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SCIENTIFIC INVESTIGATIONS

Obstructive sleep apnea and fractures in children and adolescents

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Study Objectives: To examine, among girls and boys, associations between site-specific extremity fracture and sleep apnea diagnosis or treatment.

Methods: A cross-sectional analysis of claims data from 2016 to 2018 for children aged 2–18 years. Children with sleep apnea, continuous positive airway pressure, adenotonsillectomy, and fracture were identified using *International Classification of Diseases, 10th Revision,* Current Procedural Terminology, and Healthcare Common Procedure Coding System codes. We examined sex-stratified associations between site-specific fracture, sleep apnea, and sleep apnea treatment.

Results: Among 2,327,104 children, 9,547 (0.41%) had sleep apnea and nearly 61% were treated. Girls with sleep apnea, treated or untreated, had increased odds of lower, but not upper, extremity fracture compared to those without sleep apnea (treated 1.56, 95% confidence interval 1.11, 2.21; untreated odds ratio 1.63, 95% confidence interval 1.09, 2.44). Only boys untreated for sleep apnea had increased odds of lower extremity fracture in comparison to those without a diagnosis of sleep apnea (odds ratio 1.65, 95% confidence interval 1.20, 2.27). Interestingly, boys treated for sleep apnea but not those untreated, in comparison to boys without sleep apnea, had different (reduced) odds of upper extremity fracture (odds ratio 0.74, 95% confidence interval 0.59, 0.95).

Conclusions: These large datasets provide evidence that both boys and girls with untreated sleep apnea have higher odds of lower extremity fractures. However, treatment for sleep apnea was associated with improved odds of lower extremity fracture only in boys. Upper extremity data were less clear. These data are cross-sectional and cannot show causality, but they suggest that treatment for sleep apnea may lower risk for extremity fractures in boys.

Keywords: sleep apnea, fracture, adolescent sleep, injury

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep apnea in children has been linked to neurobehavioral morbidity and increased risk for accidental injury. However, data describing the association between sleep apnea and fractures in pediatric populations are lacking.

Study Impact: This study demonstrated that both girls and boys with untreated sleep apnea, in comparison to those without diagnosed sleep apnea, have increased odds for lower extremity fracture. These odds may be improved at least for boys with sleep apnea treatment. Results were less clear for upper extremity fractures, and these data are cross-sectional, but they raise the possibility that identification and treatment for sleep apnea in children could reduce risk for fractures.

INTRODUCTION

Obstructive sleep apnea (OSA) affects 1.2%–5.7% of children[1,2] and is associated with numerous sequelae in multiple organ systems. Some of the most studied outcomes include neuropsychological and behavioral problems, but additional morbidity can include cardiac risks, growth impairment, metabolic abnormalities, and increased health care utilization.[3] Hyperactivity may be the most commonly associated behavioral abnormality associated with untreated OSA, but others include depression, aggression, and abnormal social behaviors.[4,5] Improvement in behavior and learning have been observed with treatment of OSA.[3] Treatment of pediatric OSA typically involves adenotonsillectomy or less commonly, continuous positive airway pressure (CPAP).[2,3]

Individuals with OSA may have a heightened risk for fractures, although not previously assessed in the pediatric OSA population. Pediatric OSA of any severity[6,7] may lead to impulsivity, diminished attention, or sleepiness, any of which could impair motor function and increase risk for falls and fractures. However, fractures may also be increased in OSA to the extent that OSA affects cardiovascular function. A bidirectional relationship is well-established between OSA and cardiovascular disease,[8–10] which is likely to have its roots in childhood. For example, children with OSA in comparison to those without OSA are more likely to have high diastolic blood pressure,[11] and treatment of OSA by adenotonsillectomy improves the severity of hypertension.[12]

As the skeletal system is highly vascularized, hypertension and cardiovascular diseases are associated with bone fragility[13] and are likely to increase risk of fracture through a variety of biological mechanisms.[14–18] To date, few studies have examined the association between OSA and bone health.[19] One recent study did find an increased fracture risk in adult women with OSA.[20] No studies have examined this association in children despite documented evidence of low vitamin D among children[21] and

adults[22] with OSA. Importantly, pediatric factors that affect bone mass and fracture risk can have lasting impact on bone health throughout the life span.[23–29] The potential associations between OSA and increased risk of fracture coupled with limited data in the pediatric population motivated this investigation. We hypothesized that the risk for site-specific fractures in children with OSA would exceed that of children without OSA and that fracture risk is reduced when OSA is treated.

