

Patient-reported sleep outcomes lack association with mucosal eosinophilia or neutrophilia in patients with chronic rhinosinusitis undergoing functional endoscopic sinus surgery

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Background: Chronic rhinosinusitis (CRS) is associated with sleep dysfunction, but the underlying pathophysiology is poorly understood. The purpose of this study was to determine if mucosal eosinophilia or neutrophilia were associated with sleep dysfunction severity or altered the improvement in sleep dysfunction following functional endoscopic sinus surgery (FESS).

Methods: A total of 104 patients with medically refractory CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP), completed the Pittsburgh Sleep Quality Index (PSQI) before and after FESS. Anterior ethmoid mucosa was collected during FESS and densest infiltrates of eosinophilia and neutrophilia per high-power field (HPF) were determined by microscopy. Eosinophilic (>10 eosinophils/HPF) and neutrophilic (>4 neutrophils/HPF) CRS were then compared to preoperative and postoperative PSQI measures.

Results: Of 104 study participants, 88 (85%) reported preoperative PSQI scores consistent with "poor sleep," (PSQI total > 5). The cohort overall demonstrated significant improvement in poor sleep (65%; $\chi^2 = 12.03$; $p < 0.001$) 16.8 $\pm$ 5.0 months after FESS. Regardless of nasal polyposis, neither eosinophilic nor neutrophilic CRS was associated with differences in mean postoperative PSQI improvement.

However, in patients with neutrophilic CRSsNP, there was a significant relationship between severity of neutrophilia and improvement in sleep latency ($R = -0.798$, $p = 0.003$) and sleep efficacy ($R = -0.777$, $p = 0.005$).

Conclusion: Chronic inflammation has been hypothesized to play a pathophysiologic role in sleep dysfunction associated with CRS. This study suggests that in patients with medically refractory CRS, evidence of mucosal eosinophilia and neutrophilia lack strong associations with patient-reported sleep dysfunction or improvements in sleep quality after FESS, overall. However, neutrophilia may impact sleep latency and efficacy in patients with CRSsNP. © 2020 ARS-AAOA, LLC.

Key Words:

sinusitis; chronic disease; outcome assessment (health care); quality of life; chronic rhinosinusitis

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Chronic rhinosinusitis (CRS) is a pervasive disorder, affecting nearly 30 million people in the United States.¹

The impact of CRS is profound, negatively impacting quality-of-life (QoL) with a severity equivalent to that of

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end-stage renal disease or severe asthma.²⁻⁵ Studies have also demonstrated that up to 75% of patients with CRS report sleep dysfunction.⁵⁻⁸ The negative effect on sleep quality is believed to be a significant risk factor in the overall QoL reductions reported by patients with CRS, yet very little has been done to elucidate the etiology or mechanisms of this phenomenon.

Sleep dysfunction, in and of itself, severely impacts patient lives. Patients with sleep dysfunction have reported poor daily performance, increased comorbid disease severity and healthcare costs, and reduced emotional well-being.⁹⁻¹² Additionally, chronic sleep dysfunction has been associated with the development of diabetes, cerebrovascular disease, kidney disease, and obesity.^{7,8,10-13} The prevalence and impact of long-term sleep deprivation is such that the Centers for Disease Control and Prevention declared insufficient sleep a public health epidemic in 2013.¹⁴

Given known associations between CRS and sleep dysfunction, it is imperative that the relationship be further explored to assist with guidance toward improved disease management.¹⁵ The complicated interplay between the 2 disorders is likely multifactorial and bidirectional. For example, the presence of sinonasal obstruction as well as other symptoms of CRS, such as facial pain/pressure and rhinorrhea, may impact patients' ability to fall asleep and stay asleep.^{2,16} Additionally, multiple studies indicate that various pro-inflammatory cytokines may also effect the central regulation of sleep.^{2,5,16} The chronic inflammation associated with CRS may alter expression of these somnogenic and anti-somnogenic cytokines. Conversely, studies have demonstrated that sleep deprivation, in and of itself, can induce changes in the inflammatory milieu in human subjects.^{9,13,17-20}

Though prior studies demonstrate significant associations between CRS and sleep dysfunction, they have done so in a broader sense, evaluating entire patient cohorts or stratifying by patient phenotype, based on comorbid nasal polyposis. Attempts have been made to endotype CRS patients based on histopathologic markers within the sinonasal mucosa or through clustering analysis of the inflammatory cytokine milieu.²¹⁻²³ Though inflammatory clustering analysis has become the primary means of endotyping patients with CRS, there has been renewed interest in the role of mucosal histology, specifically that of mucosal eosinophilia and neutrophilia, on patient treatment strategies. This is, in part, due to the availability of mucosal leukocyte distribution, because mucosa is routinely analyzed after FESS. Some groups have also suggested that neutrophilia play a larger role in sinonasal pathology than previously appreciated.²⁴⁻²⁶ Additionally, studies evaluating asthma have demonstrated that sleep deprivation and alterations of the circadian rhythm are associated with eosinophilia and neutrophilia in mouse models.^{20,27,28} Therefore, the purpose of this investigation was to classify variants of CRS by histologic eosinophilia or neutrophilia, and identify associations between histologic characteristics and sleep dysfunction measures in patients with CRS.

Patients and methods

Sample design and population source

Study participants presented to the Oregon Sinus Center at Oregon Health & Science University (OHSU, Portland, OR). Adult study participants were diagnosed with CRS by a fellowship-trained rhinologist using criteria outlined by the American Academy of Otolaryngology.²⁹ Patients were prospectively enrolled as part of a multicentered clinical trial designed to evaluate postoperative treatment outcomes of FESS, funded through the National Institute on Deafness and Other Communication Disorders (NIDCD, Bethesda, MD). Histology data was then retrospectively evaluated for study purposes. The Institutional Review Board (IRB) at OHSU provided ethical oversight (eIRB #7198). This heterogeneous population experienced persistent symptoms of CRS after completion of appropriate medical therapy consisting of nasal saline irrigations (~240 mL daily), topical corticosteroid sprays (≥21 days), oral corticosteroid therapy (≥5 days), and at least 1 course of culture-directed or broad-spectrum antibiotic therapy. Patients remained on medical therapy until FESS. Recalcitrant symptoms consisted of nasal congestion, mucopurulent nasal drainage, facial pain and/or pressure, or loss of smell.

