BMJ Open

Effects of birth weight and growth on childhood wheezing disorders: findings from the Born in Bradford Cohort

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ABSTRACT

Objectives: To examine the effects of birth weight and childhood growth on childhood wheezing disorders. We hypothesised that low birth weight and fast growth during early age would increase the risk of wheezing disorders.

Setting: Observational secondary analysis of data from the Born in Bradford cohort.

Participants: All children who were born at the Bradford Royal Infirmary hospital between March 2007 and December 2010 were eligible for the study. A total of 13 734 and 1598 children participated in the analyses of the effects of birth weight and growth on wheezing disorders, respectively.

Primary and secondary outcome measures: Wheezing disorders diagnosis (diagnosed as asthma or had wheezing symptom) during the ages of 0–7 years were the primary outcome measures. Diagnosis of asthma and occurrence of wheezing during the same period were secondary outcome measures. Birth weight was classified as normal (2.5–4.0 kg), low (<2.5 kg) and high (>4.0 kg). Growth mixture models were used to drive growth pattern outcomes which were classified as 'normal', 'fast' and 'slow' growth based on their velocities between birth and 36 months.

Results: The adjusted relative risks (RRs) of wheezing disorders diagnosis for the low and high birthweight children were 1.29 (95% CI 1.12 to 1.50; p=0.001) and 0.91 (95% CI 0.79 to 1.04; p=0.17), respectively. The adjusted RRs of wheezing disorders diagnosis were 1.30 (95% CI 0.56 to 3.06; p=0.54) and 0.60 (95% CI 0.16 to 2.18; p=0.44), respectively, for the 'fast' and 'slow' growth as compared with the 'normal' growth.

Conclusions: Low birth weight is associated with an increased risk of wheezing disorders; however, there is a weak evidence that suggests high birthweight children have a reduced risk in this birth cohort. Low birth weight coupled with a slower growth until 3 months and a sharp growth between 3 and 12 months has an increased risk of wheezing disorders diagnosis.

INTRODUCTION

Asthma is defined as a chronic disease of the passage of airways, characterised by smooth muscle contraction, accumulation of mucous

Strengths and limitations of this study

- A large sample, contemporary birth cohort data were used.
- Direct Acyclic Graphs (DAGs) were used to minimise potential bias due to confounding.
- Multiple imputation by chained equations was used to minimise bias due to missing data.
- Age-specific and sex-specific standardised scores and growth percentiles were used to illustrate the growth of cohort children in reference to standard growth charts.
- Selection of participants was not random.
- Number of individuals in some of the growth classes was small, so the risk estimates were not robust.
- There was a substantial missing growth data at some follow-up periods, although missing data estimation models were used to minimise bias.
- Information on potential confounding (ie, family asthma and breast feeding) was missing.

and debris in the lumen, vascular congestion and airway wall oedema which leads to breathlessness and wheezing.[1] Although it is claimed to be the most common childhood disease,[2] there is, however, a lack of consistency in its diagnosis in clinical practice.[3] This is due to the difficulty in diagnosing asthma in children, especially those of preschool age, in whom wheezing, which is the main symptom for asthma, can be caused by other illnesses.[4] In addition, although there are various asthma confirmatory tests available,[5] young children can be less cooperative in participating in such tests leading to an underdiagnosis of true asthma cases. Therefore, the word 'asthma' may not be an adequate term for what can be described as a spectrum of respiratory problems. As a result, some researchers have tended to use more inclusive terms such as 'wheezing disorders'.[6–9]

The effect of birth weight on wheezing disorders has been studied extensively with

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more than 40 observational epidemiological studies carried out to date. In our recent meta-analysis and systematic review of these studies, we reported that low birthweight children (<2.5 kg) have a 60% (OR 1.60; 95% CI 1.39 to 1.85) and 37% (OR=1.37; 95% CI 1.05 to 1.79) higher risk of wheezing disorders when compared with ≥2.5 and 2.5–4.0 kg birthweight children, respectively.[10] We also found a modest increased risk in high birthweight children (>4 kg) when compared with normal birthweight (2.5–4.0 kg) children (OR 1.02; 95% CI 0.99 to 1.04). However, we acknowledged there was substantial heterogeneity among the low birthweight risk estimates which was not accounted for by study characteristics.

