



Obstructive Sleep Apnea and Asthma: More Than Chance?

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Abstract

Purpose of Review To discuss the current evidence regarding the association and mechanistic interaction between asthma and obstructive sleep apnea (OSA).

Recent Findings The co-existence of OSA is highly prevalent in asthmatics and significantly associated with increased severity, decreased control, more frequent exacerbations, and hospitalizations despite medical management. Pre-existing asthma may also be a risk factor for new onset OSA. Rhinitis, obesity, and gastro-esophageal reflux are risk factors in both conditions. The obese asthmatic with OSA may present a unique phenotype. Positive airway pressure in severe asthma improves outcomes.

Summary Pathophysiologic mechanisms and co-morbidities overlap between OSA and asthma, but the exact link has yet to be confirmed. Screening for OSA is recommended in those with severe asthma. Further investigations are needed to delineate the cellular processes with therapeutic targets. Similarly, prospective investigations are needed to evaluate the longitudinal relationship in pre-existing asthma and the development of OSA.

Keywords Obstructive sleep apnea (OSA) · Asthma · Inflammation · Airway obstruction · Sleep fragmentation · Continuous positive airway pressure

Introduction

Over the last decade, there has been increasing interest in the relationship between asthma and obstructive sleep apnea (OSA). Both asthma and OSA are highly prevalent airway disorders with significant impact on the healthcare system [1, 2]. Evidence supports a bidirectional association where each disorder adversely affects the other and both disorders independently impair sleep quality resulting in poor daytime functioning and decreased quality of life [3•, 4–6]. Importantly, the co-existence of OSA in asthmatics has been

associated with worse asthma control and more severe exacerbations. OSA not only relates to asthma symptoms but also affects persistent daytime asthma control [5, 7–9]. In 2013, the co-existence of asthma with OSA was coined as the “alternative overlap syndrome” [10].

Asthma is a heterogeneous disease that affects approximately 6.3% of men and 9% of females in the USA and is characterized by chronic airway inflammation resulting in wheezing, shortness of breath, chest tightness, and/or cough with variable expiratory airflow limitation [1, 11]. A significant number of patients have nocturnal asthma with symptoms occurring only during sleep. Both uncontrolled asthma and nocturnal asthma have a deleterious effect on sleep quality [6].

Obstructive sleep apnea is underdiagnosed with approximately 13% of men and 6% of women in the USA estimated to have moderate to severe disease [2, 13••]. OSA causes fragmented sleep, fatigue, and excessive daytime sleepiness due to recurrent episodes of complete or partial upper airway obstruction during sleep resulting in impaired gas exchange, sympathetic overactivity, intrathoracic pressure changes, and gasping and choking [13••].

Studies have consistently demonstrated that asthmatics have an increased risk of OSA with prevalence rates as high as 70%, particularly in those with severe asthma [3•, 4]. Although most investigations have focused on the prevalence

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of OSA in the asthma population, the reverse relationship has also been demonstrated [14].

Additionally, asthma and OSA share similar underlying pathophysiology with increased airway resistance involving local and systemic inflammation and co-morbidities, such as gastro-esophageal reflux (GER), obesity, and rhinitis [15, 16, 17]. Important to asthma and OSA therapy is identification of risk factors, co-morbidities, and modifiable factors [15]. Furthermore, long-term use of continuous positive airway pressure (CPAP) has been reported to significantly alleviate asthma symptoms in patients with co-existing asthma and OSA [16, 17].

We will review the current data regarding the impact of asthma and OSA on clinical outcomes, potential pathophysiologic links between asthma and OSA, along with therapeutic information and address the role of screening (Fig. 1).

The Co-existence of Asthma and OSA: Epidemiology

OSA is typically thought to occur in obese individuals. However, like asthma, OSA also has different phenotypes largely based on craniofacial morphology. Common risk factors for OSA include male gender, age, obesity, family history, increase in neck size (> 17 inches in males and 16 inches in females), craniofacial abnormalities (i.e., micrognathia or retrognathia), and hypertension. Recently, it has been suggested that the co-existence of asthma with OSA may be a separate phenotype of asthma [12, 18]

Cross-sectional studies describe an increased prevalence of OSA in asthmatics ranging from 19 to 60% [18–22]. In severe

and difficult-to-treat asthma populations, co-existence of OSA has been reported at high rates from 50 to 95% [18]. This wide variation in prevalence rates may be due to the difference in methodology used for diagnosing OSA and asthma. Several studies used symptom-based questions where others employed well-validated questionnaires, such as the Berlin questionnaire [20, 21]. Others used limited polysomnography or home-based studies with few studies employing the gold standard overnight-attended polysomnography [14, 22]. Additionally, a variation of methods was also used for diagnosing asthma. Most studies used questionnaires related to asthma symptoms and medications or a reported physician-based diagnosis [3, 14, 22]. Only a few studies used spirometry to determine diagnosis [21–23].

