



Early inspired oxygen and intermittent hypoxemic events in extremely premature infants are associated with asthma medication use at 2 years of age

Juliann M. Di Fiore¹ · Andrew M. Dylag² · Ryan D. Honomichi³ · Anna Maria Hibbs¹ · Richard J. Martin¹ · Curtis Tatsuo³ · Thomas M. Raffay¹

Received: 29 June 2018 / Revised: 7 September 2018 / Accepted: 8 October 2018
© Springer Nature America, Inc. 2018

Abstract

Objective Extremely premature infants are at risk for childhood wheezing. Early respiratory support and intermittent hypoxemia (IH) events may be associated with adverse breathing outcomes.

Study design A single-center retrospective cohort study of 137 premature infants <28 weeks gestational age characterized the associations of cumulative oxygen, cumulative mean airway pressure, IH, and oxygen saturation (SpO₂) on the primary outcome of prescription asthma medication use at 2-year follow-up. Relative risk was calculated by generalized estimating equations.

Results Reported asthma medication use was 46%. At 1–3 days of age, elevated cumulative oxygen exposure, increased daily IH, and lower mean SpO₂ (adjusted for gestational age and sex) and increased cumulative mean airway pressure exposure (unadjusted) were associated with asthma medication use.

Conclusion Increased oxygen and frequent IH events during just the first 3 days of age may help identify extremely premature newborns at risk for symptomatic childhood wheezing requiring prescription asthma medications.

Introduction

Wheezing disorders and asthma-like symptoms are among the most common childhood pulmonary sequelae of premature birth. In the United States, one in twelve children is diagnosed with asthma [1] but in preterm infants childhood wheezing may be higher than one in three [2–4]. Extremely premature infants, <28 weeks gestational age (GA), display the highest risk of both childhood wheezing [2, 5] and obstructive lung disease [6, 7].

In preterm infants, an immature respiratory drive often leads to apnea or uncoordinated breathing [8, 9] with accompanying decreases in oxygen saturations (SpO₂) and

intermittent hypoxemic (IH) events [10, 11]. These IH events progressively increase during the first month of age [11, 12] and have been associated with multiple morbidities including retinopathy of prematurity [11, 13], neurodevelopmental impairment [13], septicemia [14], and mortality [13, 15].

Because of their immature lungs and high incidence of IH during early postnatal life, premature newborns often require supplemental oxygen and invasive or non-invasive positive pressure support. However, these life-saving neonatal interventions may themselves increase risk for future wheezing and abnormal spirometry [4, 6, 16, 17]. Therefore, we aimed to identify whether clinical markers of neonatal respiratory disease (inspired oxygen and mean airway pressure) and oxygen saturation levels (SpO₂ and IH) were associated with prescription asthma medication use and wheezing problems in early childhood.

✉ Thomas M. Raffay
tmr12@case.edu

¹ Division of Neonatology, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH, USA

² Division of Neonatology, Golisano Children's Hospital, University of Rochester, Rochester, NY, USA

³ Division of Neurology, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, OH, USA

Subjects and methods

Population

A retrospective cohort of 137 preterm infants (24 0/7 wks–27 6/7 wks GA) from 2005 to 2009 at Rainbow Babies &

Children's Hospital in Cleveland, Ohio were reviewed for birth, hospital, and respiratory follow-up data. All infants that completed a respiratory health questionnaire at their 2-year follow-up visit and had continuous oxygen saturation waveforms recorded through four weeks of age were included in the analysis.

Institutional IRB approval was obtained for the study which included a waiver of consent to collect continuous oxygen saturation waveforms from the bedside pulse oximeter during the initial hospital stay. Parents provided written consent prior to completing the respiratory questionnaire at the 2-year follow-up visit.

Data collection and analysis

Hospital charts were reviewed for birth history and hospital course. Daily levels of respiratory support with their associated mode, pressure, and fraction of inspired oxygen (FiO_2) were recorded from the respiratory flowsheets. Gestational age was calculated by the obstetrical estimated date of delivery. Severity of illness was calculated by Score for Neonatal Acute Physiology-Perinatal Extension-II (SNAPPE-II) at 24 h of life [18]. Sepsis was defined as culture-positive bacteremia or fungemia. Bronchopulmonary dysplasia was diagnosed by the National Institutes of Health (NIH) physiologic definition at 36 weeks post-menstrual age [19]. Severe intraventricular hemorrhage (IVH) was made by radiologic diagnosis of a Grade 3 or 4 IVH by head ultrasound during hospitalization. Necrotizing enterocolitis is reported as $\geq$ stage 2 by Bell's criteria [20]. Any breastmilk feeds were noted at discharge.

