Published in final edited form as:

Pediatr Pulmonol. 2017 December ; 52(12): 1583–1591. doi:10.1002/ppul.23769.

Sleep Disordered Breathing in Bronchopulmonary Dysplasia

Luis E. Ortiz, MD, Sharon A. McGrath-Morrow, MD, Laura M. Sterni, MD, and Joseph M. Collaco, MD, PhD

Johns Hopkins Medical Institutions, Baltimore, Maryland

Abstract

BACKGROUND—There are limited data on the effect of bronchopulmonary dysplasia (BPD) on sleep disordered breathing (SDB). We hypothesized that both the severity of prematurity and BPD would increase the likelihood of SDB in early childhood. Our secondary aim was to evaluate the association of demographic factors on the development of SDB.

METHODS—This is a retrospective study of patient factors and overnight polysomnogram (PSG) data of children enrolled in our BPD registry between 2008 and 2015. Association between PSG results and studied variables was assessed using multiple linear regression analysis.

RESULTS—One-hundred-forty children underwent at least one sleep study on room air. The mean respiratory disturbance index (RDI) was elevated at 9.9 events/hr (SD: 10.1). The mean obstructive apnea-hypopnea index (OAHI) was 6.5 (9.1) events/hr and the mean central event rate of 3.0 (3.7) events/hr. RDI had decreased by 22% or 1.5 events/hour (95% CI: 0.6, 1.9) with each year of age ($p=0.005$). Subjects with more severe respiratory disease had 38% more central events ($p=0.02$). Infants exposed to secondhand smoke had 2.4% lower ($p=0.04$) oxygen saturation nadirs and a pattern for more desaturation events. Non-white subjects were found to have 33% higher OAHI ($p=0.05$), while white subjects had a 61% higher rate of central events ($p<0.001$).

CONCLUSIONS—RDI was elevated in a selected BPD population compared to norms for non-preterm children. BPD severity, smoke exposure, and race may augment the severity of SDB. RDI improved with age but was still elevated by age 4, suggesting that this population is at risk for the sequelae of SDB.

Keywords

Sleep Apnea Syndromes; premature infants; sleep; polysomnogram

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that occurs most commonly in very premature infants and is characterized by chronic respiratory symptoms beyond 36 weeks corrected gestational age^{1,2}. BPD affects 12% of preterm infants or 10–15,000 births

Address correspondence to: Joseph M. Collaco, Eudowood Division of Pediatric Respiratory Sciences, 200 N. Wolfe Street, Baltimore MD, 21287, [mcollac1@jhmi.edu], 410-955-2035.

Financial Disclosure: All authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: All authors have indicated they have no potential conflicts of interest to disclose.

in the United States annually^{3,4}. BPD can be described as alveolar hypoplasia due to prematurity resulting in impaired lung function and frequent need for supplemental oxygen and respiratory support. BPD complicates postnatal development by being an independent risk factor for neurocognitive delays^{1,5–8}.

Children born prematurely are at risk for sleep disordered breathing (SDB). In addition to immature control of breathing^{9–11}, premature neonates are predisposed to upper airway obstruction due to decreased upper airway muscle tone, a smaller caliber upper airway that allows for easier collapse, and increased compliance of the chest wall^{12,13}. While this SDB is expected to resolve within the first days to weeks of life¹¹, prior work has shown that the risk for airway obstruction and/or obstructive sleep apnea syndrome (OSAS) due to prematurity persists from childhood through adulthood^{12,14–21}. The Cleveland Children's Sleep and Health Study and other studies have shown that factors such as smoke exposure, socioeconomic status, and race can also affect the development of SDB^{9,17,22–26}. This is concerning as SDB in childhood, like BPD, is associated with behavioral and developmental abnormalities, pulmonary hypertension, and failure to thrive^{27–33}.

There are limited data on the prevalence of SDB in children with a history of BPD. Studies evaluating polysomnograms (PSGs) performed on infants with BPD have found a higher rate of respiratory events compared to non-BPD infants^{34–37}. During sleep, there is a reduction in airway muscle activity and ventilatory effort. Stable breathing during sleep is achieved through chemoreceptors in the carotid body, which quickly depolarize due to hypoxia and hypercarbia. Activation of these receptors allows for an immediate and rapid rise in ventilation to compensate for hypoxemia.^{38,39} Abnormal ventilatory responses to hypoxic and hypercarbic challenges have been reported in animal models as well as in children and adults with a history of BPD.^{21,39–44} These changes in respiratory control are interconnected with abnormal carotid body development secondary to chronic hypoxemia or hyperoxia^{10,20,29,40,42,45–47}. Animal models have also shown that these changes are long lasting and thus may increase the risk of SDB in this vulnerable population.

