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Smoking in the family is most predictive of the development of childhood asthma in preterm babies <30 weeks gestation: Results of the Respiratory Outcomes Study 2 (REPOS2).

Claire F. Johnston¹, Margaret Broom², Bruce Shadbolt³ and David A. Todd^{1,2}.

¹Australian National University (ANU) Medical School, Canberra, ACT, Australia

²Department of Neonatology, Centenary Hospital for Women and Children, Garran, ACT, Australia

³Centre for Advances in Epidemiology and IT, Canberra Hospital, Garran, ACT, Australia.

Corresponding Author: David A Todd, Associate Professor, Department of Neonatology, Centenary Hospital for Women and Children, Garran, ACT Australia. Ph: 02 61747565. Email: David.todd@act.gov.au

Abstract

Objectives: The Respiratory Outcomes Study 2 (RESPOS2) investigated the relationship between neonatal outcomes (specifically, chronic lung disease [CLD]) and environmental factors on the development of asthma and atopic outcomes at primary school age for preterm babies (PBs) <30 weeks gestational age (GA).

Methods: The study included all surviving PBs <30 weeks GA admitted to the Neonatal Intensive Care Unit at Canberra Hospital, Australian Capital Territory between 2007-2009.

Parents were sent a questionnaire regarding asthma and atopy symptoms when the PBs were aged 5-7 years old. Data were compared based on CLD status.

Results: There were 103 PBs included in the study with a 68.9% response rate to the respiratory questionnaire (71/103). Of these PBs, 15/71 (21.1%) received a diagnosis of CLD. There were no significant differences with regards to asthma, hay fever or eczema in PBs either with or without CLD. The most significant predictor for the development of asthma was smoking in the family (Odds Ratio [OR]: 11.66, 95% Confidence Interval [CI]: 2.01-67.56) with a trend towards significance for family history of asthma (OR: 3.83, 95% CI: 0.85-17.25).

Conclusion: The RESPOS2 has confirmed previous reports that CLD in PBs <30 weeks GA is not associated with the development of childhood asthma, hay fever or eczema. In our group of PBs the strongest predictor of the development of asthma was smoking in the family.

Keywords:

chronic lung disease; premature, respiratory outcomes, CPAP, asthma, atopy, smoking, family history

Introduction

Respiratory morbidity is one of the complications of very premature birth < 32 weeks gestational age (GA) (1). Prior to the advent of modern ventilation techniques, synthetic surfactant and antenatal steroids, babies born prematurely presented with respiratory distress syndrome (previously known as hyaline membrane disease) and many babies that survived this initial period went on to develop bronchopulmonary dysplasia (BPD) and long term respiratory problems(2-4).

Currently there is a multifaceted approach to respiratory therapy in premature babies (PBs) including; antenatal steroids, surfactant administration, gentle ventilation and continuous positive airway pressure (CPAP) with the aim to improve respiratory outcomes(5). Previously BPD was characterised by severe lung pathology of fibrosis and necrotising bronchiolitis with poor long term outcomes for the child, including asthma and high risk of associated respiratory infections(3). Current treatments and ventilation modalities have brought with it a new form of BPD that is much less severe, with reduced necrotising bronchiolitis and moderate respiratory morbidity(6). This is now known as chronic lung disease (CLD) or chronic oxygen dependency (COD) and has various definitions, with the current one being the requirement of oxygen >36 weeks corrected GA(3, 4, 6-8). CLD/COD occurs to a higher degree in the extremely preterm <30 weeks GA and this has not changed with the introduction of surfactant except in the 30-32 weeks GA babies where it has decreased(8). The pathophysiology and predisposing factors for asthma are complex and multifactorial(9-11). Family history of asthma and atopic conditions are strongly associated with the development of asthma and atopy in offspring as has been shown in

our previous Respiratory Outcomes Study (RESPOS) from PBs <30 weeks GA born between 2001-2003(12-14). Diagnosis in children is also difficult, as spirometry and lung function measures are not accurate or even possible until children reach at least 6 years of age(15). The development of BPD in PBs has also been previously associated with development of asthma later in life(16-18). One study showed that babies who developed BPD were more likely to have a family history of asthma(19), so this raises the question of whether it is the family history that drives the development of asthma later in life rather prematurity or BPD in infancy.

