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Pediatric Sleep Apnea and Craniofacial Anomalies: A Population-Based Case–Control Study

Derek J. Lam, MD, MPH, Christine C. Jensen, MD, MPH, Beth A. Mueller, DrPH, Jacqueline R. Starr, MS, MPH, PhD, Michael L. Cunningham, MD, PhD, and Edward M. Weaver, MD, MPH

Department of Otolaryngology–Head and Neck Surgery (D.J.L., E.M.W.), University of Washington Medical Center, Seattle, Washington, U.S.A.; Department of Surgery (C.C.J.), Department of Epidemiology (B.A.M., J.R.S.), University of Washington, Seattle, Washington, U.S.A.; Fred Hutchinson Cancer Research Center (B.A.M.), Seattle, Washington, U.S.A.; Department of Pediatrics (J.R.S., M.L.C.), University of Washington, and Craniofacial Center, Seattle Children's Hospital, Seattle, Washington, U.S.A.; University of Washington Comparative Effectiveness (E.M.W.), Cost & Outcomes Research Center, Harborview Medical Center, Seattle, Washington, U.S.A

Abstract

Objective—To investigate the association between craniofacial anomalies and diagnosis with obstructive sleep apnea (OSA) in a large, population-based sample of children.

Design—Retrospective case–control study.

Methods—Cases of OSA ($n = 1,203$) were identified by International Classification of Diseases-9 codes consistent with OSA in the 1987–2003 Washington State inpatient discharge database among children 18 years of age and born in Washington state. For each case, five controls without OSA ($n = 6,015$) were randomly selected from the remaining Washington State births, frequency matched by birth year. Congenital anomaly diagnoses and covariates were extracted from discharge data for all inpatient hospitalizations during the study period and linked birth certificate data. Multiple logistic regression was used to calculate adjusted odds ratios (OR) and 95% confidence intervals (CI) for the associations between congenital anomalies (including subgroups) and OSA.

Results—An OSA diagnosis was strongly associated with the presence of any craniofacial anomaly (adjusted OR 38, 95%CI [24, 60]) and, in particular, with orofacial cleft (adjusted OR 40, 95%CI [17, 94]) and Down syndrome (adjusted OR 51, 95%CI [20, 128]). OSA was less

Send correspondence to Dr. Derek Lam, Department of Otolaryngology–Head and Neck Surgery, University of Washington Medical Center, BB1165, Box 356515, 1959 NE Pacific Street, Seattle, WA 98195. derekjlam@gmail.com.

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associated with any noncraniofacial malformation (adjusted OR 4.1, 95% CI [3.1, 5.3]), which may reflect the relatively small effect of inpatient exposure bias in the associations above.

Conclusions—The presence of congenital craniofacial anomalies is strongly associated with inpatient diagnosis of OSA. These findings persist even after control of major potential biases. Parents and clinicians should consider screening for OSA among children with craniofacial anomalies.

Keywords

Pediatric sleep apnea; craniofacial; orofacial cleft; Down syndrome

INTRODUCTION

Obstructive sleep apnea (OSA) has been extensively described in the adult population, but its impact in the pediatric population has only recently been recognized.^{1,2} OSA is characterized by repeated obstruction of the upper airway during sleep that is often associated with arousals and oxyhemoglobin desaturation. In children, symptoms of OSA include habitual snoring, frequent arousals, pauses in respiration, daytime somnolence, and neurobehavioral problems.^{3,4} Long-term sequelae of OSA in children include problems with attention and hyperactivity,⁵ learning disability,⁶ cardiorespiratory compromise, and even death.^{4,7}

Children with craniofacial anomalies frequently have anatomic features such as maxillary or mandibular hypoplasia, crowded oropharynx, macroglossia, or poor motor tone that are thought to predispose to upper airway compromise and thus are believed to be at increased risk for the development of pediatric OSA. This is a common assertion that is frequently mentioned in literature reviews on pediatric sleep apnea^{8–10} and pediatric textbooks.¹¹ However, studies that have demonstrated associations between specific craniofacial morphologic features and OSA in children have typically excluded subjects with known craniofacial abnormalities.^{12–14} Associations between craniofacial congenital anomalies and OSA have primarily been suggested by small case series or cohort studies,^{15–25} and there have been several studies focused specifically on OSA in children with orofacial clefts^{22,24–28} or Down syndrome,^{29–34} which are two of the most common conditions characterized by abnormalities of craniofacial anatomy.^{35,36} Most of these studies were uncontrolled,^{15–22,27–32} and none attempted to formally quantify an association with OSA, so the relationship between these craniofacial conditions and diagnosis with OSA remains unclear.

We conducted a population-based case–control study among children born in Washington State from 1980 to 2003 in order to quantify the association of pediatric OSA with the presence of a craniofacial anomaly in general, and with orofacial clefts and Down syndrome in particular.