The effect of early childhood growth on wheezing disorders has not been widely studied. Results from a handful of previous studies are inconsistent with some suggesting fast growth predisposes to wheezing disorders[11–20] and others reporting reduced risk of wheezing disorders.[19 21–23] In addition to that, all of these studies, with the exception of one,[18] assumed homogeneous growth among children, either used statistical techniques that can now be improved on or a non-standard growth data analysis that makes comparison and replication of results very difficult. For example, three[11 16 20] used data-driven standardised scores (SDS), three[12 19 22 23] used country-specific SDS and another one[14] used non-standardised weight measurements.

The aim of the study was twofold: (1) further investigation of the effects of birth weight on wheezing disorders; and (2) investigation of the effects of early growth on wheezing disorders using a birth cohort data.

METHODS
Study participants
The Born in Bradford (BiB) study is a prospective, mainly biethnic, cohort that examines the impact of environmental, genetic and social factors on health of the population of Bradford.[24] The methods of recruitment are explained in detail elsewhere.[24 25] In brief: recruitment of participants started in March 2007 and ended in December 2010; a total of 13 776 pregnant mothers were recruited that resulted in 13 857 births. Out of the total births, 123 died before the age of 1 week which resulted in a total of 13 734 children to be included in the birthweight and childhood wheezing disorders analyses.

At the same time, a subcohort (BiB1000) of 1735 mothers and 1763 babies were also recruited for follow-up examinations. After excluding multiple births, preterm births and death before the age of 1 week, a total of 1598 children were included in growth pattern and wheezing disorder analyses.

Data collection
We have used five data sources: (1) hospital maternity records for information on birth weight, gestational age, gender of a child and number of live births; (2) BiB1000 cohort records for weight at 6, 12, 18, 24 and 36 months of age, that is, during the first, second, third, fourth and fifth visit after birth, respectively; (3) community health records for weight at 1 and 3 months of age; (4) baseline questionnaire data collected from the mothers on recruitment about their ethnicity, smoking and socioeconomic status (SES); and (5) linked primary care data about outcome variables (wheezing disorder diagnosis terms and treatment) recorded as Read Codes (http://systems.hscic.gov.uk/data/uktc/readcodes).

Case definition and ascertainment
We drew up four disease definitions based on diagnostic codes and prescribed medication details entered by general practitioners onto the primary care database.
1. *Asthma diagnosis*: presence of asthma codes in the record;
2. *Wheezing symptoms*: presence of wheezing diagnosis codes in the record;
3. Wheezing disorder based on diagnosis (wheezing disorder diagnosis): presence of asthma or wheezing diagnosis codes in the record;
4. Wheezing disorder based on treatment (wheezing disorder treatment), existence of at least two drug prescriptions indicated for the treatment of asthma a minimum of 1 week and maximum of 12 months apart.

Drug and disease terms and codes used to confirm occurrences of wheezing disorders any time between 0 and 7 years of age are listed in online supplementary tables S1 and S2.

Variables for analysis
Primary variables
Where regression modelling was carried out, exposure variables were birth weight and growth; outcome variables were wheezing disorders (ie, asthma diagnosis, wheezing symptoms, wheezing disorders diagnosis and wheezing disorders treatment).

