

ORIGINAL ARTICLE

Respiratory outcomes study (RESPOS) for preterm infants at primary school age

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Abstract

Objective: Pulmonary function abnormalities and hospital re-admissions in survivors of neonatal lung disease remain highly prevalent. The respiratory outcomes study (RESPOS) aimed to investigate the respiratory and associated atopy outcomes in preterm infants <30 weeks gestational age (GA) and/or birth-weight (BWt) <1000 g at primary school age, and to compare these outcomes between infants with and without chronic lung disease (CLD). **Methods:** In the RESPOS 92 parents of preterm infants admitted to the Neonatal unit in Canberra Hospital between 1/1/2001 and 31/12/2003 were sent a questionnaire regarding their respiratory, atopy management and follow-up. **Results:** Fifty-three parents responded, including 28 preterm infants who had CLD and 25 who had no CLD. The gestational age was significantly lower in the CLD group compared to the non-CLD group [26.9 (26.3–27.5) CLD and 28.6 (28.3–29.0) non-CLD] [weeks [95% confidence interval (CI)]], as was the birth weight [973 (877.4–1068.8) CLD versus 1221 (1135.0–1307.0) non-CLD] [g (CI)]. CLD infants compared to non-CLD infants were significantly more likely to have been: given surfactant, ventilated and on oxygen at 28 days and 36 weeks. These neonates were also more likely to have: been discharged from the neonatal unit on oxygen, exhibit a history of PDA or sepsis and to have a current paediatrician. However, despite these differences, there was no significant difference in the proportion of asthma or atopic disease between the two groups. **Conclusions:** The RESPOS could not demonstrate respiratory and/or atopy differences between the CLD and the non-CLD groups at primary school age.

Keywords

Asthma, atopy, bronchopulmonary dysplasia, chronic lung disease, low birth weight

History

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Introduction

Historically, preterm neonates, particularly infants born <30 weeks, have required intensive respiratory support due to the immaturity of their lungs and decreased surfactant. The respiratory support they required may damage their lungs and may lead to altered lung elasticity and decreased lung compliance predisposing the infant to chronic lung disease (CLD), previously known as bronchopulmonary dysplasia (BPD) [1–7].

In the last 20 years, antenatal steroid administration to mothers in preterm labour and surfactant administration to the preterm infant has reduced the number of infants who required respiratory support as well as the duration of support [8]. These changes in neonatal medicine have led to infants with less severe forms of CLD, but overall the rates remain

high, due in some respects to the increased survival of preterm infants [3–9].

Preterm neonates have an increased risk of respiratory disorders in later life, but there is little research as to the risk of specific disorders, such as asthma and atopy, particularly in the post-surfactant era where the ‘‘classic BPD’’ is less often a problem [6–12]. Furthermore, the research that has been completed often compares preterm neonates to term controls, showing that the former have a greater risk of asthma and respiratory complications [13–15]. The research also tends to be focussed on lung function test results or analyses of the extremely preterm group of infants born <25 weeks gestation [13,14].

In the respiratory outcomes study (RESPOS), we have taken a different approach by investigating whether neonates born <30 weeks gestation and/or <1000 g with CLD have a greater risk of asthma and/or common atopic conditions at primary school age, compared to neonates born without CLD. This is a clinically relevant concern to further our knowledge as to which group of infants to target specifically for childhood asthma and atopic follow up and management.

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The primary aim of the RESPOS was to compare the respiratory and associated atopy outcomes in preterm infants born <30 weeks gestation and/or 1000 g: with and without CLD at primary school age. The null hypothesis was that there would be no difference in respiratory or atopy outcomes between infants <30 weeks with or without CLD.

Methods

Sample

The study population included all surviving preterm infants born <30 weeks gestation and/or <1000 g admitted to the Centre for Newborn Care (CNC) at Canberra Hospital born between 1 January 2001 and 31 December 2003. Infants with a congenital anomaly were excluded from the study. Infants from this era were identified using the NICUS database (Neonatal Intensive Care Units database of New South Wales (NSW) and Australian Capital Territory (ACT)) which is prospectively collected data on all infants <33 weeks gestation admitted to the neonatal intensive care unit (NICU) of NSW and ACT. This study used the data collected from the ACT as the modified questionnaire had previously been used for children born in the ACT and for future comparisons we would use this data.

