Effect of fetal and infant growth on respiratory symptoms in preterm-born children

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Abstract

Objectives: Fetal growth and rapid postnatal weight gain are associated with adverse respiratory outcomes in childhood. However, the preterm-born population is less well studied. We assessed if the increased respiratory symptoms associated with altered fetal growth and infant weight gain were mediated by early factors.

Study Design: We used data from our cohort of preterm- and term-born (n = 4284 and 2865) children, aged 1-10 years. Respiratory outcomes obtained from a respiratory questionnaire were regressed on measures of fetal growth and infant weight gain, defined as >0.67 SD change in fetal measurement or weight between birth and nine months of age, then adjusted for covariates. We used mediation analysis to investigate which variables were effect modifiers.

Results: Accelerated fetal growth between the 1st trimester and birth (OR 2.01; 95%CI 1.25, 2.32), and between the 2nd trimester and birth (1.60; 1.15, 2.22) was associated with increased wheeze-ever in preterm-born children. Rapid infant weight gain was associated with increased wheeze-ever (1.22; 1.02, 1.45); children born ≤32 weeks gestation exhibiting rapid weight gain had fivefold higher risk of wheeze-ever compared to term-born without weight gain. Current maternal smoking and gestational age were identified as candidate mediating effects.

Conclusions: Our study suggested that antenatal and postnatal growth rates are important for future respiratory health in preterm-born children, and that their effects may be mediated by modifiable factors. Minimizing exposure to environmental pollutants, especially maternal tobacco smoking, may improve outcomes.

KEYWORDS

dysanapsis, lung, prematurity

INTRODUCTION

Preterm-born (<37 weeks' gestation) children are at an increased risk of respiratory symptoms, hospital admissions and reduced lung function in childhood and beyond.1-3 These risks persist into
adulthood potentially developing into early-onset chronic obstructive pulmonary disease.\(^1\)

Recently there has been interest in both antenatal and postnatal growth patterns in children, and how these relate to risk of childhood respiratory disease. Historically, birthweight has been used as a proxy for fetal wellbeing; however, it is recognized that satisfactory birth weight results from months of development during which the fetus may be exposed to adverse intrauterine conditions.\(^5\)\(^6\) Adaptation to this adversity affects the development of organ systems,\(^7\) such as the respiratory system, which continues to develop throughout gestation.\(^8\)

Dysregulation of lung growth may be further compounded by preterm birth and pulmonary inflammation associated with neonatal respiratory distress.\(^10\) To date, the few studies investigating the association of fetal growth patterns with later childhood respiratory disease have reported inconsistent results.\(^11\)\(^-\)\(^14\)

Early infant growth is also linked to increased respiratory sequelae in childhood. However, studies have focused largely on term-born populations.\(^15\)\(^-\)\(^19\) A recent meta-analysis of 147 000 children including 7384 preterm-born individuals noted an association between greater weight gain in the first year of life and increased childhood asthma.\(^20\)

Further exploration of 24 938 children (2053 born preterm) noted an association between gestational age, infant weight gain, and measures of lung function.\(^21\) However, both studies included preterm-born subjects who were recruited in largely term-born cohorts, thus suggesting selection bias. Moreover, previous studies have reported only associations and have not explored the important early life factors that may influence the effect of fetal growth trajectories and postnatal weight gain on respiratory outcomes.

In this study, we investigated the association of fetal growth parameters and postnatal weight gain with the risk of respiratory symptoms in a cohort of preterm-born children. Furthermore, we conducted multiple regression analyses and mediation analyses to identify early-life factors that may account for the association between fetal or infant weight gain and childhood respiratory symptoms. We hypothesized that change in fetal growth trajectory, or rapid postnatal weight gain in infancy, would be associated with increased childhood respiratory symptoms in preterm-born children.

2 | METHODS

2.1 | Respiratory and neurological outcomes of children born preterm study (RANOPS)

Respiratory outcome data from RANOPS, a cross-sectional population study of preterm-born children, were used. Briefly, in 2013, all live-born preterm (<37 weeks’ gestation) surviving children born in Wales aged between 1 and 10 years, and term controls (born same gender, day, and locality) were sent the Liverpool Perinatal Symptom Questionnaire (if <5 years of age) or a modified ISAAC Questionnaire (if ≥5 years of age), n = 23 722.\(^2\) There were 7148/26 741 (27%) responders to the questionnaire survey (32% in the preterm-born group). Both questionnaires have been validated.\(^22\)\(^,\)\(^23\) Data from all responders were used in the analyses as we have previously reported similar characteristics between matched responders and all responders.\(^2\) Ethical approval for the survey was obtained from the Research Ethics Committee and parents gave consent for use of their data, and for healthcare database linkage, by returning completed questionnaires.