The primary objective of this study was to evaluate the association of prematurity and BPD on the development of SDB in early childhood after initial hospital discharge. We hypothesized that both the severity of prematurity and BPD would increase the likelihood of SDB beyond the neonatal period. Our secondary aim was to evaluate the association of demographic factors on the development of SDB in this population. To this end, we performed a retrospective analysis of PSGs from a cohort of stable preterm infants/children with BPD who were referred for overnight PSGs to assess supplemental oxygen needs and to evaluate for the presence of SDB.

PATENTS AND METHODS

Study Population

Patients referred to the Johns Hopkins Pediatric Pulmonary clinic were recruited into a bronchopulmonary dysplasia registry between January 2008 and August 2015. Patients 3 years and younger at the first visit were included in the registry if they were born at <36 weeks gestational age and had a diagnosis of BPD at NICU discharge or by the staffing

pediatric pulmonologist based on NIH criteria of treatment with oxygen > 21% for least 28 days. A subset of this population has been previously studied in McGrath, et al.³⁵. Subjects in the BPD registry were excluded from analysis if no sleep study was performed, their gestational age was < 32 weeks, they suffered from a genetic disorder, had cyanotic heart disease, have or had a tracheostomy, had a neurologic disorder not secondary to prematurity, or if their sleep studies were done beyond the age of 4 years. As oxygen therapy can improve measures of sleep disordered breathing, subjects were also excluded if their sleep studies were done while on supplemental oxygen. This study was approved by the Institutional Review Board of Johns Hopkins University (NA: 00051884).

Data Collection

Clinical data including duration of oxygen use, amount of oxygen, gestational age, birth weight, and presence of ventricular shunts were ascertained through chart review. Demographic data including the presence of a smoker residing in the home and race/ethnicity were ascertained through questionnaires. Birth weight percentile by gestational age was derived from U.S. norms⁴⁸. Tobacco exposure was ascertained by survey during recruitment into BPD registry. Median household income by residential zip code was ascertained from 2010 census data (www.census.gov).

Polysomnographic Data

Sleep studies were performed for clinical indications between January 2005 and November 2015. Indications included suspicion of OSAS or evaluation for sleep-related hypoxemia off oxygen in an infant weaning from oxygen support. Referral for sleep study for oxygen weaning was dependent on ability to wean off oxygen during the day. For polysomnography, physiologic signals that were recorded included electroencephalograms (C3-A2, C4-A1, O1-A2), left and right electrooculograms, submental and tibial electromyograms, and electrocardiogram (ECG modified V2 lead). Respiratory effort in studies prior to 2008 was measured using thoracic and abdominal piezoelectric crystal effort belts (Respironics, Murrysville, PA). Respiratory inductance plethysmography (Embla, Broomfield, CO or DyMedix, Shoreview, MN) was used for studies after 2008. Oxyhemoglobin saturation was measured via pulse oximetry (Novametrics, Marietta, GA or Natus, Pleasanton, CA) and end-tidal pCO₂ (ETCO₂) was measured at the nose by infrared capnometry (Novametrics or Smiths Medical, London, UK). Nasal air-flow was acquired with a nasal cannula (Salter Labs, Arvin, CA or Respironics, Murrysville, PA) connected to a differential pressure transducer (Pro-Tech, Mukilteo, WA), and oronasal airflow was acquired with thermistor (ProTech, Phillips Respironics). Recording systems were either Alice 3 (Healthdyne, Marietta, GA), Somnologica Studio (Medcare Flaga, Reykjavik), or RemLogic (Embla Systems, LLC, Ontario, Canada). Sleep staging and respiratory events were scored according to the AASM criteria at the time the study was done^{49–51}.

Outcome measures for the presence of sleep disordered breathing were defined as the oxygen nadir, peak ETCO₂ levels, and the number of respiratory events per hour. Chart review of the registry subjects was performed to obtain the respiratory disturbance event index (RDI), the obstructive apnea-hypopnea event index (OAH), the central apnea event index (CI), the nocturnal oxygen nadir, the peak ETCO₂ levels, and the oxygen desaturation

index (ODI) from PSG interpretation reports. RDI includes central, obstructive, and mixed apneas as well as hypopneas. Respiratory effort related arousals were not measured as part of our routine sleep studies. Raw PSG data, if available, was accessed to obtain data if measures were missing from the interpretation report.

Statistical Analyses

Analyses were conducted using STATA/IC 14.1 (StataCorp LP, College Station, TX). Excluded and included subjects were compared using two-sample t-tests, and chi-square analysis as appropriate. Owing to non-normal distributions, values for the respiratory event rates (RDI, OAH, CI, ODI) were normalized by log transformation of their value plus 1. Simple linear regression was first done to identify potential significant variables and confounders of SDB. Following this, gestational age, chronologic age, gender, race, smoke exposure status, ventricular shunt status, and need for oxygen at the first pulmonary visit were retained for regression models. Multiple linear regression analysis was performed, controlling for gestational age and chronologic age, to describe association between PSG results and variables studied. Regression models were plotted controlling for gestational age set at the geometric mean. Mean values reported in the text were calculated via integration methods.