Oxygen exposure was recorded as the FiO_2 at the end of defined 6 h intervals (0000, 0600, 1200, and 1800 h) and the maximum level for that day. For infants on nasal cannula, effective FiO_2 was estimated using the previously published equations of the STOP-ROP trial to account for cannula flow and infant body weight [21]. A daily effective FiO_2 exposure was then calculated by the weighted mean of the effective FiO_2 time points (Eff_{0000} , Eff_{0600} , Eff_{1200} , and Eff_{1800}) with an adjustment for the maximum effective FiO_2 exposure (Eff_{max}) documented that day, as described by Stevens et al. [16]:

$$\text{Daily Effective } \text{FiO}_2 = [(22 \times (\text{Eff}_{0000} + \text{Eff}_{0600} + \text{Eff}_{1200} + \text{Eff}_{1800})/4)] \\ + (2 \times \text{Eff}_{\text{max}})]/24$$

Mean airway pressure (MAP) was recorded as the highest documented exposure for each day [16, 22]. MAP estimates of nasal cannula flow were calculated using the formulae published by Wilkinson et al. [23]. Cumulative effective FiO_2 and cumulative MAP exposures were then integrated over the first 3, 7, and 28 days of age and

presented as an area under the curve (AUC) [16, 22]:

$$\text{FiO}_{2\text{AUC}} = \text{Daily Effective } \text{FiO}_2(\%) \times \text{exposure duration(days)}$$

$$\text{MAP}_{\text{AUC}} = \text{Daily MAP(cm H}_2\text{O)} \times \text{exposure duration(days)}$$

Oxygen saturation (SpO_2) was continuously recorded over the first 4 weeks of age with a 2 s averaging time and 0.5 Hz sample rate (Radical; Masimo, Irvine, CA, USA). During this time period, SpO_2 targets were historically between 85 and 95%, and there was not a hospital policy to adjust targets before 4 weeks of postnatal age. Intermittent hypoxemia (IH) events were defined as an $\text{SpO}_2 \leq 80\%$ for ≥ 10 s and ≤ 180 s, as previously described [24].

The primary outcome, asthma medication, was operationalized as parental reported prescription asthma medication use in the last 6 months (rescue inhalers/nebulizers, inhaled or systemic steroids, and/or leukotriene antagonists) from respiratory questionnaires obtained at 2-year follow-up [25, 26]. Secondary outcomes from the respiratory questionnaire included, in the last 6 months (1) wheezing or whistling in the chest more than two times in a week; (2) visit to doctor, emergency room, or hospital due to wheezing or breathing problems; and (3) change in family plans due to child's breathing problems [27–29]. Environmental exposures to pets or tobacco smokers in the child's home were also noted at the 2-year follow-up visit.

Statistics

Twenty-three of the 137 cases were the result of multiple births (10 sets of twins and 1 set of triplets). Because of the correlated nature of these observations, generalized estimating equations (GEE) for Poisson regression models with a log link were used with same family exchangeable correlation (SAS PROC GENMOD; SAS Inc, Cary, NC). Using Poisson GEE regression, unadjusted estimated relative risks are reported in Tables 1, 2, and 3. Additionally, multivariate-adjusted relative risks were estimated after controlling for GA and sex. Two-sided Type I error level is 0.05 for the primary outcome related to asthma medication, and for the secondary outcomes.

Results

Characteristics of the study population are shown in Table 1. In this retrospective cohort study of extremely premature survivors, the overall reported use of prescription asthma medication at 2-year follow-up was 46%. Maternal

Table 1 Patient characteristics, oxygen therapy, and ventilation support

Mean (SD)	Population (N = 137)	Prescription asthma medication (N = 63)	No respiratory medications (N = 74)	Relative risk (95% confidence intervals)	p-value
Perinatal characteristics					
Gestational age (weeks completed)	26.2 (1.1)	26.1 (1.0)	26.3 (1.1)	0.92 (0.77, 1.09)	0.34
Birth weight (g)	839 (179)	836 (166)	840 (190)	0.82 (0.28, 2.37)	0.71
Multiple pregnancy	17%	13%	20%	0.75 (0.36, 1.56)	0.44
Female	49%	40%	57%	0.73 (0.53, 1.02)	0.07
Race (Black)	58%	63%	53%	1.31 (0.87, 1.96)	0.19
SNAPPE-II	38.9 (17.5)	41.3(18.6)	36.9 (16.3)	1.01 (1.00, 1.01)	0.23
Maternal asthma	7%	13%	1%	1.99 (1.44, 2.75)	0.0001
Hospitalization characteristics					
Duration of hospitalization (days)	97 (36)	97(28)	97 (41)	1.00 (1.00, 1.01)	0.90
Sepsis	24%	22%	26%	0.90 (0.63, 1.29)	0.57
Bronchopulmonary dysplasia	34%	43%	27%	1.59 (1.09, 2.31)	0.02
Intraventricular hemorrhage (Grade 3 or 4)	8%	8%	8%	0.85 (0.39, 1.85)	0.69
Necrotizing enterocolitis	9%	10%	9%	0.98 (0.53, 1.82)	0.95
Hospitalization respiratory exposures					
Duration of supplemental oxygen (days)	61 (45)	64(41)	58 (49)	1.00 (1.00, 1.01)	0.33
Duration of positive pressure (days)	69 (41)	71(36)	67 (45)	1.00 (1.00, 1.01)	0.38
Mechanical ventilation	19 (20)	20(19)	18 (21)	1.00 (0.94, 1.01)	0.41
Nasal CPAP/BiPhasic	27 (13)	27(13)	27 (13)	0.98 (0.63, 1.08)	0.95
Nasal Cannula	23 (22)	25(18)	21 (25)	1.01 (1.00, 1.01)	0.20
Post-discharge characteristics					
Breastmilk at discharge	27%	24%	30%	0.89 (0.59, 1.34)	0.32
Pets in home	39%	35%	42%	0.85 (0.57, 1.27)	0.42
Tobacco exposure in home	37%	37%	38%	0.95 (0.65, 1.40)	0.81