MATERIALS AND METHODS

Study Design

A population-based case–control study design was employed to test the hypothesis that hospitalization among children for which OSA is indicated as a diagnosis code is associated with the presence of craniofacial anomalies in general, and orofacial cleft or Down syndrome in particular. These two specific diagnoses were chosen for subgroup analysis because they were the only craniofacial anomalies specifically indicated on Washington State birth certificates, and were present in sufficient numbers to allow meaningful subgroup analysis. Children with craniofacial anomalies may have increased hospital utilization and thus be more likely to obtain an inpatient diagnosis of OSA. As a control for this potential selection bias, we also measured the association between diagnosis of OSA and noncraniofacial malformations that are unlikely to be associated with OSA.

Data Sources

Two population-based databases were used to identify subjects. The Washington State Comprehensive Hospital Abstract Reporting System (CHARS), created by the Washington State Department of Health, includes International Classification of Diseases-9 (ICD-9) codes for all inpatient hospitalizations at non-federal facilities. Data were also extracted from Washington State Birth Certificates, including demographic and medical data for both the mother and infant, such as gender, maternal and child race, date of birth, gestational age, birth complications, and prenatal history. No attempt was made to access or review individual medical records of study subjects in part because of the large number of subjects included in the study, but also due to the stipulation by the Washington State Department of Health that all data extracted from these state-wide databases be deidentified prior to analysis. Procedures for data access and linkage for this project were approved by the institutional review boards of the University of Washington and the Washington State Department of Health prior to the conduct of this study.

Population

Potential cases of OSA identified in the CHARS database included all patients 18 years old born 1980–2003 with at least one hospitalization between 1987 and 2003 for which an ICD-9 diagnosis code related to OSA (780.51—insomnia with sleep apnea, unspecified; 780.53—hypersomnia with sleep apnea, unspecified; 780.57—unspecified sleep apnea) was recorded ($n = 1,495$). Although these ICD9 codes appear to exclude many symptoms associated with pediatric OSA, these are the only ICD9 codes available that are specifically related to sleep apnea. More than 96% of the cases had an ICD9 code of 780.57 (unspecified sleep apnea), so the vast majority of the cases were not limited to having either insomnia or hypersomnia. These potential cases were then linked to birth certificates to identify children born in Washington state ($n = 1,203$). For each OSA case, five controls without OSA ($n = 6,015$) were randomly sampled from the remaining Washington State births and frequency matched by birth year. This linkage to birth certificates ensured that both cases and controls were selected from the general population of children in Washington State, which allows for population-based inference, even though the ICD9 diagnostic data are based only on inpatient hospitalizations.

Because the data from the CHARS database only covers the period from 1987 to 2003, there was a possibility of an exposure bias due to unequal exposure opportunity. For example, for children born in 2002 there was only 1 year during which time an inpatient diagnosis would be captured in the database, whereas a child born in 1987 would have 15 years of exposure opportunity. In addition, for children born in 1980–1986, any hospitalizations prior to 1987 would not be captured in the database. For these reasons, all analyses were also performed on a dataset restricted to years of birth from 1987 to 1997. This restriction ensured that this dataset only included subjects with diagnoses from all inpatient admissions for at least the first 5 years of life.

Exposure Measurement

The presence of selected congenital anomalies (craniofacial, heart/great vessel, urogenital, musculoskeletal, and spine) among both cases and controls was identified from check boxes on the birth certificates indicating specific congenital anomalies as well as from ICD-9 diagnosis codes for these conditions from the birth hospitalization and all rehospitalizations within the study period (Table I). A child was considered to have a craniofacial anomaly if ICD-9 codes were present for any of the following conditions: orofacial cleft, Down syndrome, Apert syndrome, major anomalies of jaw size, anomalies of the relationship of the jaw to cranial base, and anomalies of the skull and face bones. These particular codes were chosen because they were the only ones available that were specific to craniofacial anomalies. A child was considered to have a non-craniofacial malformation if anomalies of any of the following were indicated: heart/great vessels, urogenital anatomy, musculoskeletal anatomy and spine (Table I). These two categories (craniofacial anomalies and noncraniofacial malformations) were not necessarily mutually exclusive because individuals could have multiple congenital anomalies.

Analyses

Odds ratio (OR) estimates of the relative risk were calculated by logistic regression to examine the relationship between diagnosis with OSA and the presence of 1) craniofacial anomaly, and 2) noncraniofacial malformation. Subgroup analysis was performed for the two most frequent craniofacial diagnoses, orofacial cleft and Down syndrome, as well as for malformations of heart/great vessels, musculoskeletal anatomy, and urogenital anatomy. Other exposures were not present in sufficient numbers to allow subgroup analysis.

Initial crude odds ratios were calculated using logistic regression models that tested the association between diagnosis with OSA and each of the primary exposure variables as well as their subgroups, adjusting only for year of birth (matching variable).

