Association of Early Life Factors with Prematurity-Associated Lung Disease: Prospective Cohort Study

[1,2]Kylie Hart, [1,2]Michael Cousins, [1]W John Watkins, [1]Sarah J Kotecha, [3]A John Henderson**, [1,2]Sailesh Kotecha.

**This publication is dedicated to our expert collaborator, valued mentor, and very dear late friend.

[1]Department of Child Health, Cardiff University School of Medicine, Cardiff, United Kingdom.

[2]Neonatal Unit, Cardiff and Vale University Health Board, Cardiff, United Kingdom.

[3] MRC Integrative Epidemiology Unit, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, United Kingdom.

Corresponding Author: Professor Sailesh Kotecha

Department of Child Health

School of Medicine

Cardiff University

Heath Park

Cardiff CF14 4XN

United Kingdom

Email: KotechaS@cardiff.ac.uk

Telephone: +44(0)29 20 74 4187

Fax: +44(0)29 20 74 4283

Take Home Message

Although traditionally bronchopulmonary dysplasia is thought to be associated with longer term

lung function deficits, we show that gestation and fetal growth restriction are better predictors of lung function deficits in prematurely born children.

Authors Contributors Statement:

SK and AJH conceived and designed the study. SK, AJH, KH, and MC were involved in identifying and assessing the children and in data collection and its interpretation. SK, SJK and WJW were involved in the data analysis and interpretation. SK and KH drafted the manuscript. All authors were involved in revising the manuscript and approved the final submitted version.

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Abstract – 249 words

Introduction: Although bronchopulmonary dysplasia (BPD) is associated with lung function deficits in childhood, many who develop BPD have normal lung function in childhood, and many without BPD including those born at 33-34 weeks' gestation, have lung dysfunction in childhood. Since the predictability of BPD for future lung deficits is increasingly doubted, we prospectively recruited preterm-born children to identify early life factors which are associated with lung function deficits after preterm-birth.

Methods: From 767 children aged 7-12 years, who had their respiratory symptoms assessed, and had spirometry before and after a bronchodilator in our Respiratory Health Outcomes in Neonates (RHiNO) study, 739 (544 preterm-born at ≤34 weeks' gestation and 195 term-born) had satisfactory lung function. Data were analysed using multivariable logistic regression and mediation.

Results: When preterm-born children were classified according to their lung function, low lung function (prematurity-associated lung disease, PLD) was associated with BPD, gestation and intrauterine growth restriction on univariable logistic regression analyses. However, on multivariable logistic regression analyses, gestation (Beta=-0.153, SE: 0.051, p=0.003) and intrauterine growth restriction (odds ratio 1.783, 95% confidence interval: 1.06, 3.00, p=0.029) remained significantly associated with later deficits of lung function but BPD (0.99; 0.52, 1.89, p=0.974) did not. Mediation analyses confirmed these results.

Conclusions: Although traditionally BPD has been associated with low lung function in later life, these data show that gestation and IUGR are significantly associated with PLD in childhood but BPD is not. By identifying children with PLD, we can better understand the underlying mechanisms and develop optimal therapies.

Keywords: bronchopulmonary dysplasia, chronic lung disease of prematurity, spirometry, early life factors

Introduction

It is now well-established that prematurity is associated with long-term respiratory deficits in childhood and young adulthood(1-5). These deficits are particularly marked in those who develop bronchopulmonary dysplasia (BPD, often also called chronic lung disease of prematurity, CLD) in infancy(6-8) but even those who are born at 33-34 weeks' gestation(9-12) are also at significant risk of developing respiratory disease in later life. Preterm-born infants are delivered at an early stage of lung development and may be exposed to antenatal (chorioamnionitis, maternal disease or placental dysfunction) or postnatal (mechanical ventilation, supplemental oxygen, infection) risk factors of lung injury thus lung disease may result from these different exposures(13, 14). As summarised by our systematic review(1), most individual studies reported decreased spirometry after preterm-birth, including those who did and did not develop BPD but in general were small in size. Therefore, they did not permit detailed analyses of which early life factors may be important in the development of future lung function deficits. Since BPD is increasingly questioned for predicting future lung function deficits(15, 16), it is important to assess which early life factors including gestation, BPD, intrauterine growth restriction (IUGR), sex, etc. may be important in these future lung function deficits in preterm-born children.

We, therefore, prospectively studied the largest population to date of children aged 7 – 12 years who were born at ≤34 weeks of gestation to specifically identify those with low spirometry to permit identification of which early-life factors are associated with lung function deficits associated with preterm-birth.