Following surgical counseling, patients voluntarily elected FESS as the subsequent treatment modality for symptom resolution before providing informed study consent. During preoperative study enrollment meetings, patient demographic factors, history of comorbid conditions, and prescribed medication data were collected. During the study duration, it was standard practice to provide a short course of preoperative oral corticosteroids immediately prior to FESS, unless contraindicated for comorbidity or intolerance.

Exclusion criteria

Study participants were excluded if they presented with diagnoses of comorbid ciliary dyskinesia, cystic fibrosis, immunodeficiency, allergic fungal sinusitis, odontogenic sinusitis, antrochoanal polyposis, obstructive sleep apnea (OSA), or corticosteroid dependency for CRS or asthma. Any subjects who did not accurately complete preoperative or postoperative outcome instruments were also excluded from final selection.

FESS and histopathologic markers

Surgical approach was determined after review of preoperative computed tomography (CT) imaging and endoscopic examinations. Primary or revision FESS was performed in an outpatient setting under general anesthesia. Histopathology was evaluated using mucosal tissue collected from the ethmoid cavity during FESS. Standard pathological laboratory techniques were used to prepare samples. Tissue specimens were immersed in 10% neutral buffered formalin (NBF) and fixed for at least 4 hours before submission into plastic mesh cassettes in toto and again immersed in NBF

for another 3 to 12 hours. Following a 120-second cold water rinse, the tissue cassette was immersed in an acid decalcification solution (Decal Stat; Decal Chemical Corporation, Tallman, NY) for 8 hours and again rinsed with cold water for 120 seconds. Cassettes were then treated in a 12-hour cycle in an automated processor (Sakura VIP; Sakura Finetek USA, Torrance, CA) prior to paraffin embedding (Sakura Tissue-Tec; Sakura Finetek). Histological tissue sections of 4 μ m were prepared on a microtome and the slide was placed into an automatic stainer with glass coverslip. Each hematoxylin and eosin (H&E)-stained slide was banked for histopathology review. No additional staining was performed, given that prior studies did not demonstrate any additional benefit in evaluation after myeloperoxidase staining.³⁰

Microscopy of each H&E slide was conducted by a board-certified surgical pathologist (D.S.) using a binocular microscope (Leica DM2000; Leica Microsystems Inc., Bannockburn, IL) with a graduated reticle ($\times 10$, 10 mm with 1.0-mm divisions). Histopathological review was performed with mucosal eosinophils and neutrophils quantified per high-power field (HPF) at $\times 400$ power. When viewed at $\times 400$ power magnification, the reticle field is 250 μ m with an approximate square area of 0.13 mm². Eosinophils and neutrophils were quantified on a continuous scale from the foci of densest cellular infiltrate to ensure counts were evaluated from areas of greatest inflammation.

Four phenotypic categorizations of CRS, eosinophilic CRS (eCRS), or neutrophilic CRS (nCRS), both with nasal polyposis (wNP) and without nasal polyposis (sNP), were considered the primary exposure variables of interest to this investigation. Accurate identification of eosinophilic CRS was determined if tissue eosinophils were $>10/\text{HPF}$.³¹⁻³³ Neutrophilic involvement (nCRS) was classified as tissue neutrophils $>4/\text{HPF}$. This threshold has been previously described for neutrophilic disease using tissue specimens from non-inflammatory, healthy controls in previous study.^{30,34}

Sleep-based outcome measures

All study subjects completed the Pittsburgh Sleep Quality Index (PSQI) during study enrollment meetings and at last available postoperative follow-up (≥ 6 months). The PSQI is a validated, 19-item, self-rated measure of global sleep quality and duration.³⁵⁻³⁷ Subjects were instructed to recall sleep quality during the 30 days prior to survey completion. The PSQI yields a total score (range, 0 to 21) and 7 component scores including: sleep quality, sleep medication usage, sleep duration, sleep disturbance, sleep latency, daytime dysfunction, and sleep efficiency (ranges, 0 to 3). Higher PSQI scores suggest greater sleep disturbance. A PSQI total score ≤ 5 is considered the threshold for “good” sleep quality, whereas a total score > 5 is characterized as “poor” sleep quality.³⁸ Minimal clinically important differences (MCIDs) in postoperative improvement for PSQI to-

tal score were defined as within-subject changes of at least $\frac{1}{2}$ of the standard deviation (SD) associated with the mean preoperative PSQI total score.³⁹

Sample size estimation

Sample size determinations were based on matched differences for dependent mean values for PSQI total scores between preoperative and last postoperative scores. Estimation parameters included a 2-tailed test using a conventional 0.050 error probability (α -level), 80% power ($1-\beta$), and a mean $\pm$ SD difference of 3.0 ± 4.0 points.⁸ Approximately 16 subjects were required to detect an expected mean postoperative difference of at least 3.0 points ($\sim 14\%$ difference in PSQI total score) within each phenotypic subgroup.

Database management and statistical analysis

Data collection at OHSU was facilitated by a closed-environment database (MS Access; Microsoft Corporation, Redmond, WA) protected using both unique patient identification number assignment and data safety monitoring. Retrospective, secondary data analysis of prospectively collected data was accomplished using SPSS statistical software (version 25.0; IBM Corporation, Armonk, NY). All scaled/continuous study data was evaluated for linearity and distribution. Differences in mean PSQI scores between independent subgroups were compared using either 1-way analysis of variance with F-test statistics or bivariate independent sample *t* testing. Matched pairing *t* test was used to compare within-group postoperative changes in average PSQI measures. Unadjusted, 2-tailed Spearman's rank correlation coefficients (*R*) were utilized to evaluate associations with continuous/scaled measures, where appropriate. Pearson's chi-square (χ^2) testing was used for between-group comparisons of prevalence, while McNemar's χ^2 testing was applied for within-group comparisons. Test statistics, effect estimates, 95% confidence intervals (CIs), and type-I error probabilities (*p* values) are reported.

