



Association between allergic and nonallergic rhinitis and obstructive sleep apnea

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Purpose of review

Allergic rhinitis and nonallergic rhinitis (NAR) are common disorders, which have been considered as potential risk factors for obstructive sleep apnea (OSA). This review summarizes the proposed underlying pathophysiological mechanisms to provide a better understanding of the relationship between these conditions.

Recent findings

In adults, allergic rhinitis and NAR may be considered as symptoms potentiating, rather than risk potentiating factors in the pathophysiology of OSA, whereas in children, these are considered to be independent predictors for sleep-disordered breathing (SDB) and failure of adeno-tonsillectomy, the recommended first-line therapy for children with OSA. Current advances suggest IL-6 may be important in regulating the sleep–wake cycle, and serum soluble IL-6 receptor (sIL-6R) levels may reflect the severity of OSA. Elevated Th17/Treg ratio correlates positively with apnea–hypopnea index of OSA patients, and Th17 and Treg imbalances caused by allergic rhinitis and OSA, respectively, may possibly promote each other, leading to further imbalance. Moreover, obesity is a strong risk factor for OSA, and leptin plays an important role in ventilatory function and upper airway obstruction. The variant trigeminocardiac reflex and nasotrigeminal reflex may also be involved in the association between rhinitis and OSA.

Summary

Allergic rhinitis/NAR and OSA are closely associated, and each condition can be detrimental to the other. Thus, clinicians should pay attention to the potential presence of allergic rhinitis/NAR in OSA patients and vice versa.

Keywords

allergic rhinitis, inflammatory mediators, nonallergic rhinitis, obese, obstructive sleep apnea

INTRODUCTION

An individual usually spends approximately a third of their life sleeping, which is essential for promoting the individual's health and well being [1]. However, Sleep-disordered breathing (SDB), a major cause of sleep impairment represented by a large spectrum of abnormal conditions ranging from simple snoring to obstructive sleep apnea (OSA), can lead to detrimental influence on an individual's physical and mental health. OSA is characterized by repetitive obstruction of the upper airway, which often results in oxygen desaturation and arousals from sleep [2,3]. OSA affects approximately 13% of men and 6% of women aged 30–70 years [4], and 1–4% of children [5]. As a potential life-threatening sleep disease, OSA is associated with sleep fragmentation and excessive daytime somnolence, fatigue, neuropsychiatric complications (irritability, depression), and cardiovascular complications, including pulmonary and systemic hypertension, congestive

heart failure, myocardial infarction, and stroke [3,6]. Multiple risk factors including aging, obesity, male gender, alcohol, menopause, craniofacial dysmorphism, increased pharyngeal soft tissue (such as hypertrophy of adenoids and tonsil in children), and chronic nasal congestion from rhinitis are involved in the underlying pathophysiology [3,7].

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KEY POINTS

- Doctors should constantly keep in mind the frequent coexistence of allergic rhinitis/NAR and OSA, and the potential of each condition in exacerbating the other.
- Allergic rhinitis/NAR may be regarded as symptoms potentiating, rather than risk potentiating factors for OSA, despite a relatively high prevalence in OSA patients, compared with general population.
- Increased inflammatory mediators induced by rhinitis tend to be involved in the disturbance of sleep architecture in OSA patients.
- Obesity appears to be a strong risk factor for OSA, and may influence ventilatory function and upper airway obstruction.

Some studies have suggested that OSA may develop in patients with rhinitis who experience frequent snoring and apneas [8,9].