RESULTS

Demographics

Of the 582 children enrolled in the BPD registry, 140 met inclusion criteria (Figure 1). Clinical features of the study population (n=140) and the excluded group (n=442) are summarized in Table 1. Included subjects were born at earlier gestational ages (26.3 vs. 27.3 weeks; $p<0.001$), weighed less at birth (856 vs. 1026 grams; $p<0.001$), and more likely to be on supplemental oxygen at their first pulmonary clinic visit (70.7% vs. 24.9%; $p<0.001$) than excluded subjects. No differences were observed by sex, race/ethnicity, birth weight percentile, presence of ventricular shunts, the presence of a smoker within the home, or median household income between included and excluded subjects. Of note, 24.3% of study population subjects resided with a smoker.

Polysomnographic Data

Within the study population, the mean (sd) chronologic age at the time of the first sleep study off supplemental oxygen was 1.3 (0.9) years (Table 2). Of the 140 subjects within the study population, 100 (71.4%) were on oxygen at the first pulmonary visit, which decreased to 82 (58.4%) at the time of the sleep study. For these 100 subjects the median duration of oxygen after initial hospital discharge was 240 days (intraquartile range= 216 days).

Most subjects were referred for PSG to determine their readiness to wean from supplemental oxygen (50%) or for evaluation of suspected OSA (40.7%). The remaining subjects were referred for evaluation of suspected central apnea (7.1%) or nocturnal hypoxemia or hypercarbia without concerns for obstructive or central events (2.1%). The mean oxygen saturation nadir during sleep studies was 86.4% (6.0). The mean ETCO_2 peak was 50.7 (5.1) mmHg in the 136 subjects where data were available. The median RDI was elevated at 7.2

events per hour [Range: 0–50.1]; a majority of subjects had an RDI greater than 2 events per hour (82%). Obstructive events comprised the majority of events, with the median OAHl being 3.0 events per hour [range: 0, 47.2] and the median central event index being 1.7 events per hour [range: 0, 24.2]. For the 128 subjects where data were available, the median ODI was 5.5 events per hour [range: 0–56.9]. Specific regression coefficients for selected variables can be found in Supplemental Table 1.

Gestational Age, Chronologic Age, and Severity of Disease

Increasing chronologic age was associated with improvement in RDI and central events by multiple linear regression analysis. RDI decreased by 22% or 1.5 events/hr (95% CI: 0.6, 1.9) for each year of chronologic age ($p=0.005$; Figure 2). Central events also decreased by 29% or on average 1.1 events/hr (95% CI: 0.9, 1.3) with each advancing year ($p<0.001$). There was no significant association with age in regard to obstructive events ($p=0.29$). Increasing age was also associated with higher oxygen saturation nadirs, increasing by 1.5% with every year of age ($p=0.008$). Similarly, there was a non-significant pattern of decreasing ODI by 15% with every year of chronologic age or 0.1 events/hr (95% CI: 0, 0.2; $p=0.09$). There was no significant correlation between maximum ETCO_2 measurement and chronologic age.

Subjects with more severe respiratory disease, as determined by still being on oxygen at the first pulmonary outpatient visit, had 38% more central events compared to subjects who were discharged off oxygen or weaned off supplemental oxygen between discharge and the first visit ($p=0.02$), corresponding to 0.8 (95% CI: 0.1, 1.7) more events per hour. There was no significant correlation between gestational age or birth weight percentile and sleep study measures. Ventricular shunt status was not correlated with an increased rate of respiratory events during sleep.

Sex & Race/Ethnicity

Male children had higher RDIs compared to females, or 1.7 more events per hour (32% increase), but this did not reach significance ($p=0.09$). There were no other significant associations between sex and PSG measures. Multiple linear regression modeling showed no significant differences in RDI between white and non-white subjects ($p=0.80$; Figure 3A). However, when broken down into its central and obstructive components significant differences between white and non-white subjects were found (Figure 3B). Individuals identifying as non-white were found to have 33% higher rate of obstructive events, whereas white subjects had a 61% higher rate of central events.

Household Income & Smoke Exposure

Smoke exposed infants by caregiver report, had worse nocturnal oxygen saturations, regardless of age. Smoke exposed infants had an average nadir that was 2.4% ($p=0.03$) lower than their non-smoke exposed peers. (Figure 4). No significant correlation was found between household income and PSG results. No association was found between smoke exposure status and respiratory events.

DISCUSSION

SDB has been increasingly associated with multiple sequelae in childhood such as developmental delay, failure to thrive, and pulmonary hypertension. Children with BPD are an already at risk population as BPD has been shown to be independently associated with higher rates of hospital readmissions, pulmonary morbidity, and neurocognitive delays^{1,7,8,27}. In this study we reviewed PSGs performed on children with BPD, referred for oxygen titration or evaluation for SDB. We found that our subjects had an elevated RDI that improved with age, but was still elevated by four years of age compared to general population norms. Non-white children were also found to have significantly more obstructive events. Children exposed to secondhand smoke by caregiver report had significantly lower oxygen nadirs on PSG. These findings indicate that infants and children with BPD are at an increased risk for SDB after initial hospital discharge.