Ethics approval was obtained for the study from the ACT Health and Research Ethics Committee and we obtained written consent from all parents who completed the questionnaire.

The survivors of this group were divided into those with or without CLD defined as a requirement of supplemental oxygen at 36 weeks corrected gestation, to maintain oxygen saturations between 92% and 96% for most of the time [6]. Perinatal data collected included: gestational age (GA); birth weight (BWt); gender; the presence of chorioamnionitis; antenatal steroid administration and surfactant administration. Data collected from their hospital admission were: types of ventilation; duration of intermittent positive pressure ventilation (IPPV) or continuous positive airway pressure (CPAP); days on oxygen; whether they were on ventilation/CPAP at 28 days and 36 weeks; corrected gestation age (CGA) at weaning off oxygen and therefore CLD status; postnatal steroid administration; presence of a patent ductus arteriosus (PDA); presence of sepsis during the infants neonatal stay and need for home oxygen.

Questionnaire

Parents of all surviving children were sent a questionnaire regarding respiratory and atopy symptoms. The questionnaire used was a modified version of the ‘ACT Kindergarten Health Screen’, which had already been validated [17,18]. The children were aged 5–7 years at the time the questionnaire was completed.

The asthma questions included, but is not exclusive of: does your child have asthma; in the last 12 months has your child had a wheeze, night wheeze or shortness of breath when playing; in the last 12 months how often has their normal activities, and then separately, their playing been restricted by their respiratory symptoms; in the last 12 months how many wheeze attacks have they had and what medication are they

on (list of preventers, relievers, symptom controllers, combination products and steroids provided).

The atopy questions were as follows: does your child have hay fever; does your child have eczema; has your child ever had an itchy rash for at least 6 months; has it affected eczema prone areas (typical areas listed); in the last 12 months have they had a persistent problem with sneezing or runny nose despite not having a cold; has your child ever been prescribed an epipen.

Environmental questions were also asked such as: family history of asthma or eczema or hay fever; smoking history in the household; how many children sleep in the same room as the child in the study and if they were breastfed.

Reminders were sent to parents from whom no response had been elicited and after no response from a second mail out, a telephone call was made during which they could answer a telephone questionnaire.

Analysis

Data were collected from the completed questionnaires and were analyzed using IBM SPSS version 22.0. In addition to descriptive statistics, *F* and chi-squared tests, as appropriate, were used to report univariate probability estimates of differences in study indicators between responders and non-responders to the questionnaire and between babies with and without chronic lung disease. After adjusting for potential co-founders such as GA, Bwt, gender and surfactant, study indicators significantly associated with the presence of asthma were determined using logistic regression. A two-sided probability of <0.05 was considered significant.

Results

We obtained data on 127 eligible children from 2001 to 2003 and of the 102 surviving infants (Table 1), 10 infants were excluded. Reasons for exclusion included death after discharge (3), refused consent (2) and lost to follow up (5). Parents of the 92 eligible children were sent a respiratory questionnaire, of which we had a 58% return rate (53/92), comprised of 28 preterm infants with CLD and 25 with no CLD.

The infants in the group that did not return the questionnaire were slightly younger, more were ventilated and they spent longer on CPAP (Table 1). However, and more importantly, there were no statistical differences between the groups for corrected gestational age at weaning off oxygen, or frequency of CLD or the number requiring home oxygen (Table 1). There was also no statistical difference for birth weight or gender (Table 1).

In those infants where the questionnaire was returned, those with CLD had a significantly smaller GA and BWt than those without CLD (Table 2). There was however no significant difference in gender between the CLD and no CLD infants (Table 2).

There were significant differences between the CLD group when compared to the no CLD group regarding prenatal and postnatal details (Table 2). These include increased length of ventilation, administration of surfactant, PDA and duration of oxygen (Table 2).