Rhinitis is classified as allergic rhinitis or non-allergic rhinitis (NAR), based on the results of skin prick test or serum-specific immunoglobulin E (IgE), and present with similar symptoms of nasal obstruction (congestion), rhinorrhea, sneezing, and/or itchy nose. Despite the weakness of epidemiologic data on NAR, studies from the United States and Europe have estimated that 7–19% of the adult population suffers from NAR [10,11]. A study by Westman *et al.* [12] has recently reported NAR prevalence rates of 8.1 and 6.3%, in Swedish children aged 4 and 8 years, respectively. Similarly, another study from Singapore has recently demonstrated that NAR was more common than allergic rhinitis in children younger than 6 years, although most children with allergic rhinitis (73%) presented after age 6 years [13]. Allergic rhinitis is thought to affect up to 10–20% of the worldwide population, and its prevalence is increasing. Estimates suggest that allergic rhinitis affects 20–40 million people in the United States, including up to 40% of children, while the prevalence of allergic rhinitis in Europe is estimated at 23% [14–16]. Allergic rhinitis patients often report symptoms similar to those in patients with OSA, including fatigue, irritability, depression, and daytime somnolence [17–19], of which the latter may be induced by allergy itself or by disturbance of sleep due to the troublesome symptoms. Indeed, the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline uses the degree of sleep impairment as a factor in classifying allergic rhinitis severity [20]. Recently, there is increasing consensus that NAR shares a common pathway with allergic rhinitis in an underlying syndrome

of nasal mucosal inflammation, which may lead to increased nasal congestion and consequently sleep impairment [21].

The important role of nose as the primary route of breathing during sleep has been recognized for more than 40 years since Cottle [22] suggested that ‘sleeping patterns are in great measure dependent on good nasal function’ [9]. A simple trial using a nose clip in healthy individuals to artificially induce an increase in sleep apnea and arousals has suggested that the nasal obstruction secondary to congestion has a prominent role in the underlying mechanism of SDB [23]. At present, nasal congestion is regarded extensively as a prominent and troublesome symptom in both allergic rhinitis and NAR patients [24]. Indeed, an internet survey of more than 2000 adults and children has shown that nasal congestion was the most prominent symptom, with 85% of respondents experiencing nasal congestion and almost 50% reporting it to be the most bothersome [25]. Another study demonstrated that in 30% of the patients impaired sleep was secondary to congestion [26]. It has been speculated that increased nasal congestion associated with allergic rhinitis and NAR results in negative pressure in the pharynx, and predisposes the nose to additional upper airway collapse and probably to the occurrence of OSA, when the patient is in a horizontal position [27–29].

Rhinitis has been identified as a potential risk factor in SDB, including OSA [27]. As early as 1980s, some researchers found that SDB was present in every allergic rhinitis patient, who had an average of 50 ‘microarousals’ during sleep (10 times more than healthy controls) [18] and increased episodes of apnea [30]. Hellgren *et al.* [31] demonstrated that NAR was an important, independent risk factor for difficulty in maintaining sleep, early morning awakenings, and daytime sleepiness. In addition, a polysomnography (PSG) study has shown that OSA episodes were longer and more frequent in patients with rhinitis-driven nasal congestion than in allergic rhinitis patients with no symptoms [32]. Other studies have reported that treatments for allergic rhinitis, particularly those that improve symptoms of nasal congestion, can improve patient’s sleep problems [33]. In fact, OSA and rhinitis are often common coexisting disorders, with nasal symptoms being highly prevalent in OSA patients, as confirmed by PSG, and 54% patients reporting nasal obstruction, 52% nose dryness, 33% sneezing, 33% postnasal drip, and 24% rhinorrhea [34]. Canova *et al.* [35] have demonstrated that the OSA patients have an increased prevalence of perennial allergic rhinitis (PAR) (11%) and were also more likely to be sensitized to perennial allergens such as house dust

mite (23.6 vs. 4.5%) and dog (18 vs. 4.5%) than chronic obstructive pulmonary disease patients.

However, one early study suggested that allergic rhinitis is not a major risk factor for OSA [36], and a recent study of 240 Chinese patients with OSA confirmed by standardized PSG has shown that the presence or severity of allergic rhinitis or NAR does not influence the severity of OSA [37[■]]. Thus, the precise pathophysiological mechanisms underlying the association between rhinitis and OSA are presently not clear, and there is an ongoing need for a better understanding of the relationship between rhinitis and OSA. The aim of the present study is thus to review the available information in the literature detailing the association between rhinitis and OSA and the underlying pathophysiological mechanisms.

