



Research Paper

Publication trends in obstructive sleep apnea: Evidence of need for more evidence[☆]

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Abstract *Objective:* Published research in obstructive sleep apnea (OSA) appears limited despite OSA being a highly prevalent adult and pediatric disease leading to many adverse outcomes if left untreated. We aimed to quantify the deficit in OSA scientific literature in order to provide a novel way of identifying gaps in knowledge and a need for further research inquiry.

Methods: This was a Bibliometric analysis study. Using Ovid Medline database we analyzed and compared research output (medical and surgical) between adult OSA and similarly prevalent chronic conditions (Type II diabetes (T2DM), coronary artery disease (CAD) and osteoarthritis (OA)) from December 2016 up to fifty years prior. Linear graphs were utilized to trend collected data. Utilizing same strategy, we compared publication trends for pediatric OSA to asthma and gastroesophageal reflux (GER).

Results: Adult OSA publications ($n = 9314$) were significantly underrepresented when compared to T2DM ($n = 66,023$), CAD ($n = 31,526$) and OA ($n = 34,123$). Linear plots demonstrated that despite increasing number of publications this disparity persisted annually. Surgical literature composed 10.4% ($n = 972$) of adult OSA publications and reached a plateau in the last ten years. Pediatric OSA ($n = 2994$) had less research output when compared to asthma ($n = 47,442$) and GER ($n = 6705$). However, over past five years pediatric OSA surpassed GER in annual number of publications. Surgical literature represented 23.1% ($n = 693$) of pediatric OSA publications and continued increasing over past ten years. Study methodologies for both adult and pediatric OSA showed a lack of randomized controlled trials and meta-analyses in comparison to other diseases. *Conclusion:* Our review shows substantial deficit in total, annual and surgical adult OSA published research compared to similarly prevalent diseases. This trend is not entirely observed in pediatric OSA literature.

[☆] Confirmation of original material: This material has never been published and is not currently under evaluation in any other peer-reviewed publication.

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Introduction

Obstructive sleep apnea (OSA) is a common disorder, affecting up to 7% of North American adults. OSA is characterized by partial or complete upper airway collapse during sleep. Cessation of airflow leads to disruption of gas exchange and thus causes sympathetically driven recurrent arousal from sleep.¹ Affected individuals frequently manifest excessive daytime sleepiness, cognitive dysfunction as well as decreased health-related quality of life.² Classical OSA symptoms include snoring and intermittent breathing pauses during sleep leading to frequent arousal, yet many patients are unaware of these symptoms and disease onset is insidious.^{1,2} The long-term effects of sleep fragmentation and intermittent hypoxia on health are numerous leading to systemic hypertension, impaired glucose metabolism and cardiovascular disease,¹ as well as societal effects such as increased car accidents. First line therapy for adult OSA has been in the past continuous positive airway pressure (CPAP), with surgery gradually taking on a more prominent role as evidence demonstrates benefit at or superior to CPAP in anatomically favorable patients.³

Despite sharing a common mechanism of upper airway obstruction and end pathway leading to pulmonary hypertension, OSA presents differently in pediatric population.⁴ OSA affects 0.8%–5.7% of children with peak age of 2–8 years. Prevalence of 12 and 24% has been described when ambulatory monitoring is used instead of formal polysomnogram.⁵ Cardinal symptoms of nocturnal snoring, breathing pauses may be accompanied by enuresis, impairment to cognitive development and hyperactivity.^{4,5} With an exception of children with syndromes, pediatric OSA is most commonly due to lymphoid hypertrophy of Waldeyer's ring. Therefore, childhood OSA tends to be a surgical disease, addressed with tonsillectomy or adenotonsillectomy.⁶