Despite the difference in methodology, it is difficult to ignore such results. In a large population-based study with over 38,000 newly diagnosed asthma patients evaluated over a 10-year period, the overall incidence of OSA was 2.51-fold higher in asthmatics than in non-asthmatics (12.1 vs. 4.84, respectively) [22]. Additionally, the adjusted hazard ratio (HR) for OSA was 1.78 in the asthma patients who had one or less annual emergency room (ER) visits compared to non-asthmatics. However, the risk for OSA substantially increased (HR of 23.8) for those asthmatics who had > 1 ER visit/year. This study supports that asthmatic patients have a greater risk for OSA and the risk seems to be inversely related to asthma control [22]. The risk of OSA has also shown to be positively correlated with the dose of inhaled and oral steroids [22, 23].

This is further supported by the landmark prospective longitudinal Wisconsin Sleep Cohort Study where individuals with asthma were shown to have an increased incidence of new onset OSA [3]. Over 1000 subjects have been followed

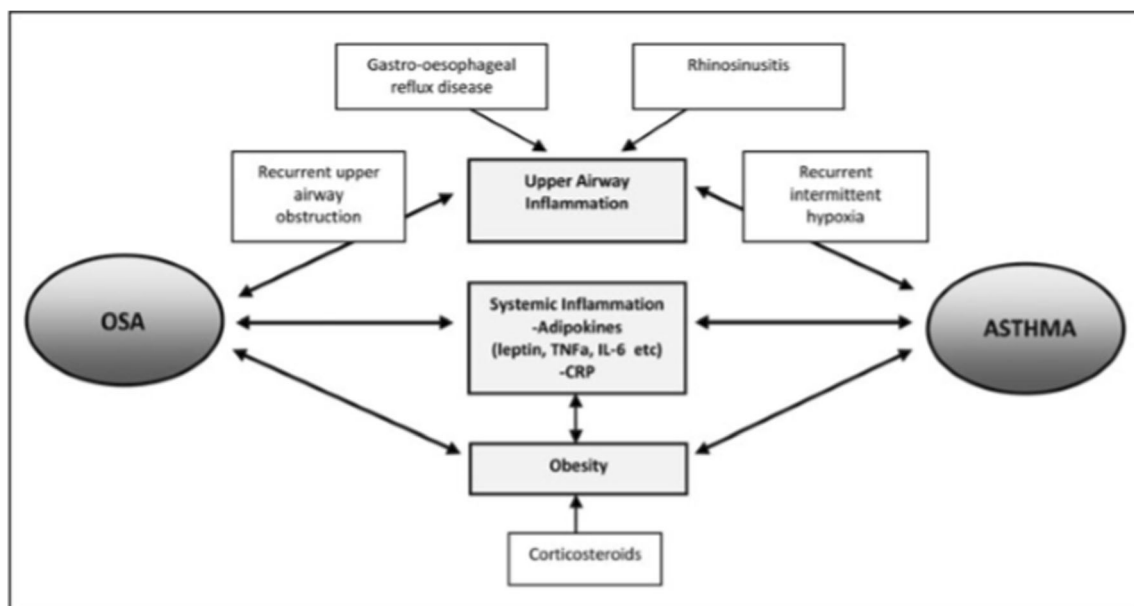


Fig. 1 Pathophysiologic links between asthma and OSA. Modified from Davies SE 2019 Reference 14. Used with permission from Taylor and Francis

since 1988 with PSG performed every 4 years. Eligible participants were identified as free of OSA (AHI < 5 events/hr and never treated) by 2 baseline PSG studies. At the very first 4-year follow-up, 27% of those with asthma developed sleep apnea compared to 16% of the non-asthmatic subjects. Over the full study period after correcting for confounders and covariates, asthma patients faced an almost 40% greater risk for sleep apnea than asthma-free participants. Furthermore, the longer an individual had asthma, the greater their increased risk for developing OSA [3•].