LINK BETWEEN ALLERGIC RHINITIS/ NONALLERGIC RHINITIS AND OBSTRUCTIVE SLEEP APNEA IN ADULTS

The 2009 Burden of Rhinitis in America survey indicated that sleep impairment played a major negative role in adult patients with rhinitis, with only 3.6% of the nearly 4000 allergic rhinitis patients surveyed experiencing 100% adequate sleep during the previous months compared with 19.2% respondents who had no symptoms of rhinitis [38]. In another survey of adult allergic rhinitis, 68% of respondents with PAR and 48% with seasonal allergic rhinitis (SAR) reported impaired sleep, due to their nasal condition [39]. Similarly, Leger *et al.* [40] indicated that sleep was impaired more significantly in patients with severe allergic rhinitis symptoms than in patients with mild allergic rhinitis symptoms, although the duration of allergic rhinitis had no effect on sleep disturbance. These findings were confirmed by Bousquet *et al.* [41], who demonstrated that for patients consulting in primary care the effect of severity of allergic rhinitis on quality of life was stronger than the duration of allergic rhinitis. Indeed, there is abundant evidence that nasal congestion induced by allergic rhinitis has a prominent role in sleep impairment [42,43]. One large population-based study involving about 5000 adults demonstrated that individuals reporting frequent nasal congestion (≥ 5 nights/month) due to allergy were almost twice as likely to have moderate-to-severe SDB than individuals without nasal congestion due to allergy [44]. Cevizci *et al.* [45[■]] examined the relationship between nasal disorders and positional or nonpositional OSA and showed that nasal congestion induced by allergic rhinitis made the patients tend to be nonpositional OSA. Allergic rhinitis associated rhinorrhea and

ocular itching have also been verified to be important in the cause of sleep impairment [20,46]. Furthermore, the types of allergen play a crucial role in the sleep impairment. Symptoms of PAR can be exacerbated during sleep because of close exposure to high concentrations of house dust mite in the bed, and thus nasal congestion is always the worst in supine position [47,48]. Similarly, a study of 25 adult SAR patients and 25 healthy volunteers undergoing two nights of PSG before and during the pollen season has demonstrated that there were significant differences in parameters of PSG between the two groups, including increases in the apnea index, hypopnea index, apnea–hypopnea index (AHI), snoring time, amount of rapid-eye movement (REM) sleep, and sleep latency when the SAR patients were symptomatic [49]. Use of actigraphy may intuitively determine the level of sleep impairment affected by rhinitis, as PAR adults were found to have a significantly increased fragmentation index value and increased sleep disturbance, compared with the healthy group [50]. Similarly, studies investigating individuals suffering from OSA have indicated that whereas about 25.0% of adult OSA patients have allergic rhinitis [51], about 70–75.0% are atopic, as demonstrated by skin prick test [52,53]. One recent study has investigated the association between allergic rhinitis and OSA in asthmatic patients with or without comorbid allergic rhinitis and demonstrated that patients with comorbid allergic rhinitis were at a greater risk of developing OSA than patients with asthma alone [54]. Furthermore, in patients with an odds ratio (OR) of 1.99, the probable increased risk of OSA was associated with the presence of concomitant allergic rhinitis, independent of other risk factors.

Compared with allergic rhinitis, there is limited information on the association between NAR and OSA. It has been reported that NAR with eosinophilia syndrome might stimulate alveolar hypoventilation, which results in an elevated hypopnea index [55]. An observational study by Kalpaklioglu *et al.* [8] investigated the prevalence of OSA in adults with allergic rhinitis and NAR and showed that a significantly greater number of NAR patients (83%) were diagnosed with OSA than allergic rhinitis patients (36%; $P=0.001$), and that severe OSA existed only in the NAR group. Furthermore, NAR was highly correlated with OSA (OR = 6.4), suggesting that adult patients with NAR were generally at higher risk for OSA than allergic rhinitis patients [8]. Similarly, a community-based sleep center study has demonstrated that 69.8% of patients diagnosed with SDB had NAR and that the rate of NAR in SDB patients was more than twice that expected and as compared with the general population [56[■]].