Table 1. A table displaying the demographics of the group whose questionnaire was returned compared to those whose questionnaire was not returned.

	Questionnaire returned <i>n</i> = 53	Questionnaire not returned <i>n</i> = 39	<i>p</i> Value
GA (weeks)	27.7 (1.6) ^a	27.0 (1.8)	0.040
BWt (g)	1090.0 (259.3)	1049.4 (292.9)	0.483
Males	20 (37.7%) ^b	19 (48.7%)	0.393
Chorioamnionitis (pathologically proven)	5 (9.4%)	8 (20.5%)	0.225
Antenatal steroids (complete course <7 days prior to birth)	24 (45.3%)	23 (59.0%)	0.165
Surfactant	38 (71.7%)	29 (74.4%)	0.817
Ventilated	42 (79.2%)	39 (100.0%)	0.002
Hours on IPPV	286.5 (480.6)	359.6 (484.4)	0.474
Hours on CPAP	411.1 (355.1)	588.8 (409.7)	0.029
Days on oxygen	62.6 (51.7)	72.0 (45.8)	0.367
CGA at weaning Oxygen (weeks)	36.7 (6.5)	37.3 (5.4)	0.643
Postnatal steroids	4 (7.5%)	7 (17.9%)	0.193
PDA	17 (32.1%)	16 (41.0%)	0.389
Proven sepsis	21 (39.6%)	14 (35.9%)	0.648
Home oxygen	17 (32.1%)	10 (25.6%)	0.644

^aMean (SD).^bNumber (percentage).

Table 2. A table displaying the perinatal and outcome variables of the 53 infants with and without CLD whose parents returned the questionnaire.

	Chronic lung disease <i>n</i> = 28	No chronic lung disease <i>n</i> = 25	Significance
GA (weeks)	26.9 (1.6) ^a	28.6 (0.9)	<0.001
BWt (g)	973.1 (246.7)	1221.0 (208.3)	<0.001
Males	12 (42.9%) ^b	8 (32.0%)	0.571
Chorioamnionitis (pathologically proven)	5 (17.9%)	5 (20.0%)	1.000
Antenatal steroids (complete course <7 days prior to birth)	13 (46.4%)	11 (44.0%)	1.000
Surfactant	24 (85.7%)	14 (56.0%)	0.031
Ventilated	26 (92.9%)	16 (64.0%)	0.016
Hours on IPPV	511.1 (576.0)	34.8 (48.4)	<0.001
Hours on CPAP	568.9 (354.5)	234.3 (265.0)	<0.001
Days on oxygen	94.9 (50.1)	26.4 (19.9)	<0.001
CGA at weaning oxygen (weeks)	40.4 (6.8)	32.4 (2.3)	<0.001
Ventilated or on CPAP at 28 days	26 (92.9%)	5 (20.0%)	<0.001
Ventilated or on CPAP at 36 weeks	6 (21.4%)	0 (0.0%)	0.024
Postnatal steroids	4 (14.3%)	0 (0.0%)	0.113
PDA	14 (50.0%)	3 (12.0%)	0.004
Proven sepsis	17 (60.7%)	4 (16.0%)	0.002
Home oxygen	17 (60.7%)	0 (0.0%)	<0.001

^aMean (SD).^bNumber (percentage).

When analyzing prevalence of asthma, there were no significant differences between the groups with 25% of children in the CLD group developing asthma compared to 32% in the no CLD group (ns, Table 3). Both the CLD and no CLD groups had a large proportion of children who had received asthma medication at some point in their life (46.4% versus 48.0% ns, respectively, Table 3). Significantly, more CLD infants compared to no CLD infants were found to have a regular paediatrician (57.1% versus 20.0%, $p = 0.013$, respectively, Table 3). There was no significant difference between the groups when assessing family history of asthma, eczema or hay fever or the presence of a smoker in the household (Table 3).

There were no significant differences in hay fever or eczema between those with or without CLD (Table 3). On further analysis, there was no significant difference when comparing GA and BWt for all of the infants in the study who had asthma, hay fever or eczema and those without respiratory/atopy complications (data not shown).

