House Dust Mite Related Allergic Rhinitis and REM Sleep Disturbances[☆]Shelley R. Berson^a, Jaclyn A. Klimczak^{b,*}, Elizabeth A. Prezio^c, Manoj T. Abraham^{b,d}^a NY Medical College, Valhalla, NY, USA^b Department of Otolaryngology Head and Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA^c University of Texas at Austin, TX, USA^d Department of Otolaryngology, New York Medical College, USA

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ABSTRACT

Purpose: Sleep disturbances are common in patients with allergic rhinitis (AR). Perennial allergens like house dust mites (HDM) are difficult to avoid and have nocturnal impacts on the respiratory system and Quality of Life (QOL). The Rapid Eye Movement (REM) sleep stage is associated with memory, cognition, dreams, and overall restfulness, which can be impaired in AR patients with Sleep Disordered Breathing (SDB) even when normal all-night apnea-hypopnea (AHI) or respiratory disturbance (RDI) indices are noted on polysomnography (PSG). We hypothesized that AR HDM allergen positive patients would show REM-specific SDB reflected in their objectively elevated REM-RDI values.

Materials and methods: This retrospective analysis of 100 patients included 47 with HDM positive allergy testing. All patients underwent PSG testing calculating the RDI during REM. Multivariate logistic regression models evaluated relationships between allergic statuses and sleep parameters while controlling for potential confounders.

Results: Compared with allergy negative patients, HDM allergen positive patients were significantly more likely (OR 4.29, 95%CI 1.26–14.62) to have a REM-RDI in the moderate/severe range (≥ 15 events/h).

Conclusions: Our study highlighted the significance of respiratory allergies to HDM in patients with SDB. We revealed a significant relationship between HDM allergen positivity and SDB characterized by elevated REM-RDI regardless of all-night AHI, RDI, or REM-AHI values. Clinical implications of knowing about disturbed REM and/or HDM allergenicity include better preparation, treatment, outcomes, and QOL for allergic, SDB, and upper airway surgery patients.

1. Introduction

Allergic rhinitis (AR) negatively impacts sleep and quality of life (QOL) [1,2]. Typical bothersome AR symptoms such as sneezing, post nasal drip, rhinorrhea, and most significantly nasal obstruction contribute to Sleep Disordered Breathing (SDB) [3]. AR affects 20 to 40 million Americans yearly placing cumbersome economic burdens directly through treatment costs and indirectly with QOL impairments including anxiety and depression when severe and prolonged [4,5].

It has been described previously that AR patients appear to have Rapid Eye Movement (REM)-specific sleep impairments and the underutilized REM-Respiratory Disturbance Index (RDI) objective sleep parameter may better reflect this relationship than commonly used Apnea Hypopnea Index (AHI), RDI, and REM-AHI values [6,7]. Normally, REM accounts for 20% of the sleep cycle, is thought responsible

for restorative sleep, memory, learning, and cognition, therefore REM disturbances likely affect some or all of these functions. Nasal congestion is known to be worst during REM sleep [8,9]. Historically, diagnosing obstructive sleep apnea (OSA) and SDB have focused on the AHI, without considering the effect of Respiratory Effort Related Arousals (RERAs) on REM sleep quality. By including apneas, hypopneas, and RERAs occurring specifically during REM, REM-RDI has clinical usefulness showing disturbed REM quality not reflected in AHI, RDI, nor REM-AHI. Increased evaluations for sleep disorders is warranted, especially since OSA is linked to chronic diseases like hypertension, coronary artery disease, stroke, cardiac arrhythmias (i.e. atrial fibrillation), insulin resistance, congestive heart failure, and pulmonary hypertension [10–14].

Impaired sleep in AR patients is multifactorial, partly related to increased nasal obstruction leading to downstream increased airway

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* Corresponding author at: 1 Gustave Levy Place, Annenberg Bldg 10th Floor, New York, NY 10029, USA.

E-mail address: jklimczak2@nyee.edu (J.A. Klimczak).

resistance and mouth breathing that reduces sleep state pharyngeal diameters [15]. Recumbent positioning influences both nasal obstruction perception and objective nasal volume and cross-sectional area measurements [4]. Anatomic upper airway blockage corrections in patients with underlying under-treated AR and/or SDB/Obstructive Sleep Apnea (OSA) present well-known surgical challenges that potentially lead to sub-optimal results [16–20].

