

# Clinical associations between allergies and rapid eye movement sleep disturbances

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**Background:** Allergic rhinitis, an immunoglobulin E inflammatory condition including nasal congestion, obstruction, sneezing, pruritus, and fatigue symptoms, has significant impact on quality of life and impairs sleep. Sleep-disordered breathing (SDB) patients often have normal all-night apnea-hypopnea (AHI) or respiratory-disturbance (RDI) indices on polysomnography (PSG). We hypothesized that the rapid eye motion-respiratory disturbance index (REM-RDI) may be a novel predictor of allergic status.

**Methods:** A retrospective analysis of 100 patients compared REM-RDI results in 67 allergen-positive patients with 33 nonallergic patients who presented with nasal blockage. Subjects completed STOP-Bang<sup>®</sup>, 22-item Sino-Nasal Outcome Test (SNOT-22)<sup>®</sup>, and Epworth Sleepiness Scale<sup>®</sup> questionnaires and underwent skin-prick testing (SPT) and PSGs including REM-RDI values. Using multivariate logistic regression models, we evaluated relationships between allergic status and sleep parameters while controlling for possible confounders including body mass index (BMI).

**Results:** Using REM-RDI as the outcome of interest, allergen-positive patients were 3.92 times more likely to have REM-RDI values in a moderate/severe range ( $\geq 15$  events/hour); and patients with moderate/severe REM-RDI values were more likely to be allergen positive ( $p < 0.05$ ). Allergic status was not significantly related to all-night AHI, RDI, or REM-AHI. BMI was not significantly related to REM-

RDI. STOP-Bang<sup>®</sup> was related to allergy status ( $p = 0.02$ ) and REM-RDI ( $p < 0.01$ ). Allergic patients had increased REM latency and less total amount of REM.

**Conclusion:** We revealed significant bidirectional associations between allergen positivity and increased REM-RDI values independent of BMI, AHI, RDI, and REM-AHI. Allergic inflammation and REM-RDI data may play important roles in diagnosing and treating fatigued SDB patients and as objective perioperative safety and outcomes measures. © 2018 The Authors International Forum of Allergy & Rhinology, published by ARSAAOA, LLC.

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### Key Words:

allergic rhinitis; AR; SNOT-22; evidence-based medicine, skin-prick test; SPT; quality of life; QOL; nasal airflow dynamics; allergens

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Allergy-related disorders are increasingly prevalent problems that have detrimental effects on quality of

life (QOL), sleep, and subsequent daytime functioning.<sup>1,2</sup> Affecting up to 40 million Americans and approximately 10% to 25% of the population worldwide, allergic upper airway disorders are an increasing socioeconomic burden.<sup>3-5</sup> Presenteeism impairments in school and work performance and absenteeism account for indirect health care costs.<sup>6-8</sup>

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Allergic disorders are caused by inflammatory processes led by inflammatory mediators, notably immunoglobulin E (IgE) in the nasal mucus membranes, eyes, Eustachian tubes, middle ears, sinuses, and throughout the pharynx.<sup>9–11</sup> Allergic rhinitis (AR) and upper airway disease are well-known risk factors for sleep-disordered breathing (SDB), a spectrum of disorders ranging from snoring to all-night obstructive sleep apnea (OSA).<sup>12</sup> Symptoms including congestion, obstruction, postnasal drip, rhinorrhea, sneezing, and pruritus can significantly impact QOL.<sup>12–15</sup> Sleep impairment is a common comorbid complaint in allergic disease, partly from nasal congestion and obstruction resulting in nocturnal mouth breathing.<sup>15–17</sup> Obstructed nasal outflow from mucosal inflammation reduces the internal nasal valve diameter, increases nasal passage resistance, escalates respiratory and arousal events, and results in sleep fragmentation.<sup>16–18</sup>