In subsequent multiple logistic regression analysis, the variables considered for their possible effects on the ORs included maternal characteristics such as age at time of birth (continuous), prenatal cigarette smoking (yes/no), prenatal alcohol consumption (yes/no), and median household income (above or below Washington state median income for birth year). Potentially confounding infant factors were also considered including gender, race (White/non-White), birth weight (continuous), gestational age (continuous), adenotonsillar hypertrophy, and the presence of other noncraniofacial malformations (yes/no).

The final multiple logistic regression models for the craniofacial anomaly exposure and all its subgroups included year of birth, gender, race, birth weight, and presence of a noncraniofacial malformation as covariates. Other covariates either did not meaningfully alter the unadjusted OR, generally by <10% (maternal age at time of birth, maternal smoking status, median income) or had too much missing data (prenatal alcohol use, gestational age, adenotonsillar hypertrophy). Adjustment for adenotonsillar hypertrophy was not possible because diagnosis of adenotonsillar hypertrophy was only found among the cases with OSA. To control for possible confounding related to adenotonsillar hypertrophy, all analyses were performed twice, once with and once without patients who had a diagnosis of adenotonsillar hypertrophy.

In the multiple logistic regression models assessing the adjusted association between OSA and noncraniofacial malformations, odds ratios were adjusted for year of birth, gender, race, birth weight, and the presence of any craniofacial anomaly. The results were not substantially different when cases with craniofacial anomalies were excluded.

All analyses were performed with Stata 9.1 (Stata Corp., College Station, TX).

RESULTS

Children with an inpatient diagnosis of OSA were more likely than controls to be male (64% vs. 36%), African-American (11% vs. 5%), and to have had birth weights <2,500 g (15% vs. 5%, Table II). A total of 639 (53%) of the cases were found to have a diagnosis of adenotonsillar hypertrophy, whereas none of the controls carried this inpatient diagnosis.

In the initial crude analysis, a diagnosis of OSA was strongly associated with the presence of craniofacial anomalies (OR 49.9, 95% CI [31.9, 78.0], Table III), with a lesser but still significant association with noncraniofacial malformations (OR 6.3, 95% CI [5.1, 7.9]). Similar magnitudes of association were noted for specific craniofacial conditions (orofacial cleft, Down syndrome) and noncraniofacial conditions (heart/great vessel, musculoskeletal, and urogenital anomalies). These odds ratios were all slightly greater but with similar relative strengths when cases with adenotonsillar hypertrophy were excluded (data not shown).

In multiple logistic regression analysis, the adjusted associations between diagnosis with OSA and diagnosis with any craniofacial anomaly, orofacial cleft, or Down syndrome were still very strong though smaller in magnitude compared to the crude ORs (OR [95% CI] 37.9 [23.9, 60.1], 39.7 [16.8, 93.9], 50.7 [20.1, 128], respectively; Table III). When the 639 cases with adenotonsillar hypertrophy were excluded, the strong positive relationship between OSA and craniofacial anomalies, orofacial cleft, or Down syndrome persisted (OR [95% CI] 49.9 [30.5, 81.4], 65.0 [26.9, 157], 48.8 [18.8, 126.8], respectively). Individuals with any noncraniofacial malformation also had a significant association with a diagnosis of OSA (OR 3.9, 95% CI [3.0, 5.2]; Table III). When the analysis was restricted to the birth years 1987 to 1997, the results were not substantially different, suggesting that the difference in exposure ascertainment was not an important source of bias (data not shown).

DISCUSSION

This study indicates that there are extremely strong population-based associations between congenital craniofacial anomalies and OSA, with adjusted odds ratios >30 . In this study, 16% of inpatient cases with OSA had a congenital craniofacial anomaly, whereas only 0.4% of inpatient controls without OSA had such an anomaly.

Children with orofacial clefts, Down syndrome, or other craniofacial anomalies (e.g., Apert or Crouzon syndromes, hemifacial microsomia, etc.) frequently have anatomic features that are thought to predispose to upper airway compromise and symptoms of OSA.^{9,10} Although the prevalence of OSA in the general pediatric population is typically reported as 1% to 3%,^{37,38} recent studies have estimated the prevalence of OSA among children with Down syndrome to be as high as 57%, with an even greater prevalence in boys.^{29,30} Another study of children with Apert, Crouzon, or Pfeiffer syndromes, which all have significant maxillary hypoplasia as a key feature, reported an estimated prevalence of OSA of 53% in this population based on symptom report on a mail-in questionnaire.¹⁵ Because long-term sequelae of OSA in children are potentially serious,⁴⁻⁷ it is important to better understand the relationship between OSA and craniofacial anomalies.