METHODS

Data source

Claims data from full calendar years 2016 through 2018 were obtained from the Optum's de-identified Clinformatics Data Mart Database. This national administrative claims database contains all medical and outpatient pharmacy claims from privately insured or Medicare Advantage beneficiaries in the United States and has been described in detail previously.[30] To be enrolled by a private payer health plan, the child's caregiver can be of any age, income, or disability status, and either pays for coverage or is covered through their employer. Therefore, this sample may be representative of a slightly more affluent sector of the population, and findings should be interpreted within the context of this privately insured sample of children. As data are deidentified, the University of Michigan Institutional Review Board approved this study as nonregulated.

Sample selection

Individuals aged 2 to 18 years who had ≥ 12 months of continuous enrollment between January 1, 2016 and December 31, 2018 were eligible for this cross-sectional analysis. The first continuous 12-month enrollment period per person was used for analysis, allowing for an adequate time period to sequester data, as is common practice with claims-based research.[31] Sleep apnea (SA) was identified by using the *International Classification of Diseases, 10th Revision Clinical Modification* codes (medical conditions), Current Procedural Terminology codes (procedures indicating medical status or treatment procedures), and Healthcare Common Procedure Coding System codes (indications for medical devices and supplies). Guided by previous studies,[32,33] SA was first defined by ≥ 1 claim for any type of sleep apnea (*International Classification of Diseases, 10th Revision Clinical Modification* codes G47.3×). The SA group was further categorized as having evidence of being treated or not treated. Treatment was defined as having ≥ 1 claim that indicated (1) CPAP or (2) CPAP machine or parts (eg, CPAP nasal mask) or (3) having undergone adenotonsillectomy during the enrollment period. An untreated SA group was defined as all other participants with sleep apnea but no evidence of treatment. Children without any claims for SA were included as a group without sleep apnea. While most pediatric research focuses on OSA, the predominant type of SA, this study included both obstructive and central sleep apnea, both of which are associated with arousals and oxygen desaturations and to this extent are functionally similar. Distinction between OSA and central SA was not made because our claims-based method of capturing SA did not allow for a clear delineation. While only 2% of combined SA from diagnostic codes was categorized as central SA, 43% of SA was "sleep apnea unspecified." Clinically, this typically denotes OSA, but it cannot be further sorted.

Fracture

The outcome measure was any claim for all-cause fracture during the child's 12-month period, at any site, as well as by anatomical location, including vertebral column, hip, lower extremities, and upper extremities as previously described.[28] Given the small number of outcome events, vertebral column and hip were combined as 1 site. Identification of fracture through administrative claims data has excellent accuracy and detection (98% positive predictive value).[34]

Statistical analysis

Descriptive characteristics were summarized for each group. Unadjusted prevalence of fracture (overall and site specific) was compared between SA and no SA groups, as well as among the 3 groups that incorporated treatment status (ie, no SA, untreated SA, and treated SA) after stratification by sex, given the difference in fracture risk between boys and girls.[35] Logistic regression models were developed before and after adjustment for age (as a continuous variable), with fracture (overall and site specific) as the outcome for girls and boys separately. Statistical significance was considered to be $P \leq .05$ (2-tailed). Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Over 2 million children and adolescents were included in this study (n = 2,327,104, **Table 1**). Of those, 9,547 (0.4%) obtained a diagnosis of SA and nearly 61% of these children were treated for SA. On average, children and adolescents with a diagnosis of SA and those treated for SA were nearly 2 years younger than those without SA diagnosis or those untreated, respectively. While the no SA group contained similar proportions of girls and boys, boys were the majority (> 55%) in the SA group. All study groups were predominantly (> 60%) White. The prevalence of any fracture during the 12-month study period per enrollee was lower in participants treated for SA (3.2%) in comparison to those untreated for SA (4.3%) and those without SA diagnosis (3.7%).