Methods

In 2013, we invited all surviving preterm-born children together with matched term-born children who were born throughout Wales, then aged 1-3, 5, 7 and 9 years, via a respiratory questionnaire(3, 17). We re-invited the responders and the non-responders from this 2013

cohort, adding additional potential participants who were born in South Wales (to permit accessibility) from the National Welsh Informatics Service if they were aged 7 – 12 years at the time of mailing the invitations. Thus, those born and cared for at all levels of neonatal care were eligible for inclusion. We mailed invitations between November 2016 and September 2019 to join the Respiratory Health Outcomes in Neonates study (RHiNO, EudraCT: 2015-003712-20) for comprehensive assessments if they were aged 7 – 12 years, born at ≤34 weeks' gestation for the preterm group or at ≥37 weeks' gestation for the control group. Ethical approval was obtained from the South-West Bristol Research Ethics Committee (15/SW/0289). For parents and children who provided informed written consent and assent respectively, two research nurses evaluated the children at their home or in hospital. After checking accuracy of the parent-completed respiratory questionnaires and conducting a physical examination, they measured the children's height, weight, fractional exhaled nitric oxide (FE_{NO}) (Circassia, Oxford, UK) and spirometry (Microloop, CareFusion, UK) before and 15-20 minutes after administration of a bronchodilator (4 x 100 mcg puffs of salbutamol administered via a spacer device) to assess reversibility (increase of >10 percent predicted forced expired volume in one second, $\%FEV_1$). Spirometry was quality controlled as per the European Respiratory Society/American Thoracic Society guidelines including independent quality control(18) and normalised against GLI reference values(19). Intrauterine growth restriction (IUGR) was defined as <10th centile for birthweight adjusted for sex and gestation using the LMS Growth program (Medical Research Council)(20). Deprivation scores and quintiles were estimated from the participants' postcodes using the Welsh Index of Multiple Deprivation (WIMD) score, which is a measure of deprivation based on 8 domains including wealth, schooling, and home ownership(21). Children with congenital malformations, significant cardiopulmonary disorder or inability to perform spirometry due to severe neurodevelopmental disorders were excluded. All children withheld their drugs prior to their assessments (short and long acting $beta_2$ agonists for 8 and 48 hours respectively; inhaled corticosteroids for 24 hours; and leukotriene receptor antagonists for 48 hours)(18, 22) and were

free of respiratory infections for at least three weeks prior to testing. Diagnosis of BPD was based on oxygen requirement at 28 days of age or at 36 weeks post-conceptual age. Information on early-life factors including gestational age, birthweight, diagnosis of BPD (according to the National Institute of Child Health and Human Development criteria using need for supplemental oxygen at 28 days of age and at 36 weeks' corrected gestation for the group born at <32 weeks' gestation at birth; and at 28 and 56 days of age for those born at ≥32 weeks at birth to classify the children into no BPD or BPD including mild, moderate or severe BPD; or into moderate/severe BPD as used in the sensitivity analyses(23)), etc. were obtained from the neonatal medical notes.

Statistical methods

The mean and 95% confidence intervals or medians and ranges are presented as appropriate. Continuous data were analysed using independent t-test or Mann-Whitney U for two groups, and one-way ANOVA or Kruskal-Wallis for multiple group comparisons with post-hoc Bonferroni correction. Pearson χ^2 was used to analyse categorical data. Univariable and multivariable logistic regression modelling were performed to identify potential predictors of low spirometry in preterm-born children. Mediation analyses was performed using M-plus (Muthén & Muthén, Los Angeles, Ca); all other analyses used SPSS V23.0 (IBM, Armonk, NY). p-values of <0.05 were considered statistically significant.

Power Calculation

We had estimated that the power of the multiple regression model using an alpha of 0.05 and 1 variable for each 100 participants recruited (estimated to 5 – 6 variables) with an R2 value of 0.2 to be conservative. There were no controlled independent variables included in the calculation, as this model was being created from scratch with no variables automatically included. This model resulted in a power of 100% and so we had sufficient power if all of the variables were retained in the model.