Nevertheless, depending on different methods used and populations surveyed, some published data on the relationship between rhinitis and OSA in adults have been shown to be negative and even paradoxical. Although one early study from Germany suggested that allergic rhinitis was not a risk factor for OSA [36], we have recently shown that the presence or severity of allergic rhinitis or NAR did not influence the severity of OSA [37[■]]. Furthermore, our study suggested that despite a comparatively high prevalence in adult OSA patients, both allergic rhinitis and NAR may be considered as symptoms potentiating, rather than risk potentiating factors in the pathophysiology of OSA [37[■]]. Indeed, one more recent study has assessed the effect of PAR on sleep quality and severity of OSA based on PSG findings, and demonstrated that there were no significant differences between adult PAR patients and healthy controls with regard to PSG parameters, including sleep architecture, arousal and respiratory index, and mean and minimal oxygen saturations [57[■]]. However, it is possible that the lack of differences between the PAR patients and healthy controls might be a consequence of selective bias because only mild PAR patients were enrolled into the study according to the ARIA classification [57[■]]. Thus, in view of the currently available data, it is clear that further well controlled studies are needed to determine the precise associations between allergic rhinitis/NAR and SDB, including OSA, and to raise awareness of the potential effects of these conditions as comorbidities among rhinologists and sleep specialists.

LINK BETWEEN ALLERGIC RHINITIS/ NONALLERGIC RHINITIS AND OBSTRUCTIVE SLEEP APNEA IN CHILDREN

Although sleep is crucial for a child's growth, development, and learning ability, a survey of Pediatric Allergies in America indicated that 40% of parents claimed allergies affected their child's sleep: 32% claimed their child had difficulty falling asleep, 26% claimed their child awakened at night due to sleep problems, and 29% claimed their children had a lack of good sleep [20]. The adverse behavioral and health effects on children induced by SDB include poor school performance, hyperactivity, growth retardation, hypertension, corpulmonale, reduced neurocognitive issues, immune function, and others. [58,59]. Thus, in view of these significant adverse effects, it is important to identify the risk factors for SDB, as well as OSA, in children. It is well known that both SDB and allergies are common problems among the children. Kalra *et al.* [60] showed that there was a significant relationship

between atopic status and simple snoring in children under the age of 1 year. This has recently been confirmed by Wang *et al.* [61], by assessing Chinese toddlers using an expanded version of the Brief Infant Sleep Questionnaire (BISQ-expanded) and standard questionnaires on allergic diseases (wheeze, eczema, food allergy, and allergic rhinitis). The authors demonstrated that snoring was significantly associated with increased odds of having any allergy, eczema, and food allergy. Similarly, Loekmanwidjaja *et al.* [62[■]] used the Children's Sleep Habits Questionnaire to assess sleep disorders in Brazilian children and demonstrated that sleep disorders were significantly higher among children with moderate-severe persistent allergic rhinitis compared with healthy controls. Chng *et al.* [63] have investigated the association between atopic disease and snoring in Singaporean children and demonstrated that snoring was significantly associated with allergic rhinitis and that atopy was the most strongly associated risk factor for snoring. Indeed, a study of children with habitual snoring referred for PSG has indicated that simple snoring children with positive radioallergosorbent test (RAST) results were significantly more likely to have OSA than children with negative RAST results [64]. However, while a retrospective descriptive study of about 300 children has reported that snoring was more common in children with NAR than in children with allergic rhinitis [65], another larger sample study investigating 5740 elementary school students demonstrated that rhinitis was an independent predictor of milder SDB [66]. Indeed, a systematic review of studies investigating the association between allergic rhinitis and SDB in children for the last 25 years has recently demonstrated that there was a higher prevalence of SDB in allergic rhinitis children [67], with habitual snoring being the most common form of SDB studied, in 56% of the studies included in the review, and OSA being studied in 33% of the studies.