We used a logistic regression analysis to identify factors that may predict asthma, with the following variables: CLD; gender; BWt; GA; surfactant; smoking in family and family history of asthma (Table 4). The only predictor for later development of asthma was a family history of asthma, with an OR of 9.25 (Table 4). CLD was not a significant predictor for later asthma (Table 4).

Table 3. A table displaying the frequency and significance of the questionnaire results for the 53 infants whose parents returned the questionnaire.

	Chronic lung disease <i>n</i> = 28	No chronic lung disease <i>n</i> = 25	Significance
Asthma currently	7 (25.0%) ^a	8 (32.0%)	0.761
Hay fever currently	4 (14.3%)	3 (12.0%)	1.000
Eczema currently	3 (10.7%)	5 (20.0%)	0.721
1st degree family history of asthma	13 (46.4%)	12 (48%)	1.000
1st degree family history of hayfever	18 (64.3%)	11 (44%)	0.213
1st degree family history of eczema	9 (32.1%)	7 (28%)	1.000
Ever taken asthma medication	13 (46.4%)	12 (48.0%)	1.000
Ever had itchy rash lasting 6 months	3 (10.7%)	3 (12.0%)	1.000
Father born in Australia	19 (67.9%)	22 (88.0%)	0.107
Mother born in Australia	24 (85.7%)	24 (96.0%)	0.355
Regular paediatrician	16 (57.1%)	5 (20.0%)	0.013
Smoker in household	8 (28.6%)	8 (32.0%)	1.000

^aNumber (percentage).

Table 4. A logistic regression analysis to predict which infants will develop asthma.

	Odds ratio	Significance
CLD	1.144 (0.18–7.15) ^a	0.885
Gender	0.484 (0.10–2.39)	0.373
BW	1.000 (0.10–1.00)	0.787
GA	1.061 (0.53–2.14)	0.868
Surfactant	0.924 (0.14–5.94)	0.934
Smoking in family	0.236 (0.04–1.59)	0.138
Family Hx asthma	9.250 (1.56–55.03)	0.014

^aOR (95% confidence interval).

Discussion

The RESPOS found that there was no significant risk of infants with CLD, when compared to infants who did not have CLD, of developing asthma, eczema or hay fever at primary school age. Also, within the eligibility parameters of <30 weeks GA and/or <1000 g BWt, the RESPOS did not find a significant association to the development of asthma, eczema or hay fever at primary school age with GA or BWt. However, the study indicated that infants with CLD were significantly lower in GA and BWt, more likely to have early respiratory complications and following discharge had follow up with a regular paediatrician. This is consistent with the previous research [4,8]. The CLD infants have better medical follow up because CLD is currently viewed as the predictive factor in later respiratory dysfunction; however this study shows that this may not be the case.

This study also did not show that gender impacted on outcomes, as other studies have suggested [5]. We also failed to show a statistical difference in gender between the CLD and no CLD groups; however, there was a slight trend towards more males in the CLD groups, which is a widely held belief [1,9,12].

As well, we found that CLD was not significantly associated with hay fever or eczema. Other studies have also shown similar results, with Vrijlandt et al. [1,12] stating that hay fever and eczema were not associated with CLD. Our rates of hay fever (13.2%, Table 3) and eczema for the whole group (15.1%, Table 3) are similar to the rates published by the ISAAC Phase 3 studies for 6- to 7-year olds in 2002–2003

(allergic rhinoconjunctivitis 12.9% and eczema 17.1%). The ISAAC study assessed the global prevalence of asthma and atopic diseases in primary school children [13].

Furthermore, no association between CLD and later asthma was demonstrated. Some authors state that CLD is a strong predictor for later respiratory dysfunction, including asthma at primary school age, wheeze and hospital readmission for respiratory symptoms or infections [11,12]. It is also suggested that the lung damage sustained as part of prematurity and ventilation damage does not resolve with age and continues into adulthood, manifesting as asthma in children and possible chronic obstructive pulmonary disease (COPD) in adults [1,8,10,12]. However, most literature discusses the risk of asthma in preterm neonates with CLD compared to term controls or focuses on lung function testing rather than symptom description [14,15]. It is true that this study was limited by not having definitive end points of lung function tests and skin prick tests, however children's asthma, hay fever and eczema are often diagnosed based on symptom reporting alone.