North American population prevalence of coronary artery disease (CAD) is 6.2% whereas prevalence of type II diabetes (T2DM) is estimated to be 9.9%.⁷ In osteoarthritis (OA) literature, prevalence is often overestimated because many studies use older age groups. Prevalence of OA is also joint-dependent with knee being the most commonly affected joint. Overall, symptomatic knee osteoarthritis affects up to 6% of North Americans.⁸ These diseases have similar prevalence to OSA, with comparable effect on quality of life. Similarly, in the pediatric population asthma is common with prevalence estimates as high as 9.5%⁹ and an estimated prevalence of gastroesophageal reflux (GER) is 5.2%.^{10,11}

Over the past fifty years, research in the aforementioned similarly prevalent adult and pediatric diseases has continued to improve survival and disease specific quality of life.^{7–11} However, evidence-based treatment strategies and management algorithms are limited with respect to OSA, and there continues to be a significant lag in quantity

as well as quality of research to guide clinical practice for this disease. With this study we aim to characterize and analyze trends of OSA publications and compare them to existing trends in similarly prevalent diseases in order to help inform researchers and consequently funding agencies about existing need for research prioritization.

Materials and methods

A literature search was performed using Ovid Medline and Embase databases (1965–2016) in December of 2016 to define existing volume of publications in OSA, T2DM, OA and CAD in the adult literature. First mention of OSA in research journals was made in 1965, therefore we used it as the start year for our analysis. For pediatric comparison, we have performed searches for asthma and GER in addition to OSA. Initial search results in Ovid Medline yielded similar search results to Embase database confirming internal validity. For the rest of the analysis Ovid Medline database was used.

Using Ovid Medline database, we then characterized overall and annual publication output for adult and pediatric research. The following key terms were used to retrieve data for OSA (term "obstructive sleep apnea"), T2DM (term "diabetes mellitus, type 2"), OA (term "osteoarthritis"), CAD (term "coronary artery disease"), asthma (term "asthma") and GER (term "gastroesophageal reflux"). For each search age limits were set as follows "19 and above" for adult and "all child 0–18" for pediatric search. To identify surgical literature Medline search sub-heading for surgery ("/su") was utilized prior to applying age limits. Ovid Medline tool "explode" was used to capture all available variations of key terms for every search. Likewise, using "AND" feature main terms were paired with "randomized controlled trial" and "meta-analysis" while using same age limits to define proportion of high quality evidence in each group.

Search results were then presented as linear graphs showing number of publications per year as well as mean number of publications calculated in five year intervals for each search term from 1965 through 2015. Standard deviations were derived for five-year interval data and presented in linear plots. Finally, Chi-square test was then used to determine differences in proportion of randomized controlled trials and meta-analyses using contingency tables.

Results

Ovid Medline literature search shown that there is a disparity in publication volumes over the past fifty years. Adult OSA publications ($n = 9314$) from 1965 through December 2016 were underrepresented when compared to T2DM ($n = 66,023$), CAD ($n = 31,526$) and OA ($n = 34,123$). Linear plots showed that despite increasing number of

publications adult OSA research output lagged annually. A similar trend was observed in mean number of publications graphed in five-year intervals with corresponding standard deviations (Fig. 1). Surgical literature composed only 10.4% ($n = 972$) of adult OSA publications. Over past ten years, linear graphs demonstrated that surgical OSA literature reached a plateau without significant increase in yearly surgical literature output (Fig. 2).

Pediatric OSA ($n = 2994$) had less overall output when compared to asthma ($n = 47,442$) and GER ($n = 6705$). Pediatric OSA has continued to lag behind asthma when we analyzed yearly publication trends. However, pediatric OSA surpassed GER in past five years in the number of annual publications. Similar trend was observed when in average number of publications in five year intervals (Fig. 3). Interestingly surgical literature represented 23.1% ($n = 693$) of total pediatric OSA publications. Moreover, unlike adult OSA pediatric surgical literature output has been steadily increasing over past ten years (Fig. 4).

