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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

1 | 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

Abbreviations: CRL, Crown-rump length; FL, Femur length; HC, Head circumference; NWIS, NHS Wales Informatics Service; OR, Odds ratio; SD, Standard deviation; WIMD, Welsh Index of Multiple Deprivation.

1 adulthood potentially developing into early-onset chronic obstructive
2 pulmonary disease.^{1,4}

3 Recently there has been interest in both antenatal and postnatal
4 growth patterns in children, and how these relate to risk of childhood
5 respiratory disease. Historically, birthweight has been used a proxy for
6 fetal wellbeing; however, it is recognized that satisfactory birth weight
7 results from months of development during which the fetus may be
8 exposed to adverse intrauterine condition.^{5,6} Adaptation to this
9 adversity affects the development of organ systems,⁷ such as the
10 respiratory system, which continues to develop throughout gestation.⁸
11 Dysregulation of lung growth may be further compounded by preterm
12 birth⁹ and pulmonary inflammation associated with neonatal respira-
13 tory distress.¹⁰ To date, the few studies investigating the association of
14 fetal growth patterns with later childhood respiratory disease have
15 reported inconsistent results.¹¹⁻¹⁴

16 Early infant growth is also linked to increased respiratory sequelae
17 in childhood. However, studies have focused largely on term-born
18 populations.¹⁵⁻¹⁹ A recent meta-analysis of 147 000 children including
19 7384 preterm-born individuals noted an association between greater
20 weight gain in the first year of life and increased childhood asthma.²⁰
21 Further exploration of 24 938 children (2053 born preterm) noted an
22 association between gestational age, infant weight gain, and measures
23 of lung function.²¹ However, both studies included preterm-born
24 subjects who were recruited in largely term-born cohorts, thus
25 suggesting selection bias. Moreover, previous studies have reported
26 only associations and have not explored the important early life factors
27 that may influence the effect of fetal growth trajectories and postnatal
28 weight gain on respiratory outcomes.

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

39 2 | METHODS

41 2.1 | Respiratory and neurological outcomes of 42 children born preterm study (RANOPS)

43 Respiratory outcome data from RANOPS, a cross-sectional population
44 study of preterm-born children, were used. Briefly, in 2013, all live-born
45 preterm (<37 weeks' gestation) surviving children born in Wales aged
46 between 1 and 10 years, and term controls (born same gender, day, and
47 locality) were sent the Liverpool Respiratory Symptom Questionnaire
48 (if <5 years of age) or a modified ISAAC Questionnaire (if ≥5 years of
49 age), $n = 23\,722$.² There were 7148/26 741 (27%) responders to the
50 questionnaire survey (32% in the preterm-born group). Both ques-
51 tionnaires have been validated.^{22,23} Data from all responders were used
52 in the analyses as we have previously reported similar characteristics

1 between matched responders and all responders.² Ethical approval for
2 the survey was obtained from the Research Ethics Committee and
3 parents gave consent for use of their data, and for healthcare database
4 linkage, by returning completed questionnaires.

6 2.2 | Perinatal data

7 Gestational age, birthweight, singleton, or multiple birth and Wales
8 Index of Multiple Deprivation (WIMD, a measure of socio-economic
9 status) were available from national healthcare databases (NHS Wales
10 Informatics Service, NWIS). Children were divided into groups based
11 on gestational age at birth: 25-32, 33-34, 35-36 weeks' gestation and
12 term controls (37-43 weeks' gestation). This approach is similar to our
13 studies on lung function²⁴ and that of others as it represents specific
14 stages in lung development and children most at risk of lung disease.⁹
15 Intrauterine growth restriction (IUGR) was defined as <10th centile for
16 standardized birthweight corrected for gestation and gender using the
17 LMS method (Medical Research Council, UK).²⁵

20 2.3 | Fetal growth data

21 Antenatal scans were obtained through NWIS for four of seven health
22 boards in Wales who share a common radiology record system. Crown
23 rump length (CRL), head circumference (HC), and femur length (FL)
24 were extracted using a method coded in C++ and checked for accuracy
25 against the original data. Multiple pregnancies were excluded as
26 identity of which fetus was scanned at 1st and 2nd trimesters was
27 uncertain.