Sleep is a crucial component of both physical and mental health; deprivation is linked to impaired immunity, poor wound healing, and to the development of chronic diseases.<sup>1</sup> More specifically, rapid eye movement (REM) sleep is the deep restorative stage of sleep that can be heavily affected by allergic disorders.<sup>19–21</sup> REM sleep occurs for approximately 20% of a normal night of sleep and is important for learning, memory, and dreaming.<sup>22–24</sup> Allergies and sleep disturbances have been linked to declines in cognitive function, learning, development, productivity, performance, and increased daytime sleepiness.<sup>24–26</sup> Although the relationship between allergies and impaired sleep has been well documented, most studies have used subjective parameters to support their findings.<sup>27–29</sup> The REM–respiratory disturbance index (REM-RDI) includes apneas, hypopneas, and respiratory effort–related arousals (RERAs) uniquely during REM.<sup>22,24–26</sup> We hypothesized that the REM-RDI could be a more specific indicator of REM-specific sleep disturbances associated with allergies than the more commonly referenced all-night apnea-hypopnea index (AHI) that volume-averages out REM-specific disturbances because its denominator reflects time spent in REM plus non-REM sleep stages. There is a paucity of literature that demonstrates a direct effect of allergy specifically on REM sleep supported by objective measurements.<sup>28,30,31</sup> The senior author (S.B.) observed abnormally high REM-RDI values in her sleep-deprived allergy-positive patients in spite of normal AHI, RDI, and REM-AHI values. The purpose of this retrospective study was to investigate the relationship between allergies and SDB using the REM-RDI sleep parameter as a novel primary outcome of interest to compare the results from a group of otherwise healthy study subjects who had allergies with nonallergic subjects.

## Subjects and methods

### Study design and setting

This was a retrospective cross-sectional study that evaluated the relationship between REM-RDI and allergic status

by comparing study subjects who presented to a suburban private otolaryngology practice between 2014 and 2015 with primary complaints of upper airway obstruction, suspected allergic inflammation, and/or SDB who tested positive for allergies compared with allergy test–negative subjects. This study was approved by the Institutional Review Board of NY Medical College in 2017.

### Study sample

Of the 296 potential study subjects, 100 met inclusion criteria, which consisted of symptoms that could be attributed to allergy or a form of SDB as determined by clinical questionnaires. They all underwent a form of allergy testing and polysomnography (PSG) with complete sleep stage documentation during the symptomatic period. A total of 196 subjects were excluded for having incomplete allergy or PSG test records; respiratory disease not attributed to allergy; significant anatomic nasal blockages such as septal deviation, polyps, or nasal valve collapse; or treatment with topical or systemic corticosteroids, decongestants, antihistamines, and/or sleep-altering medications.

### Questionnaires

STOP-Bang<sup>®</sup>, 22-item Sino-Nasal Outcome Test (SNOT-22)<sup>®</sup>, SNOT-22 sleep-subscore, and Epworth Sleepiness Scale (ESS)<sup>®</sup> questionnaires<sup>32–37</sup> were screening tools used to gauge the severity of sleep impairment and allergic symptoms. The STOP-Bang<sup>®</sup> obesity cutoff was modified from  $\geq 35$  kg/m<sup>2</sup> to  $\geq 30$  kg/m<sup>2</sup> to include obesity class 1, and a systolic blood pressure cutoff of  $\geq 135$  mmHg and/or diastolic of  $\geq 85$  mmHg defined hypertension.<sup>38</sup> The SNOT-22 sleep-subscore contained only the sleep-related questions (questions 13–17). Patient's symptoms were captured using this consistent protocol justifying appropriate allergy and/or sleep test ordering.

### Allergy testing

#### Skin-prick testing

Skin-prick testing (SPT) consisted of 46 Northeast U.S. geographic area–standardized allergen extracts (Stallergenes-Greer, London, U.K.). This included dust mites, trees, grasses, weeds, molds, and pet danders. Patients on beta-blockers or antihistamines were not skin tested. Negative glycerin and positive histamine hydrochloride (1 mg/mL) controls were placed using Multitest<sup>®</sup> II (Lincoln Diagnostics, Decatur, Illinois) applicators on the volar forearms. Results were recorded after 15 minutes. Positive reactions were determined by wheals 3 mm or greater than the negative control.