The mechanism underlying the association between rhinitis and SDB is thought to involve the lymphoid cells in the adenoids and tonsils that lie behind and below the nasal cavity, respectively. In particular, the immunologic response(s) to antigens and other inflammatory stimulation in patients with rhinitis lead to lymphoid hypertrophy, increasing the size of the tonsils and adenoids [68,69[■]]. Tonsil and adenoidal hypertrophy (ATH) subsequently lead to obstruction of the nasopharyngeal and oropharyngeal passages and result in sleep fragmentation and intermittent hypoxemia [70,71]. Indeed, adenotonsillectomy is presently recommended as the first-line therapy for children with OSA, by the American Academy of Pediatrics [72]. However, more than 20% of children with OSA still present with snoring symptoms and/or signs of snoring after adeno-

tonsillectomy [73,74]. Several clinical studies have suggested that allergic rhinitis is a risk factor for children with ATH [75,76]. Compared with healthy controls, allergic rhinitis children commonly sensitized to pollen and molds have been shown to have a significantly increased probability of adenoid hypertrophy [77]. Moreover, Dogru *et al.* [69[■]] have suggested that presence of ATH may increase the severity of allergic rhinitis and prolong the duration of allergic rhinitis. Similarly, a study of sixth grade children has shown that 30% of the children with tonsillar hypertrophy had allergic rhinitis, compared to only 8% of children without tonsillar hypertrophy having allergic rhinitis [78]. Although Huseni *et al.* [79] showed that 43% of children with OSA had rhinitis, and this comorbidity did not influence the severity of OSA or nocturnal hypoxemia children with OSA [79], a study by Warman *et al.* [80[■]] concluded that nasal obstruction in children with rhinitis may be improved after adenoidectomy, with no difference in clinical improvement between allergic rhinitis and NAR pediatric patients [80[■]]. A multivariate analysis has also identified rhinitis (OR = 1.334) as the independent predictor for the failure of adeno-tonsillectomy, similar to obesity, deviated nasal septum, tonsil size and age older than 7 years [81[■]]. Thus, in clinical practice, identifying and treating rhinitis is a very important step toward improving the symptoms and preventing deterioration of quality of life in children with OSA undergoing adeno-tonsillectomy.

ROLE OF NASAL CONGESTION IN THE PATHOGENESIS OF OBSTRUCTIVE SLEEP APNEA

Nasal resistance accounts for two-thirds of the total airway resistance. Nasal congestion occurs when capacitance vessels dilate in the cavernous tissues of the inferior turbinate and lead to a smaller internal nasal diameter and increased nasal resistance to nasal airflow [32]. Although nasal congestion in a healthy person tends to increase when the patient is supine, the compensatory mechanisms normally reduce nasal congestion, these mechanisms are not sufficient to compensate accordingly in patients with rhinitis [82]. Thus, it is not surprising that more than 50% of rhinitis patients complain of nasal congestion as their main symptom [23]. However, evidence shows that nasal congestion varies in severity with the time of day and is often worse at nighttime and during early morning hours (6 a.m.) [83[■]]. Moreover, a population-based cohort study of 4916 participants has demonstrated that chronic nasal congestion at night was a strong independent risk factor for habitual snoring, including snoring without frank sleep apnea [84]. Similarly, some early

studies have indicated that in OSA patients, the presence of nasal congestion was associated with an increase in the number and duration of episodes of apnea [30], as well as increased microarousals [18]. The degree of nasal congestion can be evaluated by use of objective methods, including peak nasal inspiratory flow, rhinomanometry, and acoustic rhinometry [85]. Although the data from one study using acoustic rhinometry indicated that OSA patients had higher congestion than non-OSA patients [86], another study using the use of rhinomanometry indicated that increased nasal resistance was an independent risk factor for OSA patients, although it accounted for 2.3% of the total AHI variance [7]. Indeed, Sugiura *et al.* [87] assessed the influence of nasal resistance before beginning continuous positive airway pressure (CPAP) treatment on the initial acceptance of CPAP in OSA patients and reported that nasal resistance quantified by rhinomanometry significantly affected the initial acceptance of CPAP in OSA patients, and hence could be a predictive parameter for the initial acceptance of CPAP in OSA patients [87].