Using cross-sectional data we found an association between age and RDI, with improvement in RDI with increasing age, which is consistent with our prior work which did use longitudinal data of a subset of subjects from the same database.³⁵ Improvement in RDI with age may be due to a maturation in control of breathing, growth of the upper airway, and post-natal alveolar development resulting in better pulmonary reserve. The frequency of oxygen desaturations with respiratory pauses and central apneas should improve in preterm children who have adequate postnatal alveolar growth during the first two years of life. Nevertheless, the average RDI by four years of age was still above normal reported values^{52,53}, averaging over 2 events per hour. This pattern of improvement, but lack of normalization is consistent with prior literature of persistent airway obstruction in former preterm infants from early childhood to adulthood^{17,19,36,37,54,55}. We did not find an association for gestational age ($p=0.49$). However, we excluded the subjects with very severe BPD who required ongoing ventilation or supplemental oxygen. Exclusion of this group of patients may have prevented the detection of an association with gestational age.

Infants with more severe BPD, as determined by need for supplemental oxygen at their first pulmonary visit, were found to have more central events by routine scoring rules. Children with BPD may have decreased pulmonary reserve due to anomalies of the pulmonary vasculature and impaired alveolar growth. In these children, brief respiratory pauses during sleep may result in significant oxygen desaturations and thus increasing the number of central apneas during a PSG. The increase in central apnea events may also represent disrupted control of breathing secondary to altered chemosensitivity.

Non-white subjects were found to have an increased rate of obstructive events compared to white subjects, which is consistent with prior studies^{24,56,57}. It is worthwhile to note that this difference can be found even at such a young age. In contrast, we found that central events were higher in white subjects suggesting that white infants with BPD may have more significant alveolar hypoplasia and decreased pulmonary reserve than non-white infants with BPD at the time of their PSG. As mentioned before, we found an association between more severe BPD and higher number of central events. Studies describing long term pulmonary outcomes of premature infants with BPD have not found racial differences, however there is little data describing the effect of race on SDB in preterm infants with BPD^{58–60}. Racial

variations in control of breathing, thoracic cavity mechanics, and upper airway anatomy may contribute to these observed racial differences in both obstructive and central events^{22,24,56,57,61}. Unlike obstructive events, it is unknown whether these brief central events affect health outcomes.

While the literature suggests that smoke exposure can result in an increased rate of airway obstruction due to upper airway inflammation and alteration in control of breathing due to smoke inhalation and chronic nicotinic receptor activation, we did not observe this^{9,23,62}. We did however find that smoke exposed infants had lower oxygen nadirs and a trend for increased rates of desaturation. The mean difference in oxygen nadirs is of sufficient magnitude to potentially influence clinical decisions regarding whether a child is ready to wean from supplemental oxygen.

Our study has several limitations. Most notably, there is a strong selection bias towards subjects with a clinical indication for a sleep study which increases the likelihood of finding an abnormal result on PSG. Tobacco exposure data was obtained from survey data, which may underestimate the true smoke exposure rate. Finally, the absence of non-BPD premature infant control data limits our ability to determine whether our observations represent the effects of BPD versus the effects of prematurity. Future research could include a prospective cohort of term, non-BPD preterm, and BPD infants with evaluation of PSGs at set periods to further describe the changes in sleep disordered breathing in this population and how BPD discretely affects it.

CONCLUSION

In conclusion, we found that preterm children with BPD have a higher rate of SDB when compared to non-BPD non-premature populations^{52,63}. While SDB improved with age, we found that standard SDB metrics by PSG were still abnormal in children with BPD when studied at four years of age. Severity of BPD, smoke exposure, and race modified the severity of SDB. Taken together, our findings suggest that BPD can be a risk factor for SDB in infants and young children. In the context of worse neurocognitive outcomes in both SDB and BPD patients,^{6,8,27,29,32,33,64} this may warrant closer follow up of BPD infants after initial discharge from the hospital with regular screening for SDB in the office and a low threshold to pursue polysomnography, even if they have been successfully weaned from oxygen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: Dr. Ortiz is supported by a T32 grant funded by the National Institutes of Health (NIH). No external funding for this manuscript.

The authors wish to thank the families who participated in the Johns Hopkins Pediatric Pulmonary Registry. Dr. Ortiz received support from the National Institutes of Health under the Ruth L. Kirschstein National Research Service Award (4T32HL072748-14) through the National Heart, Lung, and Blood Institute.