Only a limited amount of studies on the long term respiratory and atopy outcomes for extremely PBs have been conducted, as the babies receiving these new therapies have only just begun to reach school age(20). Many of the studies about respiratory and atopy outcomes at primary school age are difficult to compare due to a lack of consensus regarding: asthma diagnosis, varied control groups and populations, as well as differing modalities of treatment and follow-up(1, 14, 16, 21, 22). In 2015, our study group published an article from PBs born from 2001-2003 that reviewed the respiratory outcomes prior to changes in respiratory management such as gentle ventilation and extensive use of CPAP. In this study the strongest predictor for development of asthma was family history of asthma rather than CLD (Odds Ratio (OR): 9.25)(14). This was despite the fact that the PBs in our previous study who had CLD were much sicker than those without CLD, with significantly lower GA's, birth weights and significantly higher surfactant requirements, rates of proven sepsis, patent ductus arteriosus and more ventilation(15).

The aims of this RESPOS2 are to further investigate the relationship between neonatal outcomes (primarily CLD that occurs mainly in PB's <30 weeks GA) and home environmental factors in

the development of asthma and atopic outcomes since the introduction of multifaceted approach to respiratory therapy for PB's <30 weeks GA admitted to the NICU between 2007 and 2009. Thus we will be able to compare to our previous study of PB's <30 weeks GA(14).

Methods

A mixed methods approach was taken to address the aims of this study. Demographic and perinatal data was collected via a retrospective audit and parents of the study group were then invited to complete a questionnaire on long term respiratory outcomes.

Retrospective audit

A retrospective audit of all surviving PBs <30 weeks GA admitted to the Neonatal Intensive Care Unit (NICU) at Canberra Hospital, Australian Capital Territory (ACT) between 1 January 2007 and 31st December 2009 was conducted. PBs with a congenital abnormality or Grade 4 intraventricular haemorrhage (IVH) were excluded. Data were extracted from the NICU's database, which contains prospectively collected and collated neonatal, maternal and perinatal data.

Demographic data recorded included GA, birth weight, gender, incidence of premature rupture of membranes (PROM) and administration of antenatal steroids. Those PBs who died were included in the study to determine any differences in the populations. Perinatal data included: types of ventilation used, duration of intermittent positive pressure ventilation (IPPV) or CPAP, days on oxygen, corrected GA at weaning of oxygen (and thus their CLD status diagnosed as an oxygen and/or ventilation requirement at 36 weeks corrected GA), presence of a patent ductus arteriosus (PDA), presence of sepsis (confirmed by culture), presence of an IVH and corrected GA at discharge.

Study Recruitment

Parents of all surviving PBs were posted a questionnaire regarding respiratory and atopy symptoms during 2013-2014, when the PBs were aged 5-7 years old. Reminders were sent to parents if no response was obtained. Parents who did not respond by post were phoned and questioned using a modified phone version of the same survey (to reduce the time on the phone, questions were combined eg. did you breastfeed your child and for how long) (14).

Questionnaire

The questionnaire used was a modified version of the “ACT Kindergarten Health Screen”, which has been previously validated and used in similar studies(14). Some examples of the questions used to determine asthma status were: “Does your child have asthma?”; “In the last 12 months has your child had a wheeze, night wheeze, cough or shortness of breath?”. Asthma status for the analysis was a Yes response to the: “Does your child have asthma” question. To determine environmental impacts on the child’s respiratory outcomes, questions covered topics such as: family history of asthma, eczema or hay fever, smoking in the family, how many children sleep in the same room as the child, as well as if the child was breastfed.

Analysis

Data from the original admission, as well as the completed questionnaires were analysed using IBM SPSS version 22. Descriptive statistics, F and chi-squared tests were performed as appropriate and used to report estimates of differences in study indicators between those who completed the questionnaire and those that did not, as well as PBs with and those without CLD. Factors associated with asthma at primary school age were determined by logistic regression of study variables with adjustment for potential confounders, such as GA, birth weight and gender,

respiratory distress, ventilation, IVH, PDA and sepsis. A two-sided probability of <0.05 was considered statistically significant.

Ethics

Ethics approval for this study was obtained from the ACT Health and Research Ethics Committee (approval number: 10.09.928). Written consent was obtained from all parents who completed the study and verbal consent from those who conducted phone interviews.

Results

Overall numbers

We obtained data for 117 PBs born from 2007-2009. There were 103 surviving PBs included in the study. The total questionnaire response rate was 68.9% (71/103 [Table 1]), which included the postal as well as phone survey responses. The PBs whose parents did not complete the questionnaire (32/103 [31%]) had no significant differences compared to those who did complete the questionnaire (Table 1). This was seen as a confirmation that those who returned the questionnaire were a representative cohort of PBs.