2.2 | Perinatal data

Gestational age, birthweight, singleton, or multiple birth and Wales Index of Multiple Deprivation (WIMD, a measure of socio-economic status) were available from national healthcare databases (NHS Wales Informatics Service, NWIS). Children were divided into groups based on gestational age at birth: 25-32, 33-34, 35-36 weeks’ gestation and term controls (37-43 weeks’ gestation). This approach is similar to our studies on lung function\(^24\) and that of others as it represents specific stages in lung development and children most at risk of lung disease.\(^9\)

Intrauterine growth restriction (IUGR) was defined as <10th centile for standardized birthweight corrected for gestation and gender using the LMS method (Medical Research Council, UK).\(^25\)

2.3 | Fetal growth data

Antenatal scans were obtained through NWIS for four of seven health boards in Wales who share a common radiology record system. Crown rump length (CRL), head circumference (HC), and femur length (FL) were extracted using a method coded in C++ and checked for accuracy against the original data. Multiple pregnancies were excluded as identity of which fetus was scanned at 1st and 2nd trimesters was uncertain. Gestation (in completed weeks) was abstracted from the scan reports where possible, or, if missing, was calculated from the difference between gestation at birth and scan date. Robinson (CRL) and Chitty (HC and FL) growth charts were used to create z-scores, adjusted for gestational age and gender at the time of measurement, using the published equations.\(^26\)\(^,\)\(^27\) CRL z-score for 1st trimester scans closest to 12 weeks’ gestation (10-13 weeks’ gestation, and within 3.5 SD of mean CRL measurement) were identified for each child. For second trimester scans, HC and FL z-scores closest to 20 weeks’ gestation (17-23 weeks, and within 3.5 SD of mean HC or FL measurement) were estimated. Growth acceleration was defined as an increase in fetal measurement of >0.67 SD and growth deceleration as a decrease of >0.67 SD between each time point (1st trimester to birthweight and 2nd trimester to birthweight).

2.4 | Infant weight data

Postnatal weight data were provided by NWIS. The weight closest to 9 months of age (limited to 6-12 months) was used to derive z-scores using the LMS method, as above. Participants with birthweight or postnatal weight outside ±3.5 SD of the mean, or with unknown gestational age were excluded.

Infant weight gain between birth and 9 months of age was defined by dichotomizing the population in to those who demonstrated an increase of >0.67 SD in weight and those who did not, as previously.\(^25\)
We also used the method of Royston to calculate measures of conditional weight velocity between birth and nine months of age.28

2.5 | Respiratory outcome data

Respiratory outcomes were extracted from the RANOPS questionnaire which included wheeze-ever, recent wheeze (last 3 months for <5 years of age; last 12 months for ≥5 years of age), use of inhalers, hospital admissions for chest-related problems, and doctor-diagnosed asthma (≥5 years of age only). All outcomes were dichotomous. Rates of maternal smoking during pregnancy and current smoking were also taken from the RANOPS questionnaire.

3 | STATISTICAL ANALYSIS

Chi-squared tests were used to investigate the differences in categorical demographic data between datasets used in the fetal growth analysis, and between weight gain groups (>0.67 SD weight gain or not) in the infant growth analyses. Normality of continuous data was checked by visually inspecting Q-Q plots. Independent sample t-tests were used for normally distributed continuous variables. WIMD score was subsequently converted to quintiles for use in statistical models.

Since every case in the fetal analysis did not have a complete set of biometric data, we used sub-sets of cases with the appropriate combination of measurements (eg. CRL and HC). To assess whether this approach would introduce any bias, we compared the baseline demographics of each sub-set against the reference set (before exclusion for missing biometric data) using standardized differences. Then, univariate logistic regression models were used to investigate the association between fetal size in the first trimester (CRL) and size in the 2nd trimester (HC and FL) with childhood respiratory outcomes. Further models then investigated change in growth between 1st trimester and birth (CRL-Birthweight), between 2nd trimester and birth (HC-Birthweight and FL-Birthweight), and odds of childhood respiratory outcomes. “No change” was set as the reference category. Confounders were then included in adjusted multivariable models if they had a P-value <0.10 for association with wheeze-ever in univariate analysis (Supplementary Table S3). When a change of 0.67 SD of z-score was used to define growth trajectory, accelerated, but not decelerated growth from 1st trimester CRL to birthweight was associated with wheeze-ever (acceleration: OR 2.01; 95%CI 1.25, 2.32; deceleration: OR 1.32; 95%CI 0.89, 1.94) in the fully adjusted model when compared to those with unchanged trajectory (Table 1). Growth deceleration from 1st trimester CRL to 2nd trimester HC was associated with increased odds of wheeze-ever (OR 1.59; 95%CI 1.01, 2.51). In contrast, accelerated growth from 2nd trimester HC to birthweight was associated with increased odds of wheeze-ever (OR 1.60; 95%CI 1.15, 2.22) (Table 1). The tests of association were inconclusive (P >0.05) when FL, rather than HC, were used as the measure of 2nd trimester size (data not shown).