Mean (with standard deviation) or percentage of population by perinatal characteristics, hospitalization characteristics, and respiratory exposures through hospital discharge and in home. Relative risk (95% confidence intervals) and *p*-values reported for variable's association with reported prescription asthma medication use within the past 6 months of child's 2-year follow-up visit by generalized estimating equations for Poisson regression models with clustering of twins or triplets within one mother. SNAPPE-II (Score for Neonatal Acute Physiology-Perinatal Extension-II)

asthma was significantly increased among the group of children who had received asthma medication compared to those who had not. Bronchopulmonary dysplasia (BPD), defined as need for supplemental oxygen or positive pressure at 36 weeks postmenstrual age, was also positively associated with asthma medication use at 2-year follow-up. Other patient characteristics did not significantly differ. Durations of hospitalization, days of supplemental oxygen, days of both invasive and noninvasive positive pressure, breastmilk feeds at discharge, pets in home, and exposure to tobacco smoke were not significantly different between groups.

Early neonatal respiratory exposures ($\text{FiO}_{2\text{AUC}}$ and MAP_{AUC}) and saturation parameters (daily IH and mean SpO_2) were associated with childhood respiratory outcomes reported on the health questionnaire (Tables 2 and 3).

During the first 3 and 7 days of age, infants that had received childhood asthma medications were exposed to higher cumulative oxygen ($\text{FiO}_{2\text{AUC}}$), received greater cumulative mean airway pressure (MAP_{AUC}), had more frequent IH events, and a lower mean SpO_2 . When adjusted for GA and sex, $\text{FiO}_{2\text{AUC}}$, IH events, and mean SpO_2 remained significantly different between groups; MAP_{AUC} was no longer statistically significant after adjustment. At 4 weeks of age, respiratory exposures and saturation parameters were no longer significantly different between groups.

Secondary outcomes from the respiratory health questionnaire also revealed associations with early neonatal respiratory exposures and saturation parameters (Table 3). Parental reports of wheezing or whistling in the chest of their child >2 days/week in the last 6 months (31% of

Table 2 Respiratory parameters and prescription asthma medication

In last 6 months, any prescription asthma medication used											
Mean (SD)	Days 1–3		RR (95% CI)	p	Adjusted RR (95% CI)	p	RR (95% CI)	p	Days 1–7		Adjusted RR (95% CI)
	Yes	No							Yes	No	
FiO _{2AUC} (% × day)	96.4 (31.1)	87.7 (21.6)	1.01 (1.001, 1.01)	.02	1.01 (1.0003, 1.01)	.04	1.004 (1.001, 1.01)	.009	202.5 (50.2)	186.4 (33.9)	1.004 (1.001, 1.01)
MAP _{AUC} (cm H ₂ O × day)	19.7 (5.7)	18.0 (4.1)	1.03 (1.01, 1.06)	.02	1.03 (0.99, 1.06)	.052	1.01 (0.99, 1.02)	.04	42.9 (16.7)	38.3 (12.9)	1.01 (1.0004, 1.02)
Intermittent Hypoxemia (per day)	33 (33)	21 (17)	1.01 (1.004, 1.01)	.0002	1.01 (1.004, 1.01)	<.0001	1.01 (1.01, 1.02)	<.0001	31 (24)	21 (15)	1.01 (1.01, 1.02)
Mean SpO ₂ (%)	93.5 (2.5)	94.5 (2.2)	0.92 (0.87, 0.98)	.005	0.93 (0.88, 0.98)	.005	0.91 (0.85, 0.98)	.01	93.7 (2.3)	94.5 (1.9)	0.91 (0.86, 0.99)

Mean (standard deviation) of cumulative inspired oxygen exposure (FiO_{2AUC}), cumulative mean airway pressure (MAP_{AUC}), intermittent hypoxemia events per day, and mean oxygen saturation (SpO₂) at Days 1–3, 1–7, and 1–28 of postnatal age. Relative risk (95% confidence intervals) and *p*-values reported for variable's association with reported prescription asthma medication (Yes) or no respiratory medications (No) within the past 6 months of child's 2-year follow-up visit by generalized estimating equations (GEE) for Poisson regression models with clustering of twins or triplets within one mother. Adjusted for gestational age (weeks completed) and sex. GEE iteration limit exceeded for adjusted RR of Days 1–28 cumulative oxygen exposure and asthma medication outcome

cohort) were associated with increased IH events during the first 3 and 7 days of age. FiO_{2AUC} during the first 4 weeks of age was increased in children identified as wheezing by their parents, but the correlation was no longer significant when adjusted for GA and sex. Forty-four percent of parents reported doctor, emergency room, and/or hospital visits due to wheezing or breathing problems in their child in the past 6 months. Reported health care visits for wheezing or breathing problems were associated with increased IH events during the first 3 and 7 days of age after adjustment for GA and sex. Finally, 16% of parents reported needing to change family plans due to their child's breathing problems during the previous 6 months. When adjusted for GA and sex, this was associated with increased FiO_{2AUC} during the first 3 days of age, increased IH events and lower SpO₂ during the first 7 days of age, and a higher average SpO₂ at 4 weeks of age.