References

1. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, Wraage LA, Poole K. National Institutes of Child H, Human Development Neonatal Research N. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics*. 2005; 116(6):1353–60. [PubMed: 16322158]
2. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001; 163(7): 1723–1729. [PubMed: 11401896]
3. Van Marter LJ. Epidemiology of bronchopulmonary dysplasia. *Semin Fetal Neonatal Med*. 2009; 14(6):358–66. [PubMed: 19783238]
4. Smith VC, Zupancic JAF, McCormick MC, Croen LA, Greene J, Escobar GJ, Richardson DK. Trends in severe bronchopulmonary dysplasia rates between 1994 and 2002. *Journal of Pediatrics*. 2005; 146(4):469–473. [PubMed: 15812448]
5. Grisaru-Granovsky S, Reichman B, Lerner-Geva L, Boyko V, Hammerman C, Samueloff A, Schimmel MS, Israel Neonatal N. Population-based trends in mortality and neonatal morbidities among singleton, very preterm, very low birth weight infants over 16 years. *Early Hum Dev*. 2014; 90(12):821–7. [PubMed: 25463827]
6. Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kercsmar C, Baley J, Singer LT. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. *Pediatrics*. 2003; 112(5):E359–E366. [PubMed: 14595077]
7. Jensen EA, Schmidt B. Epidemiology of bronchopulmonary dysplasia. *Birth Defects Res A Clin Mol Teratol*. 2014; 100(3):145–57. [PubMed: 24639412]
8. Singer LT, Siegel AC, Lewis B, Hawkins S, Yamashita T, Baley J. Preschool language outcomes of children with history of bronchopulmonary dysplasia and very low birth weight. *Journal of Developmental and Behavioral Pediatrics*. 2001; 22(1):19–26. [PubMed: 11265919]
9. Gauda EB, McLemore GL, Tolosa J, Marston-Nelson J, Kwak D. Maturation of peripheral arterial chemoreceptors in relation to neonatal apnoea. *Semin Neonatol*. 2004; 9(3):181–94. [PubMed: 15050211]
10. Abu-Shaweesh JM. Maturation of respiratory reflex responses in the fetus and neonate. *Semin Neonatol*. 2004; 9(3):169–80. [PubMed: 15050210]
11. Hoppenbrouwers T, Hodgman JE, Harper RM, Hofmann E, Serman MB, McGinty DJ. Polygraphic studies of normal infants during the first six months of life: III. Incidence of apnea and periodic breathing *Pediatrics*. 1977; 60(4):418–25. [PubMed: 905004]
12. Arens R, Marcus CL. Pathophysiology of upper airway obstruction: a developmental perspective. *Sleep*. 2004; 27(5):997–1019. [PubMed: 15453561]
13. Milner AD, Greenough A. The role of the upper airway in neonatal apnoea. *Semin Neonatol*. 2004; 9(3):213–9. [PubMed: 15050214]
14. Dransfield DA, Spitzer AR, Fox WW. Episodic airway obstruction in premature infants. *American journal of diseases of children*. 1983; 137(5):441–443. [PubMed: 6846271]
15. Huang YS, Paiva T, Hsu JF, Kuo MC, Guilleminault C. Sleep and breathing in premature infants at 6 months post-natal age. *Bmc Pediatrics*. 2014;14.
16. Montgomery-Downs HE, Gozal D. Sleep habits and risk factors for sleep-disordered breathing in infants and young toddlers in Louisville, Kentucky. *Sleep Med*. 2006; 7(3):211–9. [PubMed: 16564742]
17. Rosen CL, Larkin EK, Kirchner HL, Emancipator JL, Bivins SF, Surovec SA, Martin RJ, Redline S. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. *J Pediatr*. 2003; 142(4):383–9. [PubMed: 12712055]
18. Qubty WF, Mrelashvili A, Kotagal S, Lloyd RM. Comorbidities in infants with obstructive sleep apnea. *J Clin Sleep Med*. 2014; 10(11):1213–6. [PubMed: 25325583]
19. Paavonen EJ, Strang-Karlsson S, Räikkönen K, Heinonen K, Pesonen A-K, Hovi P, Andersson S, Järvenpää A-L, Eriksson JG, Kajantie E. Very Low Birth Weight Increases Risk for Sleep-Disordered Breathing in Young Adulthood: The Helsinki Study of Very Low Birth Weight Adults. *Pediatrics*. 2007; 120(4):778–784. [PubMed: 17908765]