Chi-square analysis was performed using 4×2 contingency tables for adult and 3×2 for pediatric data to

determine differences in composition of randomized controlled trials and meta-analysis between OSA and similarly prevalent conditions from 1965 through December 2016. Adult OSA was analyzed together with T2DM, CAD and OA whereas pediatric OSA was grouped with asthma and GER. We utilized numbers of published RCTs and meta-analyses to infer quality of evidence available for each prevalent condition. Adult OSA literature search was composed of less RCTs ($n = 877$) and meta-analyses ($n = 80$) when compared to T2DM ($n = 10,548$ and 673), CAD ($n = 3046$ and 295) as well as OA ($n = 3790$ and 184). Pediatric OSA search yielded less RCTs ($n = 154$) and meta-analyses ($n = 35$) when compared to pediatric asthma ($n = 4634$ and 495). Moreover, pediatric GER had more RCTs ($n = 391$) than OSA yet less GER focused meta-analyses ($n = 32$) were identified. Using Microsoft Excel (Version 15.13.1), both Chi square analyses for adult and pediatric data demonstrated highly statistically significant ($P < 0.0001$) differences in composition of randomized controlled trials and meta-analyses when compared with their respective similarly prevalent disease groups.

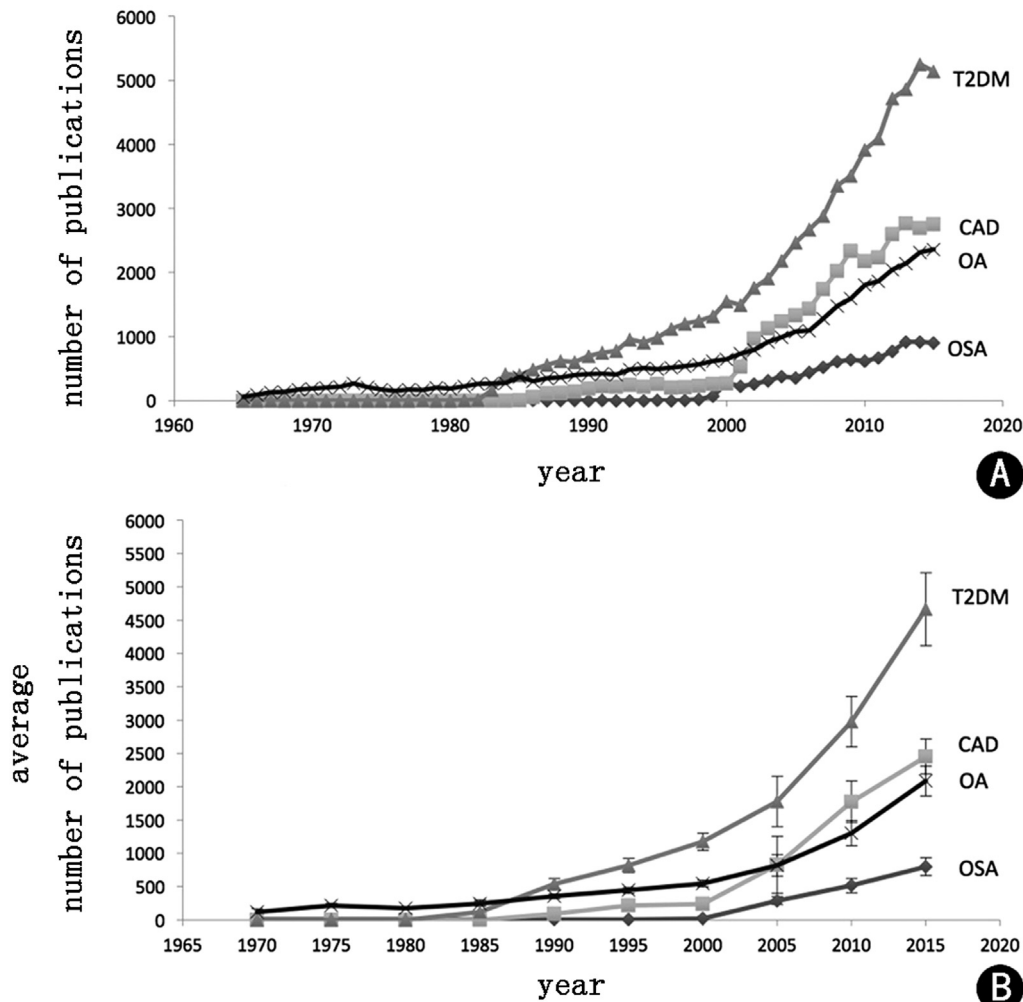


Fig. 1 A: Publication trends in adult OSA, CAD, T2DM and OA presented as number of publications per year during 1965–2015. B: Publication trends in adult OSA, CAD, T2DM and OA presented as average number of publications and associated standard deviations in five year intervals from 1965 through 2015.