Results

Final sample population

A total of 174 study participants met initial study inclusion criteria and provided voluntary consent prior to FESS conducted between April 2011 and December 2014. The final study population consisted of 104 subjects after exclusions due to comorbidity associated with cystic fibrosis (*n* = 4), allergic fungal sinusitis (*n* = 1), immunodeficiency (*n* = 1), OSA (*n* = 9), and corticosteroid dependency (*n* = 2). No study participants had clinical findings of either odontogenic sinusitis or antrochoanal polyposis. Additional exclusions were completed due to incomplete preoperative PSQI survey responses (*n* = 7) and loss to postoperative follow-up (*n* = 46). Demographic factors and health characteristics of the final study patient cohort are described

TABLE 1. Preoperative demographic factors, health characteristics, and PSQI measures of final study population (n = 104)

Characteristic	Mean $\pm$ SD	Range [LL, UL]	n (%)
Postoperative follow-up (months)	16.8 $\pm$ 5.0	[5, 29]	–
Age (years)	52.2 $\pm$ 14.8	[20, 82]	–
Male	–	–	43 (41)
Female	–	–	61 (59)
White/Caucasian (race)	–	–	101 (97)
African American (race)	–	–	1 (1)
Asian (race)	–	–	1 (1)
Hispanic/Latino (ethnicity)	–	–	3 (3)
Nasal polyposis	–	–	39 (38)
Septal deviation	–	–	53 (51)
Turbinate hypertrophy	–	–	20 (19)
Mucocele	–	–	2 (2)
Asthma	–	–	27 (26)
Aspirin sensitivity/AERD	–	–	7 (7)
Allergic rhinitis	–	–	38 (37)
Depression	–	–	23 (22)
Current tobacco use/smoker	–	–	5 (5)
Alcohol use	–	–	57 (55)
Diabetes mellitus (Type I/II)	–	–	4 (4)
GERD	–	–	4 (4)

AERD = aspirin-exacerbated respiratory disease; GERD = gastroesophageal reflux disease; LL = lower limit; n = sample size; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation; UL = upper limit.

in Table 1. Preoperative oral corticosteroids (≥ 7 -day course) were prescribed for 69 of 104 (66%) patients, whereas 22 (21%) patients did not receive preoperative oral steroid therapy. Surgical chart review could not confirm corticosteroid use for the remaining 13 (13%) of study subjects.

Histopathologic classifications

For all study participants the mean eosinophil counts from the densest cellular infiltrate was 72.0 ± 135.2 (range, 0 to 610), while the mean neutrophil count was 7.5 ± 24.0 (range, 0 to 170) for the total sample population. Phenotypic determinations based on histopathologic findings identified mucosal eosinophilia in 50 of 104 (48%) of patients and mucosal neutrophilia in 25 of 104 (24%). In patients with mucosal eosinophilia, 29 of 50 (58%) were also found to have nasal polyposis. Similarly, 14 of 25 (56%) patients with mucosal neutrophilia presented with nasal polyposis. Within the entire cohort, only 14 of 104 (14%) of patients presented with both mucosal eosinophilia and neutrophilia.

Preoperative PSQI measures between independent histopathologic subgroups

Unadjusted, global comparisons of both mean and ranked median differences in preoperative PSQI total or component scores found no significant differences between any 2 independent patient subgroups with and without eosinophilia (non-eCRS) and nasal polyposis, though there was a trend toward worse PSQI total scores in eCRSwNP over non-eCRSwNP ($F \leq 1.59$; all $p \geq 0.196$). Similarly, no significant differences in PSQI total or component scores were noted for any 2 patient subgroups with and without neutrophilia (non-nCRS) and nasal polyposis ($F \leq 1.51$; all $p \geq 0.217$).

In addition, only weak significant correlation coefficients were found between some preoperative PSQI scores and histopathologic density counts within each independent histopathologic subgroup (Table 2). For all study participants with eCRS (n = 50) significant correlations were identified between higher eosinophilic counts and worse preoperative sleep quality as measured by PSQI total scores ($R = 0.340$; $p = 0.016$) and daytime dysfunction scores ($R = 0.354$; $p = 0.012$) without pairwise adjustment. For

TABLE 2. Unadjusted Spearman's rho correlations (*R*) between preoperative PSQI measures and counts of highest density histopathologic markers*

	Total eCRS (n = 50)		Total nCRS (n = 25)	
Sleep-based measures	<i>R</i>	<i>p</i>	<i>R</i>	<i>p</i>
PSQI total score	0.340	0.016	−0.038	0.858
Sleep quality score	0.200	0.163	0.173	0.407
Sleep medication score	0.052	0.720	−0.247	0.234
Sleep duration score	0.197	0.170	0.137	0.514
Sleep disturbance score	0.207	0.149	−0.038	0.856
Sleep latency score	0.145	0.315	−0.397	0.049
Sleep daytime dysfunction score	0.354	0.012	−0.136	0.517
Sleep efficiency score	0.192	0.181	0.111	0.599
CRSsNP	eCRSsNP (n = 29)		nCRSsNP (n = 14)	
PSQI total score	0.363	0.053	−0.051	0.861
Sleep quality score	0.178	0.355	0.194	0.506
Sleep medication score	−0.068	0.727	−0.101	0.732
Sleep duration score	0.257	0.179	0.170	0.561
Sleep disturbance score	0.356	0.058	−0.167	0.567
Sleep latency score	0.217	0.258	−0.372	0.190
Sleep daytime dysfunction score	0.327	0.084	−0.169	0.565
Sleep efficiency score	0.369	0.049	−0.128	0.664
CRSsNP	eCRSsNP (n = 21)		nCRSsNP (n = 11)	
PSQI total score	0.240	0.294	−0.204	0.547
Sleep quality score	0.260	0.255	0.027	0.937
Sleep medication score	0.109	0.639	−0.337	0.311
Sleep duration score	−0.019	0.935	−0.086	0.802
Sleep disturbance score	0.145	0.530	−0.097	0.777
Sleep latency score	0.172	0.456	−0.525	0.097
Sleep daytime dysfunction score	0.389	0.081	−0.158	0.642
Sleep efficiency score	−0.125	0.588	0.343	0.302

*Bold values indicate significance.