Discussion

Childhood wheezing is a substantial long-term respiratory sequelae in former preterm infants. This study maintains that symptomatic wheezing continues to be a major problem facing children born prematurely, with nearly half of our cohort receiving prescription asthma medications at 2 years of age. We observed that an increased relative risk of asthma medication use was associated with elevated inspired oxygen and early postnatal patterns of oxygenation, including a higher number of daily intermittent hypoxemia events and a lower mean SpO₂ during the first 3 and 7 days of age.

It has been well documented that premature infants are at increased risk for developing wheezing disorders during childhood, with more premature infants showing the greatest childhood risk [2, 3, 30]. Previous studies have suggested causal pathway models encompassing genetic and environmental factors and preterm birth [17, 31–33]. While often diagnosed and treated as asthmatics, the wheezing of premature infants may be unique in that patients often display less pronounced airway reversibility, less atopy/allergy, with decreased inflammation and exhaled nitric oxide than childhood asthmatics [34].

Childhood wheezing disorders in these preterm infants have traditionally been associated with prolonged courses of supplemental oxygen and/or mechanical ventilation and the diagnosis of BPD [4, 17]. Yet, Doyle et al. has reported that measurements of childhood airflow obstruction have increased in recent preterm cohorts despite less invasive ventilation and consistent monitoring by pulse oximetry [6]. In this

Table 3 Respiratory parameters and secondary respiratory health outcomes

In last 6 months, wheezing or whistling in the chest >2 days/week																		
Mean (SD)	Days 1–3		RR (95% CI)	p	Adjusted RR (95% CI)	Days 1–7		RR (95% CI)	p	Adjusted RR (95% CI)	Days 1–28		RR (95% CI)	p	Adjusted RR (95% CI)			
	Yes	No				Yes	No				Yes	No						
FI _{O2} AUC (% × day)	96.0 (33.1)	89.8 (23.2)	1.01 (1.00,1.01)	.13	1.01 (1.00,1.01)	.18	202.5 (51.4)	190.0 (38.0)	1.00 (1.00,1.01)	.07	1.00 (1.00,1.01)	.20	955.1 (269.3)	861.9 (246.6)	1.001 (1.00,1.002)	.02	1.00 (1.00,1.00)	.30
MAP _{AUC} (cm H ₂ O × day)	19.4 (5.4)	18.6 (4.8)	1.02 (0.98,1.07)	.30	1.02 (0.97,1.08)	.50	41.1 (16.4)	40.1 (14.2)	1.00 (0.99,1.02)	.70	1.00 (0.98,1.02)	.89	166.5 (74.8)	161.0 (72.8)	1.00 (1.00,1.00)	.69	1.00 (0.99,1.00)	.38
Intermittent Hypoxemia (per day)	34 (35)	23 (20)	1.01 (1.004,1.01)	.0005	1.01 (1.004,1.02)	.0002	30 (25)	23 (18)	1.01 (1.003,1.02)	.01	1.01 (1.002,1.02)	.02	96 (57)	87(54)	1.00 (0.98,1.01)	.34	1.00 (0.96,1.01)	.93
Mean SpO ₂ (%)	93.8 (2.3)	94.2 (2.4)	0.95 (0.86,1.04)	.27	0.96 (0.87,1.07)	.46	93.8 (2.1)	94.2 (2.1)	0.93 (0.83,1.04)	.21	0.96 (0.85,1.08)	.49	92.6 (2.1)	93.2 (2.5)	0.93 (0.84,1.02)	.12	0.97 (0.88,1.07)	.58
In last 6 months, visit to doctor, emergency room, or hospital due to wheezing/breathing problems																		
Mean (SD)	Days 1–3		RR (95% CI)	p	Adjusted RR (95% CI)	Days 1–7		RR (95% CI)	p	Adjusted RR (95% CI)	Days 1–28		RR (95% CI)	p	Adjusted RR (95% CI)			
	Yes	No				Yes	No				Yes	No						
FI _{O2} AUC (% × day)	93.8 (32.1)	90.1 (21.5)	1.00 (1.00,1.01)	.14	1.01 (1.00,1.01)	.05	195.2 (47.8)	192.7 (38.6)	1.00 (1.00,1.01)	.34	1.01 (1.00,1.01)	.07	867.6 (224.0)	908.3 (279.2)	1.00 (1.00,1.00)	.34	1.00 (1.00,1.00)	.11
MAP _{AUC} (cm H ₂ O × day)	18.9 (5.6)	18.7 (4.4)	1.01 (0.97,1.04)	.66	1.01 (0.98,1.05)	.47	39.8 (16.3)	40.8 (13.7)	0.99 (0.99,1.01)	.70	1.00 (0.98,1.01)	.70	155.2 (66.8)	168.5 (77.7)	1.00 (1.00,1.00)	.28	1.00 (0.99,1.00)	.07
Intermittent Hypoxemia (per day)	31 (33)	23 (18)	1.01 (1.002,1.01)	.002	1.01 (1.003,1.01)	.002	29 (24)	23 (16)	1.01 (1.003,1.02)	.003	1.01 (1.004,1.02)	.002	94 (55)	87 (54)	1.00 (0.98,1.00)	.64	1.00 (0.97,1.00)	.92
Mean SpO ₂ (%)	93.8 (26)	94.2 (2.2)	0.97 (0.91,1.03)	.28	0.97 (0.93,1.03)	.39	94.0 (2.3)	94.2 (2.0)	.099 (0.92,1.06)	.73	1.00 (0.93,1.07)	.96	93.0 (2.2)	93.1 (2.5)	0.98 (0.93,1.06)	.73	1.00 (0.94,1.06)	.93
In last 6 months, had to change family plans due to child's breathing problems																		
Mean (SD)	Days 1–3		RR (95% CI)	p	Adjusted RR (95% CI)	Day 1–7		RR (95% CI)	p	Adjusted RR (95% CI)	Day 1–28		RR (95% CI)	p	Adjusted RR (95% CI)			
	Yes	No				Yes	No				Yes	No						
FI _{O2} AUC (% × day)	102.6 (37.1)	89.6 (23.8)	1.01 (1.003,1.02)	.008	1.01 (1.001,1.02)	.03	213.5 (54.1)	190.0 (39.4)	1.01 (1.003,1.01)	.003	1.01 (0.99,1.01)	.05	1009.7 (264.8)	867.7 (249.5)	1.001 (1.0004,1.002)	.008	1.00 (1.00,1.00)	.18
MAP _{AUC} (cm H ₂ O × day)	20.1 (5.1)	18.6 (4.9)	1.05 (0.98,1.12)	.13	1.04 (0.96,1.13)	.32	43.0 (13.0)	39.9 (15.2)	1.01 (0.99,1.03)	.27	1.00 (0.98,1.03)	.78	186.0 (74.5)	158.2 (72.4)	1.00 (1.00,1.01)	.07	1.002 (1.00,1.01)	.66
	31 (23)	25 (27)	1.01 (0.96,1.02)	.26	1.01 (0.98,1.02)	.13	33 (24)	24 (20)	1.02 (1.001,1.03)	.03	1.02 (1.002,1.03)	.02	97 (48)	89 (56)	1.00 (0.97,1.01)	.44	0.99 (0.93,1.01)	.79