Cohort Demographics

Of the 103 PBs included 23 (22.3%) had a CLD diagnosis and 80 no CLD, while 15/71 (21.1%) PBs received a diagnosis of CLD where the questionnaire was completed (Table 2, Figure 1). Those PBs with a diagnosis of CLD had significantly lower GA and birth weight compared to those without CLD (Table 2). They also had a significantly longer duration of CPAP and had a significantly higher corrected GA at the time of oxygen weaning. There were also trends towards longer days of IPPV and a higher percentage with a PDA in the CLD vs no CLD groups (Table 2).

Results of Respiratory and Atopy Questionnaire

Comparison of PBs with and without CLD in this study population showed no significant differences in asthma and atopy outcomes (Table 3). The proportion of children with asthma in those with CLD is 14.3% while the proportion for those without CLD was 23.6%. Similarly, for hay fever 14.3% compared to 1.9% and eczema 28.6% compared to 13.5% respectively (Table 3). Logistic regression was used to identify factors that could predict asthma in primary school age (Table 4). The most significant predictor for the development of asthma was smoking in the family with an odds ratio (OR) of 11.66 (95% confidence interval (CI) 2.01-67.56). Family history of asthma and GA showed a trend towards influencing asthma development with odds ratios of 3.83 and 1.24 respectively; but did not reach significance (Table 4).

Discussion

The RESPOS2 has shown that respiratory outcomes in PBs <30 weeks GA in the study site have improved since 2003. We have shown that both CLD and the incidence of asthma has reduced when comparing study data to our previous study (CLD: 21.1% vs. 52.8% and asthma: 23.8% vs. 28.3%, respectively) undertaken 7 years earlier(14). We have also confirmed that there was no correlation between CLD and the rate of asthma, hay fever or eczema development in this study cohort(6, 14). The strongest predictor of the development of asthma at primary school age was smoking in the family. Our study provides further evidence that the risk of CLD is associated with lower GA and birth weight as well as longer respiratory support(14, 23).

While the asthma rates in this specific population may be decreasing over time, it is still more than double the Australian national average (10.2% adults, 9.3% of 0-14 year olds) (24)and the local community rate (11% of 4-6 year olds in 2005)(25). This is consistent with both United

States (US) and Norwegian studies. The US study showed PBs born at 34-36 weeks GA were significantly more likely to develop asthma at 18 months compared to those at term (9.3% vs 7.6%, respectively)(19). The Norwegian study showed an association between premature birth and development of severe asthma (23-31 weeks GA, OR: 3.63 for developing asthma compared to 37-41 weeks GA)(26).

In the RESPOS2 it was shown that smoking in the family (mother, father or anyone living in the household) was the most significant factor in the prediction of asthma at primary school age. However, in our previous RESPOS, this was not the case(14). It may be that we are reducing the overall injury to the lungs of the current generation of PBs compared to previous study participants; e.g.: corrected GA to cease oxygen was 36.7 ± 6.5 weeks previously(14), and 32.9 ± 3.6 weeks currently (Table 1). With that reduction in overall damage to the premature lung, environmental and other factors may now play a more important role in the development of asthma.

It has long been known that smoking is associated with the development and worsening symptoms of pre-existing asthma(27-29). There are several papers linking parental smoking or second hand smoke exposure in infancy with the development of asthma later on in life(30-33). A previous study found a strong interaction effect of smoking on the development of asthma, where maternal prenatal smoking was linked to low birth weight, which then also contributed to the development of asthma(31). Another study found that extremely preterm children born at <26 weeks GA have a continuum of poor respiratory health over the first 6 years, which is exacerbated by smoking during pregnancy and in the home(31). In addition, researchers have shown that even smoking by a grandparent is associated with the development of asthma(34).

There is good biological plausibility for this as prenatal exposure to smoking can lead to airway inflammation and low birth weight predisposes to underdeveloped airways(31). These factors, combined with the extreme prematurity of birth of the present cohort, could account for the strength of the association with smoking by the family. To expand current research, it may be of interest to include in the data collection a greater breakdown of: exactly who smokes in the household, the level of smoking, whether the family smokes inside or out of the home and whether there was prenatal exposure from maternal smoking or passive smoking. Consistent with the previous RESPOS study, family history was the most significant predictor of asthma development when smoking in the family was excluded(14).