In sex-stratified analysis, increased odds of lower extremity fracture were apparent among girls with SA, untreated or treated, compared with girls who were not diagnosed with SA; age-adjusted odds ratio = 1.63, 95% confidence interval (1.09, 2.44) and odds ratio = 1.56, 95% confidence interval (1.11, 2.21) for untreated and treated girls with SA, respectively. There were no associations between SA and upper extremity fracture among girls.

Boys who were untreated for SA in comparison to boys without SA had increased odds of lower extremity fracture, with an age-adjusted odds ratio = 1.65, 95% confidence interval (1.20, 2.27). As expected, boys who were treated for SA in comparison to boys without SA had similar odds of lower extremity fracture. Findings for upper extremity fracture were mixed. While there was no association between untreated SA and upper extremity

Table 1—Demographic characteristics of 2,327,104 children.

	No SA	SA	SA untreated	SA treated
	n (column %)	n (column %)	n (column %)	n (column %)
Sample size, n	2,317,557 (99.6)	9,547 (0.4)	3,762 (NA)	5,785 (NA)
Age, y, mean [SD]	10.2 [4.9]	8.3 [4.7]	9.3 [4.9]	7.6 [4.5]
2–5 y	526,278 (22.7)	3,501 (36.7)	1,064 (28.3)	2,437 (42.1)
6–11 y	801,281 (34.6)	3,558 (37.3)	1,410 (37.5)	2,148 (37.1)
12–18 y	989,998 (42.7)	2,488 (26.1)	1,288 (34.2)	1,200 (20.7)
Sex				
Female	1,142,105 (49.3)	4,113 (43.1)	1,563 (41.6)	2,550 (44.1)
Male	1,175,452 (50.7)	5,434 (56.9)	2,199 (58.5)	3,235 (55.9)
Race				
White	1,470,975 (63.5)	6,124 (64.2)	2,267 (60.3)	3,857 (66.7)
Black	150,069 (6.5)	683 (7.2)	311 (8.3)	372 (6.4)
Hispanic	264,607 (11.4)	1,117 (11.7)	487 (13.0)	630 (10.9)
Asian	117,962 (5.1)	347 (3.6)	174 (4.6)	173 (3.0)
Other/unknown	313,944 (13.6)	1,276 (13.4)	523 (13.9)	753 (13.0)
U.S. region of residence				
West	500,367 (21.6)	2,158 (22.6)	878 (23.3)	1,280 (22.1)
Midwest	631,484 (27.3)	2,524 (26.4)	807 (21.5)	1,717 (29.7)
South	960,919 (41.5)	3,925 (41.1)	1,632 (43.4)	2,293 (39.6)
Northeast	224,787 (9.7)	940 (9.9)	445 (11.8)	495 (8.6)
Fracture characteristics				
Any fracture	86,332 (3.7)	345 (3.6)	162 (4.3)	183 (3.2)
Unspecified location	*	0 (0)	0 (0)	0 (0)
Vertebral column or hip	2,374 (0.1)	23 (0.2)	14 (0.4)	9 (0.2)
Lower extremities	25,045 (1.1)	131 (1.4)	63 (1.7)	68 (1.2)
Upper extremities	61,353 (2.7)	212 (2.2)	97 (2.6)	115 (2.0)

*n between 1 and 10 patients and not reported to maintain patient de-identification. NA = not applicable, SA = sleep apnea.

fracture, treated SA in comparison to absence of SA was associated with lower odds of upper extremity fracture, with an age-adjusted odds ratio = 0.74, 95% confidence interval (0.59, 0.95) (**Figure 1**).