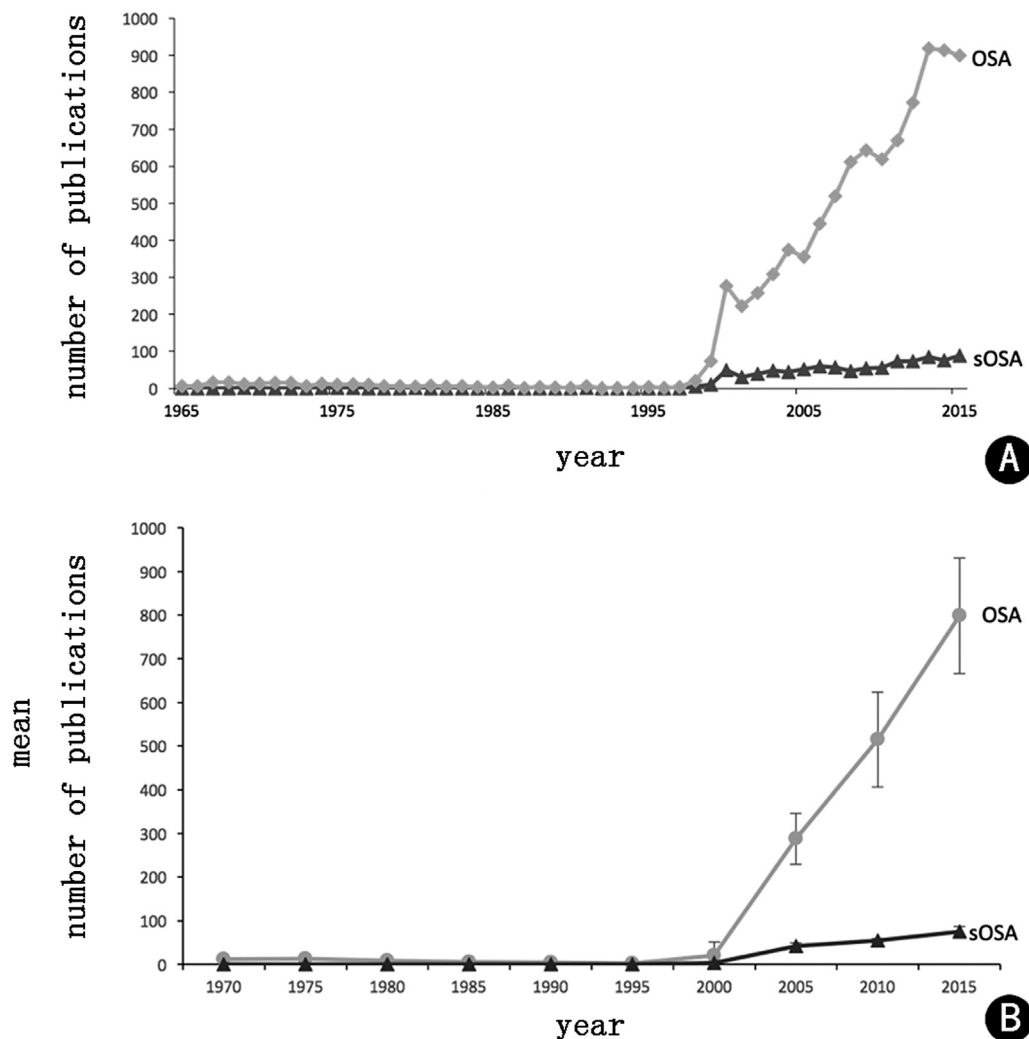


Fig. 2 A: Publication trends in OSA and surgical OSA (sOSA) literature presented as number of publications per year. B: Mean number of publications during five year intervals with associated standard deviations for all OSA and surgical OSA (sOSA) publications during 1965–2015.

Discussion

Obstructive sleep apnea emerged as an important disease process over fifty years ago yet our novel data showed a modest increase in overall and annual research output when compared to similarly prevalent diseases (Fig. 1). Numerous studies have confirmed that OSA is highly prevalent disease estimated to affect up to 7% of North American adult population.¹ Tishler et al¹² also showed that 5-year incidence of moderately severe sleep apnea is 7.5% and 16% for mild to moderately severe in an urban adult population. Therefore, long-term prevalence of OSA is projected to continue increasing, which makes the relatively smaller research output all the more perplexing.

Bibliometric analysis by Huang¹³ has previously shown that OSA publications steadily increased over sixteen years and surpassed general scientific literature. Instead of using similarly prevalent conditions, Huang¹³ compared productivity index of OSA publications to that of all publication available through Ovid Medline. In addition, their analysis

grouped adult and pediatric OSA research together.¹³ Whereas, separating pediatric and adult OSA data is indicated since pathophysiology, first line treatments, as well as similarly prevalent conditions differ between these age groups. Our data adds in depth insight showing the striking OSA publication lag when compared to similarly prevalent CAD, T2DM and OA. This trend is not entirely followed by pediatric OSA research.

Our data shows a surge of interest in pediatric OSA research compared to adults. Despite lagging behind asthma, pediatric OSA surpassed GER in annual publications in the past five years (Fig. 3). Interestingly, asthma’s relationship with pediatric sleep disordered breathing appears to be bidirectional. Adenotonsillectomy for pediatric OSA improves asthma control.¹⁴ Few chronic conditions affect children without syndromes, so heightened interest in OSA is unsurprising. In the past five years, many pediatric prevalence studies have emerged both using polysomnography and ambulatory monitoring.^{4–6} In addition, our data demonstrated a steady increase in pediatric