Most investigations have focused on prevalence of OSA in the asthma population; the reverse relationship has also been demonstrated. Alharbi et al. investigated 616 patients with pre-existing OSA demonstrated by polysomnography and found that asthma was present in 35.1% [14••]. This illustrates the need for further prospective investigations to evaluate the subsequent development of asthma in individuals with OSA.

Co-morbidities Associated with the Alternative Overlap Syndrome

Rhinitis, obesity, and gastro-esophageal reflux (GER) are shared co-morbidities in developing asthma and OSA. These conditions have both direct and indirect effects on the pathophysiology between asthma and OSA.

Rhinitis

Asthmatics have higher rates of allergic and non-allergic rhinitis, as well as nasal polyposis [24]. Rhinitis causes chronic inflammation and nasal obstruction which results in higher negative oropharyngeal pressure during inspiration and predisposes to airway collapse and symptoms of OSA with snoring and apneic episodes [25]. Additionally, cortisol's normal circadian regulation results in a nocturnal dip that leads to increased nasal resistance and inflammatory mediators perpetuating nocturnal asthma symptoms, nasal congestion/rhinitis, and OSA symptoms [26, 27]

Gastro-esophageal Reflux

GER is a common disorder and is self-reported in approximately 58–65% of individuals with OSA and up to 80% of asthmatics, independent of other confounders [15, 28]. Increased snoring and excessive daytime sleepiness have been reported in subjects with nocturnal GER as compared to those without nocturnal GER suggesting that GER may be an independent risk factor for development of OSA [28]. Persistent GER can cause direct injury to the upper airway resulting in inflammation and edema, which can precipitate nocturnal arousals and sleep fragmentation, snoring, and choking episodes [29].

OSA reciprocally promotes GER via increased negative intrathoracic pressure during inspiration causing reflux of gastric contents. Micro-aspiration directly injures the airway mucosa causing inflammation and reflex-mediated vagal-induced bronchoconstriction. Hence, OSA-induced acid reflux may play a role in triggering asthma symptoms [30].

However, it is not completely clear why asthmatics without co-existing OSA still have a higher prevalence of GER. One postulation is the change in intrathoracic pressure much like that in OSA creates retrograde movement of gastric contents. Additionally, medications used in treating asthma, such as beta-agonist, reduce lower esophageal sphincter tone and promote GER [15, 31]

Obesity

Obesity is a well-known risk factor for developing OSA but is also an independent risk factor for asthma [31, 32]. In a 4-year longitudinal study, a 10% increase in body weight predicted a 32% increase in AHI and a 6-fold increase in the odds of developing moderate to severe OSA (AHI > 15). Importantly, a weight loss of 10% predicted a 26% reduction in AHI, indicating that weight management is important in treatment of OSA [33]. Obesity is a complex entity that impairs breathing by altering mechanical and physiologic processes. Fat deposition causes narrowing of the upper airway, increased airway resistance, and collapsibility. In addition, excessive adipose tissue surrounding the chest and abdomen creates a restrictive process where functional residual capacity (FRC) is reduced, ventilatory drive is impaired, and oxygen demand and work of breathing are increased. Because FRC is decreased, exhalation must occur at a lower lung volume further compromising expiratory air flow rates and increasing airway obstruction [34, 35].

Obesity is also independent predictor of asthma even after adjusting for demographics, smoking status, oral corticosteroid use, and GER and is associated with poorer outcomes [36]. Whereas OSA is more common in obese men than obese women, the opposite occurs in obesity-related asthma: asthma is twice as likely to develop in obese women than in obese men suggesting a potential hormonal influence [37]. Obese asthmatics present a specific phenotype with more frequent or more severe asthma exacerbations, difficult-to-control symptoms with less eosinophilic inflammation, and relative resistance to glucocorticoids [36]. An improvement in asthma symptoms and reduction in medication requirements have been observed after weight loss in the obese asthmatics [7].

Pathophysiologic Links

In addition to the shared risk factors and co-morbidities associated with OSA and asthma, there are various intrinsic

mechanisms that each disorder may contribute to the development of the other. These mechanisms include neuro-mechanical, hypoxia, cardiovascular, sleep fragmentation, and chronic inflammation.