Results

The CONSORT diagram shows the details of the invitees and responders (Online Figure 1). From 1,122 (827 preterm, 295 term) responders, 767 (565 preterm, 202 term) were comprehensively assessed with satisfactory spirometry data available from 544 preterm- and 195 term-born children. When the responders and non-responders were compared, there were small differences for gestational age and birthweight and fewer of the most-deprived population responded (Online Table 1). To identify which early risk factors were associated with low lung function observed after preterm-birth, we classified preterm-born children into those with $\%FEV_1 \leq 85\%$ (PT_{low}) and $\%FEV_1 > 85\%$ (PT_c) groups (Table 1). The PT_{low} group had lower birthweight and gestation but had greater rates of IUGR, BPD, neonatal complications and greater respiratory symptoms in childhood when compared to the preterm and term control groups. They did not have greater family history of atopy nor greater exposure to antenatal or postnatal smoking when compared to the preterm control group. Interestingly, although a greater proportion of the preterm-born children who had BPD in infancy (38%, 41/108) had low spirometry, a significant proportion of the preterm subjects without BPD (23%, 100/436) also had low spirometry. When the analysis was restricted to those born at ≤32 weeks' gestation, 38% of the BPD group and 25% of the preterm control group had low lung function. As expected, the PT_{low} group had low spirometry values as they were classified using low $\%FEV_1$ but a greater proportion of the PT_{low} group had FE_{NO} >35 ppb (28/124, 23%) when compared to the PT_c (33/350, 9%) or term (20/183, 11%) groups (Table 2). Similarly, the low lung function group had greater bronchodilator responses with an increase in $\%FEV_1$ of 7.9% compared to 4.4% and 3.6% for the preterm and term control groups respectively after administration of salbutamol. Furthermore, a greater proportion had a positive bronchodilator response in the PT_{low} group (39/134, 29%) when compared to the control groups (PT_c: 27/382, 7%; term: 10/183, 6%).

We next identified which early life factors were associated with low spirometry in the preterm group. Univariable analyses showed that gestation, IUGR and diagnosis of BPD were significantly associated with low %FEV_1 but sex, mode of delivery, maternal smoking and WIMD quintile were not (Table 3). With multivariable logistic regression analyses, gestation (Beta=-0.153, SE: 0.051, p=0.003) and IUGR (odds ratio: 1.783; 95% confidence interval: 1.06, 3.00, p=0.029) remained significantly associated with low %FEV_1 but BPD (0.99; 0.52, 1.89, p=0.964) did not (Table 4) thus suggesting that gestation and fetal growth restriction, but not BPD, are important determinants of future deficits in FEV_1. We next assessed if mild (n=40) or moderate/severe BPD (n=68) were better predictors of decreased spirometry. On univariable analyses both mild (2.016; 95%CI 1.023, 3.971) and moderate/severe BPD (2.080; 95%CI 1.215, 3.561) were significantly associated with low lung function, but neither was in a multivariable model (mild 1.099; 95%CI 0.493, 2.449, p=0.818; moderate/severe 0.917; 95%CI 0.439, 1.917, p=0.818) also including gestation and IUGR (Online Table 2 and 3). To further elucidate the relationships between the early life factors and low lung function, we used mediation analyses (Figure 1). Using mediation analyses, gestation was significantly associated with BPD but not with IUGR when the two preterm groups with and without low spirometry were compared. However, IUGR was significantly associated with low lung function in the preterm group but BPD was not thus consolidating the multivariable logistic regression results that gestation and IUGR were associated with low lung function in the preterm-born group.

Discussion

In this study, we investigated preterm-born children who had low lung function in childhood to determine which early-life factors could explain these deficits noting that gestation and IUGR were strongly associated with the lung function deficits but mild BPD and moderate/severe BPD, although both were associated with low lung function in univariable analyses, were not following adjustments for gestation and IUGR. Mediation analyses showed that gestation led to an

association with both low spirometry and development of BPD, and IUGR was independently associated with low spirometry, but BPD was not.

It is well-established that preterm-born children who had BPD in infancy have decreased lung function(7, 8, 24) but it is increasingly recognised that BPD is not an optimal marker of future lung function decrements. It can be argued that a better definition of BPD(25, 26) can potentially improve this predictability, but any refined definition is unlikely to optimally identify lung disease in preterm-born children who did not have BPD in infancy, especially those born at 32 weeks' gestation or more who are less likely to develop BPD. Thus, in this study, since we and others have shown that children who are born late-preterm are at risk of future lung dysfunction(3, 9, 10), we included children who were born at 33-34 weeks' gestation as well those born ≤32 weeks' gestation who are traditionally considered to be at risk of developing BPD(6). Indeed, although 38% (41/108) of the BPD group had low spirometry, a significant proportion (23%, 100/436) from those without BPD including those born late preterm also had low lung function. The results remained similar with 38% of the BPD group and 25% of the preterm controls having low lung function when we confined the analyses to those born at ≤32 weeks' gestation. The greater proportion in the BPD group was most likely due to the lower gestation observed in this group.