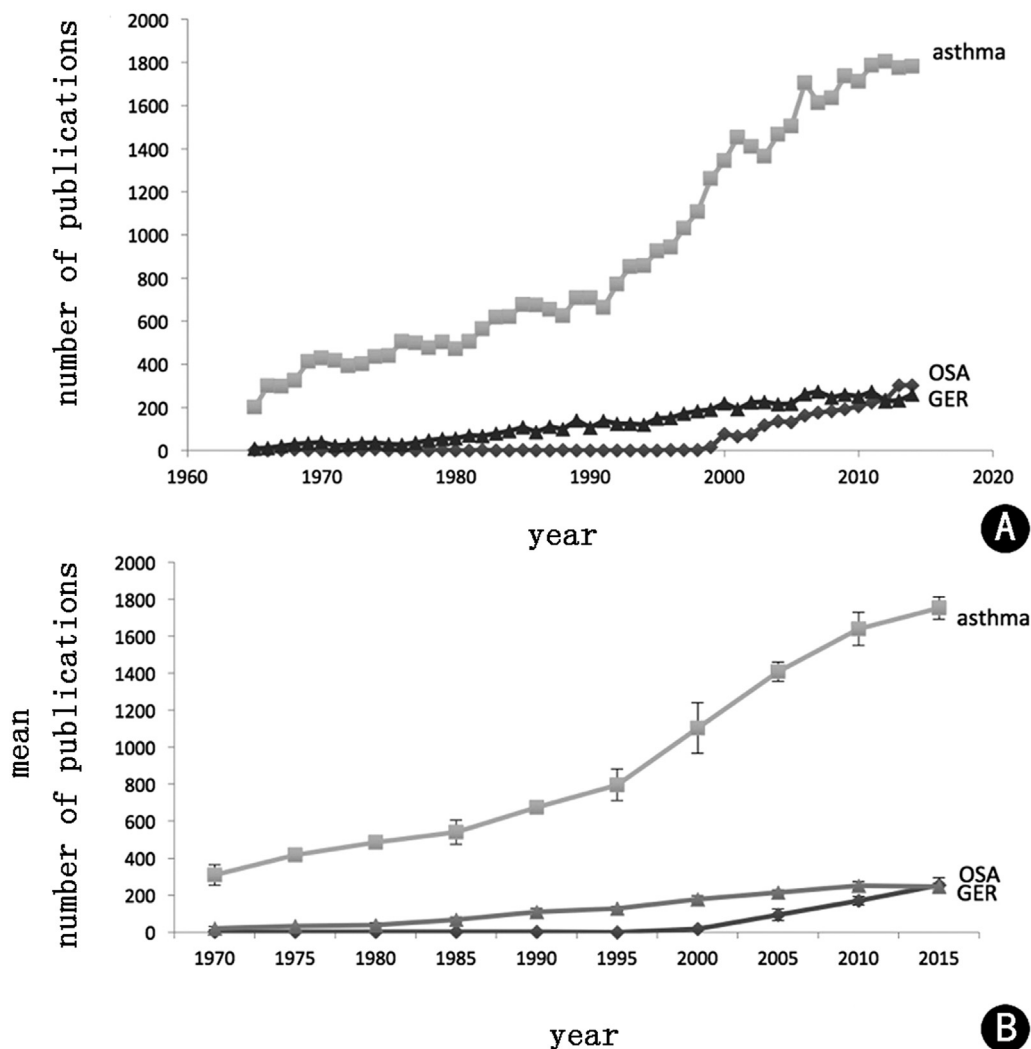


Fig. 3 A: Publication trends in pediatric OSA, asthma and GER presented as total number of publications per year 1965–2015. B: Publication trends in pediatric OSA, asthma and GER presented as mean number of publications with associated standard deviations in five year intervals during 1965–2015.

surgical OSA literature over past ten years (Fig. 4). First line treatment for children without syndromes is adenotonsillectomy, which is estimated to be 81% effective in improving multiple sleep parameters, including apnea–hypopnea index. The effectiveness decreases to 61% in children with obesity.¹⁵

Despite steady relative increase in publications in pediatric OSA, absolute numbers of pediatric OSA publications significantly lag behind adult OSA research (Figs. 1 and 3). In general, research funding prioritization is adult-focused partly owing to the greater burden of disease in adults. Pediatric research also faces specific ethical and methodological obstacles as well as lack of financial support from pharmaceutical industry.¹⁶ Therefore, ongoing pediatric research efforts and consequently funding is necessary as many areas of uncertainty in pediatric OSA management exist. Treatment of persistent OSA after pediatric adenotonsillectomy is challenging and robust treatment algorithms are lacking. The definition of surgical success is

another area of controversy in pediatric literature with some studies accepting mild OSA as a successful outcome.¹⁵

High prevalence of adult OSA along with associated adverse health and quality of life effects indicate that more resources should be allocated to OSA research akin to current efforts in CAD, T2DM and OA. Lifestyle plays a key role in development of CAD, T2DM and OA. However, frequently congenital and anatomical factors such as micrognathia, macroglossia and tonsillar hypertrophy predispose to development of adult OSA yet are not easily modifiable. Moreover, OSA has been shown to be an important concurrent condition in T2DM and CAD patients, thus contributing to adverse patient outcomes in these patient groups. OSA has shown to be a highly prevalent comorbidity in CAD, affecting 83% of patients undergoing cardiovascular rehabilitation.¹⁷ Approximately 37.4% of T2DM patients have OSA.¹⁸ Since adult OSA plays a key role as a comorbid condition, redistributing research effort towards addressing OSA may consequently improve quality of life, reduce