CRSsNP = chronic rhinosinusitis without nasal polyposis; CRSwNP = chronic rhinosinusitis with nasal polyposis; eCRS = eosinophilic chronic rhinosinusitis; eCRSsNP = eosinophilic CRS without nasal polyposis; eCRSwNP = eosinophilic CRS with nasal polyposis; nCRS = neutrophilic chronic rhinosinusitis; nCRSsNP = neutrophilic CRS without nasal polyposis; nCRSwNP = neutrophilic CRS with nasal polyposis; PSQI = Pittsburgh Sleep Quality Index; *R* = Spearman's rank correlation coefficient.

all study participants with nCRS (n = 25) significant correlations were only identified between higher neutrophilic counts and better preoperative sleep latency scores without adjustment (*R* = −0.397; *p* = 0.049).

Total postoperative changes in PSQI measures

For all study patients (n = 104), postoperative improvement in PSQI total scores were reported (10.4 ± 4.1 to 8.2

± 4.5 ; $\Delta = -2.1$; 95% CI, −3.0 to −1.3; *t* = 4.90; *p* < 0.001) with similar statistically significant improvements in sleep quality, sleep duration, sleep disturbance, sleep latency, and daytime dysfunction component scores (*p* ≤ 0.006). The prevalence of overall “poor” sleep quality significantly improved from 85% to 65% following sinus surgery ($\chi^2 = 12.03$; *p* < 0.001) for all study participants. Likewise, the prevalence of all study participants reporting improvement

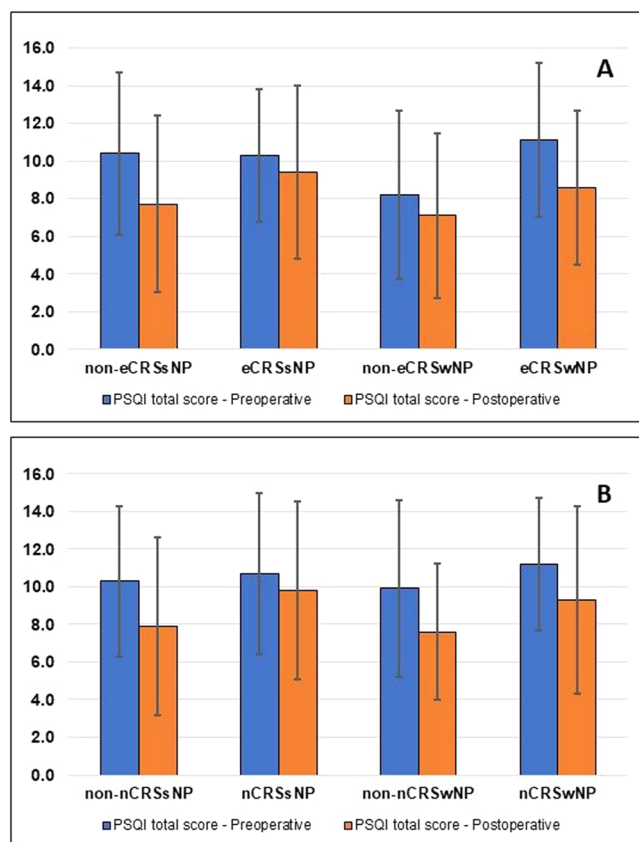


FIGURE 1. Comparisons of average preoperative and postoperative PSQI total scores between both (A) study participants with and without both eosinophilia and nasal polyposis, and (B) study participants with and without both neutrophilia and nasal polyposis in CRS. non-eCRSsNP ($n = 44$); eCRSsNP ($n = 21$); non-eCRSwNP ($n = 10$); eCRSwNP ($n = 29$); non-nCRSsNP ($n = 54$); nCRSsNP ($n = 11$); non-nCRSwNP ($n = 25$); nCRSwNP ($n = 14$). Error bars represent 1 standard deviation above/below the mean. CRS = chronic rhinosinusitis; eCRSsNP = eosinophilic CRS without nasal polyposis; eCRSwNP = eosinophilic CRS with nasal polyposis; nCRSsNP = neutrophilic CRS without nasal polyposis; non-eCRSsNP = non-eosinophilic CRS without nasal polyposis; non-eCRSwNP = non-eosinophilic CRS with nasal polyposis; non-nCRSsNP = non-neutrophilic CRS without nasal polyposis; non-nCRSwNP = non-neutrophilic CRS with nasal polyposis; PSQI = Pittsburgh Sleep Quality Index.

in PSQI total scores equaling at least an MCID value (ie, ≥ 2.05) was 50 of 104 (48%) with improvement scores ranging from -13 ("better"; $n = 2$) to 8 ("worse"; $n = 2$).

Postoperative PSQI measures between independent histopathologic subgroups

After adjustment for pairwise comparisons of postoperative mean improvements in PSQI total measures, no significant differences between any 2 independent patient subgroups with and without eosinophilia and nasal polyposis were found ($p \geq 0.196$; Fig. 1A). Additional comparison of postoperative differences in PSQI total scores between patient subgroups with and without neutrophilia and nasal polyposis found no significant between-subject differences after adjustment ($p \geq 0.217$; Fig. 1B). Similar findings were identified for all PSQI component scores.

Bivariate correlations between postoperative changes in PSQI scores and counts of highest density histopathologic counts/HPF were evaluated for subgroups with and without nasal polyposis (Table 3). For all patients with eosinophilia, a weak correlation was identified between higher counts/HPF and greater postoperative improvement in daytime dysfunction scores. Additionally, in subjects without polyposis, higher counts of neutrophilia/HPF highly correlated with greater postoperative improvement in both sleep latency and efficiency scores without adjustment for pairwise comparisons.

Bivariate comparisons between independent study participants with and without eCRS, regardless of nasal polyposis, found no significant differences in the prevalence of postoperative improvement equal to at least 1 MCID in PSQI total scores (48% vs 48%; $\chi^2 = 0.01$; $p = 0.988$). Additional omnibus comparisons of between independent groups with and without nasal polyposis, with or without eosinophilia also found no significant difference in MCID prevalence ($\chi^2 = 0.71$; $p = 0.871$) or postoperative poor sleep (PSQI > 5 ; $\chi^2 = 5.24$; $p = 0.155$). Bivariate comparison between study participants with and without neutrophilic CRS, regardless of nasal polyposis, also found no significant differences in the proportion of improvement equal to 1 MCID in PSQI total scores (52% vs 47%; $\chi^2 = 0.20$; $p = 0.652$). Further omnibus comparisons between independent groups with nCRS, with and without nasal polyposis also found no differences in MCID prevalence ($\chi^2 = 0.66$; $p = 0.883$) or postoperative poor sleep (PSQI > 5 ; $\chi^2 = 2.47$; $p = 0.481$).