Inflammatory mediators released from IgE-primed-mast cells include: Histamine, cytokines (IL4, 5, TNF alpha), proteases, prostaglandins and leukotrienes. IgE-mediated allergic reactions to airborne particles irritate, inflame, and congest respiratory epithelium [21–24]. Proinflammatory mediators associated with AR can have suppressive actions on Rapid Eye Movement (REM) and Non-rapid Eye Movement (NREM) sleep [21,24]. Nasal obstruction from AR can lead to a spectrum of breathing events from snoring to RERAs to hypopneas to apneas progressing to SDB then OSA [1,25,26]. Normally restorative REM sleep, when impaired, can diminish memory, cognitive ability, concentration, and productivity [1,7,21]. Apneas, hypopneas, and less often reported RERAs are prevalent during REM sleep in AR patients. There is a heightened clinical awareness of OSA, yet even mild degrees of SDB or REM-OSA can lead to significant morbidity and increased healthcare costs [27–31]. Berson et al. noted that since RERAs are integral to REM-RDI, it may be a useful objective sleep parameter to gauge SDB severity within AR patient populations [6]. When compared with non-allergic patients, those with AR were 3.92 times more likely to have a REM-RDI in the moderate to severe range, regardless of BMI. Stuck et al. demonstrated statistically significant daytime sleepiness and poorer QOL parameters in seasonal AR patients compared with healthy volunteers using questionnaires and polysomnography (PSG) before and during pollen seasons [32].

Specific AR aggravating allergens can be determined via allergy testing. Commonly tested allergens include grass, tree, weed pollens, cat, dog, cockroach, molds, and house dust mites (HDM) that may cause upper respiratory system problems like AR and lower respiratory system problems like allergic asthma [33–35]. Four main species of allergenic Arachnid class HDMs include commonly tested and clinically relevant *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* [36]. HDM allergic rhinitis affects between 65 and 130 million persons worldwide. HDMs are prevalent, difficult to avoid in sleeping environments year round, and worse in the winter [36–38]. AR symptom severity and durations vary with frequent sleep disturbances reported. The DREAMS study showed sleep was significantly worse in severe versus mild AR patients [26]. There was increased insomnia, hypersomnia, sleep apnea, daytime sleepiness, and cognitive impairments compared with healthy controls. A study evaluating the subjective effect of HDM allergy on sleep using Epworth Sleepiness Scale (ESS), the Insomnia Severity Index (ISI), and modified Hotel Dieu-42 (HD-42) sleep disorder questionnaires found those with severe persistent HDM related AR were more sleep impaired than those with intermittent or mild symptoms [39]. A multicenter observational study of 1750 patients with HDM specific AR showed higher likelihoods of difficulty falling asleep, nocturnal awakenings, clinical insomnia, and poor-quality sleep than non-HDM AR patients [39].

Leger et al. conducted a prospective observational study among HDM-related allergy participants who were initiating Sublingual Immunotherapy (SLIT) [39]. The majority of participants (73.5% of adults and 65.8% of children) sought medical treatment for primary sleep disorder complaints rather than allergy. Furthermore, subjects suffering from severe persistent HDM-related AR had more subjective sleep complaints than those who suffered from non-HDM AR.

A paucity of scientific literature associates specific AR allergens with objective sleep disturbances. We suspected that all-night exposures to strong prevalent bedroom allergens such as HDM may significantly affect REM sleep. In this retrospective study we investigated relationships between HDM allergen positive patients and SDB using the REM-RDI parameter and compared them with healthy non-HDM allergic and

non-allergic patients.

2. Methods

2.1. Study design and participants

This retrospective study was directed by a board-certified Sleep Medicine Otolaryngologist and approved by the Institutional Review Board of New York Medical College. Data were extracted from 2014 to 2016 clinic medical records by a trained research assistant who identified patients with AR or SDB symptoms. Patients presenting with symptoms suspicious for allergic rhinitis underwent Skin Prick Testing (SPT), ImmunoCAP® blood testing, or Intradermal Testing (IDT/MQT) including HDM, grass, tree, weed pollens, cat, dog, cockroach, and common molds, with in-lab polysomnogram (PSG) or Home Sleep Testing (HST) approximately within a month of their allergy symptoms documenting all sleep stages, apneas, hypopneas and RERAs. Patients using corticosteroids, sleep-aid medications, unable to remain off antihistamines, or having incomplete medical records were excluded.

Questionnaires included “STOP-Bang®, Epworth Sleepiness Scale (ESS)®, and SNOT-22®, gauging subjective sleep impairment and allergy severity [6]. Demographic data included age, gender, and body mass index (BMI). Of 296 subjects identified with allergic and/or sleep complaints, 100 patients met study inclusion criteria.