Two types of growth variables were used: age-based and visits-based. For the age-based growth, age of a child when the measurement of weight occurred was used as a time score. The data were collected through maternity records, BiB1000 questionnaire and the community health records, so the time points: 0, 1, 3, 6, 12, 18, 24 and 36 months were used as time scores. In the visits-based, however, only maternity records and the BiB1000 questionnaire data were considered. Therefore, 0, 1, 2, 3, 4 and 5 were used as times scores. Note that 0 stands for time when birth weight was measured (ie, birth), and 1, 2, 3, 4 and 5 represent 6, 12, 18, 24 and 36 months of BiB1000 questionnaires, respectively.

The aim of using the age-based and visits-based time scores was to explore the effects of growth in terms of latent growth factors (ie, intercept and slope) and weight status (ie, underweight, normal, overweight or obese based on the weight percentiles) at every visit, respectively. In the age-based approach, the age of the children at each time point needed to be identical or

weight values were constrained to be missing if the recorded weight measurement did not reflect the time points. In the visits-based approach, however, the age of the children at each time point did not need to be identical and no constraint was imposed. The main difference between these two approaches was that in the age-based, group classification was based on how fast or slow the children grow as their age was identical or constrained to be identical. On the visits-based, however, although the group classification was similar to the age-based, the outputted intercept and slope were artificial and were not used to characterise how fast or slow the children grew between two times points as the age of children was not constrained to be identical. In addition, the age-based data had more missing value than the visits-based due to the constraint of age to be identical during the respective time points.

Confounding variables

Selection of variables was carried out based on the criteria that confounding variable must have an effect on the exposure and outcome variables, and should not be on the causal pathway.[26–28] In order to minimise bias due to confounding and overadjustment, Direct Acyclic Graphs (DAGs) were used[27 29] and models were tested using DAGitty software.[28] Drawing a relationship between variables of interest (ie, confounding and main variables) was guided by epidemiological, biological and clinical knowledge. Online supplementary figures S1 and S2 illustrate the schematic view of adjustment and output for the list of 'minimally sufficient' confounding sets using DAGitty software.

In assessing the effect of birth weight on wheezing disorders, ethnicity, family asthma, gender, gestational age, maternal smoking, number of live births, parity and SES were selected as 'minimally sufficient' set of confounding variables. In assessing the effect of childhood growth on wheezing disorders, birth weight, ethnicity, family asthma, breast feeding, gender, maternal smoking, parity and SES were selected as 'minimally sufficient' set of confounding variables.

However, note that selection among sets of confounding variables was carried out retrospectively. Hence, availability of information on variables was also a factor during the selection process. As such, although the selected sets were better than the other candidate sets, no data were available for the variables 'family asthma' and 'breast feeding'.

Missing data estimation variables

Where imputations were carried out, missing data were estimated under Missing Data at Random (MAR) assumption that the missingness on outcome variables does not depend on the outcome variables themselves but can be explained by (or related to) other variables included in the imputation models (also known as *auxiliary* variables).[30] The *auxiliary* variables included in the imputation process were: exposure variables, confounding variables and variables that can be related to the missingness. The first two types of variables were those included in the analysis models, whereas the third types of variables (maternal hypertension and diabetes) were included only in the imputation models.

A brief check on the variables before carrying out imputations showed that birth weight, gestational age and outcome variables (ie, asthma diagnosis, wheezing symptoms, wheezing disorder treatment and wheezing disorder diagnosis) were completely observed. To further explore if imputations were necessary or beneficial, dummy variables (ie, yes or no) were created as missing data indicator for each covariate with missing observations. When the missingness indicator variables and outcome variables were tested for correlations, the results consistently showed that there were no significant associations which also indicate that complete cases analysis could produce unbiased, albeit less precise, parameter estimates.[31] However, there were consistent significant associations between the missing indicator variables and other confounding variables which also suggest that imputations with inclusion of these covariates may improve the precision of the parameter estimates.[30 31]

Statistical analysis and software

Birth weight was classified according to the Centre of Diseases Prevention and Control (CDC)[32] and WHO methods[33] where <2.5 kg=low, 2.5–4.0 kg=normal and >4.0 kg=high. Age-specific and sex-specific SDS of weight were derived according to WHO growth standards[34] in LMSgrowth Microsoft excel add-in software.[35] The WHO growth standards population that we used to derive the SDS was made up of singleton term births. Hence, multiple and preterm births were excluded from the growth patterns and wheezing disorders analyses.