Table 3 (continued)

In last 6 months, had to change family plans due to child's breathing problems											
Mean (SD)	Days 1–3		RR (95% CI)	<i>p</i>	Day 1–7		RR (95% CI)	<i>p</i>	Day 1–28		Adjusted RR (95% CI)
	Yes	No			Yes	No			Yes	No	
Intermittent Hypoxemia (per day)											
Mean SpO ₂ (%)	93.3 (2.0)	94.2 (2.4)	0.87 (0.77,0.99)	.04	0.88 (0.77,1.02)	93.1 (2.1)	94.3 (2.1)	0.81 (0.69,0.94)	.007	0.84 (0.71,0.99)	0.04
									93.3 (2.3)	91.9 (2.2)	0.82 (0.72,0.94)
											.03
											(0.74,0.98)

Mean (standard deviation) of cumulative inspired oxygen exposure (FiO_{2AUC}), cumulative mean airway pressure (MAP_{AUC}), intermittent hypoxemia events per day, and mean oxygen saturation (SpO₂) at Days 1–3, 1–7, and 1–28 of postnatal age. Relative risk (95% confidence intervals) and *p*-values reported for variable's association with parental reported respiratory outcomes (Yes or No) within the past 6 months of child's 2-year follow-up visit by generalized estimating equations for Poisson regression models with clustering of twins or triplets within one mother. Adjusted for gestational age (weeks completed) and sex

study, we chose to concentrate on the associations between early postnatal parameters on later respiratory outcomes, isolated from intermediate diagnoses such as BPD and allergy which may be part of the causal pathway. Stevens et al. investigated the newborn and childhood exposures of premature infants without BPD that went on to have symptomatic airway dysfunction, finding strong associations with cumulative supplemental oxygen exposures in just the first few days of age [16]. Use of asthma medication in our cohort was also associated with elevated FiO_{2AUC} during the first 3 and 7 days of age, even when controlling for GA and sex. We found an increased prevalence of BPD in the 2-year-old children who had received asthma medication (43% compared to 27%), but contrary to previous reports [4, 17], the duration of supplemental oxygen through hospitalization and the duration of both invasive and noninvasive pressure support did not have an apparent association on the primary outcome.