20. Wong-Riley MT, Liu Q, Gao XP. Peripheral-central chemoreceptor interaction and the significance of a critical period in the development of respiratory control. *Respir Physiol Neurobiol*. 2013; 185(1):156–69. [PubMed: 22684042]
21. Beshish A, Bates ML, Farrell ET, Pegelow DF, Eldridge MW. Blunted hypoxic ventilatory drive in adult humans with a history of premature birth. *The FASEB Journal*. 2012; 26:1090.11. 1_MeetingAbstracts.
22. Hibbs AM, Johnson NL, Rosen CL, Kirchner HL, Martin R, Storfer-Isser A, Redline S. Prenatal and neonatal risk factors for sleep disordered breathing in school-aged children born preterm. *J Pediatr*. 2008; 153(2):176–82. [PubMed: 18534222]
23. Johansson A, Ludvigsson J, Hermansson G. Adverse health effects related to tobacco smoke exposure in a cohort of three-year olds. *Acta Paediatr*. 2008; 97(3):354–7. [PubMed: 18241297]
24. Calhoun S, Vgontzas AN, Mayes SD, Tsaousoglou BS, Sauder K, Mahr F, Karippot A, Wisner K, Bixler EO. Prenatal and Perinatal Complications: Is It the Link Between Race and SES and Childhood Sleep Disordered Breathing? *J Clin Sleep Med*. 2010; 6(3):264–269. [PubMed: 20572420]
25. Marcus CL. The toll of poverty: no respite even in sleep. *J Pediatr*. 2006; 149(3):293–4. [PubMed: 16939735]
26. Spilsbury JC, Storfer-Isser A, Kirchner HL, Nelson L, Rosen CL, Drotar D, Redline S. Neighborhood disadvantage as a risk factor for pediatric obstructive sleep apnea. *J Pediatr*. 2006; 149(3):342–7. [PubMed: 16939744]
27. Hunter SJ, Gozal D, Smith DL, Philby MF, Kaylegian J, Kheirandish-Gozal L. Effect of Sleep-disordered Breathing Severity on Cognitive Performance Measures in a Large Community Cohort of Young School-aged Children. *Am J Respir Crit Care Med*. 2016; 194(6):739–47. [PubMed: 26930303]
28. Bonuck K, Parikh S, Bassila M. Growth failure and sleep disordered breathing: a review of the literature. *Int J Pediatr Otorhinolaryngol*. 2006; 70(5):769–78. [PubMed: 16460816]
29. Karpinski AC, Scullin MH, Montgomery-Downs HE. Risk for sleep-disordered breathing and executive function in preschoolers. *Sleep Med*. 2008; 9(4):418–24. [PubMed: 17689143]
30. Lind MG, Lundell BP. Tonsillar hyperplasia in children. A cause of obstructive sleep apneas, CO₂ retention, and retarded growth. *Arch Otolaryngol*. 1982; 108(10):650–4. [PubMed: 6812557]
31. Marcus CL. Sleep-disordered breathing in children. *Am J Respir Crit Care Med*. 2001; 164(1):16–30. [PubMed: 11435234]
32. Zhang XM, Shi J, Meng GZ, Chen HS, Zhang LN, Wang ZY, Wu H. The effect of obstructive sleep apnea syndrome on growth and development in nonobese children: a parallel study of twins. *J Pediatr*. 2015; 166(3):646–50. e1. [PubMed: 25722268]
33. Emancipator JL, Storfer-Isser A, Taylor H, et al. Variation of cognition and achievement with sleep-disordered breathing in full-term and preterm children. *Archives of Pediatrics & Adolescent Medicine*. 2006; 160(2):203–210. [PubMed: 16461879]
34. Fajardo C, Alvarez J, Wong A, Kwiatkowski K, Rigatto H. The incidence of obstructive apneas in preterm infants with and without bronchopulmonary dysplasia. *Early Hum Dev*. 1993; 32(2–3):197–206. [PubMed: 8486121]
35. McGrath-Morrow SA, Ryan T, McGinley BM, Okelo SO, Sterni LM, Collaco JM. Polysomnography in preterm infants and children with chronic lung disease. *Pediatr Pulmonol*. 2012; 47(2):172–9. [PubMed: 21815283]
36. Sekar KC, Duke JC. Sleep-Apnea and Hypoxemia in Recently Weaned Premature-Infants with and without Bronchopulmonary Dysplasia. *Pediatric Pulmonology*. 1991; 10(2):112–116. [PubMed: 2030919]
37. Van Mastrigt E, Pichardo J, Reiss I, Kroon A, De Jongste J, Duijts L, Joosten K, Pijnenburg M. Polysomnography findings in infants with severe bronchopulmonary dysplasia (BPD). *European Respiratory Journal*. 2015; 46(suppl 59):PA2419.
38. Katz ES, Mitchell RB, D'Ambrosio CM. Obstructive sleep apnea in infants. *Am J Respir Crit Care Med*. 2012; 185(8):805–16. [PubMed: 22135346]