Associations between histopathology and perioperative steroid use

Patients who received corticosteroid therapy immediately prior to FESS ($n = 69$) were compared against patient who did not ($n = 22$) across histopathologic subgroups. Mean histopathologic counts/HPF were not significantly different between corticosteroid groups for either eosinophilia (81.8 ± 141.1 vs 39.8 ± 112.4 eosinophils/HPF; $\Delta = 42.0$; 95% CI, -23.6 to 107.6; $p = 0.206$) or neutrophilia (6.9 ± 21.8 vs 2.9 ± 5.2 neutrophils/HPF; $\Delta = 4.0$; 95% CI, -5.3 to 13.4; $p = 0.393$). Preoperative PSQI survey responses were, on average, not significantly different between patients completing a course of corticosteroid therapy immediately before FESS compared to those patients who did not (all $p \geq 0.367$; Fig. 2). No statistically significant differences in the prevalence of subjects receiving preoperative corticosteroid were found based on eosinophilic phenotypes including: non-eCRSsNP (67%) compared to eCRSsNP (70%; $\chi^2 = 0.07$; $p = 0.795$) or non-eCRSwNP (86%) compared to eCRSwNP (92%; $\chi^2 = 0.25$; $p = 0.614$). Additionally, similar frequency of preoperative steroids were prescribed to non-nCRSsNP (66%) compared to nCRSsNP (78%; $\chi^2 = 0.49$; $p = 0.486$) or non-nCRSwNP (86%) compared to nCRSwNP (100%; $\chi^2 = 1.51$; $p = 0.220$).

TABLE 3. Unadjusted Spearman's rho correlations (*R*) between postoperative PSQI differences and counts of highest density preoperative histopathologic markers*

Sleep-based measures	Total eCRS (n = 50)		Total nCRS (n = 25)	
	<i>R</i>	<i>P</i>	<i>R</i>	<i>P</i>
PSQI total score	−0.063	0.663	−0.334	0.103
Sleep quality score	−0.046	0.751	−0.093	0.657
Sleep medication score	0.241	0.092	−0.320	0.119
Sleep duration score	−0.245	0.087	−0.203	0.330
Sleep disturbance score	0.082	0.570	−0.079	0.706
Sleep latency score	0.080	0.581	−0.268	0.196
Sleep daytime dysfunction score	−0.330	0.019	−0.015	0.943
Sleep efficiency score	−0.155	0.283	−0.380	0.061
CRSwNP	eCRSwNP (n = 29)		nCRSwNP (n = 14)	
PSQI total score	−0.097	0.617	−0.097	0.741
Sleep quality score	0.011	0.953	−0.004	0.990
Sleep medication score	0.225	0.241	−0.506	0.065
Sleep duration score	−0.223	0.246	−0.147	0.616
Sleep disturbance score	0.106	0.584	0.067	0.820
Sleep latency score	0.122	0.529	0.041	0.889
Sleep daytime dysfunction score	−0.236	0.218	0.026	0.930
Sleep efficiency score	−0.208	0.278	−0.096	0.744
CRSSNP	eCRSSNP (n = 21)		nCRSSNP (n = 11)	
PSQI total score	0.148	0.521	−0.643	0.033
Sleep quality score	−0.084	0.716	−0.155	0.648
Sleep medication score	0.259	0.257	−0.048	0.889
Sleep duration score	−0.147	0.524	−0.230	0.497
Sleep disturbance score	−0.028	0.906	−0.352	0.288
Sleep latency score	0.105	0.650	−0.798	0.003
Sleep daytime dysfunction score	−0.139	0.548	−0.130	0.703
Sleep efficiency score	0.184	0.425	−0.777	0.005

*Bold values indicate significance.

CRSSNP = chronic rhinosinusitis without nasal polyposis; CRSwNP = chronic rhinosinusitis with nasal polyposis; eCRS = eosinophilic chronic rhinosinusitis; eCRSSNP = eosinophilic CRS without nasal polyposis; eCRSwNP = eosinophilic CRS with nasal polyposis; nCRS = neutrophilic chronic rhinosinusitis; nCRSSNP = neutrophilic CRS without nasal polyposis; nCRSwNP = neutrophilic CRS with nasal polyposis; PSQI = Pittsburgh Sleep Quality Index; *R* = Spearman's rank correlation coefficient.

Discussion

The relationship between CRS and sleep is complex and likely bidirectional, with a poorly understood pathophysiology.^{2,5,7,8,16} The predominant theory proposes that there are 2 primary components of CRS that impact sleep: physical sinonasal changes, which impact airflow, and the presence of chronic inflammation. Chronic inflam-

mation associated with CRS is also known to impact other components of patient QoL and many attempts have been made to elucidate these relationships.⁴⁰ Recent literature has even suggested that analysis of the mucosal histopathology should be a feature in the management in patients with CRS.^{24,30} For that reason, the purpose of this study was to determine if the presence of mucosal eosinophilia or neutrophilia was associated with patient-reported evaluations