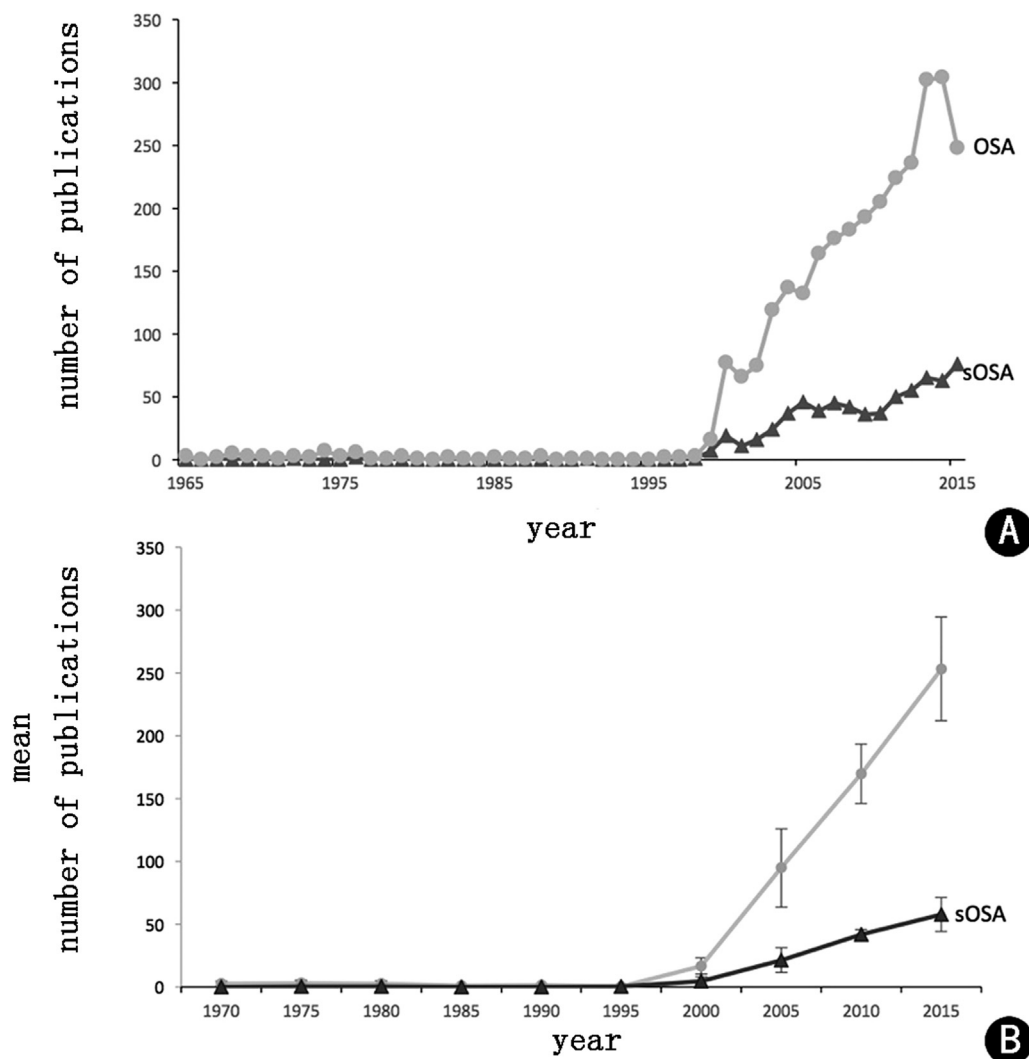


Fig. 4 A: Publication trends in pediatric OSA and surgical OSA (sOSA) literature presented as number of publications per year. B: Mean number of publications during five year intervals with associated standard deviations for all pediatric OSA and surgical OSA (sOSA) publications from 1965 through 2015.

morbidity and affect overall mortality of patients living with CAD and T2DM. Conversely, the observed higher research output in OA compared to OSA is puzzling since OA primarily affects patient’s quality of life without directly contributing to mortality.