28 Gestation (in completed weeks) was abstracted from the scan
29 reports where possible, or, if missing, was calculated from the
30 difference between gestation at birth and scan date. Robinson (CRL)
31 and Chitty (HC and FL) growth charts were used to create z-scores,
32 adjusted for gestational age and gender at the time of measurement,
33 using the published equations.^{26,27} CRL z-score for 1st trimester scans
34 closest to 12 weeks' gestation (10-13 weeks' gestation, and within
35 3.5 SD of mean CRL measurement) were identified for each child. For
36 second trimester scans, HC and FL z-scores closest to 20 weeks'
37 gestation (17-23 weeks, and within 3.5 SD of mean HC or FL
38 measurement) were estimated. Growth acceleration was defined as
39 an increase in fetal measurement of >0.67 SD and growth deceleration
40 as a decrease of >0.67 SD between each time point (1st trimester to
41 birthweight and 2nd trimester to birthweight).

44 2.4 | Infant weight data

45 Postnatal weight data were provided by NWIS. The weight closest to
46 9 months of age (limited to 6-12 months) was used to derive z-scores
47 using the LMS method, as above. Participants with birthweight or
48 postnatal weight outside ± 3.5 SD of the mean, or with unknown
49 gestational age were excluded.

50 Infant weight gain between birth and 9 months of age was defined
51 by dichotomizing the population in to those who demonstrated an
52 increase of >0.67 SD in weight and those who did not, as previously.²⁵
53

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 questionnaires 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.² 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 in 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," which was the considered the primary outcome for all analyses. A similar modeling approach was applied to the infant weight gain data, using both weight gain >0.67 SD (or not) then conditional weight gain as the primary exposure variables.

Next, we considered the whole cohort population (including preterm and term groups) and used interaction terms to investigate the combined effects of gestation groups and infant weight gain when defined as >0.67 SD change between birthweight and weight at 9 months. Term-born children with "no change" for weight gain were used as the control category. Both univariate, and multivariable modeling including covariates with a *P*-value <0.10, were performed. All modeling was performed using SPSS (version 20, IBM, Chicago IL). *P* < 0.05 was considered statistically significant.

Finally, to assess if the relationship between weight gain and "wheeze-ever" was mediated through gestational age and other significant covariates, we performed mediation analysis using

structural equation modeling (Mplus version 7, Muthen and Muthen, Los Angeles, CA); all potential mediators were entered in parallel.

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 3125/5012 individuals of which 1880 (60%) were born preterm. In total, 615 CRL, 1,196 HC, and 1,326 FL measurements were available 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.

TABLE 1 Association between fetal growth trajectories and respiratory symptoms in preterm-born children

	Wheeze-ever	Recent wheeze	Inhaler use	Hospital admission
1st trimester CRL to birthweight				
Preterm all measurements N = 615 (adjusted) ^a				
Deceleration N = 306	1.32 (0.89, 1.94)	1.00 (0.65, 1.54)	0.71 (0.45, 1.13)	0.80 (0.39, 1.64)
Acceleration N = 142	2.01* (1.25, 2.32)	1.42 (0.86, 2.34)	1.35 (0.81, 2.26)	1.70 (0.78, 3.70)
No change N = 167	Ref	Ref	Ref	Ref
1st trimester CRL to 2nd trimester HC				
Preterm all measurements N = 615 (adjusted) ^a				
Deceleration N = 306	1.59* (1.01, 2.51)	1.29 (0.79, 2.11)	1.60 (0.94, 2.70)	3.84* (1.56, 9.51)
Acceleration N = 142	1.07 (0.70, 1.62)	0.94 (0.59, 1.50)	1.00 (0.60, 1.66)	2.57* (1.08, 6.09)
No change N = 167	Ref	Ref	Ref	Ref
2nd trimester HC to birthweight				
Preterm all measurements N = 1196 (adjusted) ^a				
Deceleration N = 486	1.24 (0.95, 1.62)	0.94 (0.74, 1.26)	0.95 (0.70, 1.31)	0.92 (0.58, 1.46)
Acceleration N = 238	1.60* (1.15, 2.22)	1.39 (0.99, 1.96)	1.22 (0.84, 1.77)	1.39 (0.23, 2.34)
No change N = 472	Ref	Ref	Ref	Ref

Data are odds ratios (95% confidence intervals).

*P < 0.05.

^aAdjusted for gestational age, gender, ethnicity, current maternal smoking, family history of asthma/atopy, breastfeeding, WIMD, and child <5 or ≥5 years of age.