4 | RESULTS

4.1 | Fetal size and growth patterns

After excluding participants who did not consent for database linkage or who resided in the three health boards where radiology database linkage was not possible, 5012/7148 (70%) of participants remained eligible. Finally, after excluding those with missing maternal demographic data, 10 428 antenatal ultrasound scans were obtained from preterm-born children (Supplementary Figure S1). When compared to the whole dataset, there were small differences (standardized differences <0.10) in demographics when alternative fetal measurements were used in the analysis (Supplementary Table S1).

For first trimester CRL size at 12 weeks’ and 2nd trimester HC or FL at 20 weeks’ gestation, association with childhood respiratory outcomes were negligible (Supplementary Table S2).

Gestational age, gender, ethnicity, current maternal smoking, family history of asthma/atopy, breastfeeding, WIMD, and whether the child was aged over or under 5 years were all statistically significantly associated with wheeze-ever in univariate analysis (Supplementary Table S3). When a change of 0.67 SD of z-score was used to define growth trajectory, accelerated, but not decelerated growth from 1st trimester CRL to birthweight was associated with wheeze-ever (acceleration: OR 2.01; 95%CI 1.25, 2.32; deceleration: OR 1.32; 95%CI 0.89, 1.94) in the fully adjusted model when compared to those with unchanged trajectory (Table 1). Growth deceleration from 1st trimester CRL to 2nd trimester HC was associated with increased odds of wheeze-ever (OR 1.59; 95%CI 1.01, 2.51). In contrast, accelerated growth from 2nd trimester HC to birthweight was associated with increased odds of wheeze-ever (OR 1.60; 95%CI 1.15, 2.22) (Table 1). The tests of association were inconclusive (P >0.05) when FL, rather than HC, were used as the measure of 2nd trimester size (data not shown).

4.2 | Infant weight gain

Following exclusions for missing birthweight, missing weight at 9 months, and weight z-score ±3.5 SD, 5824/7149 (81%) of responders to the questionnaire survey had valid data; 3425 participants were born preterm and 2399 were born at term (Supplementary Figure S1).

Demographics of preterm-born children with, and without weight gain of >0.67 SD are presented in Supplementary Table S4. Children of lower birthweight, whose mothers smoked during pregnancy, of lowest WIMD quintile, and whose mothers currently smoke, were more likely to exhibit weight gain >0.67 SD between birth and 9 months of age. Children born with IUGR, delivered by caesarean section, and as one of multiple birth were also more likely to exhibit weight gain.
In univariate analysis, increased wheeze-ever was associated with infant weight gain (OR 1.20; 95%CI 1.03, 1.41), lower gestational age, male gender, maternal smoking in pregnancy, current maternal smoking, family history of asthma/atopy, breastfeeding, WIMD, and child <5 or ≥5 years of age. Moreover, the size of the direct effect (β = 0.07, P = 0.22) diminished relative to the adjusted regression model presented in Supplementary Table S5 (β = 0.19, P = 0.03), further indicating the mediating effect of these two factors.

### DISCUSSION

In our cohort of preterm-born children, we have reported that rapid weight gain in the first year of life is statistically significantly correlated with increased wheeze in childhood. We also noted the interaction between birth at the extremes of prematurity and postnatal weight gain resulted in the poorest respiratory outcome (OR 5.04). Using mediation analysis, we have identified modifiable factors that may have an important influence on the relationship between weight gain and childhood respiratory symptoms. We also reported increased odds for wheeze-ever for fetal growth deceleration between the 1st-2nd trimester (OR 1.59), and for growth acceleration between the 2nd trimester and birth (OR 1.60).