In order to explore factors that may be associated with respiratory disease in the future, we, initially, classified the preterm-born children into those with low and normal spirometry, basing the classification on a pragmatic approach for the research nurses to use a cut-off value of 85% predicted FEV_1 which was close to lower limit of normal for the group we studied to identify children who could join RHiNO which includes a randomised control trial of inhalers (EudraCT: 2015-003712-20). Although it is tempting to attribute the lower findings to the diagnosis of BPD, in multivariable logistic regression modelling, gestation was more influential for future spirometry deficits, but the diagnosis of BPD was not. The data suggest that gestation and IUGR are strong

determinants of low lung function in preterm-born children thus suggesting that delivery at an early stage of lung development is most likely to be most associated with future lung dysfunction(27). Traditionally, studies have compared lung function, including spirometry and impulse oscillometry, in preterm-born children with and without BPD generally showing that BPD is associated with decreased lung function. Hurst and colleagues showed decreased measures of spirometry in young adults born at <26 weeks' gestation with BPD when compared to those without or with term-born controls (7). In contrast, Manti et al did not show a significant difference in impulse oscillometry between preschool age children with and without BPD(28). Some studies have investigated early life factors that could explain later lung function. In a longitudinal study, Levin et al. reported that duration of mechanical ventilation and neonatal corticosteroid exposure in a multivariable model adjusting for BPD and gestation were associated with lower rate of rise in $\%FEV_1$ in those with BPD(29). In contrast, another study of 88 six-year-olds, including 78 with BPD, reported that Nissen's fundoplication was associated with lower FEV_1(30). Studies thus far have been limited by power suggesting the need for larger studies such as ours.

FE_{NO} has, previously, not shown to be increased in preterm groups who do or do not have BPD in infancy(31-33). Therefore, it was interesting to note that FE_{NO} was increased in 23% of the PT_{low} group and only 9% and 11% in the PT_c and T_c groups suggesting that at least some of these children are likely to have an inflammatory process occurring. Similarly, a greater proportion of the PT_{low} group responded to single administration of salbutamol (29% vs 7% vs 6% for the PT_{low}, PT_c and T_c groups respectively). Taken together these data suggest that the PT_c group are similar to the Tc group and are likely to have good respiratory health in the future. In contrast, the PT_c group appears to have some individuals who have high FE_{NO}, and some who respond to

bronchodilators, suggesting that different phenotypes(34) are likely to exist within this group, which requires further dissection.

The strengths of this study are the large number of prospectively and comprehensively studied preterm-born children together with term controls with standardised methods by two highly trained research nurses. Weaknesses, include fewer responses than we had anticipated. Differences noted especially for the deprivation score is unlikely to introduce any bias as the main aim was to study preterm-born children with low lung function to identify their associations with early life factors so the findings should remain robust and are clearly independent of response rates. In addition, the questionnaire data may be subject to parental recall bias. Thus, we have concentrated more on objective measures of spirometry as outcome measures.

In summary, we have shown that although moderate/severe BPD is associated with longer term lung function deficits, gestation and IUGR are better determinants of decreases of lung function. In addition, these children had increased FE_{NO} and greater bronchodilator responses when compared to preterm and term controls. By identifying children with low lung function, which we have termed PLD or prematurity-associated lung disease, we can better study the underlying mechanisms of why these children continue to have lung function decrements in the future, and to optimise therapies (35).

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Declaration of interest:

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Table 1 Characteristics of participants based upon $\%FEV_1$