Neuro-mechanical

OSA and asthma alter mechanical properties of the airway. Intermittent collapse of the upper airway associated with OSA leads to increased airway resistance caused from direct mechanical trauma due to vibratory damage from snoring. Additionally, inhalation against a closed glottis (Muller maneuver) causes increased intrathoracic pressure triggering a vagal reflex that stimulates the muscarinic receptors in the central airways potentiating bronchoconstriction [38].

Reciprocally, mechanical consequences of asthma can contribute to the development of OSA. Asthmatic patients have hyperinflation resulting in an increased functional residual capacity (FRC) compared to healthy controls. During sleep, FRC normally decreases, but asthmatics have a much greater FRC reduction, which may contribute to airway resistance and precipitate nocturnal symptoms of snoring, gasping, and choking [38]. The abrupt decline in lung volume also causes a decrease in tracheal tug resulting in altered pharyngeal airway stiffness further impacting resistance [39].

Corticosteroids used to treat asthma may further impair upper airway diameter due to excessive intrapharyngeal fat deposition. Prolonged oral corticosteroids used in treating severe asthmatics may also induce a muscle myopathy and decrease contractile properties of the pharyngeal dilator muscles making the airway more “floppy”, prone to collapse, and increase the risk for obstruction during sleep [23, 40].

Hypoxia

Hypoxia associated with airway obstruction results in increased sympathetic discharge causing vasoconstriction, deoxygenation-reoxygenation (redox) injury, platelet activation, inflammation, and ultimately endothelial dysfunction. Intermittent hypoxia also stimulates the carotid body receptors and may create a reflex bronchoconstriction and precipitate nocturnal asthma symptoms [41].

The increased sympathetic tone from hypoxia and negative intrathoracic pressure associated with intermittent airway obstruction leads to increased afterload of left ventricular causing or worsening heart failure. Congestive heart failure itself has been known to worsen the asthma symptoms by inducing airway hyper-responsiveness [41].

Additionally, vascular endothelial growth factors (VEGF) may play a role in the pathogenesis of both asthma and OSA [41, 42]. VEGF is a hypoxia-sensitive glycoprotein, and both OSA and asthma can promote its expression. VEGF contributes to bronchial inflammation, hyper-responsiveness, and

vascular remodeling. Studies indicate that the concentration of VEGF correlates with the severity of obstructive events in OSA and the degree of hypoxia but also with the severity of airway obstruction in asthmatics [42].

Sleep Fragmentation

The hallmark of OSA is intermittent upper airway obstruction leading to hypoxia and central nervous system (CNS) activation causing sleep fragmentation with cortical arousals and awakenings with daytime sleepiness. Disturbance in the sleep architecture itself may contribute to the bidirectional interactions of OSA and asthma. Frequent persistent obstruction can result in blunting of the arousal response to hypoxia, as well as to bronchoconstriction. Asthmatics are reported to have more frequent sleep disruption with more irregular breathing, hypopneas, and snoring, particularly during REM sleep, than those without asthma [43]. This may be related to the increased cholinergic activity that occurs during REM sleep, which in turn modulates airway caliber and reactivity via the muscarinic receptors.

Inflammation

OSA is becoming more commonly thought of as a chronic inflammatory disease by inducing both airway and systemic inflammation via repeated upper airway mechanical stress. The repetitive partial or complete upper airway collapse leads to hypoxia and oxidative stress not just locally but systemically, with increased serum cytokines, including C-reactive protein (CRP), tumor necrosis factor (TNF- α), and interleukin-6 (IL-6) [44]. Repeated snoring has been shown to cause edema and damage to the soft tissue resulting in direct mechanical trauma and airway inflammation [44, 45]. Biopsies from nasal and tonsillar tissue have shown increased polymorphonuclear cells (PMN's), bradykinin, vasoactive intestinal peptide (VIP), and increased leukotriene receptors (LTR-1 and 2). These are known mediators of inflammation, bronchoconstriction, microvascular permeability, and eosinophilic recruitment and may cause similar changes in central airways precipitating bronchoconstriction that may impact or promote asthma [46].