Furthermore, consideration of OSA diagnosis in children with craniofacial anomalies is particularly important because of the overlapping morbidity. Some craniofacial syndromes are associated with learning disabilities, neurocognitive deficits, or failure to thrive. Because pediatric OSA also can result in these sequelae, it is possible that in children with craniofacial anomalies, these morbidities might be due in part to the associated OSA, which often can be treated. Thus, it appears important to identify and treat OSA in this population.

To date, no large-scale epidemiologic studies have quantified the association between OSA and the presence of one or more craniofacial anomalies. One cross-sectional study of 850 children aged 8 to 11 years demonstrated an increased risk of OSA in former preterm infants compared to term infants (OR 3.0 [1.5, 6.5]) but did not address whether these children had any congenital anomalies.³⁹ Another study investigated the rate of tracheotomy among a sample of patients from a craniofacial clinic at a tertiary-care pediatric medical center and found that 19% required tracheotomy to relieve airway obstruction (awake or asleep) caused by various abnormalities of their craniofacial anatomy.⁴⁰ However, this was a retrospective case series that used tracheotomy as an outcome measure rather than diagnosis with OSA, and there was no control group with which to calculate an association between craniofacial anomalies and tracheotomy. To our knowledge, the current case-control study is the first population-based assessment of the association between OSA diagnosis and presence of craniofacial anomalies. The use of large population-based databases provided the opportunity to study uncommon exposures like craniofacial anomalies which would be difficult to study adequately in single-site series.

There are several important limitations to this study. First, adjustment for the presence of adenotonsillar hypertrophy, the principal risk factor for sleep apnea in the general pediatric population, was not possible because inpatient diagnosis with adenotonsillar hypertrophy occurred exclusively among cases of OSA (Table II). It is highly unlikely that among all the

controls there were no individuals diagnosed with adenotonsillar hypertrophy. We interpret this result to be an artifact of the inpatient database used to identify adenotonsillar hypertrophy. In general, children are diagnosed with adenotonsillar hypertrophy in an outpatient setting, but because our analysis relied on inpatient diagnostic data, only those children admitted to the hospital with a diagnosis of adenotonsillar hypertrophy, probably at the time of adenotonsillectomy, were captured in the database screen. In this context, individuals from the general population with adenotonsillar hypertrophy would not be captured in the CHARS database because they would be treated as outpatients, whereas those with sleep apnea would be far more likely to be admitted overnight for airway monitoring. To account for this skewed rate of inpatient diagnosis of adenotonsillar hypertrophy, we analyzed the data two ways: 1) including all patients, and 2) excluding patients with adenotonsillar hypertrophy. Although the magnitudes of the ORs tended to be greater for the primary exposures when patients with adenotonsillar hypertrophy were excluded, the results were comparable, which suggests that the skewed distribution of adenotonsillar hypertrophy diagnosis does not explain the relationship between craniofacial anomalies and OSA.

Second, because cases of sleep apnea were ascertained by screening for ICD9 codes, it is unclear how the diagnosis of OSA was made. We could not assess whether this was based on sleep study data or some other method of diagnosis. The aggregate deidentified state-wide data sources used did not allow review of individual-level records that might have included polysomnography data. However, given the time frame included in this study, modern polysomnography was not widely available as a diagnostic tool for much of the study period. Therefore, it is reasonable to conclude that a large proportion of the OSA diagnoses were based on clinical assessment only. Previous studies have shown that clinical assessment has a positive predictive value of approximately 30% to 85% for diagnosis of OSA by polysomnography, depending on the method of assessment used.^{41–43} In this setting, patients with undiagnosed OSA or outpatient diagnoses of OSA could be potentially misclassified as controls if they were admitted for an unrelated reason and never given an inpatient diagnosis of OSA. Regardless of how OSA was diagnosed among these inpatients, it seems unlikely that the magnitude of the associations observed can be wholly accounted for by such potential misclassification.

Third, in addition to misclassification of cases and controls, it is possible that there was misclassification of the primary exposures (craniofacial and noncraniofacial malformations) due to inaccurate or incomplete coding at the time of discharge or on the birth certificates. Such misclassification could, in part, account for the magnitude of association observed for both craniofacial and noncraniofacial malformations if only patients predisposed to airway obstruction such as those with one or more congenital anomalies were admitted to the hospital specifically for airway monitoring and assigned a diagnosis of OSA.

Fourth, there is a potential selection bias because the OSA diagnosis data are all derived from inpatient data, whereas in general, initial OSA diagnosis is usually made in an outpatient setting. It is possible that the use of only inpatient data may exaggerate the association between craniofacial anomalies and OSA diagnosis. We can estimate the associations in the absence of this selection bias by using results from another epidemiologic

study that quantified the prevalence of craniofacial anomalies (5.6%) in pediatric tracheotomy patients.⁴⁴ Tracheotomies are generally only done in an inpatient setting, so there is no inpatient selection bias in that sample. Using this value (5.6%) as a rough approximation for the true underlying prevalence of craniofacial anomalies in patients with airway disorders, instead of the 16% found in our potentially biased inpatient OSA sample, we recalculated an OR of 16.1, 95%CI [9.7, 27.4] for the association between craniofacial anomalies and OSA in our sample. This odds ratio still indicates a very strong association between a diagnosis of OSA and craniofacial anomalies, and it suggests that the strong association is not explained by a bias of analyzing only inpatient OSA.