2.2. Outcome measures

REM-RDI was reported as events per hour: normal (0–4.9), mild (5–14.9), moderate (15–29.9), and severe (≥ 30). Allergy testing was performed via SPT (Stallergenes-Greer or ALK Abello allergens) or ImmunoCAP® Blood testing (if dermatographia or beta blocker usage precluded SPT). Intradermal Testing (IDT/MQT) was performed if clinical suspicion persisted for allergy in negative SPT patients. All tests included HDMs *D. pteronyssinus* and *D. farinae*. SPT wheal diameters 3 mm or larger than the negative control after 15 min were considered positive. IDT/MQT positivity was a wheal diameter at least 7 mm and at least 2 mm wider than the glycerin control. ImmunoCAP® blood testing was considered positive at or above 0.35 kU/L [2].

PSG sleep quality assessment used American Academy of Sleep Medicine definitions (AASM) and were recorded by certified sleep lab technicians [40–42]. Sleep stage percentages obtained via electroencephalography or Peripheral Arterial Tone were REM or NREM stages 1, 2, and deep slow wave sleep (SWS stages 3 & 4). Relevant objective measurements included apnea index, hypopnea index, RERAs, sleep latency, REM latency, all-night apnea hypopnea and respiratory disturbance indices (AHI and RDI), REM-AHI, and REM-RDI values. Apnea was a cessation of breathing or greater than 90% drop in peak airflow for at least a ten-second duration. Hypopnea was defined as a 30% decrease in peak respiratory airflow signal excursion from baseline for at least 10 s resulting in a greater than 3% oxygen desaturation. RERAs were increases in respiratory effort for greater than 10 s leading to arousals not meeting the criteria for apneas or hypopneas. The RDI included apneas, hypopneas, and RERAs, whereas the AHI only included apneas and hypopneas notably excluding RERA arousals.

2.3. Statistical analysis

Subjects were stratified based on allergy test results as non-allergic, allergic to HDM (*D. pteronyssinus* and/or *D. farinae*), or allergic to one or more non-HDM antigens. Pearson χ^2 for categorical variables and independent-samples *t*-tests for continuous variables were used to evaluate allergy positive subjects compared with non-allergic subjects. Logistic regression models adjusted for age, gender, hypertension, and BMI were used to evaluate relationships between REM-AHI and REM-RDI (reference category normal to mild defined as 0–14.9 events/h) and HDM allergen positive or non-HDM allergen positive (reference

Table 1
Demographics, clinical measures and indices of sleep disordered disease severity.

	Allergy negative (n = 33)	Allergy positive to HDM (n = 47)	<i>p</i>	Allergy positive to allergens other than HDM (n = 20)	<i>p</i>
Gender: n (%) ^a					
Male	18(55)	29(62)	0.13	7(35)	0.18
Female	15(45)	18(38)		13(65)	
Age: mean ± S.D. ^b	55(15.8)	46(15.4)	0.02 _{ns}	48(16.1)	0.12
BMI: mean ± S.D. ^b	30.5(5.9)	28.4(5.6)	0.11	29(7)	0.44
HTN: n (%) ^a	16(48.5)	19(40.4)	0.21	7(35)	0.21
AHI (events/h): mean ± S.D. ^b	14.1(15)	13.5(15)	0.86	12.9(17.4)	0.78
RDI (events/h): mean ± S.D. ^b	19.3(13.9)	19(14.5)	0.93	17.9(16.2)	0.74
REM-RDI (events/h): mean ± S.D. ^b	22.7(15.9)	26.9(15.4)	0.24	23.6(17.2)	0.84
REM-AHI (events/h): mean ± S.D. ^b	17.4(17)	19.5(17.9)	0.59	17(18.8)	0.93

Note: BMI: body mass index; HTN: hypertension; AHI: apnea hypopnea index; RDI: respiratory disturbance index; REM-RDI: rapid eye movement respiratory disturbance index; REM: rapid eye movement; HDM: house dust mites.

^a Pearson χ^2 (HDM positive or other allergen positive vs allergen negative).

^b Independent-samples *t*-test (HDM positive or other allergen positive vs. allergen negative).

* *p* < 0.05.

category allergen negative). Statistical significance was defined as *p* < 0.05. Stata Statistical Software: Release 12 (StataCorp, College Station, TX) was used for statistical analysis.

3. Results

The study population comprised 54 males and 46 females. Allergy negative subjects were significantly older than HDM allergic subjects (*p* = 0.02). No significant differences were found between HDM allergic or non-HDM allergic groups and non-allergic subjects for AHI, RDI, REM-AHI, or REM-RDI mean values (Table 1).