Asthma has several underlying pathologies which include atopic causes and viral induced wheeze. It is difficult to accurately diagnose the underlying cause of asthma in children, a limitation that most studies recognise, as a viral wheeze can appear similar to chronic airway inflammation when the children present at a young age [16,19]. However, it is more likely that premature infants have smaller caliber airways which may cause recurrent wheeze, particularly viral, and this may be mis-labeled as asthma. The difference is that this should improve as the children become older, which is what our study suggests, whereas an atopic aetiology would not. Our only predictive factor of an asthma diagnosis, was a family history of asthma and it may be that this or a family history of atopy influences the diagnosis that a physician gives to a child's wheeze. The EPICure study repeatedly assessed the respiratory function of its cohort of extremely premature infants, finding that poor respiratory function, primarily based on lung function tests, is worse in infants with CLD but that the difference decreases with age. EPICure results concluded that CLD children at primary school age showed significant differences in their respiratory function: they used a bronchodilator or steroid inhaler more frequently

and had a higher incidence of respiratory symptoms such as wheezing or coughing at night [14]. However, the study commented on how asthma symptoms, treatment and hospitalization reduced significantly between 30 months and 6 years [14]. The children in our study were between 5 and 7 years of age when the parents completed the questionnaire. Furthermore, the infants in the EPICure were <25 weeks gestational age, whereas the RESPOS focused on infants born <30 weeks gestation and/or <1000 g.

It may also be that the label of CLD is a poor predictor for later respiratory dysfunction. Jobe et al. [8] claimed that radiographic evidence of CLD at 36 weeks was a far better indicator of risk of later asthma, compared to the need for oxygen at 36 weeks. In our study, significantly, more infants in the CLD group required respiratory support at 36 weeks corrected GA (Table 2).

Another possible reason for the lower rates of asthma symptoms in the CLD infants compared to EPICure, is that the infants with CLD were found to be significantly more likely to have a regular paediatrician and frequent doctor consultations could result in a better health status, including less respiratory symptoms [20]. The Australian government had increased funding for asthma management as part of the ‘‘asthma management program’’, and other studies have shown that the use of inhaled corticosteroids is increasing, which indicates that asthma management is improving [21–24]. Studies have shown that the prevalence of asthma decreased from 2000 to 2005 and if this trend has continued, previous research may no longer be appropriate in the current treatment group [22,23].

As discussed the RESPOS showed that the prevalence of asthma in infants who were born <30 weeks gestation and or <1000 g BWt with CLD was 25% and for infants without CLD was 32%. The prevalence in both of these groups is more than twice the national average for asthma in children aged 0–14 years [22,25]. Reporting bias is a possibility, and previous studies have shown that parental reports can over estimate respiratory symptoms [24]. However, this cannot fully account for the large difference and RESPOS researchers believe that the greater prevalence is not associated with CLD but instead related to these infants being more premature than the majority of the population whom are born as term infants [25,26]. This premise that those born preterm are at greatest risk of asthma, is well supported [16,19].

Conclusion

This study indicates that it is the lower GA of preterm infants, which leads to an increased rate of asthma regardless of CLD status. There were no associated risks of developing asthma, hay fever or eczema in the CLD infants compared to infants without CLD.

Overall, preterm infants as a group are at a greater risk of developing asthma compared to term controls. The clinical importance of this finding is that it implies that premature infants of low GA and BWt should have regular paediatric or GP follow up regardless of CLD status to optimize long-term outcomes. Family history of asthma also has a significant impact on later development of asthma in this group of preterm infants.

Asthma and its management has large impacts upon patients and the economy and so there is a great need to focus research upon preterm birth and the prevention of asthma.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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