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, and lower WIMD quintile. Non-white ethnicity, breastfeeding and being ≥5 years of age were associated with decreased odds of wheeze-ever (Supplementary Table S5). In the adjusted model, an increase in weight >0.67 SD between birth and 9 months of age was associated with wheeze-ever in preterm-born children (OR 1.22; 95%CI 1.02, 1.45) (Table 2). All other covariates remained significant aside from breastfeeding and maternal smoking in pregnancy. Excluding children from multiple births did not affect the results (data not shown). When the cohort was stratified in to those aged <5 years and those aged ≥5 years, wheeze-ever was significant in the fully adjusted model in ≥5 years age group only (OR 1.37; 95%CI 1.06, 1.77), Table 2. Sensitivity analysis using conditional growth showed similar results, with marginally attenuated ORs (Supplementary Table S6).

Compared to term-born children who did not demonstrate weight gain of >0.67 SD between birth and the age of 9 months, children born ≤32 weeks' gestation with infant weight gain of >0.67 SD had increased odds of wheeze-ever (OR 5.04; 95%CI 3.36, 7.54, Figure 1).

Results of the mediation analysis are summarized in Figure 2. Gestational age, maternal smoking in pregnancy, current maternal smoking, and breastfeeding all had statistically significant univariate associations with weight gain; the test for association was inconclusive for gender, being ≥5 years of age, ethnicity and family history of asthma/atopy. All of these factors were statistically significant predictors (P < 0.05) of wheeze aside from maternal smoking in pregnancy. Of the above covariates, bootstrapped confidence intervals for specific indirect effects did not include zero for gestational

age and current maternal smoking, indicating strong evidence that weight gain influenced wheeze-ever via gestational age and current maternal smoking. Moreover, the size of the direct effect (B = 0.07, P = 0.22) diminished relative to the adjusted regression model presented in [Supplementary Table S5](#) (B = 0.19, P = 0.03), further indicating the mediating effect of these two factors.

5 | DISCUSSION

In our cohort of preterm-born children, we have reported that rapid weight gain in the first year of life is statistically significantly associated 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.^{29,30} 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

All	Wheeze-ever	Recent wheeze	Wheeze last 12 months	Wheeze last 3 months	Inhaler use	Hospital admission	Doctor diagnosed asthma
Whole population							
Preterm ^a							
>0.67 N = 684	1.22* (1.02, 1.45)	1.15 (0.95, 1.40)	-	-	1.07 (0.86, 1.33)	1.01 (0.79, 1.53)	-
No change N = 2358	Ref	Ref	-	-	Ref	Ref	-
<5 years of age							
Preterm ^b							
>0.67 N = 353	1.11 (0.86, 1.42)	-	-	1.11 (0.85, 1.44)	1.11 (0.83, 1.49)	1.13 (0.79, 1.62)	-
No change N = 1231	Ref	-	-	Ref	Ref	Ref	-
≥5 years of age							
Preterm ^b							
>0.67 N = 331	1.37* (1.06, 1.77)	-	1.25 (0.93, 1.68)	-	1.03 (0.74, 1.44)	1.01 (0.45, 2.29)	1.21 (0.89, 1.64)
No change N = 1127	Ref	-	Ref	-	Ref	Ref	Ref

Data ⁰ are odds ratios (95% confidence intervals).

*P < 0.05; **P < 0.001.

^aAdjusted for gestation, gender, maternal smoking (pregnancy), maternal smoking (current), family history of asthma/atopy, breastfeeding at birth, ethnicity, WIMD, <5/≥5 years of age.

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

Three groups have investigated similar hypotheses to ours, all of which were conducted in term-born cohorts. In common with our study, the Generation-R cohort did not detect any association between fetal size and childhood respiratory outcomes in early childhood.¹⁴ In contrast, Turner and colleagues reported decreased odds for respiratory symptoms and improved lung function per millimeter increase in fetal measurement in term-born children at 5 and 10 years of age.^{12,13} The mechanisms of how change in growth rate impacts upon the developing organs are not yet known, however, the main structures of the respiratory system are established by the early second trimester, whereas differentiation and maturation occur between the 2nd trimester and birth.³¹ One possibility is that structural deficits established early in gestation manifest later as airway obstruction due to smaller airways. For example, growth faltering between the 1st and 2nd trimesters was statistically significantly associated with increased respiratory symptoms in the Aberdeen cohort.³² Our results also noted that growth deceleration between the 1st and 2nd trimester was associated with increased odds of wheeze-ever (OR 1.59 95%CI 1.01, 2.51). An interesting finding within the Southampton cohort was that growth faltering between the 1st and 2nd trimester was also linked to non-atopic wheeze, whereas faltering between second to third trimesters was statistically significantly associated with atopic wheeze.¹¹ The authors speculate this may relate to altered immunological status. To date, the RANOPS cohort does not have any direct data on atopic status (ie, results of skin prick testing); however, family history of atopy was abstracted from the questionnaire. Although family history was strongly related to respiratory outcomes in univariate analysis, it was not significant in the statistical analysis performed when modeling with measures of foetal growth change. This is in keeping with the primary analysis of the RANOPS cohort which established that “prematurity-associated wheeze” phenotype is unlikely to include atopy as one of its determinants.² In our results, acceleration from the 2nd to 3rd trimester was statistically significantly associated with wheeze-ever. This has not been widely reported in respiratory studies, although the latter Aberdeen study reported increased asthma with current wheeze for growth acceleration between the first and second trimesters, when compared to the reference category of consistently high growth.¹² Moreover, growth acceleration has been noted to be a risk factor for early adiposity gain at 6 months³³ and 3 years of age.³⁴ These potential adverse effects of both growth restraint and growth acceleration are consistent with the “predictive adaptive response,” whereby altered fetal growth may dispose the infant to a developmental mismatch with the postnatal environment.⁷