Studies have demonstrated significantly higher neutrophil percentage, independent of other cofounders, in patients with high OSA risk as compared to those without OSA, whereas sputum eosinophil percentages were similar [47]. Similar results were observed in another study where patients with OSA and severe asthma showed airway inflammation and remodeling with a higher proportion of neutrophils and lower proportion of macrophages, elevated interleukin-8 (IL-8), and matrix metalloproteinase 9 (MMP-9) in sputum and thinner bronchial basement membrane, compared to non-OSA patients with severe asthma. The thickness of the bronchial basement membrane was negatively associated with the severity of

sleep apnea [7, 47]. This supports that OSA may be an important contributor to neutrophilic asthma and may contribute to airway remodeling eventually leading to difficult-to-treat asthma. However, further studies are necessary to confirm those findings and better understand the mechanisms.

Inflammatory changes associated with asthma may reciprocally promote upper airway obstruction. Chronic coughing leads to persistent inflammation causing thickening of the upper airways. Radiographic studies have demonstrated decreased pharyngeal cross-sectional area in asthmatics during bronchoprovocation [48]. This creates upper airway resistance and high negative pressure on inspiration thus increasing the risk of upper airway collapse [38].

Furthermore, leptin may be a linking component between asthma and OSA. Leptin is a protein hormone produced by adipose tissue that circulates systemically and acts on the hypothalamus to induce satiety and increase metabolism. However, leptin is also proinflammatory and stimulates the release of IL-6 and TNF- α by adipocytes, as well monocytes and macrophages to express cytokines, and increases T cell proliferation [41, 49]. Obesity is known to induce a chronic low-grade state of inflammation by directly releasing pro-inflammatory mediators, such as leptin, resistin, and other adipokines. This triggers systemic inflammation, as well as airway inflammation independently of the inflammation associated with asthma. However, patients with OSA have also been shown to have increased levels of serum leptin compared with non-apneic patients irrelevant to obesity [41]. Furthermore, leptin has been shown to be increased in asthmatic patients compared with non-asthmatics even after controlling for obesity and may also contribute to airway hyper-responsiveness [41, 49].

This supports that increased levels of serum leptin observed in both OSA and asthma independently of obesity suggest leptin may play a pivotal role in the pathogenesis of these respiratory disorders. Obesity further compounds the severity of inflammation and adversely impacts both OSA and asthma [50].

Clinical Outcome of Asthma-OSA Overlap

Not only does OSA seem to be associated with development of nocturnal asthma, it is also associated with persistent daytime asthma symptoms, particularly in those with severe and difficult-to-treat asthma. Thus, unrecognized OSA may be the cause of persistent daytime and nocturnal asthma [8].

There is still little evidence on the impact of OSA on asthmatic patients' pulmonary function. Based on a 15-year follow-up study of ventilatory function in asthmatic patients, the unadjusted decline in forced expiratory volume in one second (FEV1) was 38 ml/year [51]. There are several factors identified for the decline of FEV1 in asthma, including age, sex, asthma exacerbation, smoking status, obesity, and hypoxia [52]. In a recent retrospective study, asthmatic patients with

OSA were followed for more than 5 years with spirometry and showed a greater decline in FEV1 compared to those without OSA [53•]. In this study, the decline of FEV1 among asthmatic patients with severe OSA was 72.4 ml/year compared to 41.9 ml/year in those with mild to moderate OSA and 24.3 ml/year in those without OSA. After adjusting for confounder, OSA severity was the only independent factor affecting pulmonary function decline [53•]. However, in another recent meta-analysis, no significant difference of FEV1 was seen between asthmatic patients with and without OSA [54]. Larger prospective studies are needed to verify long-term effects on pulmonary function.

Sleep quality is known to be poor in individuals with OSA and in asthmatics. A recent evaluated sleep architecture in adult women showed that both asthma and OSA subjects have more light sleep and less time in REM sleep compared to either condition alone. In those with both asthma and OSA, mean oxygen saturation was lower than those with only OSA. The results were consistent even after adjustment of age, BMI, and smoking status. The authors concluded that the combination of OSA and asthma is associated with poorer sleep quality with more profound hypoxemia than with either condition alone [21]. Similar results have been described difficult-to-treat asthmatics with longer periods of oxygen saturations remaining <90% [55].