#### ImmunoCAP<sup>®</sup> allergy blood testing

ImmunoCAP<sup>®</sup> (ThermoFisher Scientific, Portage, MI) testing was performed in patients unable to undergo SPT; ie, patients with dermatographia or on beta-blockers. Using quantitative radioimmunoassay blood testing,

allergen-specific IgE antibodies can be detected. ImmunoCAP<sup>®</sup> results vary from 0.1 to 100 kU/L and are ranked by class severity from 0 to 6. Class 1 (very low allergen) at 0.35 kU/L is commonly used as the optimal lower cutoff for positive atopy.

### *Intradermal dilutional testing/modified quantitative testing*

Patients with allergic symptoms interested in immunotherapy underwent intradermal testing (intradermal dilutional testing [IDT]/modified quantitative testing [MQT]) to reveal possibly clinically significant low-sensitivity allergens; ie, molds. Using a thin 26G needle, a diluted allergen was injected into the superficial dermis on the outer upper arms over the deltoid muscles. Positive results were wheals at least 7 mm in diameter or 2 mm larger than the 2% glycerin control.

### *PSG*

Sleep quality, stages, respiratory events, and REM correlative data were obtained using in-laboratory PSG software or home sleep test (HST) medical devices (WatchPAT, Itamar Medical Ltd., Caesarea, Israel) with certified respiratory/sleep technicians or proprietary algorithms scoring the respiratory disturbance index values. WatchPAT was extensively validated against in-laboratory PSG (“the gold standard”), with a documented correlation of 90%.<sup>39</sup> Sleep study physiologic parameters for both in-laboratory PSG and HST devices were recorded and standardized in accordance with American Academy of Sleep Medicine definitions (AASM)<sup>40–42</sup> including: total sleep time, sleep and REM latencies, wakefulness, Non-REM N1, N2, slow wave sleep, and REM stage %, all-night AHI, RDI, REM-AHI, and REM-RDI values. Since there are no established reference ranges for REM-RDI, we used cutoffs based on accepted AHI and RDI ranges: normal (0–4.9 events per hour) to mild (5–14.9 events per hour) and moderate (15–29.9 events per hour) to severe ( $\geq 30$  events per hour); our statistical analysis stratified into normal-mild (0–14.9) and moderate to severe ( $\geq 15$ ) groups.

Apneas were defined as larger than 90% drops in peak airflow signal excursions for at least 10-second durations. Hypopneas were events lasting at least 10 seconds with at least 30% reductions in thoracoabdominal movement or airflow with at least 4% declines in oxygen saturation and/or electroencephalographic arousal or 50% reductions in thoracoabdominal movement or airflow with at least 3% reductions in oxygen saturation. RERAs were events of increasing respiratory effort for greater than 10 seconds leading to arousals from sleep not fulfilling apnea or hypopnea criterion. The REM-RDI index isolates these 3 types of events only during the REM sleep stage specifically, excluding respiratory events during non-REM sleep.

### **Statistical analysis**

Data were extracted from patient charts and entered into a database by a trained research assistant, triple-checked for errors, and cross-referenced with the electronic health record. Demographic, clinical, and sleep study parameters were compared using independent samples *t* tests for continuous variables and Pearson  $\chi^2$  for categorical variables. Being allergic was established as positive testing to at least 1 antigen. Sleep-related questionnaires were scored and results compared between nonallergic and allergic subjects using independent samples *t* tests. Linear regression models were used to evaluate the relationship between REM-RDI and score results from the sleep-related questionnaires using allergy status as a predictor.

Multiple logistic regression models were used to evaluate associations between various outcomes including allergic status, all night AHI, all-night RDI, REM-AHI, and REM-RDI adjusted for age, gender, BMI, %REM sleep, and AHI and REM-RDI as covariates. Statistical significance was defined as  $p < 0.05$ . Stata Statistical Software: Release 12 (StataCorp, College Station, TX) was used for all analyses.<sup>43</sup>

### **Results**

Demographic characteristics, clinical measures of disease, and indices of sleep-disordered disease severity are found in Table 1. Study subjects who tested positive for allergies were significantly younger than those who did not ( $p = 0.01$ ). The time to REM ( $p < 0.001$ ) was significantly longer and the percentage of REM sleep ( $p = 0.04$ ) was significantly less in patients with allergen positivity.

The results from the comparison of the scores of 4 sleep-related questionnaires in nonallergic vs allergic subjects are presented in Table 2. There was a statistically significant higher modified STOP-Bang<sup>®</sup> score in nonallergic vs allergic subjects ( $p = 0.02$ ).