Despite these limitations, our results demonstrated a very strong association between an inpatient OSA diagnosis and the presence of craniofacial anomalies in children less than 18 years of age. Analyses of craniofacial subgroups such as orofacial clefts and Down syndrome also demonstrated strong associations. The adjusted associations between OSA and noncraniofacial malformations were also significantly increased, but were an order of magnitude less than for children with craniofacial anomalies. One possible explanation for this association is that individuals with noncraniofacial malformations are also more likely to have craniofacial abnormalities. However, the persistence of this association even after adjusting for the presence of a craniofacial anomaly suggests that coexistence of craniofacial anomalies and noncraniofacial malformations does not completely account for this observed association.

Two phenomena may explain the association between diagnosis with OSA and a diagnosis with non-craniofacial malformations. First, the observed association may reflect an exposure bias where children with one or more congenital malformations may have an increased likelihood of hospital admission and are therefore more likely to be diagnosed with OSA as an inpatient simply through greater exposure to inpatient medical care. Second, such malformations may be part of syndromes that include neuromuscular disorders resulting in poor neuromotor tone or other anatomic features that predispose to OSA but are not explicitly listed in the diagnosis coding of the CHARS discharge database. Regardless, because this association is an order of magnitude smaller than that found for craniofacial anomalies and OSA, this provides evidence that anomalies of craniofacial structures are very strongly associated with OSA, even beyond the factors mentioned above. Moreover, the magnitude of the association between OSA and craniofacial anomalies remained robust after adjusting for the presence of noncraniofacial malformations and other potential confounders in multiple regression analysis and after excluding all cases diagnosed with adenotonsillar hypertrophy.

As another way to address the potential bias of using inpatient data, future analyses using outpatient diagnostic data could provide a more comprehensive and representative sampling of the general pediatric population. In addition, expanding the dataset to include similar data from other state or national databases might allow for analysis of other subgroups of interest and provide more generalizable findings.

CONCLUSION

This population-based study demonstrated very strong associations between craniofacial anomalies and OSA among children aged 0 to 18 years identified using a hospital discharge database and birth records. These findings persist even after control of major potential biases. The significant associations between noncraniofacial malformations and OSA suggest a possible exposure bias where patients with any anomalies have greater opportunity to receive an inpatient OSA diagnosis. In addition, the limitation of having only inpatient data for OSA diagnosis may introduce a selection bias. However, based on our quantifications, these possible biases appear to account for only a fraction of the very strong associations observed between craniofacial anomalies and OSA. As with any administrative data analysis, mis-classification may distort the association; however, the strength of the association is unlikely to be explained by miscellaneous or random misclassifications. Given the potential morbidity associated with untreated OSA, we suggest that screening for OSA should be considered for all children with significant craniofacial anomalies.

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BIBLIOGRAPHY

- Guilleminault C, Eldridge FL, Simmons FB, Dement WC. Sleep apnea in eight children. *Pediatrics*. 1976; 58:23–30. [PubMed: 934781]
- Guilleminault C, Winkle R, Korobkin R, Simmons B. Children and nocturnal snoring: evaluation of the effects of sleep related respiratory resistive load and daytime functioning. *Eur J Pediatr*. 1982; 139:165–171. [PubMed: 7160405]
- Archbold KH, Pituch KJ, Panahi P, Chervin RD. Symptoms of sleep disturbances among children at two general pediatric clinics. *J Pediatr*. 2002; 140:97–102. [PubMed: 11815771]
- Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2002; 109:704–712. [PubMed: 11927718]
- Chervin RD, Archbold KH, Dillon JE, et al. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. *Pediatrics*. 2002; 109:449–456. [PubMed: 11875140]
- Gozal D. Sleep-disordered breathing and school performance in children. *Pediatrics*. 1998; 102:616–620. [PubMed: 9738185]
- Brouillette RT, Fernbach SK, Hunt CE. Obstructive sleep apnea in infants and children. *J Pediatr*. 1982; 100:31–40. [PubMed: 7057314]
- Singer LP, Saenger P. Complications of pediatric obstructive sleep apnea. *Otolaryngol Clin North Am*. 1990; 23:665–676. [PubMed: 2199900]
- Erlor T, Paditz E. Obstructive sleep apnea syndrome in children: a state-of-the-art review. *Treat Respir Med*. 2004; 3:107–122. [PubMed: 15182212]
- Ward SL, Marcus CL. Obstructive sleep apnea in infants and young children. *J Clin Neurophysiol*. 1996; 13:198–207. [PubMed: 8714340]
- Rosen, CL.; Kass, LJ.; Haddad, GG. Obstructive sleep apnea and hypoventilation. In: Behrman, RE., editor. *Nelson Textbook of Pediatrics*. Philadelphia, PA: Saunders; 2004. p. 1397-1401.
- Arens R, McDonough JM, Corbin AM, et al. Upper airway size analysis by magnetic resonance imaging of children with obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 2003; 167:65–70. [PubMed: 12406826]