A large retrospective analysis of very low birthweight infants enrolled in the Canadian Oxygen Trial (COT) revealed an association between increased time spent in hypoxemia and multiple morbidities including neurodevelopmental impairment and ROP [13]. In a more detailed analysis of transient patterns of IH we have previously shown that the frequency of IH events progressively increases during the first postnatal month and that a sustained increase in IH events after 5 weeks of age was associated with morbidity [11]. In contrast, our current study showed that longer-term respiratory morbidity may be influenced by early patterns of IH during the first 3 and 7 days of age, where the incidence of IH was relatively low. This may be reflective of an early postnatal window of vulnerability where an increase in both IH and oxygen exposure predisposes the infant to longer term airway hyperreactivity. In adults, obstructive sleep apnea IH induces airway inflammation and oxidative stress [35, 36] but data describing the relationship between IH and inflammation/oxidative stress in infants is severely limited [8, 37, 38]. In animal models, exposure to intermittent hypoxia induces a proinflammatory response [39, 40] and reactive oxygen species generation [41–43], suggesting multiple causal pathways that may induce a pathological cascade leading to lung injury and childhood wheezing [32].

Supplemental oxygen has been used in various newborn animal models to induce airway hyperreactivity [44–46]. Additionally, newborn hyperoxic animal models have suggested that the addition of recurrent postnatal hypoxia events may contribute to longer-term pulmonary changes [44, 47–49]. Specifically, airway reactivity studies in recovered rodents exposed to frequent intermittent hypoxia in the setting of underlying hyperoxia during the first week of age show juvenile airway hyperreactivity to methacholine challenge when compared to room air controls [44], suggesting

that exposure to recurrent desaturation events treated with supplemental oxygen may contribute to longer-term wheezing. Importantly, this animal study also indicated that intermittent hypoxia alone does not increase airway hyperreactivity and corresponds to the current study findings of both increased IH and increased oxygen exposure predisposing infants to long-term respiratory morbidity.

The Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT) randomly assigned extremely premature infants to mandatory intubation and surfactant versus continuous positive airway pressure (CPAP) in the delivery room [50]. At 6–22 months corrected age, less respiratory morbidity was observed among infants initially randomized to receive CPAP and a limited ventilation strategy [29], although subanalyses of the delivered level and duration of positive pressure were not reported. We did not observe significant associations between modes of ventilation nor cumulative mean airway pressure exposures (after adjusting for GA and sex) on the various childhood wheezing outcomes, which is congruent with the previous MAP_{AUC} data of Stevens et al. [16]. We speculate that infants in our cohort having frequent IH events and a lower mean SpO₂ during the first week of age are preferentially treated with increased supplemental oxygen and secondarily with modestly elevated positive airway pressure in attempts to alleviate IH episodes.

At 2-year follow-up, approximately a third of our cohort had recurrent wheezing and nearly half reported healthcare visits for wheezing or breathing problems in the past 6 months. These secondary respiratory health outcomes were also associated with early increases in IH frequency. Despite the relatively high incidence of doctor, emergency room, or hospital visits, only 16% of parents reported changing family plans due to their child's breathing problem. Change in family plans was associated with increased IH events and lower SpO₂ during the first 7 days of age, and an unexpected higher SpO₂ at 4 weeks of age. The higher SpO₂ is most likely a result of the increased oxygen exposure at 4 weeks of age.

The strengths of this study include the continuous recordings of oxygen saturation during the first month of age, the daily documentation of inspired oxygen and mean airway pressure, and the use of prescribed asthma medications to substantiate respiratory morbidity by a clinical care provider. Our primary outcome of prescription asthma medication has been previously used in follow-up studies of preterm populations [25, 26] and reflects a need for medical treatment due to breathing problems as evaluated by a physician and the child's caregiver. The respiratory questionnaire was structured similar to the Tucson Asthma Study previously validated in a term cohort [27] and used in the SUPPORT preterm infant follow-up study [29]. Additionally, parental questionnaire reports of wheezing or whistling

in the chest in a preterm population have shown test–retest reliability and convergence with other respiratory outcomes, including inhaled medications and oral steroids [28].

Among potential limitations of this retrospective cohort study, only parent–child dyads that returned for follow-up were included and their respiratory outcomes were reported by parental questionnaires, which may be predisposed to selection and recall biases for all outcomes. Given the study design, we cannot attribute causality nor exclude the possibility that more critically-ill infants required increased inspired oxygen, had increased IH events, lower SpO₂, and were more likely to be on asthma medications as children. While a history of maternal asthma was notably increased in subjects receiving asthma medications, the adjustment models failed to converge when maternal asthma was included as a covariate, likely due to inadequate sample size (10 of the 137 infant cohort). Future cohort studies of childhood wheezing would benefit from more detailed accounting of family medical histories and postnatal exposures as they pertain to allergy or asthma.

In summary, cumulative inspired oxygen exposure and frequent IH events during just the first 3 and 7 days of age in extremely premature newborns were associated with childhood use of prescription asthma medications. Increased neonatal IH events were also associated with wheezing and substantial demands on the healthcare system and families. Risk for childhood wheezing disorders remain high despite efforts to decrease early exposures to excessive hyperoxia and invasive ventilation. Early recognition of premature infants prone to developing symptomatic wheezing has the potential to enhance patient care by allowing targeted surveillance and intervention, family education, and preventative measures against environmental triggers.