Mortality associated with OSA in asthmatics has been poorly investigated. To our awareness, the literature is limited to an isolated study that investigated the risk of mortality in asthmatics with various sleep disorders. Asthmatic patients with sleep disorders had increased risk of death compared to those asthma patients alone even with adjusting for possible confounders (HR 1.451, 95% confidence interval: 1.253–1.681) [56]. Although this study is limited by inclusion of many types of sleep disorders, it suggests that sleep fragmentation may negatively impact outcomes in asthma.

Therapeutic Implications

Early studies which evaluated the effect of CPAP on asthma were limited by small sample size and short follow-up period. A large survey study was conducted in a group of patients with OSA and asthma to investigate the effect of long-term use of CPAP on control of asthma symptoms [57]. Thirteen percent of CPAP users had co-existing asthma and used CPAP for over 5 years with a daily duration of 6.3 h. Self-reported asthma severity decreased significantly, and the asthma control test score improved despite no significant change in body mass index. The percentage of patients using daily rescue medication also decreased from 36 to 8% with CPAP usage ($p < 0.001$) [57]. In another prospective, multicenter study, asthma outcomes were examined after 6 months of CPAP use in 99 adult asthma patients with OSA [16]. The study assessed asthma control and

quality of life using the Asthma Control Questionnaire (ACQ) and mini asthma quality of life questionnaire (MiniAQLQ), respectively. Both disease control and quality of life significantly improved. But when diseases were stratified according to severity, only patients with moderate-severe asthma and severe OSA who used CPAP > 4 h/day showed significance in improvement. Asthma exacerbations also decreased from 35.4 to 17.2%. Bronchial reversibility, gastro-esophageal reflux, rhinitis, and exhaled nitric oxide levels all significantly improved. All changes occurred without significant asthma drug therapy modification, change in body weight, and other asthma comorbidities [16].

Data is conflicting regarding the effect of CPAP treatment on FEV1 decline in asthmatic patients. A retrospective study in asthmatics with severe OSA demonstrated a positive effect, however this was not confirmed in other studies [16, 17, 53]. Additionally, a single study reported a decrease in airway reactivity with even a short 7-day nocturnal CPAP [58]. Randomized trials are needed to scientifically investigate the effect of PAP therapy on pulmonary function and airway responsiveness to medication management.

Equally important is treatment of the underlying risk factors, namely, allergic rhinitis, obesity, and GER [28]. A meta-analysis showed significant improvement in OSA among those that received intranasal corticosteroid therapy [59, 60]. Obesity is a well-recognized risk factor for asthma and OSA, and their interplay has been recognized in an outpatient setting [50]. Bariatric surgery is known to improve OSA, as well as asthma control and pulmonary function [61, 62].

Role of Screening

Given the high prevalence and the adverse effect of OSA and asthma on each other, it is important to consider screening for OSA in asthma patients. A recent study in China evaluated the predictive performance of the two most common OSA screening questionnaires, the Berlin questionnaire (BQ) and STOP-BANG questionnaire (SBQ) in asthmatic patients. In comparison with BQ, SBQ was easier and demonstrated higher diagnostic sensitivity (84.4% vs 60%), lower specificity (79.5% vs 91%), lower positive predictive value (70.4% vs 79.4%), and higher negative predictive value (90% vs 80%), in detecting moderate-to-severe OSA with an AHI > 15. The SBQ seems to be the preferable sleep questionnaire over BQ in the detection of moderate and severe OSA but needs to be further validated with a larger asthma population [18, 63].

Conclusion

The co-existence of OSA in asthma patients is significantly associated with duration, severity, and control of asthma with increased daytime and nocturnal symptoms, worsening

nocturnal hypoxemia, and sleep quality, leading to increased asthma exacerbations and hospitalizations. Although most studies have demonstrated that OSA impacts asthma, data has also shown that asthma may be a risk factor for new onset OSA. Pathophysiologic mechanisms and co-morbidities overlap between OSA and asthma, but a causal relationship has yet to be confirmed. Further investigations are needed to delineate cellular processes with therapeutic targets, as well as to validate the effect of current therapies, such as CPAP on pulmonary function. Additionally, given the high prevalence of OSA in asthmatics and significant adverse impact, screening for OSA should be considered.

Authors' Contribution DP and KH conducted literature review, synthesized the literature, and wrote the manuscript. JM edited and reviewed references.

Compliance with Ethical Standards

Conflict of Interest Donna L. Pepito, Jamal M. Mohammed, and Kimberly A. Hardin declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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