The relationship between REM-RDI and scores on sleep-related questionnaires (adjusted for allergic status) is shown in Table 3. For every 1-unit increase in the STOP-Bang<sup>®</sup> score, the REM-RDI was increased by 4.48 units holding allergy status constant.

The relationships between the outcomes allergic status, all night AHI and RDI, REM-AHI, and REM-RDI with predictive variables using regression modeling are found in Table 4. Using allergic status as the outcome, every 1-unit increase in BMI resulted in subjects who were 1.1 times less likely to be allergic. A 1% increase in REM sleep resulted in 1.2 times lower likelihood of being allergic. Subjects with a moderate to severe REM-RDI range ( $\geq 15$  events per hour of sleep) were 5.1 times more likely to be allergic compared with subjects who had a REM-RDI in the normal to mild range (0–14.9) adjusted for other covariates.

With AHI as the outcome, every 1-unit increase in BMI had a 1.24 increased chance of having a moderate to severe AHI ( $p < 0.001$ ). With RDI as the outcome, for every 1-unit increase in AHI there was a 1.55 times

**TABLE 1.** Demographics, clinical measures, and indices of sleep-disordered disease severity

	Allergy-negative (n = 33)	Allergy-positive (n = 67)	p
Gender, n (%) <sup>a</sup>			0.94
Male	18 (18)	36 (36)	
Female	15 (15)	31 (31)	
Age (years), mean ± SD <sup>b</sup>	55.03 ± 15.80	46.70 ± 15.69	0.01*
BMI, mean ± SD <sup>b</sup>	30.45 ± 5.90	28.58 ± 5.99	0.20
HTN, n (%) <sup>a</sup>	16 (48.5)	26 (38.8)	0.36
Sleep study parameters (events/hour of sleep)			
AHI, mean ± SD <sup>b</sup>	14.13 ± 15.03	13.33 ± 15.60	0.81
RDI, mean ± SD <sup>b</sup>	19.26 ± 13.91	18.64 ± 14.92	0.84
REM-RDI, mean ± SD <sup>b</sup>	22.68 ± 15.95	25.91 ± 15.89	0.34
ODI, mean ± SD <sup>b</sup>	8.93 ± 12.26	7.31 ± 11.64	0.49
Number of respiratory events, n (%) <sup>a</sup>	118.42 (81.57)	111.97 (86.97)	0.72
Number of times awake, n (%) <sup>a</sup>	3.2 (10.26)	13.6 (36.63)	0.16
Oxygen %, mean ± SD <sup>b</sup>	93.48 ± 2.18	94.37 ± 2.19	0.06
Time below 80% (units), mean ± SD <sup>b</sup>	0.32 ± 1.67	1.92 ± 12.69	0.47
Time to REM (minutes), mean ± SD <sup>b</sup>	87.28 ± 49.30	115.85 ± 69.65	<0.001*
REM sleep %, mean ± SD <sup>b</sup>	25.76 ± 7.75	22.35 ± 7.81	0.04*

<sup>a</sup>Pearson  $\chi^2$ .<sup>b</sup>Independent samples t test.\*Significant at  $p < 0.05$ .

AHI = apnea hypopnea index; BMI = body mass index; HTN = hypertension; ODI = oxygen desaturation index; RDI = respiratory disturbance index; REM = rapid eye movement; REM-RDI = rapid eye movement respiratory disturbance index; SD = standard deviation.

**TABLE 2.** Results from sleep-related questionnaires in nonallergic and allergic subjects

Questionnaire	Nonallergic		Allergic		p <sup>a</sup>
	n	Mean ± SD	n	Mean ± SD	
STOP-Bang <sup>®</sup>	33	5.12 ± 1.60	67	4.21 ± 1.88	0.02
Epworth Sleepiness Scale <sup>®</sup>	23	8.39 ± 4.81	46	8.13 ± 4.96	0.84
SNOT-22 <sup>®</sup>	19	29.32 ± 15.76	32	31.2 ± 19.25	0.72
SNOT-22 <sup>®</sup> Sleep Subscore	17	11.41 ± 6.79	28	11.67 ± 7.26	0.9

<sup>a</sup>Independent samples t test.

SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

greater likelihood that a subject would have an RDI in the moderate to severe range ( $p < 0.001$ ). When REM-AHI was the outcome, for every 1-unit increase in BMI, there was a 1.3 times greater likelihood that a subject would have a REM-AHI in the moderate to severe range ( $p < 0.05$ ) holding all other variables constant. Every 1-unit increase in the moderate to severe REM-RDI value had a 1.36 times higher chance of having a REM-AHI in the moderate to severe range. The status of being allergic was not significantly related to AHI, RDI, or the REM-AHI.

With REM-RDI as the outcome of interest, being allergic did show a 3.92 times greater chance of having a REM-RDI in the moderate to severe range ( $p < 0.05$ ). Every 1-unit increase in the AHI had a 1.2 times greater chance of having a moderate to severe REM-RDI ( $p < 0.01$ ).

## Discussion

Our investigation found a significant relationship between allergic status and REM-RDI independent of BMI. To our

**TABLE 3.** Relationship between REM-RDI and sleep-related questionnaires

	REM-RDI	Nonallergic (n)	Allergic (n)	Coefficient ( $\beta$ ) <sup>a</sup>	95% CI
<b>STOP-Bang<sup>®</sup></b>					
	<5	3	2		
	5–14.9	10	13		
	15–30	11	29		
	≥30	9	23		
	Total	33	67	4.48 <sup>*</sup>	(2.93,6.02)
<b>Epworth Sleepiness Scale<sup>®</sup></b>					
	<5	2	2		
	5–14.9	7	8		
	15–30	8	20		
	≥30	6	16		
	Total	23	46	–0.1	(–0.95,0.74)
<b>SNOT-22<sup>®</sup></b>					
	<5	3	2		
	5–14.9	3	4		
	15–30	6	15		
	≥30	7	11		
	Total	19	32	0.11	(–0.13,0.36)
<b>SNOT-22<sup>®</sup> Sleep Subscore<sup>e</sup></b>					
	<5	3	2		
	5–14.9	3	4		
	15–30	6	11		
	≥30	5	11		
	Total	17	28	0.15	(–0.54,0.86)

<sup>a</sup>Linear regression.

<sup>b</sup>Reference for STOP-Bang<sup>®</sup> adjusted for obesity class I (BMI ≥30 kg/m<sup>2</sup>).<sup>32–34</sup>

<sup>c</sup>Reference for Epworth-Sleepiness scale<sup>®</sup>.<sup>37</sup>

<sup>d</sup>Reference for SNOT-22<sup>®</sup>.<sup>35,36</sup>

<sup>e</sup>Reference for SNOT-22<sup>®</sup> Sleep Subscore.<sup>35,36</sup>

\* $p < 0.01$ .

BMI = body mass index; CI = confidence interval; REM-RDI = rapid eye movement respiratory disturbance index; SNOT-22 = 22-item Sino-Nasal Outcome Test.

knowledge, this is the first study to support the clinical use of REM-RDI to evaluate fatigue and suspected allergy in otolaryngology patients. Our data supports an influence of allergens on sleep disturbances, especially during REM.

Many patients affected by OSA and SDB fail to resolve their sleep disorders with weight loss alone.<sup>44</sup> Some patients affected by SDB fail to fit into a category of BMI-defined obesity (BMI ≥30) so other clinically relevant factors such as allergies must be impacting their sleep quality.<sup>44–46</sup> Traditionally, REM-OSA has been diagnosed by looking at REM-AHI values. Focusing upon RERA events during REM, the REM-RDI was elevated uniquely in our allergic patients regardless of BMI increases. Our allergic patients

were statistically younger than nonallergic individuals, an observation previously noted possibly because of decreases in immune system skin test responses as patients age.<sup>47</sup>

We were able to demonstrate the bidirectionality of allergen positivity resulting in higher REM-RDI values as well as higher REM-RDI values predicting allergic status. Although OSA has been linked to AR, it has not been established whether AR is associated with OSA.<sup>4</sup> Our results confirmed this known prevalence and bidirectionality of sleep problems in upper airway allergy sufferers, and provides for a currently underappreciated role of otolaryngologists testing and providing for medical and surgical management of these burdensome diseases.<sup>45</sup>