The physiologic mechanism of how increased nasal congestion induces upper airway collapse is best described by use of the Starling resistor model, first described by Blakley and Mahowald [88]. In this model, the whole upper airway is viewed as a tube, in which under normal airflow conditions the intraluminal pressure is equal to the surrounding pressure, and thus the transmural pressure is zero. The Venturi effect states that air must pass through a small tube faster than through a large tube if the passing volume of air and time are equal. Thus, a decreased cross-sectional area of nasal passage induced by congestion will lead to a faster airflow. According to the Bernoulli principle, the higher the velocity of airflow is, the lower the intraluminal pressure is. As a result, the conductive intraluminal pressure is smaller than surrounding pressure in the velopharyngeal or retropalatal segments, which are the soft regions, considering the nasal cavity is relatively rigid. The elevated negative transmural pressure in the pharynx will thus promote additional pharyngeal collapse, increasing the risk of OSA (Fig. 1). Indeed, credence of this mechanism is strengthened by the positive effect of intranasal corticosteroid treatment on OSA and rhinitis [89].

ROLE OF INFLAMMATORY CELLS AND MEDIATORS INDUCED BY ALLERGIC RHINITIS IN OBSTRUCTIVE SLEEP APNEA

In addition to the evident effect of the symptoms of allergic rhinitis on sleep, the underlying pathophysiologic changes, such as inflammatory cells

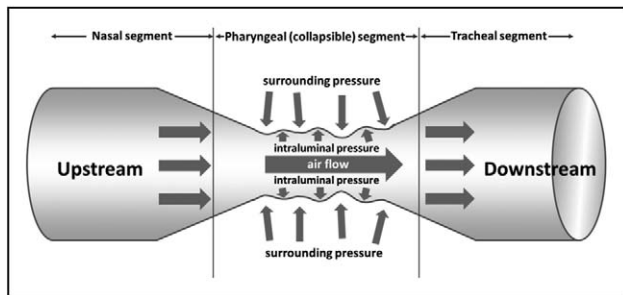


FIGURE 1. Schematic diagram for the Starling resistor model of upper airway collapse in obstructive sleep apnea (OSA).

imbalance and an inflammatory cytokine-rich milieu, present in symptomatic allergic rhinitis patients can also directly contribute to OSA. The disturbance of sleep architecture can lead to both nocturnal events and daytime symptoms such as fatigue, depression, somnolence, etc. The mediators released in the early/late phase responses of allergic rhinitis include histamine, cysteinyl leukotrienes (CysLTs), cytokines, chemotactic factors, and enzymes, all of which contribute to the different symptoms of allergic rhinitis [90,91]. Additionally, histamine participates in the regulation of the sleep–wake cycle, arousal, cognition, and memory [92], whereas CysLTs increase slow-wave sleep and are also involved in increased eosinophil presence and function, congestion and rhinorrhea, leading to sleep disruption [93,94]. An exploratory study by Krouse *et al.* [95] demonstrated levels of IL-1 β , IL-4, and IL-10 were higher in allergic rhinitis patients, compared with nonallergic patients, and correlated with increased latency to REM sleep, decreased time in REM sleep, and decreased latency to sleep onset. Given the role of REM sleep in enhancing restoration function, disruption in REM sleep may contribute to daytime fatigue, difficulty concentrating, and worse performance in allergic rhinitis patients. Moreover, elevated levels of TNF- α , IL-6, and IL-1 β in both allergic rhinitis and OSA patients can result in fatigue and other nonspecific mental symptoms, such as stress and depression [96]. Animal models have also indicated that exogenous administration of IL-1 β , IL-2, IL-6, IL-18, and TNF- α promote non-REM (NREM) sleep, whereas IL-4, IL-10, IL-13, and TGF- β inhibit NREM sleep [97]. Indeed, IL-6, a key factor in controlling the switching of Treg and Th17, has been proposed to be a ‘sleep factor’ that improves circadian rhythm and regulates the sleep–wake cycle [98,99]. Furthermore, serum levels of soluble IL-6 receptor (sIL-6R) have been shown to reflect the severity of OSA [100]. However, whether these mediators are simply associated with or actually induce OSA in allergic rhinitis patients remains