Atopic conditions such as asthma, eczema and hay fever have an associated genetic link(13, 30), although the specifics of this link are unclear(34). There has also been some association of family history of asthma with the development of BPD(19, 35). Some papers have suggested that maternal asthma is more likely to confer an increased risk of developing early asthma, while a paternal asthma is linked to more severe disease and later onset of asthma(12, 34). One of these studies showed an increased risk over time for developing asthma when both parents had asthma(34). There has also been shown to be an interaction between family history of asthma/allergies, environmental factors and asthma(17, 36). Kuiper et al showed within a Dutch community, that both parental smoking and exposure to inhaled dust mite increased the effects of family history(36). Whilst breastfeeding reduces this effect by reducing odds ratios for tonsillitis and acute otitis media(36); in our study there was no significant difference in breastfeeding rates between those with and without asthma (11/14[78.6%] versus 47/52[90.3%] breastfed, $p=0.35$

respectively), although there was a trend towards higher rates of breastfeeding in those without asthma.

In regard to hay fever and eczema, Guimaraes et al., found that in very low birth weight PBs with and without BPD, that there was no difference in atopy or family history of atopy(21). This was despite the fact that the PBs with BPD were significantly shorter in GA (27 weeks GA [23-30 range] versus 30 weeks GA [26-35 range] $p<0.001$)(21). The rate of atopy was 30.8% in the BPD group and 26.6% in the no BPD group(21). This is consistent with the current results and with our previous study although their rates are slightly higher (Table 3)(14).

The RESPOS2 had a number of strengths including the relatively high response rate for the respiratory questionnaire (compared to the previous RESPOS(14)) and use of validated study tools(22). There are also limitations to the RESPOS2 that are acknowledged. Given this is a relatively small cohort of PBs from a single study centre these results may not be generalisable to the wider Australian and International community. Further studies may concentrate on a greater breakdown of smoking patterns. We would also further investigate the home environment, including if it is a more rural or urban location. The respiratory outcomes and asthma prevalence were all self-reported by the parents, which would be ideally collected from more objective sources such as medical records or testing(37).

Future studies should include longer follow up, more solid endpoints, such as spirometry-confirmed asthma diagnosis or skin prick tests for atopy(15, 20). Another important confounder could be the presence of early, significant respiratory infection, which was not investigated in the current study. This study has focused on asthma and atopy morbidity; however, there are many

other endpoints that are also associated with both premature birth and CLD, such as cognitive and motor developmental delay(38, 39).

Conclusion

The RESPOS2 has shown that factors other than CLD are associated more strongly with the development of asthma in PBs at primary school age. The strongest predicting factor for the development of asthma was smoking in the family, followed by family history of asthma, confirming a previous study(14). Smoking is an important public health issue that can be seen as a preventable cause of morbidity and mortality worldwide(32). It may be important, going forward, to target and better inform these families to help prevent some of the risk of developing asthma later in life and a significant health burden.

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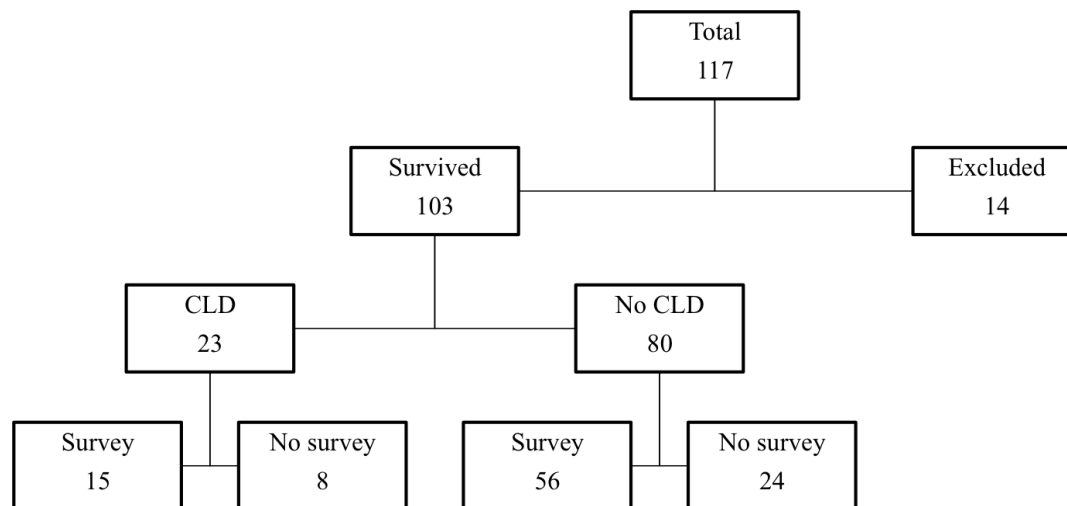


Figure 1: Consort diagram showing total number of PBs assessed, those included and excluded in the study, as well as the breakdown of those who had chronic lung disease (CLD) and those who completed the respiratory survey.