**TABLE 4. Relationship between predictive variables and allergic status, AHI, RDI, REM-AHI, REM-RDI†**

Outcomes	Predictors											
	Allergic status		AHI		BMI		% REM Sleep		REM-RDI			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Allergic status <sup>a</sup>	–	–	1.02	(0.98,1.07)	<b>0.84**</b>	(0.75,0.96)	<b>0.89**</b>	(0.83,0.96)	<b>5.08*</b>	(1.41,18.27)		
AHI <sup>b</sup>	3.22	(0.68,15.36)	–	–	<b>1.24***</b>	(1.08,1.42)	1.1	(0.99,1.2)	6.54	(0.98,43.45)		
RDI <sup>c</sup>	0.45	(0.09,2.17)	<b>1.55***</b>	(1.28,1.88)	0.92	(0.79,1.08)	1.03	(0.93,1.13)	–	–		
REM-AHI <sup>d</sup>	2.64	(0.22,32.23)	–	–	<b>1.28*</b>	(1.05,1.56)	1.00	(0.88,1.16)	<b>1.36**</b>	(1.13,1.64)		
REM-RDI <sup>e</sup>	<b>3.92*</b>	(1.05,14.59)	<b>1.2*</b>	(1.06,1.36)	1.08	(0.96,1.21)	1.03	(0.95,1.12)	–	–		

†Bold values are significant.

AHI = apnea hypopnea index; BMI = body mass index; CI = confidence interval; OR = odds ratio; RDI = respiratory disturbance index; REM = rapid eye movement; REM-AHI = rapid eye movement apnea hypopnea index; REM-RDI = rapid eye movement respiratory disturbance index.

<sup>a</sup>Logistic regression adjusted for age and gender. RDI reference category: "0–14.9 events per hour."

<sup>b</sup>Logistic regression adjusted for age and gender. REM-RDI reference category: "0–14.9 events per hour."

<sup>c</sup>Logistic regression adjusted for age and gender. REM-AHI reference category: "0–14.9 events per hour."

<sup>d</sup>Logistic regression adjusted for age and gender. AHI reference category: "0–14.9 events per hour."

<sup>e</sup>Logistic regression adjusted for age and gender. Allergic status reference category: "non-allergic."

\**P* < 0.05.

\*\**P* < 0.01.

\*\*\**P* < 0.001.

We administered validated subjective screening questionnaires but only the STOP-Bang<sup>®</sup> questionnaire significantly correlated with allergy status. This was consistent with prior studies whereby rhinitis was associated with a 1.44 times higher odds ratio for having increased OSA risk defined in accordance with STOP-Bang<sup>®</sup>.<sup>48</sup> It is very likely that when sleep disturbance is combined with allergies, symptom severity is subjectively higher. When focusing on REM-RDI among allergen-positive subjects, there was a significant increase in REM-RDI severity for every 1-unit increase in STOP-Bang<sup>®</sup>. Although the SNOT-22<sup>®</sup> and SNOT-22 sleep subscores showed no significant difference between allergy-positive and allergy-negative subjects, we found them to be useful screening tools.<sup>49</sup> Practitioners should maintain a high suspicion in sleep-disturbed populations that there may be an underlying allergic component and should be encouraged to elicit allergy and OSA symptoms.

We add allergen-positive status to a growing list of conditions that have REM abnormalities in common such as fatigue, diabetes, and hypertension.<sup>50–52</sup> It is suspected that the obstructive symptoms of AR worsen at night partly because of the circadian pattern most inflammatory diseases follow through a cascade of autonomic nervous system activation, histamine release, and vagal tone leading to vasodilation and an increase in secretions.<sup>1,52–55</sup> Continued exposures to bedroom dust mites and mold allergens from adjacent bathrooms and water leakages might trigger this inflammation.<sup>56</sup> Nasal airflow seems to follow a similar endogenous circadian rhythm pattern with our metabolic, immunologic, and endocrine systems as obstruction/congestion increases throughout the night and peaks in the early morning.<sup>57</sup> These labile autonomic changes during REM sleep periods coincide with significantly longer desaturations that profoundly affect sleep and systemic health.<sup>46,50,51,58</sup> BMI-independent microarousals most likely emerge during REM sleep.