39. Katz-Salamon M, Jonsson B, Lagercrantz H. Blunted peripheral chemoreceptor response to hyperoxia in a group of infants with bronchopulmonary dysplasia. *Pediatr Pulmonol.* 1995; 20(2): 101–6. [PubMed: 8570299]
40. Di Fiore JM, Martin RJ, Gauda EB. Apnea of prematurity--perfect storm. *Respir Physiol Neurobiol.* 2013; 189(2):213–22. [PubMed: 23727228]
41. Calder N, Williams B, Smyth J. Absence of respiratory chemoreflex responses to mild hypoxia in infants who have suffered bronchopulmonary dysplasia. *Pediatr Res.* 1994; 35:677–681. [PubMed: 7936817]
42. Ling L, Olson EB Jr, Vidruk EH, Mitchell GS. Attenuation of the hypoxic ventilatory response in adult rats following one month of perinatal hyperoxia. *J Physiol.* 1996; 495(Pt 2):561–71. [PubMed: 8887766]
43. Coste F, Ferkol T, Hamvas A, Cleveland C, Linneman L, Hoffman J, Kemp J. Ventilatory control and supplemental oxygen in premature infants with apparent chronic lung disease. *Arch Dis Child Fetal Neonatal Ed.* 2015; 100(3):F233–7. [PubMed: 25716677]
44. Durand M, Cabal LA, Gonzalez F, Georgie S, Barberis C, Hoppenbrouwers T, Hodgman JE. Ventilatory control and carbon dioxide response in preterm infants with idiopathic apnea. *Am J Dis Child.* 1985; 139(7):717–20. [PubMed: 3925757]
45. MacFarlane PM, Ribeiro AP, Martin RJ. Carotid chemoreceptor development and neonatal apnea. *Respiratory physiology & neurobiology.* 2013; 185(1):170–176. [PubMed: 22842008]
46. Sterni LM, Bamford OS, Wasicko MJ, Carroll JL. Chronic hypoxia abolished the postnatal increase in carotid body type I cell sensitivity to hypoxia. *Am J Physiol.* 1999; 277(3 Pt 1):L645–52. [PubMed: 10484473]
47. Bamford OS, Sterni LM, Wasicko MJ, Montrose MH, Carroll JL. Postnatal maturation of carotid body and type I cell chemoreception in the rat. *Am J Physiol.* 1999; 276(5 Pt 1):L875–84. [PubMed: 10330044]
48. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr.* 2003; 3:6. [PubMed: 12848901]
49. Berry, RB., Brooks, R., Gamaldo, CE., Harding, SM., Lloyd, RM., Marcus, CL., Vaughn, BV. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.2. Darien, Illinois: American Academy of Sleep Medicine; 2015. <http://www.aasmnet.org>
50. Iber, C., Ancoli-Israel, S., LCA, Quan, SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
51. Berry, RB., Brooks, R., Gamaldo, CE., Harding, SM., Lloyd, RM., Marcus, CL., Vaughn, BV. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.0. Darien, Illinois: American Academy of Sleep Medicine; 2012. <http://www.aasmnet.org>
52. Traeger N, Schultz B, Pollock AN, Mason T, Marcus CL, Arens R. Polysomnographic values in children 2–9 years old: Additional data and review of the literature. *Pediatric Pulmonology.* 2005; 40(1):22–30. [PubMed: 15858805]
53. Montgomery-Downs HE, O'Brien LM, Gulliver TE, Gozal D. Polysomnographic characteristics in normal preschool and early school-aged children. *Pediatrics.* 2006; 117(3):741–53. [PubMed: 16510654]
54. Scher MS, Richardson GA, Salerno DG, Day NL, Guthrie RD. Sleep architecture and continuity measures of neonates with chronic lung disease. *Sleep.* 1992; 15(3):195–201. [PubMed: 1621019]
55. Sharma PB, Baroody F, Gozal D, Lester LA. Obstructive sleep apnea in the formerly preterm infant: an overlooked diagnosis. *Front Neurol.* 2011; 2:73. [PubMed: 22144976]
56. Chen X, Wang R, Zee P, Lutsey PL, Javaheri S, Alcantara C, Jackson CL, Williams MA, Redline S. Racial/Ethnic Differences in Sleep Disturbances: The Multi-Ethnic Study of Atherosclerosis (MESA). *Sleep.* 2015; 38(6):877–88. [PubMed: 25409106]

57. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. *Am J Respir Crit Care Med*. 1999; 159(5 Pt 1):1527–32. [PubMed: 10228121]
58. Singer L, Yamashita T, Lilien L, Collin M, Baley J. A longitudinal study of developmental outcome of infants with bronchopulmonary dysplasia and very low birth weight. *Pediatrics*. 1997; 100(6):987–993. [PubMed: 9374570]
59. Petrova A, Mehta R, Anwar M, Hiatt M, Hegyi T. Impact of race and ethnicity on the outcome of preterm infants below 32 weeks gestation. *J Perinatol*. 2003; 23(5):404–8. [PubMed: 12847537]
60. Cristea AI, Carroll AE, Davis SD, Swigonski NL, Ackerman VL. Outcomes of Children With Severe Bronchopulmonary Dysplasia Who Were Ventilator Dependent at Home. *Pediatrics*. 2013; 132(3):E727–E734. [PubMed: 23918888]
61. Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spry K. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. *Am J Respir Crit Care Med*. 1997; 155(1):186–92. [PubMed: 9001310]
62. Weinstock TG, Rosen CL, Marcus CL, Garetz S, Mitchell RB, Amin R, Paruthi S, Katz E, Arens R, Weng J, et al. Predictors of obstructive sleep apnea severity in adenotonsillectomy candidates. *Sleep*. 2014; 37(2):261–9. [PubMed: 24497655]
63. Sanchez I, Vega-Briceno L, Munoz C, Mobarec S, Brockman P, Mesa T, Harris P. Polysomnographic findings in 320 infants evaluated for apneic events. *Pediatr Pulmonol*. 2006; 41(3):215–21. [PubMed: 16429436]
64. Hunt CE. Neurocognitive outcomes in sleep-disordered breathing. *J Pediatr*. 2004; 145(4):430–2. [PubMed: 15480358]