The effectiveness of surgery over CPAP for treatment of adult OSA in anatomically favorable patients was recently demonstrated,³ yet our analysis showed that surgical literature represents a small fraction (10.4%) of existing evidence. The low rates of CPAP adherence further question its role as primary therapy.^{19,20} Instead, surgery may be curative especially when levels of upper airway obstruction can be reliably identified and then targeted. Drug-induced sleep endoscopy (DISE) is a novel approach shown to be superior to awake physical examination in identifying anatomical sources of OSA. During DISE sleeping patients are examined with flexible nasal pharyngolaryngoscopy in real-time allowing surgeons to personalize surgical OSA treatment depending on visualized levels of obstruction.²¹ Despite these advances, our data

demonstrate that surgical literature output has not significantly increased over the past ten years (Fig. 2), hence identifying a clear need for focused research inquiry. Unlike CPAP, combined surgery and DISE pose a promising and potentially curative approach to treating adult OSA, therefore warranting greater attention and consequently further research efforts focusing on surgical outcomes.

Our study showcases a novel way of quantifying existing gaps in knowledge which can guide future research inquiry. Bibliometric trends using Ovid Medline searches is a telling way to reflect research productivity in each field and consequently infer current resource allocation. Perhaps an observed plateau in adult surgical OSA literature productivity over past ten years is reflective of underrepresentation of surgeon scientists in receiving major funding agency awards. National Institute of Health (NIH) awards to surgical investigators represented 3% or less of total NIH grants over the last two decades. In addition, awards to practicing surgeons composed 1%–2% of the NIH total.²² Conversely, pediatric surgical literature output continued to increase

over the past ten years and represented 23.1% of all pediatric OSA publications. Unlike adult OSA first line treatment for pediatric sleep disordered breathing is surgical.^{4–6} Despite relative increase, absolute numbers for surgical OSA literature continued to lag behind adult surgical OSA publications indicating an ongoing need in pediatric surgical research. Such a difference can be partly attributed to the specific ethical, funding and methodological challenges facing research in children.¹⁶

With this study we have highlighted a need for further research in adult and pediatric OSA research based on prevalence, rate of adverse outcomes, and current level of evidence. However, since Ovid Medline database grows continuously with daily additions of research publications, bibliometric data from the database accepts inherent variability in annual and total number of publications for each search term. We have assumed that the database variability stays constant between OSA and similarly prevalent adult and pediatric diseases as long as searches are conducted in the same time frame. Embase database searches using the same terms demonstrate that relative differences in publications between OSA and similarly prevalent conditions were preserved. Another limitation of our study is selection bias of comparators as we were identifying chronic conditions with similar prevalence. Perhaps these striking differences may not be observed if other comparators are selected.

Conclusion

Resource prioritization in research must consider the prevalence, mortality and effect on patient's quality of life. Compared to similarly prevalent diseases, adult OSA is understudied. Herein we propose a novel method of advocating for resource allocation by showing an existing deficit in OSA annual publications. Furthermore, we want to emphasize the need for surgical literature in adult OSA. Pediatric OSA data showed greater progress in annual number of publications, which is responsible for recent emergence of evidence-based algorithms. However, absolute numbers show that pediatric OSA literature lags significantly behind adult OSA thus reflecting an ongoing need in pediatric research. We therefore hope to inform researchers about this existing gap in knowledge in adult and pediatric OSA to guide future scientific investment.

Financial disclosures

None.

Conflicts of interest

None.

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