### 5.1 Fetal growth

Previous studies in term-born cohorts have used birthweight as proxy for fetal growth and examined associations with respiratory outcomes, with mixed results. By assessing growth over gestational ranges, we have attempted to investigate the impact of growth trajectory in preterm-born children during key periods of development.
### TABLE 2  Associations between infant weight gain from birth to 9 months of age and respiratory outcomes in preterm-born children

<table>
<thead>
<tr>
<th>Whole population</th>
<th>Wheeze-ever</th>
<th>Recent wheeze</th>
<th>Wheeze last 12 months</th>
<th>Wheeze last 3 months</th>
<th>Inhaler use</th>
<th>Hospital admission</th>
<th>Doctor diagnosed asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preterm</strong></td>
<td></td>
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<tr>
<td>&gt;0.67 N = 684</td>
<td>1.22 (1.02, 1.45)</td>
<td>1.15 (0.95, 1.40)</td>
<td>-</td>
<td>-</td>
<td>1.07 (0.86, 1.33)</td>
<td>1.01 (0.79, 1.53)</td>
<td>-</td>
</tr>
<tr>
<td>No change N = 2358</td>
<td>Ref</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
<td>Ref</td>
<td>Ref</td>
<td>-</td>
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<tr>
<td>&lt;5 years of age</td>
<td></td>
<td></td>
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<tr>
<td><strong>Preterm</strong></td>
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<tr>
<td>&gt;0.67 N = 353</td>
<td>1.11 (0.86, 1.42)</td>
<td>-</td>
<td>-</td>
<td>1.11 (0.85, 1.44)</td>
<td>1.11 (0.83, 1.49)</td>
<td>1.13 (0.79, 1.62)</td>
<td>-</td>
</tr>
<tr>
<td>No change N = 1231</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>-</td>
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<tr>
<td>≥5 years of age</td>
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<tr>
<td><strong>Preterm</strong></td>
<td></td>
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</tr>
<tr>
<td>&gt;0.67 N = 331</td>
<td>1.37 (1.06, 1.77)</td>
<td>-</td>
<td>-</td>
<td>1.25 (0.93, 1.68)</td>
<td>-</td>
<td>1.03 (0.74, 1.44)</td>
<td>1.01 (0.45, 2.29)</td>
</tr>
<tr>
<td>No change N = 1127</td>
<td>Ref</td>
<td>Ref</td>
<td>-</td>
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</tbody>
</table>

Data are odds ratios (95% confidence intervals).
*p < 0.05; **p < 0.001.

*Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, breastfeeding at birth, ethnicity, WIMD.

**Adjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, breastfeeding at birth, ethnicity, WIMD.

### 5.2 | Postnatal weight gain in preterm-born children

Few studies in preterm-born cohorts have investigated the association between early weight gain in infancy and respiratory health in childhood and adolescence. A study of the NINFeA cohort demonstrated that rapid growth and accelerated growth during early weight gain in infancy is a significant predictor of increased wheeze during the first 18 months of life in term-born infants.27 Two recent studies in term-born children reported increased wheeze in the first 12 months of life in term-born infants.28,29 Among preterm-born infants, Kasznica et al.27 noted that rapid growth and accelerated growth during early infancy were significant predictors of increased wheeze during the first 12 months of life. However, the study did not adjust for gestational age, gender, or family history of asthma, which are known risk factors for wheeze.

Moreover, growth acceleration in the second trimester was significantly associated with increased wheeze.30 This has not been widely reported in respiratory studies, although it is consistent with the predictive adaptive response, whereby altered growth trajectories in utero may influence the postnatal environment.17 Therefore, the early acceleration of growth in the second trimester may be a marker of increased risk for wheeze.

The mechanisms underlying these associations are not fully understood. One possibility is that the rapid growth and accelerated growth during early infancy may be a response to altered maternal-fetal adaptation. For example, increased fetal growth velocity may be a significant predictor of respiratory symptoms in the first year of life.30 Other studies have suggested that rapid fetal growth is associated with a developmental mismatch with the postnatal environment, which may contribute to respiratory symptoms in early childhood.31

In the postnatal period, growth acceleration in the second trimester was associated with increased wheeze.30 This is consistent with previous studies in term-born children, which have reported that rapid growth velocity was a significant predictor of respiratory symptoms in the first year of life.30 However, further studies are needed to investigate the mechanisms underlying this association and to determine whether growth acceleration in the second trimester is a risk factor for wheeze in the first year of life.

