaction in narcolepsy with cataplexy: effects of hypocretin deficiency in humans. *Sleep*. 2012;35(4):519–528. doi:10.5665/sleep.1738
24. Miano S, Kheirandish-Gozal L, De Pieri M. Comorbidity of obstructive sleep apnea and narcolepsy: a challenging diagnosis and complex management. *Sleep Med*. 2024;8:100126.
25. Spinieli RL, Ben Musa R, Cornelius-Green J, Hasser EM, Cummings KJ. Orexin facilitates the ventilatory and behavioral responses of rats to hypoxia. *Am J Physiol Regul Integr Comp Physiol*. 2022;322(6):R581–r596. doi:10.1152/ajpregu.00334.2021
26. Hoshino T, Sasanabe R, Mano M, et al. Prevalence of rapid eye movement-related obstructive sleep apnea in adult narcolepsy. *Intern Med*. 2019;58 (15):2151–2157. doi:10.2169/internalmedicine.2601-18
27. Almeneessier AS, Alballa NS, Alsalman BH, Aleissi S, Olaish AH, BaHammam AS. A 10-year longitudinal observational study of cataplexy in a cohort of narcolepsy type 1 patients. *Nat Sci Sleep*. 2019;11:231–239. doi:10.2147/NSS.S229105
28. Benchimol EI, Smeeth L, Guttmann A, et al. The reporting of studies conducted using observational routinely-collected health data (RECORD) statement. *PLoS Med*. 2015;12(10):e1001885. doi:10.1371/journal.pmed.1001885
29. Sedgwick P. Retrospective cohort studies: advantages and disadvantages. *BMJ*. 2014;348(g1072).
30. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Int J Surg*. 2014;12(12):1500–1524. doi:10.1016/j.ijsu.2014.07.014
31. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Ann Intern Med*. 2007;147(8):W163–194. doi:10.7326/0003-4819-147-8-200710160-00010-w1
32. Kanbr O, Wali S, Wasfi L, et al. Prevalence and characteristics of rapid eye movement-related sleep apnea in a population-based cohort. *Ann Thorac Med*. 2025;20(2):117–124. doi:10.4103/atm.atm_188_24
33. Berry RB, Brooks R, Gamaldo CE, et al. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.1*. Darien, Illinois: American Academy of Sleep Medicine; 2014.
34. AASM. American Academy of Sleep Medicine (AASM). *International Classification of Sleep Disorders (ICSD)*. 3rd ed. Darien, IL: AASM; 2014.
35. Conwell W, Patel B, Doeing D, et al. Prevalence, clinical features, and CPAP adherence in REM-related sleep-disordered breathing: a cross-sectional analysis of a large clinical population. *Sleep Breath*. 2012;16(2):519–526. doi:10.1007/s11325-011-0537-6
36. Sakao S, Sakurai T, Yahaba M, et al. Features of REM-related sleep disordered breathing in the Japanese population. *Intern Med*. 2015;54 (12):1481–1487. doi:10.2169/internalmedicine.54.4248
37. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996;49(12):1373–1379. doi:10.1016/S0895-4356(96)00236-3
38. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. *Am J Epidemiol*. 2007;165(6):710–718. doi:10.1093/aje/kwk052
39. Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G*power 3.1: tests for correlation and regression analyses. *Behavior Research Methods*. 2009;41(4):1149–1160. doi:10.3758/BRM.41.4.1149
40. Cohen J. *Statistical Power Analysis for the Behavioral Sciences (2nd Ed.)*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
41. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Stat Sci*. 2001;16(2):101–133,133. doi:10.1214/ss/1009213286
42. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med*. 1998;17(8):857–872. doi:10.1002/(SICI)1097-0258(19980430)17:8<857::AID-SIM777>3.0.CO;2-E
43. Pizza F, Tartarotti S, Poryazova R, Baumann CR, Bassetti CL. Sleep-disordered breathing and periodic limb movements in narcolepsy with cataplexy: a systematic analysis of 35 consecutive patients. *Eur Neurol*. 2013;70(1–2):22–26. doi:10.1159/000348719
44. Frauscher B, Ehrmann L, Mitterling T, et al. Delayed diagnosis, range of severity, and multiple sleep comorbidities: a clinical and polysomnographic analysis of 100 patients of the innsbruck narcolepsy cohort. *J Clin Sleep Med*. 2013;9(8):805–812. doi:10.5664/jcsm.2926
45. BaHammam AS, Alenezi AM. Narcolepsy in Saudi Arabia. Demographic and clinical perspective of an under-recognized disorder. *Saudi Med J*. 2006;27(9):1352–1357.