to be unclear. There is evidence that OSA may impact the number and function of inflammatory cells, enhance cytokines release and even lead to persistent or worsening systemic inflammatory immune functioning [101–103]. Moreover, several studies have shown that snoring may result in repeated episodes of hypoxemia. Periodic hypoxia-induced norepinephrine and epinephrine secretion leads to increased levels of IL-6 and TNF- α and reduced immunologic tolerance to allergen and triggering of allergic reactions [104–106]. Ye *et al.* [107] have reported that the Th17/Treg ratio is elevated in OSA patients and correlates positively with AHI [107]. Similarly, Ni *et al.* [108^{***}] have shown that the Th17/Treg ratio was significantly higher in OSA children with allergic rhinitis compared to OSA children with ATH. The authors hypothesized that Th17 and Treg imbalance caused by allergic rhinitis and OSA, respectively, may mutually promote each other and lead to further imbalance. Thus, regardless of which pathological changes appear first, both allergic rhinitis and OSA will cause Th17/Treg imbalance disorders [108^{***}]. Table 1 presents a summary of the effects of different inflammatory mediators on sleep architecture and impairment and nasal pathophysiology [23,24,33,92–95,109–113].

POSSIBLE ROLE OF NEUROMECHANICAL REFLEX IN THE LINK BETWEEN RHINITIS AND OBSTRUCTIVE SLEEP APNEA

There is evidence that the inferior turbinates are dominated by both sympathetic and parasympathetic nerves and that while sympathetic activity in the nasal mucosa of inferior turbinate declines at night, relative parasympathetic hyperactivity is responsible for increased nasal congestion in the sleep [114,115]. Abnormalities of autonomic nervous activity present in rhinitis are characterized by excessive cholinergic tone and decreased adrenergic tone [116]. Some scholars have speculated that imbalance of autonomic system, in the form of sympathetic withdrawal and parasympathetic activation, plays a potential role in the pathophysiology of sleep impairment induced by rhinitis, especially by NAR [24,42]. Moreover, it has been suggested that in NAR with eosinophilia syndrome, a clinical subtype of NAR, activation and augmentation of nasal-pulmonary reflex may cause alveolar hypoventilation, which subsequently results in an increase in hypopnea index in the sleep [55,117]. Woodson *et al.* [118] showed that disturbances of the autonomic system were associated with mild OSA and suggested that abnormalities of autonomic system may be secondary or precede OSA and possibly may

Table 1. The effect of inflammatory mediators on sleep and nose

Mediators	Effect on sleep	Effect on nose	References
Histamine	Regulates the sleep–wake cycle and arousal	Slightly increases congestion and rhinorrhea	[92]
CysLTs	Increases slow-wave sleep and leads to sleep disruption	Increases eosinophil presence and function, congestion and rhinorrhea,	[93,94]
IL-1 β	Increases REM sleep and decreases time in REM sleep, and decreases latency to sleep onset	Upregulates the late-phase response of allergic rhinitis and increases congestion	[95,109]
IL-4	Increases REM sleep and decreases time in REM sleep, and decreases latency to sleep onset	Major Th2 cytokine and increases congestion	[95,110]
IL-10	Increases REM sleep and decreases time in REM sleep, and decreases latency to sleep onset	Unknown	[95]
IL-6	Improves circadian rhythm and regulates the sleep–wake cycle and increases slow wave sleep, as the ‘sleep factor’. Promotes mucosal thickening of upper airway and increases the risk of OSA. sIL-6R reflects the severity of OSA	Promotes Th2 cell phenotypes and increases congestion	[99,24,111]
TNF- α	Promotes mucosal thickening of upper airway and increases the risk of OSA	Promote Th2 cell phenotypes and increases congestion	[24,33]
Prostaglandin D2	Promotes sleep. Increases both REM and NREM sleep	Increases congestion	[112,113]
Bradykinin	Increases sleep apnea	Increases congestion and rhinorrhea	[23,113]
Substance P	Increases REM latency and arousal	Increases congestion	[113]