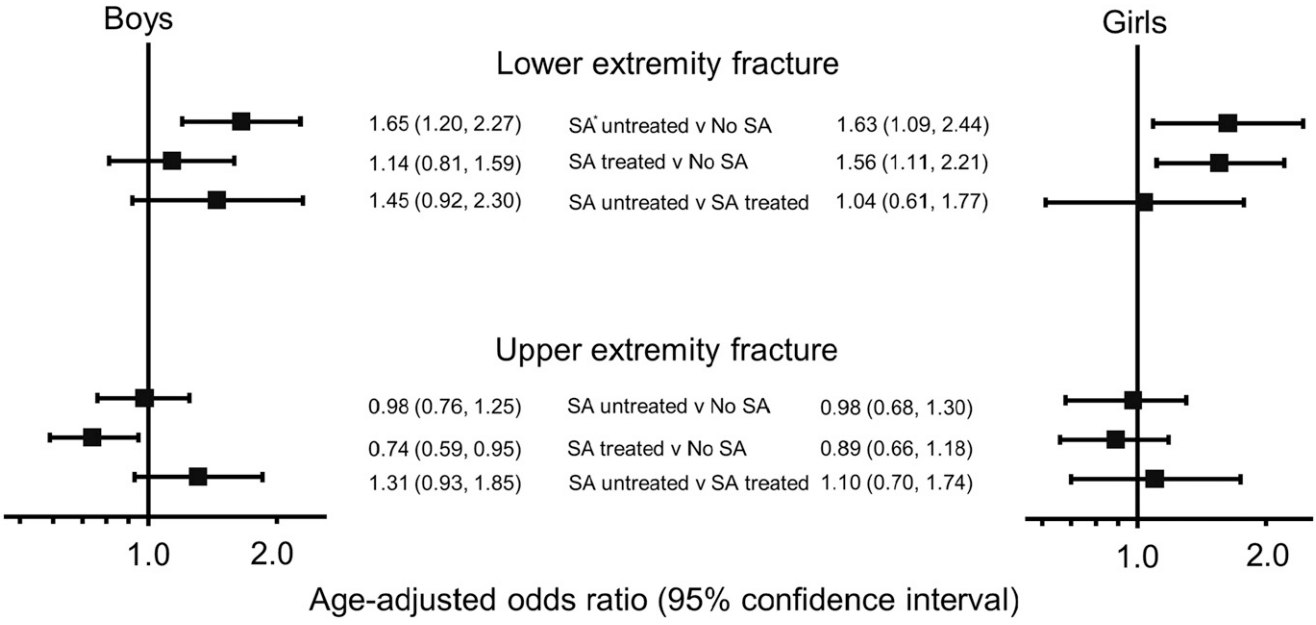
DISCUSSION

In this analysis of claims data from over 2 million children and adolescents, we report sex-specific associations between sleep apnea status and odds of fracture during a 12-month period. For lower extremity fractures, we found that in comparison to same-sex youth with no SA, boys with untreated SA had 65% higher odds of fracture, whereas girls with both treated and untreated SA had 56% and 63% higher odds, respectively. For upper extremity fractures, associations with SA were less clear: although no associations emerged among girls, among boys treated SA in comparison to no SA was unexpectedly linked with lower odds of fractures.

The finding that both boys and girls with untreated SA had elevated odds of lower extremity fractures confirmed our original hypothesis. Although we could identify no prior studies that have examined associations between SA and fracture risk in children, a relationship is biologically plausible. Children with SA are at increased risk for fractures for numerous reasons. SA is associated with excessive daytime sleepiness,[2] which may cause errors in judgment leading to accidents and therefore bone fractures.[36] Children with SA are more likely to have attention-deficit hyperactivity disorder[37,38] with corresponding impulsive behavior. Diagnosed attention-deficit hyperactivity disorder is associated with increased fracture risk.[39] Children with attention-deficit hyperactivity disorder commonly use stimulant medications, which have a negative effect on growth, including (indirectly) bone growth and epiphyseal maturation.[40] Additionally, children with sleep apnea are prone to hypovitaminosis D,[21] which can increase risk for fracture. Additional suggested mechanisms include intermittent hypoxia from SA, resulting in vascular endothelial dysfunction that in turn can decrease blood flow to bones and promote bone loss.[41] Sleep disturbance, another common feature of SA, can increase inflammation,[42] which in turn may suppress bone formation.[20]

A few of our findings were counter to expectations. First was that girls who were treated for SA still had higher odds of lower

Figure 1—Site-specific fracture by sleep apnea diagnosis and treatment stratified by sex.