Figure 1. Subject Selection Flow Diagram. Genetic and congenital disorders excluded from analysis (N=7) include: 15q13 Deletion, Achondroplasia, DiGeorge Syndrome, Myotonic Dystrophy, Ehlers-Danlos Syndrome, Trisomy 21, and an Unidentified Genetic Disorder

Figure 2.

RDI as a Function of Age. Each dot represents an individual subject's first sleep study done completely off of oxygen (N=140). Dashed line represents multiple linear regression model ($r=0.24$; $p=0.005$) controlling for the geometric mean for gestational age (26.2 weeks).

Figure 3.

Differences in Respiratory Events Between Caregiver-Identified Race. Lines represent regression models based on logarithmic transformation of respiratory events across age, controlling for gestational age and comparing between race. A: No significant difference in RDI between whites and non-whites ($p=0.80$). B: Whites have a significantly lower OAH ($r=0.23$, $p=0.05$) and higher CI ($r=0.52$, $p<0.001$) compared to non-whites.

Figure 4. Difference in Oxygen Nadir between Tobacco Exposure Status. Scatterplot showing distribution of nocturnal oxygen nadir across age amongst individual subjects' first study off oxygen (N=140). Lines represent regression analysis controlling for gestational age (geometric mean: 26.2 weeks), showing a difference between smoke exposed and unexposed children ($r=0.29$; $p=0.035$).

Table 1

Characteristics of Infants and Children in BPD Registry

Mean (SD) [Range]	BPD Registry (N = 582)	Study Population (N = 140)	Excluded Population (N = 442)	P value
Sex (% male)	60.7	67.1	58.6	0.07
Self-Identified Race (%)				
African-American	56.4	60.0	55.2	0.32
White	35.9	35.0	36.2	
Mixed/Other	7.7	5.0	8.6	
Gestational Age (weeks)	27.1 (2.9) [22.7, 36.0]	26.3 (2.1) [23.0, 31.9]	27.3 (3.1) [22.7, 36.0]	<0.001
Birth Weight (grams)	985 (479) [380, 3181] (N = 566)	856 (328) [390, 2069] (N = 136)	1026 (511) [380, 3181] (N = 430)	<0.001
Birth Weight Percentile (%)	40.1 (23.4) [1, 95] (N = 566)	38.2 (22.3) [1, 90] (N = 136)	40.7 (23.7) [1, 95] (N = 430)	0.27
Chronologic Age at First Pulmonary Visit (years)	0.65 (0.49) [0.07, 4.27]	0.58 (0.37) [0.16, 3.14]	0.67 (0.53) [0.07, 4.27]	0.07
On Supplemental Oxygen at First Visit (% yes)	35.9	71.4	24.9	<0.001
Shunt for Cerebrospinal Fluid (% yes)	8.6	11.4	7.7	0.17
Residing with a Smoker (% yes)	28.4 (N = 581)	24.3	29.7 (N = 441)	0.22
Estimated Median Household Income (\$'000s)	63.8 (22.0) [15.6, 156.6]	61.4 (22.0) [25.2, 156.6]	64.6 (22.00) [15.6, 139.3]	0.14

Table 2

Polysomnography Results (First study performed off of supplemental oxygen)

Mean/Median (SD) [Range]		Study Population (N=140)
Chronologic Age at First Pulmonary Visit (years)		0.6 (0.4) [0.2, 3.1]
Chronologic Age at Sleep Study (years)		1.3 (0.9) [0.2, 4.0]
Oxygen Status (% yes)	On oxygen at first clinic visit	71.4
	On oxygen prior to sleep study	58.6
Reason for Study (%)	Evaluation of oxygen requirement	50.0
	Evaluation for OSA	40.7
	Evaluation for CSA	2.1
	Evaluation for nocturnal hypoxia/hypercarbia	7.1
PSG Results	Oxygen saturation nadir, mean (%)	86.4 (6.0) [67.0, 97.0]
	Peak pCO ₂ , mean (mm Hg)	50.7 (5.1) [42, 68] (n=136)
	Respiratory Disturbance Index, median (events per hour)	7.2 [0, 50.1]
	OAHI, median (events per hour)	3.0 [0, 47.2]
	Central Apnea Index, median (events per hour)	1.7 [0, 24.2]
	Oxygen Desaturation Index, median (events per hour)	5.5 [0, 56.9] (n=128)