The relationship between sleep parameters (REM-AHI and REM-RDI) and allergy status can be found in Table 2. Patients who were allergic to HDM were significantly more likely to have a REM-RDI (OR 4.29, 95% CI 1.26–14.62) and a REM-AHI (OR 3.98, 95% CI 1.08–14.68) in the moderate to severe range compared with allergen negative subjects. Patients allergic to allergens other than HDM were significantly more likely to have a REM-AHI (OR 4.76, 95% CI 1.05–21.55) in the moderate to severe range compared with allergen negative patients. However, when comparing the REM-RDI between the patients allergic to allergens other than HDM and allergen negative patients, there was no significant difference (OR 3.03, 95% CI (0.73,12.57)). BMI was an independent predictor of REM-AHI and REM-RDI in the moderate to severe range in both regression models.

Patients in three allergy test groups (Non-allergic, Allergic to HDM, Non-HDM allergic) were stratified by REM-RDI score (Fig. 1). Significantly more patients with HDM allergies had a REM-RDI ≥ 30 events/h compared with allergen negative patients (*p* = 0.016).

Table 2
Relationship between allergic status and sleep parameters¹.

	Allergic to dust mites		Allergic to other than dust mites		BMI	
	OR	95%CI	OR	95%CI	OR	95%CI
REM-RDI	4.29 _*	(1.26,14.62)	3.03	(0.73,12.57)	1.17 _{**}	(1.04,1.3)
REM-AHI	3.98	(1.08,14.68)	4.76 _*	(1.05,21.55)	1.27 _{***}	(1.13,1.44)

Note. BMI: body mass index; CI: confidence interval; OR: odds ratio;

REM-AHI: rapid eye movement apnea hypopnea index; REM-RDI: rapid eye movement respiratory disturbance index.

¹ Logistic regression adjusted for age, gender hypertension and BMI. REM-RDI reference category: “< 15 events per hour.” REM-AHI reference category: “< 15 events per hour.”

* *p* < 0.05.

** *p* < 0.01.

*** *p* < 0.001.

4. Discussion

Perennial bedroom HDM allergens may have negative effects on the upper respiratory tract [43]. HDM are ubiquitous, difficult to eliminate, are associated with poor health outcomes, and reduce QOL. Suspecting that QOL can potentially improve with HDM treatment, we analyzed objective allergy and sleep test data in sleep challenged patients with allergy symptoms. Our findings suggest that HDM allergic patients can have disturbed REM sleep; HDM allergen positive patients in this sample were significantly more likely to have a REM-RDI in the moderate to severe range when compared to patients with no allergies and those allergic to allergens other than HDM. Of note, REM-AHI was significantly more likely to be in the moderate to severe range for study subjects allergic to both HDM and non-HDM. The sleep parameter REM-RDI which uniquely includes RERAs may be indicated in evaluating sleep disturbances specifically in HDM allergic patients and it should be routinely calculated and reported upon in sleep study reports. Previous studies have demonstrated the relationship between higher BMI and sleep disturbances including OSA [44]. We controlled for the independent predictor, BMI, in our models. We also used age as a covariate in our models to adjust for our sample in which allergy negative subjects were significantly older than HDM allergic subjects. Having an elevated REM-RDI in the setting of HDM allergies makes a case for using available targeted HDM therapies. A placebo-controlled double blind study has demonstrated that HDM SLIT therapy significantly improved subjective sleep quality [45].

Novakova et al. looked at QOL scores in 191 patients with moderate to severe AR with clinically relevant sensitization to either HDM or grass pollen before and one year after SLIT [46]. In the HDM group, overall QOL scores showed the greatest improvement in “nasal symptoms” and significant sleep score improvement from 2.48 to 0.31;