Table 1: Comparison of demographic data for those PBs for which a questionnaire was returned compared to those who did not return the questionnaire.

	Questionnaire completed (n= 71)	Questionnaire not completed (n= 32)	p value
GA (weeks)	27.6 ±1.5	27.8 ±1.5	0.64
Birth weight (kg)	1.1 ±0.3	1.1 ±0.3	0.99
Females	39 (54.9)	16 (50.0)	0.40
CLD	15 (21.1)	8 (25.0)	0.42
PROM	18 (25.3)	8 (25.0)	1.00
Intrauterine steroids	50 (70.4)	26 (81.3)	0.16
Intubated	63 (88.7)	23 (71.9)	0.18
Days of IPPV	7.5 ±12.1	9.2 ±25.2	0.64
Days CPAP	17.2 ±16.2	15.3 ±20.4	0.95
Days on oxygen	37.1 ±30.3	35.6 ±38.4	0.84
GA at O2 weaning (weeks)	32.9 ±3.6	33.5 ±4.9	0.54
PDA	37 (52.1)	13 (40.6)	0.24
Sepsis (proven)	20 (28.2)	7 (21.9)	0.37
IVH	14 (19.7)	3 (9.4)	0.17

Data presented as mean ± standard deviation (SD) or total number (%). GA: gestational age;

CLD: chronic lung disease; PROM: premature rupture of membranes; IPPV: intermittent positive pressure ventilation; CPAP: continuous positive airway pressure; CGA: corrected gestational age; PDA: patent ductus arteriosus; IVH: intraventricular haemorrhage.

Table 2: Comparison of demographic and outcome details of PBs with chronic lung disease (CLD) compared to those without CLD, for those 71 PBs who had a survey returned (via mail or phone).

	CLD n= 15	No CLD n= 56	p value
GA (weeks)	26.8 ±1.4	27.8 ±1.5	0.02
Birth weight (kg)	0.9 ±0.2	1.1 ±0.3	0.009
Females	8 (53.3)	24 (42.9)	0.33
PROM	6 (40.0)	12 (22.2)	0.15
Antenatal steroids given	9 (60.0)	41 (75.9)	0.18
Ventilated	14 (93.3)	49 (87.5)	0.46
Days of IPPV	12.3 ±12.3	6.2 ±11.4	0.09
Days CPAP	30.9 ±21.7	12.5 ±13.7	0.00
Days on oxygen	80.3 ±17.2	26.3 ±22.1	0.00
CGA at O ₂ weaning (weeks)	38.2 ±1.5	31.5 ±2.5	0.00
PDA	11 (73.3)	26 (48.1)	0.07
Sepsis (proven)	5 (33.3)	15 (27.8)	0.45
IVH	3 (20.0)	11 (20.4)	0.64

Data presented as mean ± Standard Deviation (SD) or total number (%). GA: gestational age; PROM: premature rupture of membranes; IPPV: intermittent positive pressure ventilation; CPAP: continuous positive airway pressure; CGA: corrected gestational age; PDA: patent ductus arteriosus; IVH: intraventricular haemorrhage.

Table 3: Comparison of significant respiratory questionnaire results for those with chronic lung disease (CLD) compared to those without CLD for those who returned the questionnaire.

	CLD n= 14 (22%)	No CLD n= 49 (78%)	p value
Asthma	2 (14.3)	13 (23.6)	0.36
Hay fever	2 (14.3)	1 (1.9)	0.11
Eczema	4 (28.6)	7 (13.5)	0.17
1 st degree family history of asthma	4 (28.6)	24 (51.1)	0.12
1 st degree family history of hay fever	8 (57.1)	26 (53.1)	0.52
1 st degree family history of any atopy	10 (71.4)	37 (74.0)	0.55
Smoker in the household	5 (35.7)	13 (23.2)	0.26

Data presented as total number (%). Note the total numbers differ from Table 2 due to incomplete survey responses for some of these items.

Table 4: Prediction of asthma development by logistic regression analysis.

	Odds Ratio ^a (Exp [B])	Significance (CI)	p value
GA	1.24	0.50-3.05	0.65
Birth weight	0.17	0.00-49.37	0.54
Gender	0.36	0.07-1.75	0.20
Family history of asthma	3.83	0.85-17.25	0.08
Smoking in the family	11.66	2.01-67.56	0.006

GA: gestational age, ^a Adjusted Odds Ratios