We demonstrated that allergens have a significant effect preferentially on the REM-RDI independent of all-night AHI, RDI, and REM-AHI. Earlier studies have concluded that nasal congestion in AR is a primary contributor to the increase in the number of apneic episodes, RERAs, and microarousals that cause sleep disturbances.<sup>59–61</sup> In children with AR and moderate to severe OSA, a significantly elevated AHI was seen during REM sleep.<sup>62</sup> Our results showed our allergic patients to have disturbed REM sleep. Not only did they take longer to enter REM, but they also had less total percent REM sleep and more disturbed REM quality. We found no significant relationships with allergy-positive subjects when using all-night AHI, RDI, or REM-AHI as outcomes of interest, which highlights the importance of using moderate-to-severe REM-RDI values in a novel way to suspect allergies.

We had hypothesized that already inflamed situationally paralyzed upper airway structures would preferentially narrow air passages during REM due to REM stage-specific


skeletal muscle atonia. Despite the pharynx often being focused on as the primary area of obstruction in OSA, upstream nasal resistance can limit downstream pharyngeal airflow.<sup>61,63</sup> Throughout human evolution, narrowing of the upper aerodigestive tract compensated for the predisposition to speech and language. Stupak<sup>64</sup> proposed the function of the external nose is to facilitate a curvilinear airflow into the nasopharynx, lifting the soft palate to permit airway opening. While this is negligible in the awake state due to pharyngeal tone, during sleep a change in the curvilinear airflow creates a propensity for OSA.<sup>64</sup> As demonstrated by Kimura et al.,<sup>60</sup> an increase in nasal resistance has a direct association with the nasal cycle occurring primarily around REM sleep, and never occurs during non-REM (NREM) slow-wave sleep. The association of increased congestion during REM sleep has been demonstrated through objective serial acoustic rhinometry and is followed by decongestion in the NREM stages.<sup>59,62</sup> Increases in nocturnal nasal congestion, often exacerbated by lying in a supine position, may be even more relevant during REM sleep where muscle paralysis plays a role in the collapse of an already obstructed nose.<sup>61,65-67</sup>

We suspect patients who were allergen-positive but who had no REM-RDI disturbances might have greater nasal patency and therefore minimized REM nasal obstruction even in the setting of mucosal inflammation; they might also have been sleep tested during a nonallergic season. Although there are no consistent objective efficacy measures for previous immunotherapy, patients treated with allergy injection, subcutaneous immunotherapy (SCIT), or sublingual immunotherapy (SLIT) may show reduced REM-RDI values. To the contrary, patients with negative allergy testing and REM-RDI elevations may have persistent nasal obstructions or downstream mechanical obstructions at the level of the oropharynx, hypopharynx, and/or larynx

amenable to future surgery; REM-RDI improvements after upper airway surgical procedures might be useful objective outcomes measures.

This study has its limitations. The comparison groups allergic and nonallergic were a convenience sample from 1 physician's practice that limits the generalizability of our findings. The subject matter of sleep quality questionnaires may result in reporting biases because patients might underreport their symptoms if their employment depends upon daytime alertness. In addition, not all of our patients underwent sleep testing at the same facility nor were the same home sleep testing devices used, possibly resulting in measurement biases.

## Conclusion

We conclude that the REM-RDI is an underutilized, clinically relevant, and knowable sleep parameter that is significantly related to allergic status. Further studies are needed to firmly establish the relationships between allergic status and SDB that we have identified in our patient population. Other subjective allergy and sleep questionnaires might meaningfully correlate to REM-RDI values. This represents a new and clinically significant bidirectional bridge between sleep and allergies that justifies further studies on anti-inflammatory, medical, device, and surgical treatments. Investigations to evaluate improvements in REM-RDI values following various interventions would be informative. The effect of specific allergens on REM-RDI values may prove to be clinically relevant. Our future goal is to determine seasonal trends and specific allergen triggers in allergic SDB patients experiencing upper airway blockages. Managing SDB in AR patients with customized medical, device, and surgical strategies is an achievable enhanced safety and improved outcomes goal. 

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