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 velocity was a significant predictor of increased wheeze during the first 18 months of life in term-born infants.¹⁷ Two recent studies in term-born children reported

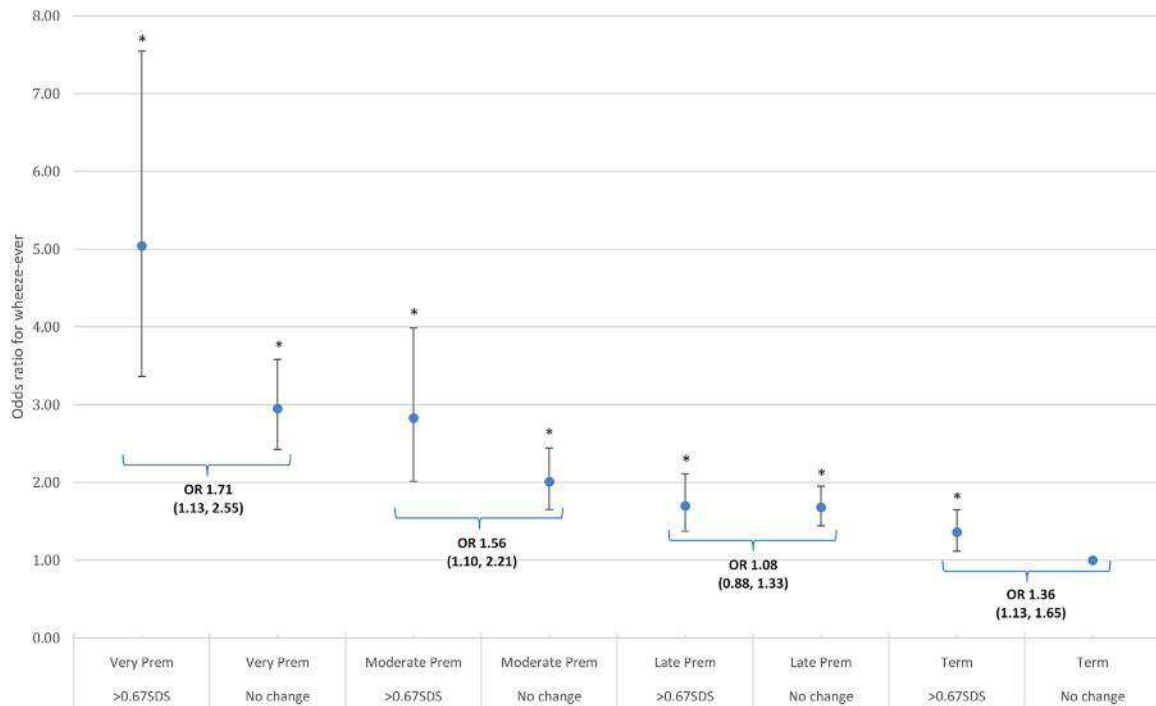
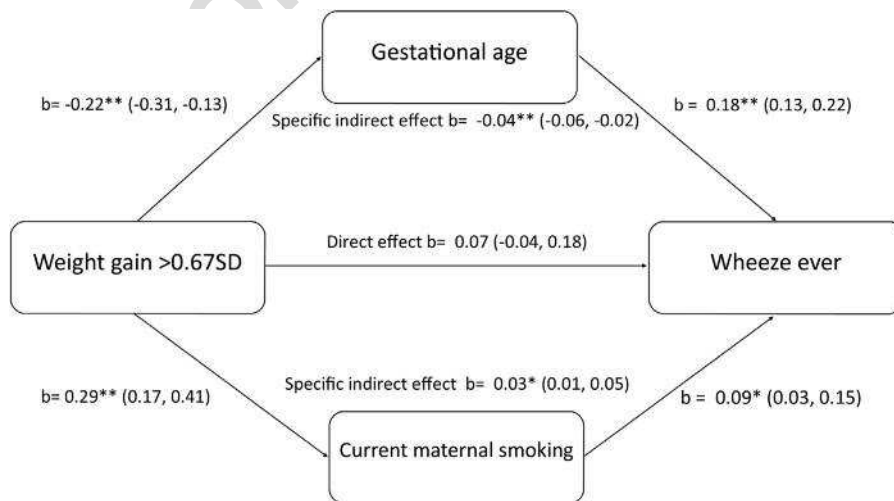