SA = sleep apnea

extremity fracture compared to girls with no SA. We can only speculate about potential explanations. One, which would limit our findings in a conservative manner (for girls as well as boys), is that treatment for SA initiated only late within the 12-month observation period might have had little opportunity within the remaining portion of that period to exert any beneficial effect on risk of fractures. Another is that SA is not always eliminated after adenotonsillectomy. Inadequate CPAP adherence can diminish its effectiveness. Finally, treatment of SA in children may not completely reverse neurobehavioral impact, underlying brain damage, or a trajectory that leads to phenotypic expression later in life. For example, a remote history of OSA symptoms, even after they have resolved, is still associated with an elevated risk for emergence of problematic behavior later in childhood.[43–45] However, why such mechanisms might be more salient among girls than boys remains unclear.

The second unexpected finding was that boys who were treated for SA had 26% lower odds of upper extremity fracture than boys with no SA. Again, we can only speculate at reasons. Children with SA were 2 years younger than those without SA, and fracture risk increases in boys between ages 8 and 10 years, possibly as boys become more involved with sports.[46] Perhaps a similar age-related reduced risk of upper extremity fracture would have been observed in untreated SA if not for an adverse impact of that condition on fracture risk. Another potential confound that could explain our paradoxical results could be lifestyle differences, such that boys with SA, who are also more likely to have excess adiposity, may engage in fewer physical activities that would otherwise raise risk for upper extremity fractures.

This study examined novel relationships between SA diagnosis and treatment on the one hand and odds of fractures in boys and girls on the other. The large sample size with over 2 million children and adolescents provided an unusual opportunity for analysis of fractures even if they are not highly likely to occur within any given 12-month interval. However, this study has several limitations. First, the sensitivity and specificity of pediatric sleep apnea diagnosis and treatment codes as listed in administrative claims data are unknown and, therefore, interpretations should be made with caution. Efficacy of adenotonsillectomy and CPAP compliance are < 100%, and therefore a misclassification of treatment status is possible. However, sensitivity is more likely to be compromised than specificity. The missed patients with SA and fracture in the large pool of people identified as not having these conditions are likely vastly diluted by those who truly experienced neither of these conditions. Thus, we expect that the directionality of our estimate is conservative: we would expect an even larger difference between SA and non-SA groups than we demonstrated. Second, surgical therapy for SA (adenotonsillectomy) is generally performed at a younger age, thus the use of adenotonsillectomy detected in our dataset may be skewed toward the younger population and may miss children who had the surgery prior to the enrollment period. Third, although this study showed associations between SA or SA treatment and odds of fracture, its cross-sectional design does not permit temporal analysis of these findings. However, SA is a chronic condition highly likely to have been present for up to a year before diagnosis. Finally, we did not separate central SA from OSA in these analyses due to the methodologic limitations noted above. However, the present findings can be anticipated to reflect similarities of effects known to occur in both types of SA, and also the high predominance of OSA at the ages studied.

CONCLUSIONS

In conclusion, these analyses highlight the relationship between pediatric SA and the odds of lower and upper extremity fractures. At this point, we can only speculate on the clinical implications of these findings. It could mean that children with fractures that occur from preventable accidents should be screened for SA. Moreover, it could spur considerably more investigation to confirm these findings in the pediatric population and to assess whether adults may also be vulnerable in a similar manner to the impact of impaired or deficient sleep.

ABBREVIATIONS

CPAP, continuous positive airway pressure
OSA, obstructive sleep apnea
SA, sleep apnea

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DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. Work for this study was performed at the University of Michigan. The authors report no conflicts of interest.