In identifying the best fitting growth patterns, growth mixture models (GMMs) were fitted,[36 37] and in selecting the optimal number of classes and best growth model, we used model classification quality and model fit statistics. In addition, interpretability was also considered where we rejected models that consist of a class with ≤1% of the total population. When comparing growth patterns of children in our GMMs, we used WHO growth standards charts[34] as a point of reference. In converting weight SDS into percentiles, we used a one-sided normal standard distribution. For example, weight SDS of −1.64, 0, 1.04 and 1.64 are equivalent to the 5th, 50th, 85th and 95th centiles, respectively.

Missing data on covariates were estimated using Multiple Imputations by Chained Equation (MICE) models under MAR assumptions.[38 39] In deciding how many data sets to be imputed, we took the number of imputations (n) to be greater than the percentage or fraction of incomplete cases.[38 40] Missing growth data were estimated using a Full Information Maximum Likelihood (FIML) method in which parameters are

estimated using all available observations in the data set, under MAR assumption.[41 42]

GMM was carried out in Mplus V.7.11, and covariates' missing data estimation and regression modelling were carried out in Stata V.12. Five per cent significance levels and 95% CIs were adopted throughout.

RESULTS

Birth weight and wheezing disorders

The cohort was made up of 13 734 children that yielded 74 940 person years of follow-up. In total, 37.3% and 32.8% were Pakistani and white British origin, respectively; 12.6% were minority and 17.3% with missing ethnicity data. In total, 50.4% and 47.3% were male and female, respectively, and 2.3% of children had missing information on sex. In total, 82.6%, 9.1% and 8.3% of the cohort were 'normal', 'high' and 'low' birthweight children, respectively (table 1). Out of 13 734 children, 6.1% were diagnosed as asthmatic, 14.5% had wheezing symptoms, 17.1% were either diagnosed for asthma or had wheezing symptoms, and 22.1% children were

treated with asthma drugs based on primary care data available up to November 2014 (table 1).

Low birth weight

Low birth weight was associated with all four disease definitions. The adjusted relative risks (RRs) for 'asthma' diagnosis, 'wheezing' symptoms, 'wheezing disorder' diagnosis and 'wheezing disorder' treatment were 1.53 (95% CI 1.20 to 1.96), 1.29 (95% CI 1.10 to 1.52), 1.29 (95% CI 1.12 to 1.50) and 1.25 (95% CI 1.10 to 1.42), respectively (table 2). The respective unadjusted RRs were 1.55 (95% CI 1.27 to 1.89), 1.29 (95% CI 1.13 to 1.46), 1.28 (95% CI 1.14 to 1.45) and 1.27 (95% CI 1.15 to 1.40).

High birth weight

There was a consistent but weak evidence for a reduction of wheezing disorders risk for those children who were classified as being of high birth weight. The adjusted RRs for 'asthma' diagnosis, 'wheezing' symptoms, 'wheezing disorder' diagnosis and 'wheezing disorder' treatment were 0.95 (95% CI 0.74 to 1.22), 0.90

Table 1 Characteristics of 13 734 children with complete data on wheezing disorders and covariates