13. Finkelstein Y, Wexler D, Berger G, Nachmany A, Shapiro-Feinberg M, Ophir D. Anatomical basis of sleep-related breathing abnormalities in children with nasal obstruction. *Arch Otolaryngol Head Neck Surg.* 2000; 126:593–600. [PubMed: 10807326]
14. Kulnis R, Nelson S, Strohl K, Hans M. Cephalometric assessment of snoring and nonsnoring children. *Chest.* 2000; 118:596–603. [PubMed: 10988178]
15. Pijpers M, Poels PJ, Vaandrager JM, et al. Undiagnosed obstructive sleep apnea syndrome in children with syndromal craniofacial synostosis. *J Craniofac Surg.* 2004; 15:670–674. [PubMed: 15213550]
16. Mogayzel PJ Jr, Carroll JL, Loughlin GM, Hurko O, Francomano CA, Marcus CL. Sleep-disordered breathing in children with achondroplasia. *J Pediatr.* 1998; 132:667–671. [PubMed: 9580768]
17. Cohen SR, Levitt CA, Simms C, Burstein FD. Airway disorders in hemifacial microsomia. *Plast Reconstr Surg.* 1999; 103:27–33. [PubMed: 9915160]
18. Cohen SR, Ross DA, Burstein FD, Lefaivre JF, Riski JE, Simms C. Skeletal expansion combined with soft-tissue reduction in the treatment of obstructive sleep apnea in children: physiologic results. *Otolaryngol Head Neck Surg.* 1998; 119:476–485. [PubMed: 9807073]
19. Cohen MM Jr, Kreiborg S. Upper and lower airway compromise in the Apert syndrome. *Am J Med Genet.* 1992; 44:90–93. [PubMed: 1519659]
20. Spier S, Rivlin J, Rowe RD, Egan T. Sleep in Pierre Robin syndrome. *Chest.* 1986; 90:711–715. [PubMed: 3769574]
21. James D, Ma L. Mandibular reconstruction in children with obstructive sleep apnea due to micrognathia. *Plast Reconstruct Surg.* 1997; 100:1131–1137. discussion 1138.
22. Liao YF, Yun C, Huang CS, et al. Longitudinal follow-up of obstructive sleep apnea following Furlow palatoplasty in children with cleft palate: a preliminary report. *Cleft Palate Craniofac J.* 2003; 40:269–273. [PubMed: 12733955]
23. Onodera K, Niikuni N, Chigono T, Nakajima I, Sakata H, Motizuki H. Sleep disordered breathing in children with achondroplasia. Part 2. Relationship with craniofacial and airway morphology. *Int J Pediatr Otorhinolaryngol.* 2006; 70:453–461. [PubMed: 16406083]
24. Rose E, Thissen U, Otten JE, Jonas I. Cephalometric assessment of the posterior airway space in patients with cleft palate after palatoplasty. *Cleft Palate Craniofac J.* 2003; 40:498–503. [PubMed: 12943438]
25. Rose E, Staats R, Thissen U, Otten JE, Schmelzeisen R, Jonas I. Sleep-related obstructive disordered breathing in cleft palate patients after palatoplasty. *Plast Reconstruct Surg.* 2002; 110:392–396.
26. Abramson DL, Marrinan EM, Mulliken JB. Robin sequence: obstructive sleep apnea following pharyngeal flap. *Cleft Palate Craniofac J.* 1997; 34:256–260. [PubMed: 9167078]
27. Liao YF, Chuang ML, Chen PK, Chen NH, Yun C, Huang CS. Incidence and severity of obstructive sleep apnea following pharyngeal flap surgery in patients with cleft palate. *Cleft Palate Craniofac J.* 2002; 39:312–316. [PubMed: 12019007]
28. Liao YF, Noordhoff MS, Huang CS, et al. Comparison of obstructive sleep apnea syndrome in children with cleft palate following Furlow palatoplasty or pharyngeal flap for velopharyngeal insufficiency. *Cleft Palate Craniofac J.* 2004; 41:152–156. [PubMed: 14989690]
29. de Miguel-Diez J, Villa-Asensi JR, Alvarez-Sala JL. Prevalence of sleep-disordered breathing in children with Down syndrome: polygraphic findings in 108 children. *Sleep.* 2003; 26:1006–1009. [PubMed: 14746382]
30. Shott SR, Amin R, Chini B, Heubi C, Hotze S, Akers R. Obstructive sleep apnea: Should all children with Down syndrome be tested? *Arch Otolaryngol Head Neck Surg.* 2006; 132:432–436. [PubMed: 16618913]
31. Dyken ME, Lin-Dyken DC, Poulton S, Zimmerman MB, Sedars E. Prospective polysomnographic analysis of obstructive sleep apnea in down syndrome. *Arch Pediatr Adolesc Med.* 2003; 157:655–660. [PubMed: 12860786]
32. Marcus CL, Keens TG, Bautista DB, von Pechmann WS, Ward SL. Obstructive sleep apnea in children with Down syndrome. *Pediatrics.* 1991; 88:132–139. [PubMed: 1829151]