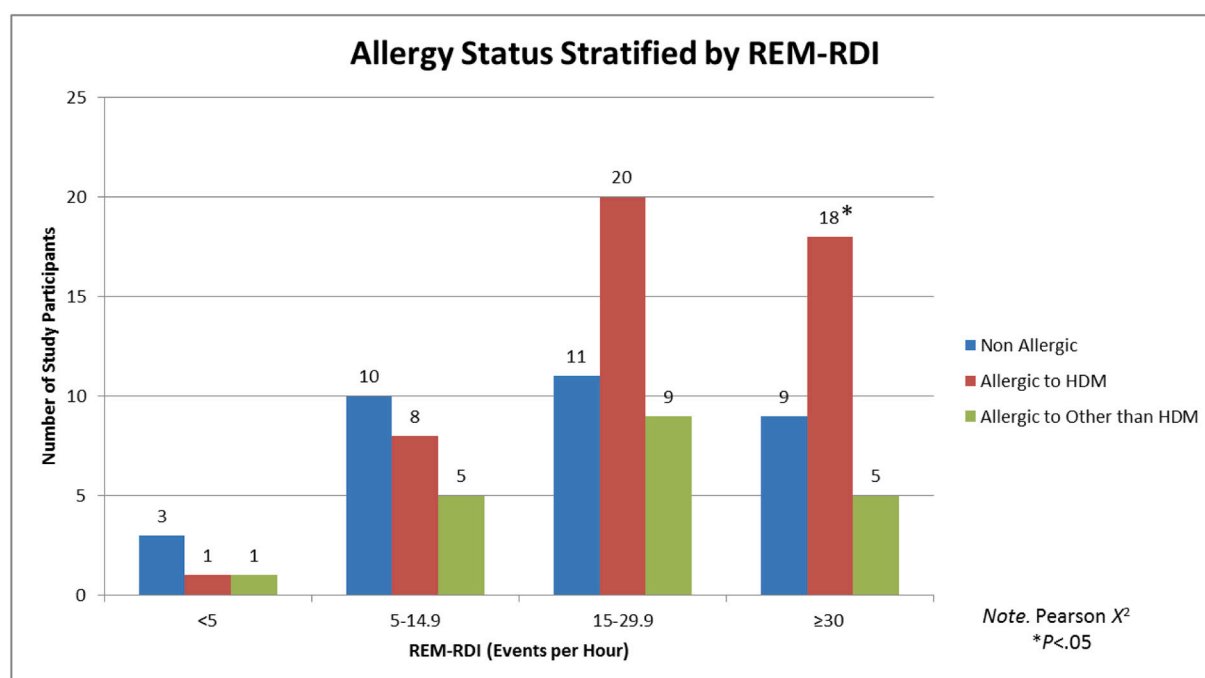


Fig. 1. Allergy status stratified by REM-RDI.

$p < 0.001$ after treatment. This suggests that once patients are able to breathe from the nose, mouth breathing, snoring, and sleep improve. Early sensitization to HDM has detrimental effects on long term lung function and is associated with poorer respiratory health outcomes. Complete elimination of HDM from the home and bedroom by cleaning, laundry methods, or protective barriers is difficult to achieve and there is variable evidence to prove improvement when HDM are even partially removed [47,48]. To our knowledge, no studies have reported objective REM-inclusive sleep stages in home sleep studies performed on HDM allergic patients.

This study has its limitations. The results obtained were from a single clinic population and there is no direct comparison group, which limits generalizability of these findings to the population as a whole. With only 20 subjects in the non-HDM allergic group the study may have been underpowered to demonstrate a statistical difference for REM-RDI between the non-HDM allergy group and the non-allergic group. It is not possible to conclude from this study that only HDM allergy sensitivity affects REM-RDI; larger sample sized future studies are warranted to further elucidate the REM-RDI differences in HDM vs. Non-HDM allergic subjects. Retrospective reviews are subject to selection bias. Allergy and polysomnography testing, while standardized, can result in misclassification of subjects. In addition, patients were evaluated using a variety of polysomnography and allergy tests.

5. Conclusion

HDM are among the most prevalent ubiquitous, difficult to eliminate, perennial allergens that induce allergic inflammation, cause nasal obstruction, and disturb sleep. We have demonstrated a statistically significant relationship between HDM allergy and elevated REM-RDI. The findings in this study need to be confirmed using controlled study conditions with adequate power. Further studies are needed to evaluate REM-RDI before and after SLIT/SCIT immunotherapy treatments. Also of interest would be an assessment of REM-RDI values before and after HDM environmental cleanup with and/or without immunotherapy, as well as the effects of non-HDM allergen treatments on objective sleep parameters. Multi-faceted form-function approaches facilitate not only more precise diagnoses but also more effective allergy, surgical, as well

as sleep treatments. Medical or surgical-only treatments might under-treat patients resulting in sub-optimal outcomes. Whether patients seek help for sleep, allergy, or anatomic nasal obstruction complaints, they deserve proper examinations of their upper airways beginning in the nose, administration of REM-RDI inclusive sleep tests, and gathering of HDM and customized seasonal and perennial allergic data. Consequently, clinicians need to not only consider surgically correctable upper airway problems and undertreated sleep impairments in patients who present with AR, but they should also consider diagnosing and treating specific allergens like HDM in sleep impaired patients.

Declaration of competing interest

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