FIGURE 1 Graphical representation of interaction analysis (adjusted). All ORs for wheeze-ever are compared to the reference category of Term-born, no change in weight gain between birth and 9 months of age (* $P < 0.05$ compared to reference category). Error bars represent 95% confidence intervals for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

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



Values in parenthesis are 95% confidence intervals

* $p < 0.05$ ** $p < 0.001$

FIGURE 2 Diagrammatic representation of mediation analysis results in preterm-born children

1 respiratory infections in the first years of life,¹⁶ asthma in school-age
2 children,^{19,38} and decreased measures of peripheral airway flow in
3 adolescence.¹⁵ Along with our data in preterm-born children, these
4 studies further support the concept that rate of weight gain is an
5 important factor in influencing later respiratory health, possibly
6 because the airways may be small in comparison to lung capacity
7 (dysanapsis). Further data on lung function complement this hypothe-
8 sis.³⁹ We repeated our analysis using weight data at 24 months, and
9 failed to detect associations with respiratory symptoms (data not
10 shown). Methodological differences in calculating weight gain may be
11 responsible for these differences, however, one possibility is that the
12 deleterious effects of early weight gain on respiratory health may be
13 mitigated if “catch-up” lung growth occurs over a longer period of time.
14 Our previous data suggest that deficits in FEV₁ present in IUGR term-
15 born children are ameliorated by catch-up growth by 8 years of age.²⁵

16 Similar to others,²⁰ we observed an incremental increase in odds of
17 wheeze-ever for decreasing gestational age with infant weight gain, when
18 compared to a term-born control growth without weight gain (OR 5.04).
19 We extended our findings by identifying current maternal smoking, as well
20 as gestation, as a mediator of the relationship between weight gain and
21 wheeze-ever in preterm-born children. Maternal smoking can be
22 considered a proxy of socio-economic status and may represent higher
23 rates of formula feeding.⁴⁰ Thus, nutrition may be key in balancing the
24 beneficial effects of growth versus potential harm of excess weight gain in
25 preterm-born infants. Exclusive breastfeeding ameliorated the association
26 between postnatal weight gain and increased early transient wheeze in
27 term-born children in the study by Turner et al.³²

29 5.3 | Strengths and limitations

30 In common with many cohort studies, the main limitation of our work is
31 the attrition of cases available for analysis due to non-response to the
32 questionnaire survey, absence of consent for data linkage, and
33 challenges with database accessibility. Moreover, we cannot rule
34 out residual confounding in our data by unmeasured covariates. We
35 conducted an additional sensitivity analysis by modeling wheeze-ever
36 on the interaction between each variable in our final model with infant
37 weight gain. The results indicated that weight gain may have a
38 differential effect in certain sub-groups (eg, gender), Supplementary
39 Table S7. Another limitation of our study is its use of an exploratory
40 approach to model-building and the lack of overall control for
41 the multiplicity of hypothesis tests which involved multiple outcome
42 variables, multiple definitions of the exposure variables, and multiple
43 inclusion criteria (eg, subgroups). Thus, some results may have
44 occurred by chance and this must be considered when interpreting
45 the data. In the cohort at-large, non-responders to the questionnaire
46 were of lower socio-economic status.² However, given that infants
47 born into such conditions are more likely to be born preterm, IUGR and
48 have been exposed to a less favorable intrauterine growth environ-
49 ment, we conjecture that inclusion of these children might have
50 strengthened the associations we have observed.

51 The main strength of our study is the use of a contemporary cohort of
52 preterm-born children for exploration of growth patterns and exposures
53

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.

16 6 | CONCLUSION

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

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30 CONFLICT OF INTEREST

31 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.

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