The study design and methodology may have limitations. The data were collected retrospectively, and the sample size was relatively small. Future studies should include larger and more diverse populations to confirm these findings. Moreover, the study did not control for other potential risk factors for wheeze, such as maternal smoking, infection, and family history of asthma. Further research is needed to investigate the role of these factors in the development of wheeze and to identify effective strategies for preventing respiratory symptoms in early childhood.
decrements in lung function and increased respiratory symptoms at age 5 when rapid postnatal growth was observed between birth and 3 months of age, the latter of which was independent of fetal growth.14,18 Both the Southampton and Aberdeen groups noted that early childhood wheeze at age 3 was statistically significantly associated with weight gain throughout the first year of life.13,35 The report by Belfort noted an association between asthma at the age of 8 years and postnatal growth in preterm infants.36 This was not compensated by increased linear growth, indicating the potential developmental mismatch between somatic and organ growth which may promote later obesity and lung disease, possibly through the pro-inflammatory immunological effects.37 Other studies in term-born cohorts have investigated longer periods over which to define weight gain and noted increased

**FIGURE 1** Graphical representation of interaction analysis (adjusted). All ORs for wheeze-ever are compared to the reference category of Term-born, no change in weight gain between birth and 9 months of age (* P < 0.05 compared to reference category). Error bars represent 95% confidence intervals for ORs

**FIGURE 2** Diagrammatic representation of mediation analysis results in preterm-born children
respiratory infections in the first years of life, asthma in school-age children, and decreased measures of peripheral airway flow in adolescence. Along with our data in preterm-born children, these studies further support the concept that rate of weight gain is an important factor in influencing later respiratory health, possibly because the airways may be small in comparison to lung capacity (dysanapsis). Further data on lung function complement this hypothesis. We repeated our analysis using weight data at 24 months, and failed to detect associations with respiratory symptoms (data not shown). Methodological differences in calculating weight gain may be responsible for these differences, however, one possibility is that the deleterious effects of early weight gain on respiratory health may be mitigated if “catch-up” lung growth occurs over a longer period of time. Our previous data suggest that deficits in FEV₁ in IUGR term-born children are ameliorated by catch-up growth by 8 years of age.

Similar to others, we observed an incremental increase in odds of wheeze-ever for decreasing gestational age with infant weight gain, when compared to a term-born control growth without weight gain (OR 5.04). We extended our findings by identifying current maternal smoking, as well as gestation, as a mediator of the relationship between weight gain and wheeze-ever in preterm-born children. Maternal smoking can be considered a proxy of socio-economic status and may represent higher rates of formula feeding. Thus, nutrition may be key in balancing the beneficial effects of growth versus potential harm of excess weight gain in preterm-born infants. Exclusive breastfeeding ameliorated the association between postnatal weight gain and increased early transient wheeze in term-born children in the study by Turner et al.

5.3 Strengths and limitations

In common with many cohort studies, the main limitation of our work is the attrition of cases available for analysis due to non-response to the questionnaire survey, absence of consent for data linkage, and challenges with database accessibility. Moreover, we cannot rule out residual confounding in our data by unmeasured covariates. We conducted an additional sensitivity analysis by modeling wheeze-ever on the interaction between each variable in our final model with infant weight gain. The results indicated that weight gain may have a differential effect in certain sub-groups (eg, gender). Supplementary Table S7. Another limitation of our study is its use of an exploratory approach to model-building and the lack of overall control for the multiplicity of hypothesis tests which involved multiple outcome variables, multiple definitions of the exposure variables, and multiple inclusion criteria (eg, subgroups). Thus, some results may have occurred by chance and this must be considered when interpreting the data. In the cohort at-large, non-responders to the questionnaire were of lower socio-economic status. However, given that infants born into such conditions are more likely to be born preterm, IUGR and have been exposed to a less favorable intrauterine growth environment, we conjecture that inclusion of these children might have strengthened the associations we have observed.

The main strength of our study is the use of a contemporary cohort of preterm-born children for exploration of growth patterns and exposures that may be risk factors for wheezing symptoms in childhood. We used well-established, validated questionnaires; this allows comparison with other studies. Moreover, we were able to link to national databases to obtain both antenatal and postnatal measurements for the majority of the cohort who provided respiratory symptom data; however, we were limited to only routinely collected data. The sample sizes and numbers of non-missing values varied across the measured predictors and outcomes. Some cases had valid fetal data only, whereas some had valid postnatal data only, and as such different cases were included in the two analyses. Data were obtained retrospectively; we acknowledge that prospective collection of data may have improved the accuracy of the results and there will be some variation due to differences between equipment and use by the operator. Notwithstanding, we used two methods of defining weight gain and obtained similar results.

6 | CONCLUSION

In conclusion, our study suggests that antenatal and postnatal growth rates are important for future respiratory health in preterm-born children. Since they are unlikely to have the same etiology of lung disease as their term-born peers, it is important to consider strategies for ensuring appropriate growth. Optimizing nutrition in the neonatal period and diminishing exposure to environmental pollutants, such as anti-and-postnatal tobacco smoking, present two potential interventions.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.