46. Black J, Reaven NL, Funk SE, et al. Medical comorbidity in narcolepsy: findings from the burden of narcolepsy disease (BOND) study. *Sleep Med*. 2017;33:13–18. doi:10.1016/j.sleep.2016.04.004
47. Maski K, Mignot E, Plazzi G, Dauvilliers Y. Disrupted nighttime sleep and sleep instability in narcolepsy. *J Clin Sleep Med*. 2022;18(1):289–304. doi:10.5664/jcsm.9638
48. Terada J, Nakamura A, Zhang W, et al. Ventilatory long-term facilitation in mice can be observed during both sleep and wake periods and depends on orexin. *J Appl Physiol*. 2008;104(2):499–507. doi:10.1152/japplphysiol.00919.2007
49. Zhang GH, Liu ZL, Zhang BJ, et al. Orexin A activates hypoglossal motoneurons and enhances genioglossus muscle activity in rats. *Br J Pharmacol*. 2014;171(18):4233–4246. doi:10.1111/bph.12784
50. Yamada R, Koike T, Nakakariya M, Kimura H. Orexin receptor 2 agonist activates diaphragm and genioglossus muscle through stimulating inspiratory neurons in the pre-Bötzinger complex, and phrenic and hypoglossal motoneurons in rodents. *PLoS One*. 2024;19(6):e0306099. doi:10.1371/journal.pone.0306099

51. Bonsignore MR, Mazzuca E, Baiamonte P, Bouckaert B, Verbeke W, Pevernagie DA. REM sleep obstructive sleep apnoea. *Eur Respir Rev*. 2024;33(171):230166. doi:10.1183/16000617.0166-2023
52. Vilela M, Tracey B, Volfson D, et al. Identifying time-resolved features of nocturnal sleep characteristics of narcolepsy using machine learning. *J Sleep Res*. 2024;33(6):e14216. doi:10.1111/jsr.14216
53. Hoshino T, Sasanabe R, Murotani K, et al. Estimated respiratory arousal threshold in patients with rapid eye movement obstructive sleep apnea. *Sleep Breath*. 2022;26(1):347–353. doi:10.1007/s11325-021-02399-9
54. Zhou R, Suo C, Jiang Y, et al. Association of sleep pattern and genetic susceptibility with obstructive sleep apnea: a prospective analysis of the UK biobank. *Nat Sci Sleep*. 2024;16:503–515. doi:10.2147/NSS.S443721
55. Huang EI, Huang SY, Lin YC, et al. Respiratory arousals in patients with very severe obstructive sleep apnea and how they change after a non-framework surgery. *Healthcare*. 2022;10(5). doi:10.3390/healthcare10050902
56. Suzuki M, Shimamoto K, Sekiguchi H, et al. Arousal index as a marker of carotid artery atherosclerosis in patients with obstructive sleep apnea syndrome. *Sleep Breath*. 2019;23(1):87–94. doi:10.1007/s11325-018-1664-0
57. Mokhlesi B, Varga AW. Obstructive sleep apnea and cardiovascular disease. rem sleep matters! *Am J Respir Crit Care Med*. 2018;197(5):554–556. doi:10.1164/rccm.201710-2147ED
58. Kwon Y, Gami AS, Javaheri S, et al. Cardiovascular risks in people with narcolepsy: expert panel consensus recommendations. *J Am Heart Assoc*. 2024;13(16):e035168. doi:10.1161/JAHA.124.035168
59. BaHammam AS. Cardiovascular disease risk and comorbidities in narcolepsy. In: BaHammam AS, Sharafkhaneh A, Pandi-Perumal SR, editors. *Narcolepsy: Integrating Basic and Clinical Knowledge*. London, United Kingdom: Academic Press, Elsevier; 2025:221–234.
60. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea – new pathways for targeted therapy. *Sleep Med Rev*. 2018;37:45–59. doi:10.1016/j.smrv.2016.12.003
61. Sullivan SS, Guilleminault C. Emerging drugs for common conditions of sleepiness: obstructive sleep apnea and narcolepsy. *Expert Opin Emerg Drugs*. 2015;20(4):571–582. doi:10.1517/14728214.2015.1115480
62. Mallampalli A. More than just narcolepsy: the importance of recognizing concurrent sleep disorders. In: BaHammam AS, Sharafkhaneh A, Pandi-Perumal SR, editors. *Narcolepsy: Integrating Basic and Clinical Knowledge*. Chennai, India: Elseveir; 2025:235–249.
63. Zinchuk A, Yaggi HK. Phenotypic subtypes of OSA: a challenge and opportunity for precision medicine. *Chest*. 2020;157(2):403–420. doi:10.1016/j.chest.2019.09.002