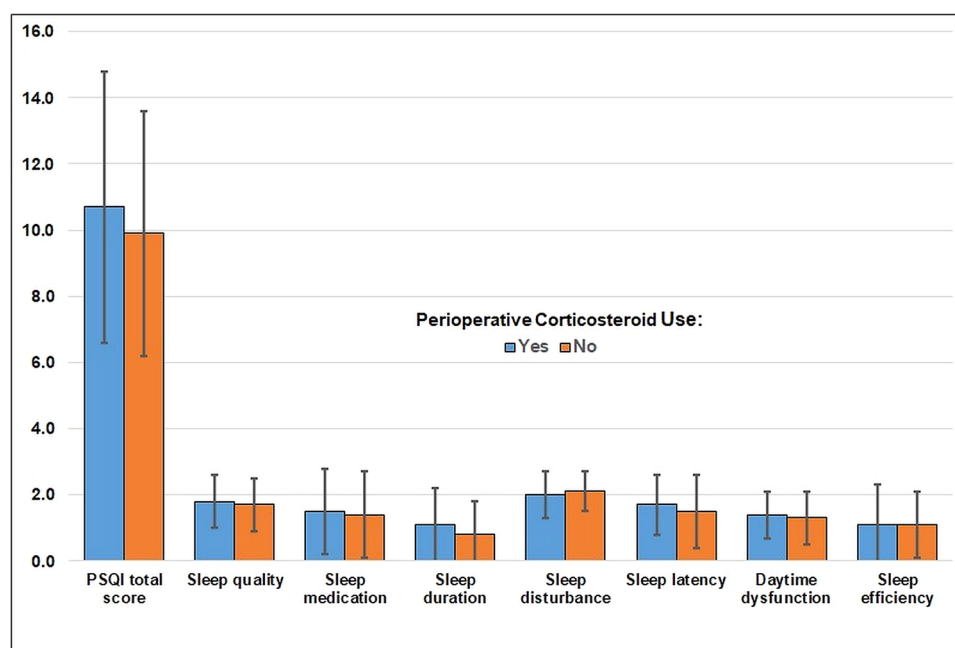


FIGURE 2. Comparisons of average preoperative PSQI measures between patients with and without completion of perioperative corticosteroids. Error bars represent 1 standard deviation above/below the mean. PSQI = Pittsburgh Sleep Quality Index.

of the severity of sleep dysfunction in patients with CRS or with postoperative improvement after FESS. This study demonstrated that 84% of our patients with CRS report “poor” sleep overall. Additionally, consistent with prior studies, our cohort demonstrated significant improvement in PSQI total scores and subdomain scores after FESS.⁸ Overall, the presence of either mucosal eosinophilia or neutrophilia did not significantly associate with either the severity of preoperative sleep dysfunction or postoperative improvement in sleep dysfunction as measured by the PSQI.

Patients with CRS typically note a combination of nasal obstruction, facial pain/pressure, and rhinorrhea.²⁹ Any one of those symptoms alone could impact a patient’s ability to fall asleep and stay asleep. Additionally, studies in healthy subjects have demonstrated that nasal obstruction can induce intermittent hypoxia and apneas that directly impact sleep quality.^{41–43} Therefore, it is surprising that our cohort of patients with CRSwNP, in whom we have previously found worse rhinologic symptoms, including nasal obstruction (unpublished data), had no significant differences in preoperative metrics of sleep dysfunction. These findings contradict findings from a study in France which demonstrated that subjects with CRSwNP had 2 times higher risk of sleep disturbance compared to control subjects.⁴⁴ That study, however, was a survey of the general French population and only evaluated self-reported nasal polyposis and sleep disturbance. Though our results contradict those findings, neither study directly evaluated nasal obstruction severity and its relationship to sleep dysfunction. The lack of associations between rhinologic symptoms on baseline sleep dysfunction measures, however, gives credence to the role of other mechanisms, such as cytokine

imbalance, driving the resultant sleep dysfunction in these patients.

Chronic inflammation likely plays a bidirectional role in sleep dysfunction in patients with CRS. Evaluations of patients with other chronic inflammatory disease including allergic rhinitis, atopic dermatitis, and inflammatory bowel disease have implicated somnogenic and anti-somnogenic cytokines in resultant sleep dysfunction.^{45–47} The potential relationship of inflammation and sleep has also been explored in more depth for other chronic airway diseases, such as asthma. One such study demonstrated that alterations in brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1), a circadian rhythm regulator, resulted in much higher levels of interleukin 5 (IL-5) and eosinophils in asthma mouse models.²⁸ Another study demonstrated that mice with allergic airway disease who were subjected to sleep deprivation developed intense neutrophilic pulmonary inflammation with increased tumor necrosis factor α (TNF α) and IL-17 production.²⁰ From a sinonasal perspective, Alt et al.¹⁶ demonstrated that cytokines associated with CRS may promote changes in the central regulation of sleep, resulting in fatigue, sleep deprivation, and impaired cognition. These studies demonstrate that in chronic inflammatory conditions, the somnogenic cytokines IL-1 β and TNF α are released and can promote non-rapid eye movement sleep, either through centrally acting mechanisms or the activation of downstream regulators that affect sleep.¹⁶ Cytokine studies of patients with CRS have demonstrated upregulation of IL-4, IL-13, and transforming growth factor β (TGF β), which antagonize IL-1 β and TNF α , decreasing sleep.² Because those cytokines are presumably released from the leukocytes present in chronic

inflammatory conditions, we hypothesized that predominant neutrophilic or eosinophilic mucosal inflammation would affect cytokine expression and ultimately impact sleep regulation in patients with CRS. Interestingly, within our patient subgroup of nCRSsNP, there was a significant correlation between higher neutrophils/HPF and improvement in sleep latency and sleep efficiency dysfunction; however, there was not an improvement in overall sleep quality. This relationship is the opposite of what we would expect. In fact, multiple studies evaluating various inflammatory conditions have demonstrated that neutrophilia correlates with worse sleep outcomes.^{17,48} As such, additional evaluation is indicated to better understand this relationship between extent of neutrophilia and the postoperative effect on sleep efficacy and latency.

Sleep dysfunction associated with CRS may also have a bidirectional component, with sleep deprivation induced by inflammation-based symptoms of CRS that cause greater sleep dysfunction. Prior studies evaluating otherwise healthy individuals have demonstrated that chronic sleep deprivation can, in and of itself, induce the production of inflammatory cytokines and neutrophilia.^{13,49,50} Additionally, studies in allergic rats have demonstrated that chronic sleep deprivation changes the inflammatory milieu of the lung parenchyma, with an influx of neutrophils, eosinophils, IL-6, TNF α , and IL-17. Conversely, the lung parenchyma of allergic mice with healthy sleep has primarily eosinophilic inflammation with prevalence of IL-4.²⁰ Though similar studies have not been done to evaluate sinonasal mucosa, it is possible that sleep deprivation could induce similar inflammatory changes in the upper airway.