	Preterm group with $\%FEV_1 \leq 85\%$ (PT_{low})	Preterm control group with $\%FEV_1 > 85\%$ (PT_C)	≥37/40 Term born controls (TC)
Subjects (n)	141 (26%)	403 (74%)	195 (26%)
Current status			
Sex - Male	68/141 (52%)	211/403 (52%)	100/195 (51%)
Current age (y)	9.9 (9.7 to 10.2) **	9.5 (9.4 to 9.7)	9.7 (9.5 to 9.8)
Current height (cm)	140.7 (139.1 to 142.4)	139.5 (138.4 to 140.5) ‡	142.0 (140.7 to 143.3)
Current weight (kg) (range) #	32.4 (18.2 to 62.8)	32.8 (17.7 to 88.9) ‡	34.8 (21.4 to 78.2)
Current BMI (range) #	16.5 (12.2 to 28.0)	17.0 (12.8 to 32.5)	17.1 (13.2 to 30.9)
Neonatal history			
Gestational age (weeks) (range) #	31 (24 to 34) **, †††	32 (23 to 34) ‡‡‡	40 (37 to 42)
Birthweight (g) (range) #	1450 (482 to 2930) **, †††	1758 (450 to 3912) ‡‡‡	3430 (2155 to 4916)
Birthweight (z-score after adjustments for gestation and sex)	-0.087 (-0.312 to 0.139) *	0.256 (0.124 to 0.387)	0.062 (-0.076 to 0.199)
Intrauterine growth restriction	28/141 (20%) *, †††	48/403 (12%) ‡‡	9/195 (5%)
Caesarean section	79/141 (56%) †††	227/401 (57%) ‡‡‡	49/195 (25%)
Antenatal steroids	122/135 (90%) †††	329/376 (88%) ‡‡‡	4/195 (2%)
Postnatal steroids	6/131 (5%) ††	8/383 (2%) ‡	0/194 (0%)
BPD	41/141 (29%) **	67/403 (16%)	0/195
Retinopathy of prematurity (ROP)	13/141 (9%) †††	19/403 (5%) ‡‡‡	0/195 (0%)
IVH	26/141 (18%) ***, †††	30/403 (7%) ‡‡‡	0/195 (0%)
NEC	13/137 (10%) †††	18/390 (4%) ‡‡	0/194 (0%)
PDA	14/138 (10%) †††	21/388 (5%) ‡‡‡	0/195 (0%)
Combined Illness	41/139 (30%) ***, †††	53/391 (14%) ‡‡‡	0/194 (0%)
Family history			
Maternal antenatal smoking	14/138 (10%)	48/394 (12%) ‡‡	11/194 (6%)
Maternal postnatal smoking	16/140 (11%) †	58/399 (15%) ‡‡‡	8/195 (4%)
Family history of asthma	83/140 (59%) †	213/399 (53%)	91/195 (47%)
Family history hay fever	72/138 (52%)	217/396 (55%)	115/194 (59%)
Family history eczema	59/138 (43%)	183/393 (47%)	90/195 (46%)
Family history allergies	52/138 (38%)	156/393 (40%)	81/193 (42%)
Respiratory Symptoms			
Bronchiolitis	39/141 (28%) **, †††	58/401 (15%) ‡‡‡	10/194 (5%)
Wheeze-ever	87/138 (63%) *, †††	194/385 (50%)	51/191 (27%)
Wheeze last 12 months	48/141 (34%) †††	104/403 (26%) ‡‡‡	25/195 (13%)
Inhalers last 12 months	32/141 (23%) †††	61/403 (15%) ‡‡	12/195 (6%)
Diagnosed asthma	35/140 (25%) **, †††	53/403 (13%) ‡‡	10/193 (5%)

95% confidence intervals or percentages shown in brackets unless ranges specified. [a] = % of total population, [b] = %preterm population.

PT_C v TC ‡ p<0.05, ‡‡ p<0.01, ‡‡‡ p<0.001; PT_{low} v PT_C * p<0.05, ** p<0.01, *** p<0.001; PT_{low} v TC † p<0.05, †† p<0.01, ††† p<0.001.

Abbreviations: BPD = mild and moderate/severe bronchopulmonary dysplasia, IVH = intraventricular/cerebral haemorrhage of all grades, NEC = necrotising enterocolitis requiring medical or surgical treatment, ROP = retinopathy of prematurity of all grades, PDA = patent ductus arteriosus requiring medical or surgical treatment, Combined Illness = IVH or ROP or NEC in the neonatal period.

Table 2 Preterm population classified into low (PT_{low}) and normal (PT_C) lung function