NREM, non-rapid-eye movement; OSA, obstructive sleep apnea; REM, rapid-eye movement.

even be part of the pathological mechanism underlying OSA. Cook *et al.* [119] suggested that the variant trigeminocardiac reflex (TCR) was exaggerated in NAR patients and potentially mediated the association between nasal congestion and SDB in these patients [119]. More recently, Bindu *et al.* [120] have hypothesized that the nasotrigeminal reflex, a peripheral form of TCR, may be involved in REM sleep apnea [120]. Presently, as one of the most powerful autonomic nerve reflexes, TCR is considered to have a direct role in SDB, including OSA [121[■]]. Thus, further studies aimed at elucidating the role of neurogenic pathway should help to better understand the pathogenic link between rhinitis and OSA.

ROLE OF OBESITY IN THE ASSOCIATION BETWEEN RHINITIS AND OBSTRUCTIVE SLEEP APNEA

Obesity represents an important challenge for public health systems all over the world, similar to rhinitis and OSA. A population-based longitudinal study involving nearly 700 individuals monitored for a period of 11 years, has demonstrated that obesity was a strong risk factor associated with OSA, and a moderate reduction of obesity was effective in reducing the incidence of OSA [122]. While it has generally been recognized that anatomic alterations due to more fat deposition

predispose to upper airway collapse during sleep in obese patients [123], a more recent review of studies investigating the role of leptin, a peptide hormone mainly produced in white adipose tissue, has indicated that leptin plays a role in ventilatory function and upper airway obstruction, and thus, may also play a role in OSA [124[■]]. Indeed, administration of leptin in leptin-deficient animals has been shown to attenuate impaired ventilatory control and inspiratory flow limitation during sleep, as well as attenuate obstructive hypopneas in a leptin-deficient animal model [125[■]]. However, unlike the close relationship noted between obesity and elevated leptin in wild type mice with diet-induced obesity, obesity in humans is associated with more variable leptin levels, and thus raises the possibility leptin deficiency or leptin resistance may play a role in obesity-related OSA [126]. Moreover, some researchers have indicated that obesity was linked with allergy symptoms or higher serum IgE levels [127]. One study has demonstrated that obese patients had a higher frequency of serum-specific IgE positivity than nonobese patients, suggesting that obesity might decrease the immunologic tolerance to antigen and result in atopic disease [128]. It has been hypothesized that the effect of adipose tissue on the immune system in obese patients may be the development of chronic inflammatory changes, including higher levels of IL-6 and TNF- α and

lower levels of IL-10, which all lead to Th17/Treg imbalance and development of allergic disease [129]. Several epidemiological studies have reported that the prevalence of allergic rhinitis is increased in obese adolescents and children [130,131]. Additionally, higher BMI has been shown to be an important predictor for allergic rhinitis in teenage girls [132]. A large-scale household-based survey of healthcare has recently reported that the adjusted OR for allergic rhinitis when obesity was present was 1.22, and concluded that increased prevalence of adult obesity was associated with allergic rhinitis [133]. Similarly, Han *et al.* [129] have reported that obesity was associated with increased OR of NAR, particularly in male adults. This is consistent with the findings of Schleich *et al.* [134], which have shown that also adult asthmatic patients with comorbid obesity have a predominantly neutrophilic airway inflammation.

CONCLUSION

Evidence indicates that allergic rhinitis/NAR and OSA are detrimental to each other. Although epidemiologic, pathologic, and physiologic studies have demonstrated a link between rhinitis and OSA, many available cross-sectional studies have merely confirmed the close association rather than a cause-effect relation between allergic rhinitis/NAR and OSA until now. Thus, future studies need to explore this hypothetical link for causality and therapy between rhinitis and OSA. It is possible that a better understanding of the nature of these disorders and underlying pathogenic mechanisms will provide further information on optimal treatment choices for the management of these disorders, and even the opportunity to prevent the progression of one to the other.

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Conflicts of interest

All the authors declare that they have seen and approved the manuscript and they have no conflict of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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