Acknowledgements AMD was supported by the NIH T32HD060537 (PI Richard Martin) and TMR by the NIH K08HL133459-01A1. The study was also supported by NIH R01HL056470 (PI Richard Martin). The authors thank Marissa Mancuso and Dominic Camperchiolo for assisting with chart recovery and data entry. AMD and TMR are participants in the NIH Loan Repayment Program.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Zahran HS, Bailey CM, Damon SA, Garbe PL, Breyse PN. Vital signs: asthma in children - United States, 2001-2016. *MMWR Morb Mortal Wkly Rep.* 2018;67:149–55.
2. Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, et al. Preterm birth and childhood wheezing

- disorders: a systematic review and meta-analysis. *PLoS Med.* 2014;11:e1001596.
3. Jaakkola JJ, Ahmed P, Ieromnimon A, Goepfert P, Laiou E, Quansah R, et al. Preterm delivery and asthma: a systematic review and meta-analysis. *J Allergy Clin Immunol.* 2006;118:823–30.
 4. Grischkan J, Storfer-Isser A, Rosen CL, Larkin EK, Kirchner HL, South A, et al. Variation in childhood asthma among former preterm infants. *J Pediatr.* 2004;144:321–6.
 5. Edwards MO, Kotecha SJ, Lowe J, Richards L, Watkins WJ, Kotecha S. Management of prematurity-associated wheeze and its association with atopy. *PLoS ONE.* 2016;11:e0155695.
 6. Doyle LW, Carse E, Adams AM, Ranganathan S, Opie G, Cheong JLY, et al. Ventilation in extremely preterm infants and respiratory function at 8 years. *N Engl J Med.* 2017;377:329–37.
 7. Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V, et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. *Am J Respir Crit Care Med.* 2010;182:237–45.
 8. Di Fiore JM, Martin RJ, Gauda EB. Apnea of prematurity—perfect storm. *Respir Physiol Neurobiol.* 2013;189:213–22.
 9. Bancalari E, Claure N. Respiratory instability and hypoxemia episodes in preterm infants. *Am J Perinatol.* 2018;35:534–6.
 10. Di Fiore JM, Walsh M, Wraga L, Rich W, Finer N, Carlo WA, et al. Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia. *J Pediatr.* 2012;161:1047–52.
 11. Di Fiore JM, Bloom JN, Orge F, Schutt A, Schluchter M, Cheruvu VK, et al. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J Pediatr.* 2010;157:69–73.
 12. Abu Jawdeh EG, Martin RJ, Dick TE, Walsh MC, Di Fiore JM. The effect of red blood cell transfusion on intermittent hypoxemia in ELBW infants. *J Perinatol.* 2014;34:921–5.
 13. Poets CF, Roberts RS, Schmidt B, Whyte RK, Asztalos EV, Bader D, et al. Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. *JAMA.* 2015;314:595–603.
 14. Fairchild KD, Lake DE. Cross-correlation of heart rate and oxygen saturation in very low birthweight infants: association with apnea and adverse events. *Am J Perinatol.* 2018;35:463–9.
 15. Di Fiore JM, Martin RJ, Li H, Morris N, Carlo WA, Finer N, et al. Patterns of oxygenation, mortality, and growth status in the Surfactant Positive Pressure and Oxygen Trial cohort. *J Pediatr.* 2017;186:49–56.e41.
 16. Stevens TP, Dylag A, Panthagani I, Pryhuber G, Halterman J. Effect of cumulative oxygen exposure on respiratory symptoms during infancy among VLBW infants without bronchopulmonary dysplasia. *Ped Pulmonol.* 2010;45:371–9.
 17. Halvorsen T, Skadberg BT, Eide GE, Roksund O, Aksnes L, Oymar K. Characteristics of asthma and airway hyper-responsiveness after premature birth. *Pediatr Allergy Immunol.* 2005;16:487–94.
 18. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: simplified newborn illness severity and mortality risk scores. *J Pediatr.* 2001;138:92–100.
 19. Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. *J Perinatol.* 2003;23:451–6.
 20. Bell MJ, Temberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg.* 1978;187:1–7.
 21. The Stop-ROP Multi-Center Study Group. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. *Pediatrics.* 2000;105:295–310.
 22. Wai KC, Kohn MA, Ballard RA, Truog WE, Black DM, Asselin JM, et al. Early cumulative supplemental oxygen predicts bronchopulmonary dysplasia in high risk extremely low gestational age newborns. *J Pediatr.* 2016;177:97–102 e102.
 23. Wilkinson DJ, Andersen CC, Smith K, Holberton J. Pharyngeal pressure with high-flow nasal cannulae in premature infants. *J Perinatol.* 2008;28:42–47.
 24. Di Fiore JM, Kaffashi F, Loparo K, Sattar A, Schluchter M, Foglyano R, et al. The relationship between patterns of intermittent hypoxia and retinopathy of prematurity in preterm infants. *Pediatr Res.* 2012;72:606–12.
 25. Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Andreias L, et al. Chronic conditions, functional limitations, and special health care needs of school-aged children born with extremely low-birth-weight in the 1990s. *JAMA.* 2005;294:318–25.
 26. Hack M, Schluchter M, Andreias L, Margevicius S, Taylor HG, Drotar D, et al. Change in prevalence of chronic conditions between childhood and adolescence among extremely low-birth-weight children. *JAMA.* 2011;306:394–401.
 27. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med.* 1995;332:133–8.
 28. Boggs E, Minich N, Hibbs AM. Performance of commonly used respiratory questionnaire items in a cohort of infants born preterm. *Open J Pediatr.* 2013;3:260–5.
 29. Stevens TP, Finer NN, Carlo WA, Szilagyi PG, Phelps DL, Walsh MC, et al. Respiratory outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT). *J Pediatr.* 2014;165:240–9.
 30. Kotecha SJ, Edwards MO, Watkins WJ, Henderson AJ, Paranjothy S, Dunstan FD, et al. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. *Thorax.* 2013;68:760–6.
 31. Filippone M, Carraro S, Baraldi E. The term “asthma” should be avoided in describing the chronic pulmonary disease of prematurity. *Eur Respir J.* 2013;42:1430–1.
 32. Reyburn B, Martin RJ, Prakash YS, MacFarlane PM. Mechanisms of injury to the preterm lung and airway: implications for long-term pulmonary outcome. *Neonatology.* 2012;101:345–52.
 33. McEvoy CT, Park BS, Spindel ER. Sensitive windows for in utero exposures and asthma development. Layers of complexity. *Am J Respir Crit Care Med.* 2017;196:1362–4.
 34. Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med.* 2007;357:1946–55.
 35. Liu J, Li Z, Liu Z, Zhu F, Li W, Jiang H, et al. Exhaled nitric oxide from the central airway and alveoli in OSAHS patients: the potential correlations and clinical implications. *Sleep Breath.* 2016;20:145–54.
 36. Tichanon P, Wilaiwan K, Sopida S, Orapin P, Watchara B, Banjamas I. Effect of continuous positive airway pressure on airway inflammation and oxidative stress in patients with obstructive sleep apnea. *Can Respir J.* 2016;2016:3107324.
 37. Cornette L. Fetal and neonatal inflammatory response and adverse outcome. *Semin Fetal Neonatal Med.* 2004;9:459–70.
 38. Kalikstad B, Kulthia HG, Andersstuen TK, Klungland A, Isaksson A. Gene expression profiles in preterm infants on continuous longterm oxygen therapy suggest reduced oxidative stress-dependent signaling during hypoxia. *Mol Med Rep.* 2017;15:1513–26.
 39. Bowser JL, Lee JW, Yuan X, Eltzschig HK. The hypoxia-adenosine link during inflammation. *J Appl Physiol (1985).* 2017;123:1303–20.
 40. Del Rio R, Moya EA, Iturriaga R. Differential expression of pro-inflammatory cytokines, endothelin-1 and nitric oxide synthases in the rat carotid body exposed to intermittent hypoxia. *Brain Res.* 2011;1395:74–85.