The main strength of this study is the use of prospectively collected data within a relatively large cohort representing patients in phenotypical subcategories of CRS. This allowed us to provide a comparison of CRSwNP to those without nasal polyps and to subcategorize by the presence of mucosal eosinophilia or neutrophilia. Our definition of eosinophilia (>10 eosinophils/HPF) is consistent with current literature.³¹⁻³³ Some previous studies have used lower eosinophilia thresholds (>5 /HPF),^{51,52} which may potentially misclassify some patients. Applying this alternative cellular staging to our cohort would have only reclassified 5 subjects as eCRS, including both eCRSsNP ($n = 3$) and eCRSwNP ($n = 2$), and provided only nominal changes to our statistical power. Similarly, there are no universally accepted guidelines of what defines mucosal neutrophilia.^{30,34} For this investigation and consistent with prior study we elected >4 neutrophils/HPF; however, prior studies defined this threshold by adding 2 SDs to the average neutrophil count of healthy control subjects without CRS.³⁰ Future studies should be performed to confirm whether this threshold accurately represents CRS patients with a confirmed di-

agnosis of neutrophilia. Ultimately, these efforts could serve as a basis for defining neutrophilia in future investigations which cluster CRS patients by histopathology.

There are multiple limitations to this study. First, 66% of our patients received preoperative corticosteroids as part of the standard of care provided by the enrolling surgeon to control and minimize blood loss during FESS. Although corticosteroids have the potential of altering the mucosal inflammatory makeup, no significant differences were noted in patients who did or did not receive preoperative corticosteroids. This is consistent with past literature, which has demonstrated that oral corticosteroids do not alter the mucosal histopathologic makeup.^{53,54} Another limitation of this study is that the PSQI surveys were completed on average 4.7 weeks prior to FESS. Therefore, it is possible that the mucosal histology changed in between the time that the patient's completed preoperative sleep evaluations and the time of specimen collection. Although this could theoretically impact our results, there were no new interventions implemented between the time of preoperative survey completion and FESS so it is unlikely that the histopathologic markers would change significantly. The PSQI was utilized to determine patients with poor sleep and symptoms of sleep dysfunction, rather than quantitative polysomnography. As such, our results could be influenced by unmeasured confounding factors or underlying sleep disturbances that may impact patient responses. Additionally, other survey instruments may provide alternative information about sleep dysfunction in patients with CRS. Last, this study broadly classified patients as those with or without nasal polyposis and did not further subclassify patients into known cohorts, such as those with aspirin-exacerbated respiratory disease (AERD). Additionally, other patient comorbidities, such as asthma and depression, have known influences on sleep. Additional study would be indicated to further evaluate the relationship of mucosal leukocyte distribution on outcomes in additional subtypes of CRS and in those with comorbidities that are known to influence sleep quality.

Conclusion

CRS is associated with significant sleep dysfunction, with a large majority of patients reporting poor sleep. Current theories include a multifactorial, bidirectional relationship between CRS and sleep, with symptoms resulting from a combination of sinonasal symptoms as well as inflammatory effects on central regulators of sleep. Although the inflammatory milieu of CRS patients may play a role in sleep dysfunction, the presence of sinonasal mucosal eosinophilia or neutrophilia does not associate with changes in baseline sleep symptoms or improvement after FESS as measured by the PSQI. 