33. Stebbens VA, Dennis J, Samuels MP, Croft CB, Southall DP. Sleep related upper airway obstruction in a cohort with Down's syndrome. *Arch Dis Child*. 1991; 66:1333–1338. [PubMed: 1836718]
34. Southall DP, Stebbens VA, Mirza R, Lang MH, Croft CB, Shinebourne EA. Upper airway obstruction with hypoxaemia and sleep disruption in Down syndrome. *Dev Med Child Neurol*. 1987; 29:734–742. [PubMed: 2961643]
35. Global strategies to reduce the health care burden of craniofacial anomalies: report of WHO meetings on international collaborative research on craniofacial anomalies. *Cleft Palate Craniofac J*. 2004; 41:238–243. [PubMed: 15151440]
36. Adams MM, Erickson JD, Layde PM, Oakley GP. Down's syndrome. Recent trends in the United States. *JAMA*. 1981; 246:758–760. [PubMed: 6454794]
37. Ali NJ, Pitson DJ, Stradling JR. Snoring, sleep disturbance, and behaviour in 4–5 year olds. *Arch Dis Child*. 1993; 68:360–366. [PubMed: 8280201]
38. Gislason T, Benediktsdottir B. Snoring, apneic episodes, and nocturnal hypoxemia among children 6 months to 6 years old. An epidemiologic study of lower limit of prevalence. *Chest*. 1995; 107:963–966. [PubMed: 7705162]
39. Rosen CL, Larkin EK, Kirchner HL, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. *J Pediatr*. 2003; 142:383–389. [PubMed: 12712055]
40. Sculerati N, Gottlieb MD, Zimble MS, Chibbaro PD, McCarthy JG. Airway management in children with major craniofacial anomalies. *Laryngoscope*. 1998; 108:1806–1812. [PubMed: 9851495]
41. Carroll JL, McColley SA, Marcus CL, Curtis S, Loughlin GM. Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children. *Chest*. 1995; 108:610–618. [PubMed: 7656605]
42. Goldstein NA, Pugazhendhi V, Rao SM, et al. Clinical assessment of pediatric obstructive sleep apnea. *Pediatrics*. 2004; 114:33–43. [PubMed: 15231905]
43. Montgomery-Downs HE, O'Brien LM, Holbrook CR, Gozal D. Snoring and sleep-disordered breathing in young children: subjective and objective correlates. *Sleep*. 2004; 27:87–94. [PubMed: 14998242]
44. Lewis CW, Carron JD, Perkins JA, Sie KC, Feudtner C. Tracheotomy in pediatric patients: a national perspective. *Arch Otolaryngol Head Neck Surg*. 2003; 129:523–529. [PubMed: 12759264]

TABLE I

Coding of Congenital Anomaly Exposure Variables.

Exposure	Birth Certificate Congenital Anomaly Variable(s)	CHARS ICD-9 Diagnosis Code(s)
Craniofacial Anomalies		
Cleft lip and/or palate	Cleft lip with/without cleft palate	749.0x Cleft palate
	Cleft palate alone	749.1x Cleft lip
		749.2x Cleft palate with cleft lip
Down Syndrome	Down Syndrome	758.0 Down Syndrome
Other craniofacial anomalies	–	524.0x Major anomalies of jaw size
		524.1x Anomalies of relationship of jaw to cranial base (incl. retrognathism and maxillary or jaw asymmetry)
		744.8x Mouth/lip anomalies
		750.15 Macroglossia
		755.55 Apert Syndrome
		756.0x Anomalies of skull and face bones (incl Crouzon Syndrome)
		748.0x Choanal atresia
		744.0x Ear anomalies with hearing loss
		744.2x Ear anomalies without hearing loss, microtia
		744.3x Unspecified ear anomalies
		744.9x Unspecified face and neck anomalies
		754.0x Hemifacial microsomia
Noncraniofacial Congenital Malformations		
Heart/great vessel anomaly	Heart malformations	745.xx Anomalies of bulbis cordis and septal closure (incl. ASD, VSD, Tetralogy of Fallot)
	Circulatory/respiratory Anomalies	746.xx Other congenital heart anomalies
		747.xx Other congenital anomalies of circulatory system (incl PDA)
Musculoskeletal anomaly	Musculoskeletal anomalies	754.3x-754.8x
		Congenital musculoskeletal deformities (incl. hip dislocation, scoliosis, club foot)
		755.xx (excl 755.55)
		Limb deformities (incl. poly/syndactyly)
Urogenital anomaly	Urogenital anomalies	752.xx Genital anomalies
		753.xx Urinary anomalies
Spine anomaly	Spina bifida	741.xx Spina bifida