41. Nanduri J, Wang N, Yuan G, Khan SA, Souvannakitti D, Peng YJ, et al. Intermittent hypoxia degrades HIF-2alpha via calpains resulting in oxidative stress: implications for recurrent apnea-induced morbidities. *Proc Natl Acad Sci USA*. 2009;106:1199–204.
42. Yuan G, Nanduri J, Khan S, Semenza GL, Prabhakar NR. Induction of HIF-1alpha expression by intermittent hypoxia: involvement of NADPH oxidase, Ca²⁺ signaling, prolyl hydroxylases, and mTOR. *J Cell Physiol*. 2008;217:674–85.
43. Wang Y, Zhang SX, Gozal D. Reactive oxygen species and the brain in sleep apnea. *Respir Physiol Neurobiol*. 2010;174:307–16.
44. Dylag AM, Mayer CA, Raffay TM, Martin RJ, Jafri A, MacFarlane PM. Long-term effects of recurrent intermittent hypoxia and hyperoxia on respiratory system mechanics in neonatal mice. *Pediatr Res*. 2017;81:565–71.
45. Kumar VH, Lakshminrusimha S, Kishkurno S, Paturi BS, Gugino SF, Nielsen L, et al. Neonatal hyperoxia increases airway reactivity and inflammation in adult mice. *Pediatr Pulmonol*. 2016;51:1131–41.
46. Raffay TM, Dylag AM, Di Fiore JM, Smith LA, Einisman HJ, Li Y, et al. S-nitrosoglutathione attenuates airway hyperresponsiveness in murine bronchopulmonary dysplasia. *Mol Pharmacol*. 2016;90:418–26.
47. Chang M, Bany-Mohammed F, Kenney MC, Beharry KD. Effects of a superoxide dismutase mimetic on biomarkers of lung angiogenesis and alveolarization during hyperoxia with intermittent hypoxia. *Am J Transl Res*. 2013;5:594–607.
48. Mankouski A, Kantores C, Wong MJ, Ivanovska J, Jain A, Benner EJ, et al. Intermittent hypoxia during recovery from neonatal hyperoxic lung injury causes long-term impairment of alveolar development: A new rat model of BPD. *Am J Physiol Lung Cell Mol Physiol*. 2017;312:L208–L216.
49. Ratner V, Slinko S, Utkina-Sosunova I, Starkov A, Polin RA, Ten VS. Hypoxic stress exacerbates hyperoxia-induced lung injury in a neonatal mouse model of bronchopulmonary dysplasia. *Neonatology*. 2009;95:299–305.
50. Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010;362:1970–9.