References

- National Center for Health Statistics. Chronic sinusitis. Atlanta, GA: Centers for Disease Control and Prevention; 2020. <https://www.cdc.gov/nchs/fastats/sinuses.htm>. Accessed August 8, 2020.
- Alt J, Orb Q, Orlandi RR. The role of sinus surgery in sleep outcomes. *Curr Opin Otolaryngol Head Neck Surg*. 2017;25:47-53.
- Wyld M, Morton RL, Hayen A, Howard K, Webster AC. A systematic review and meta-analysis of utility-based quality of life in chronic kidney disease treatments. *PLoS Med*. 2012;9:e1001307.
- Szende A, Leidy NK, Stahl E, Svensson K. Estimating health utilities in patients with asthma and COPD: evidence on the performance of EQ-5D and SF-6D. *Qual Life Res*. 2009;18:267-272.
- Mahdavinia M, Schleimer RP, Keshavarzian A. Sleep disruption in chronic rhinosinusitis. *Expert Rev Anti Infect Ther*. 2017;15:457-465.
- Bengtsson C, Lindberg E, Jonsson L, et al. Chronic rhinosinusitis impairs sleep quality: results of the GA2LEN Study. *Sleep*. 2017;40(1):zsw021. <https://doi.org/10.1093/sleep/zsw021>. Accessed August 8, 2020.
- Alt JA, Smith TL. Chronic rhinosinusitis and sleep: a contemporary review. *Int Forum Allergy Rhinol*. 2013;3:941-949.
- Alt JA, Smith TL, Schlosser RJ, Mace JC, Soler ZM. Sleep and quality of life improvements after endoscopic sinus surgery in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2014;4:693-701.
- Liu H, Wang G, Luan G, Liu Q. Effects of sleep and sleep deprivation on blood cell count and hemostasis parameters in healthy humans. *J Thromb Thrombolysis*. 2009;28:46-49.
- Cappuccio FP, Miller MA. Sleep and mortality: cause, consequence, or symptom? *Sleep Med*. 2013;14:587-588.
- Azevedo Da Silva M, Singh-Manoux A, Shipley MJ, et al. Sleep duration and sleep disturbances partly explain the association between depressive symptoms and cardiovascular mortality: the Whitehall II cohort study. *J Sleep Res*. 2014;23:94-97.
- Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep*. 2010;33:585-592.
- Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry*. 2016;80:40-52.
- Perry GS, Patil SP, Presley-Cantrell LR. Raising awareness of sleep as a healthy behavior. *Prev Chronic Dis*. 2013;10:E133.
- Sukato DC, Abramowitz JM, Boruk M, Goldstein NA, Rosenfeld RM. Endoscopic sinus surgery improves sleep quality in chronic rhinosinusitis: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2018;158:249-256.
- Alt JA, Sautter NB, Mace JC, Detwiller KY, Smith TL. Antisomnogenic cytokines, quality of life, and chronic rhinosinusitis: a pilot study. *Laryngoscope*. 2014;124:E107-E114.
- Taille C, Rouvel-Tallec A, Stoica M, et al. Obstructive sleep apnoea modulates airway inflammation and remodelling in severe asthma. *PLoS One*. 2016;11:e0150042.
- Teodorescu M, Broymann O, Curran-Everett D, et al. Obstructive sleep apnea risk, asthma burden, and lower airway inflammation in adults in the Severe Asthma Research Program (SARP) II. *J Allergy Clin Immunol Pract*. 2015;3:566-575.e1.
- Said EA, Al-Abri MA, Al-Saidi I, et al. Sleep deprivation alters neutrophil functions and levels of Th1-related chemokines and CD4(+) T cells in the blood. *Sleep Breath*. 2019;23:1331-1339.
- Nunes JOF, Apostolico JS, Andrade DAG, et al. Sleep deprivation predisposes allergic mice to neutrophilic lung inflammation. *J Allergy Clin Immunol*. 2018;141:1018-1027.e4.
- Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology*. 2012;50:1-12.
- Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(Suppl 1):S22-S209.
- Tomassen P, Vandeplass G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol*. 2016;137:1449-1456.e4.
- Lal D, Borish L, Detwiller KY, et al. A case for multidisciplinary management of chronic rhinosinusitis with nasal polyposis. *Int Forum Allergy Rhinol*. 2020;10:795-797.
- Sharbel D, Li M, Unsal AA, et al. Use of mucosal eosinophil count as a guide in the management of chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2020;10:474-480.
- Smith TL. Scientific abstracts for RhinoWorld 2019. *Int Forum Allergy Rhinol*. 2019;9(S2):S49-S124.
- Kavanagh J, Jackson DJ, Kent BD. Sleep and asthma. *Curr Opin Pulm Med*. 2018;24:569-573.
- Zaslona Z, Case S, Early JO, et al. The circadian protein BMAL1 in myeloid cells is a negative regulator of allergic asthma. *Am J Physiol Lung Cell Mol Physiol*. 2017;312:L855-L860.
- Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg*. 2007;137(3 Suppl):S1-S31.
- Succar EF, Li P, Ely KA, Chowdhury NI, Chandra RK, Turner JH. Neutrophils are underrecognized contributors to inflammatory burden and quality of life in chronic rhinosinusitis. *Allergy*. 2020;75:713-716.
- Soler ZM, Sauer DA, Mace J, Smith TL. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2009;141:454-461.
- Soler ZM, Sauer D, Mace J, Smith TL. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg*. 2010;142:64-71.
- Soler ZM, Sauer DA, Mace JC, Smith TL. Ethmoid histopathology does not predict olfactory outcomes after endoscopic sinus surgery. *Am J Rhinol Allergy*. 2010;24:281-285.
- Wen W, Liu W, Zhang L, et al. Increased neutrophilia in nasal polyps reduces the response to oral corticosteroid therapy. *J Allergy Clin Immunol*. 2012;129:1522-1528.e5.
- Ulus Y, Akyol Y, Tander B, Durmus D, Bilgili A, Kuru O. Sleep quality in fibromyalgia and rheumatoid arthritis: associations with pain, fatigue, depression, and disease activity. *Clin Exp Rheumatol*. 2011;29(6 Suppl 69):S92-S96.
- Milross MA, Piper AJ, Norman M, et al. Subjective sleep quality in cystic fibrosis. *Sleep Med*. 2002;3:205-212.
- Merlino G, Fratticci L, Lenchig C, et al. Prevalence of 'poor sleep' among patients with multiple sclerosis: an independent predictor of mental and physical status. *Sleep Med*. 2009;10:26-34.
- Buyse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193-213.
- Norman GR, Sloan JA, Wywich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003;41:582-592.
- Smith TL, Mendolia-Loffredo S, Loehrl TA, Sparapani R, Laud PW, Nattiger AB. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. *Laryngoscope*. 2005;115:2199-2205.
- Olsen KD, Kern EB, Westbrook PR. Sleep and breathing disturbance secondary to nasal obstruction. *Otolaryngol Head Neck Surg*. 1981;89:804-810.
- Zwillich CW, Pickett C, Hanson FN, Weil JV. Disturbed sleep and prolonged apnea during nasal obstruction in normal men. *Am Rev Respir Dis*. 1981;124:158-160.
- Duzenli U, Bozan N, Sonkaya Y, Cetin YS, Demir H. Evaluation of the relationship between nasal septum deviation and oxidative stress markers. *J Craniofac Surg*. 2019;30:851-853.
- Serrano E, Neukirch F, Pribil C, et al. Nasal polyposis in France: impact on sleep and quality of life. *J Laryngol Otol*. 2005;119:543-549.
- Craig TJ, Hanks CD, Fisher LH. How do topical nasal corticosteroids improve sleep and daytime somnolence in allergic rhinitis? *J Allergy Clin Immunol*. 2005;116:1264-1266.
- Chang YS, Chiang BL. Sleep disorders and atopic dermatitis: a 2-way street? *J Allergy Clin Immunol*. 2018;142:1033-1040.
- Keefer L, Stepanski EJ, Ranjbaran Z, Benson LM, Keshavarzian A. An initial report of sleep disturbance in inactive inflammatory bowel disease. *J Clin Sleep Med*. 2006;2:409-416.
- Fang SH, Suzuki K, Lim CL, Chung MS, Ku PW, Chen LJ. Associations between sleep quality and inflammatory markers in patients with schizophrenia. *Psychiatry Res*. 2016;246:154-160.
- Besedovsky L, Lange T, Born J. Sleep and immune function. *Pflugers Arch*. 2012;463:121-137.
- Gamaldo CE, Shaikh AK, McArthur JC. The sleep-immunity relationship. *Neurol Clin*. 2012;30:1313-1343.
- Kountakis SE, Arango P, Bradley D, Wade ZK, Borish L. Molecular and cellular staging for the severity of chronic rhinosinusitis. *Laryngoscope*. 2004;114:1895-1905.
- Snidvongs K, Lam M, Sacks R, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *Int Forum Allergy Rhinol*. 2012;2:376-385.
- Kuhar HN, Tajudeen BA, Mahdavinia M, Gattuso P, Ghai R, Batra PS. Inflammatory infiltrate and mucosal remodeling in chronic rhinosinusitis with and without polyps: structured histopathologic analysis. *Int Forum Allergy Rhinol*. 2017;7:679-689.
- Gitomer SA, Fountain CR, Kingdom TT, et al. Clinical examination of tissue eosinophilia in patients with chronic rhinosinusitis and nasal polyposis. *Otolaryngol Head Neck Surg*. 2016;155:173-178.