	Preterm group with $\%FEV_1 \leq 85\%$ (PT_{low})	Preterm control group with $\%FEV_1 > 85\%$ (PT_C)	≥37/40 Term born controls (TC)
Baseline spirometry	**n = 141**	**n = 403**	**n = 195**
%predicted FEV_1	75.6 (74.0 to 77.1) †††, ***	96.6 (95.8 to 97.4)	95.7 (94.2 to 97.0)
%predicted FVC	83.2 (81.8 to 84.6) †††, ***	98.2 (97.2 to 99.1)	96.2 (94.8 to 97.7)
FEV_1/FVC ratio	0.80 (0.78 to 0.81) †††, ***	0.86 (0.86 to 0.87)	0.87 (0.86 to 0.88)
%predicted $FEF_{25-75\%}$	57.0 (54.2 to 59.7) †††, ***	84.0 (82.3 to 85.6)	86.4 (83.6 to 89.1)
Post BD spirometry	**n = 134**	**n = 382**	**n = 183**
%predicted FEV_1	83.3 (81.8 to 84.9) †††, ***	101.0 (100.1 to 102.0)	99.0 (97.5 to 100.5)
%predicted FVC	86.4 (84.7 to 88.2) †††, ***	99.0 (98.0 to 100.0) ‡	96.7 (95.2 to 98.3)
FEV_1/FVC ratio	0.85 (0.83 to 0.86) †††, ***	0.89 (0.89 to 0.90)	0.89 (0.89 to 0.90)
%predicted $FEF_{25-75\%}$	71.8 (68.8 to 74.8) †††, ***	97.0 (95.3 to 98.8)	96.2 (93.4 to 99.1)
Mean change in pre-/post-bronchodilator spirometry	**n = 134**	**n = 382**	**n = 183**
%predicted FEV_1	7.9 (6.5 to 9.3) †††, ***	4.4 (3.9 to 4.8)	3.6 (2.9 to 4.3)
%predicted FVC	3.0 (1.8 to 4.2) †††, ***	0.6 (0.1 to 1.0)	0.5 (-0.1 to 1.1)
FEV_1/FVC ratio	0.054 (0.044 to 0.064) †††, ***	0.032 (0.028 to 0.036)	0.029 (0.023 to 0.035)
%predicted $FEF_{25-75\%}$	15.5 (13.6 to 17.4) ††	13.3 (12.1 to 14.6)	11.0 (8.9 to 13.0)
Positive bronchodilator response	39 (29%) †††, ***	27 (7%)	10 (6%)
	n = 124	**n = 350**	**n = 183**
FE_{NO} >35ppb	28 (23%) ††, ***	33 (9%)	20 (11%)

95% confidence intervals or percentages shown in brackets.
PT_C v TC ‡ $p<0.05$; PT_{low} v PT_C *** $p<0.001$; PT_{low} v TC †† $p<0.01$, ††† $p<0.001$

Table 3: Univariable analysis of predictors of low lung function in the preterm-born population

Covariates	**Beta**	**Standard error**	**Significance**
Gestational age	-0.153	**0.036**	**0.000**
Factors	**Beta**	**Odds ratio (95% confidence interval)**	**Significance**
Intrauterine growth restriction (ref = No)	0.606	**1.83 (1.10, 3.06)**	**0.020**
BPD (ref = No)	0.721	**2.06 (1.31, 3.22)**	**0.002**
Family history of asthma* (ref = No)	0.240	1.27 (0.86, 1.88)	0.228
Sex (ref = Female)	-0.165	0.85 (0.58, 1.24)	0.399
Antenatal smoking* (ref = No)	-0.206	0.81 (0.43, 1.53)	0.521
Postnatal smoking* (ref = No)	-0.276	0.76 (0.42 to 1.37	0.359
Caesarean section * (ref = No)	-0.024	0.98 (0.66 to 1.44)	0.905
WIMD Quintiles			
1 – Most deprived	-0.110	0.99 (0.54 to 1.80)	0.971
2	-0.181	0.84 (0.46 to 1.51)	0.550
3	0.242	1.27 (0.73 to 2.23)	0.397
4	-0.184	0.83 (0.47 to 1.48)	0.532
5 – Least deprived	Ref	-	-

Covariates presented as Beta value and SE. Beta value and Odds ratios with (95%CI) presented for all factors.

*Missing cases: Family history of asthma = 5, Antenatal smoking = 12, Postnatal smoking = 5, Caesarean section = 2.

Abbreviation: WIMD: Welsh Index of Multiple Deprivation 2019.

Table 4: Multivariable modelling for low lung function in the preterm-born population

Model 1			
Covariates	**Beta**	**Standard error**	**Significance**
Gestational age	-0.153	0.051	**0.003**
Factors	**Beta**	**Odds ratio (95% confidence interval)**	**Significance**
IUGR (ref = No)	0.579	**1.783 (1.06, 3.00)**	**0.029**
BPD (ref = No)	-0.11	0.99 (0.52, 1.89)	0.974

Covariates presented as Beta value and SE. Beta value and Odds Ratios with 95%CI presented for all factors.