TABLE II

Infant and Maternal Characteristics of OSA Cases and Controls, Washington State 1987–2003 *

	Cases of OSA (N = 1,203)		Controls without OSA (N = 6,015)	
	N	(%)	N	(%)
Child Characteristics				
Year of birth				
1980–1984	83	(6.9)	415	(6.9)
1985–1989	202	(16.8)	1,010	(16.8)
1990–1994	373	(31.0)	1,865	(31.0)
1995–1999	363	(30.2)	1,815	(30.2)
2000–2003	182	(15.1)	910	(15.1)
Gender				
Male	768	(63.8)	3,058	(50.8)
Female	436	(36.2)	2,957	(49.2)
Race/ethnicity				
White	815	(75.0)	4,427	(78.9)
Black	121	(11.0)	290	(5.2)
Asian [†]	19	(1.7)	115	(2.1)
Hispanic	103	(9.4)	614	(10.9)
Other [‡]	44	(4.0)	167	(3.0)
Estimated gestational age (weeks)				
Mean ± SD	41 ± 10		40 ± 10	
<37 weeks	162	(13.5)	278	(4.6)
Birthweight (g)				
Mean ± SD	3,274 ± 917		3,448 ± 626	
<2,500	174	(14.5)	274	(4.6)
Maternal Characteristics				
Mother's age (years, mean ± SD)	28 ± 6		27 ± 6	
Mother's race/ethnicity				
White	870	(72.3)	5,490	(77.4)
Black	99	(8.2)	249	(3.5)
Asian [†]	75	(6.2)	431	(6.1)
Hispanic	83	(6.9)	581	(8.2)
Other [‡]	34	(2.8)	152	(2.1)
Ever smoked	460	(38.2)	2,131	(35.4)
Consumed alcohol during Pregnancy	24	(3.0)	95	(2.3)
Socioeconomic Indicators				
Household income median	456	(43.2)	2,413	(45.7)

* Frequencies and percentages may not sum to total due to missing data.

[†] Includes Chinese, Japanese, Filipino, Asian Indian, Korean, and Vietnamese.

[‡]Includes Native American, Hawaiian, Guamanian, Samoan, and other Non-White.

OSA = obstructive sleep apnea.

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TABLE III

Presence of Selected Congenital Anomalies in OSA Cases and Controls, Washington State, 1987–2003.

Congenital Anomaly*	OSA Cases (N = 1,203)		Controls (N = 6,015)		Crude		Adjusted	
	n	(%)	n	(%)	OR [†]	95% CI [‡]	OR ^{†,§}	95% CI [‡]
Any anomaly or malformation	327	(27.2)	241	(4.0)	8.9	[7.5, 10.7]	8.4	[7.0, 10.2]
Any craniofacial anomaly	186	(15.5)	22	(0.4)	49.9	[31.9, 78.0]	37.9	[23.9, 60.1]
Orofacial cleft	57	(4.7)	7	(0.1)	42.7	[19.4, 93.9]	39.7	[16.8, 93.9]
Down syndrome	74	(6.2)	5	(0.1)	79.0	[31.8, 196]	50.7	[20.1, 128]
Any noncraniofacial malformation	180	(15.0)	163	(2.7)	6.3	[5.1, 7.9]	4.1	[3.1, 5.3]
Heart/great vessel malformation	109	(8.1)	47	(0.8)	12.7	[8.9, 18.0]	7.7	[5.0, 11.7]
Muskuloskeletal malformation	53	(4.4)	62	(1.0)	4.4	[3.1, 6.4]	3.5	[2.3, 5.3]
Urogenital malformation	35	(2.9)	53	(0.9)	3.4	[2.2, 5.2]	2.3	[1.4, 3.7]

* Individuals may have more than one anomaly.

[†] Adjusted for year of birth (matching variable) only.

[‡] For any craniofacial anomaly and its subgroups, odds ratios were adjusted for year of birth, gender, race, birth weight, and presence of noncraniofacial malformation.

[§] For any noncraniofacial malformation and its subgroups, odds ratios were adjusted for year of birth, gender, race, birth weight, and presence of craniofacial anomaly.

OR = odds ratio; CI = confidence interval; OSA = obstructive sleep apnea.