	Asthma diagnosis		Wheezing symptoms		Wheezing disorder diagnosis		Wheezing disorder treatment	
	Yes/no	Yes (%)	Yes/no	Yes (%)	Yes/no	Yes (%)	Yes/no	Yes (%)
Birth weight (kg)								
Normal (2.5–4.0)	668/10 673	5.9	1622/9719	14.3	1907/9434	16.8	2444/8897	21.6
Low (<2.5)	104/1035	9.1	209/930	18.3	246/893	21.6	311/828	27.3
High (>4.0)	69/1185	5.5	163/1091	13.0	194/1060	15.5	280/974	22.3
Ethnicity								
White British	217/4284	4.8	586/3915	13.1	706/3795	15.7	1074/3427	23.9
Pakistani	382/4735	7.5	857/4260	16.7	985/4132	19.2	1150/3967	22.5
Others	86/1647	5.0	207/1526	11.9	243/1490	14.0	308/1425	17.8
Gender								
Male	502/6415	7.3	1220/5697	17.6	1416/5501	20.5	1775/5142	25.7
Female	318/6172	4.9	742/5748	11.4	890/5600	13.7	1190/5300	18.3
Gestational age								
Term	769/12 100	6.0	1841/11 028	14.3	2166/10 703	16.8	2792/10 077	21.7
Preterm	72/793	8.3	153/712	17.7	181/684	20.9	243/622	28.1
Number of births								
Singleton	803/12 281	6.1	1923/11 161	14.7	2262/10 822	17.3	2911/10 173	22.2
Twins	17/297	5.4	38/276	12.1	43/271	13.7	52/262	16.6
Triplets	0/9	0	1/8	11.1	1/8	11.1	2/7	22.2
Maternal smoking								
No	520/7371	6.6	1162/6729	14.7	1359/6532	17.2	1710/6181	21.7
Yes	167/3295	4.8	490/2972	14.2	578/2884	16.7	823/2639	23.8
Parity								
Primiparous	292/4823	5.7	686/4429	13.4	821/4294	16.1	1128/3987	22.1
Multiparous	489/7311	6.3	1210/6590	15.5	1401/6399	18.0	1728/6072	22.2
IMD 2010 quintile score								
1	487/7048	6.5	1182/6353	15.7	1372/6163	18.2	1721/5814	22.8
2	115/1939	5.6	253/1801	12.3	304/1750	14.8	435/1619	21.2
3	59/1196	4.7	148/1107	11.8	177/1078	14.1	247/1008	19.7
4	18/317	5.4	41/294	12.2	53/282	15.8	84/251	25.1
5	8/184	4.2	30/162	15.6	33/159	17.2	49/143	25.5

IMD, index of multiple deprivation with 1 and 5 indicating the least deprived and most deprived scores, respectively.

Table 2 Adjusted relative risks and 95% CIs of covariates using 40 imputed data sets

	Asthma diagnosis	Wheezing symptoms	Wheezing disorder diagnosis	Wheezing disorder treatment
Birth weight (kg)				
Normal (2.5–4.0)	1	1	1	1
High (>4.0)	0.95 (0.75 to 1.22)	0.90 (0.77 to 1.04)	0.91 (0.79 to 1.04)	0.99 (0.89 to1.11)
Low (<2.5)	1.53 (1.20 to 1.96)	1.29 (1.10 to 1.52)	1.29 (1.12 to 1.50)	1.25 (1.10 to 1.42)
Ethnicity				
White British	1	1	1	1
Pakistani	1.36 (1.11 to 1.66)	1.26 (1.12 to 1.42)	1.21(1.08 to 1.35)	0.95 (0.87 to 1.05)
Others	0.96 (0.74 to 1.25)	0.93 (0.79 to 1.08)	0.90 (0.78 to 1.04)	0.76 (0.67 to 0.85)
Gender				
Male	1	1	1	1
Female	0.67 (0.58 to 0.76)	0.64 (0.59 to 0.70)	0.66 (0.61 to 0.72)	0.71 (0.67 to 0.76)
Gestational age				
Term	1	1	1	1
Preterm	1.11 (0.83 to 1.48)	1.08 (0.90 to 1.30)	1.09 (0.92 to 1.29)	1.16 (1.01 to 1.34)
Number of births				
Singleton	1	1	1	1
Twins	0.68 (0.42 to 1.10)	0.71 (0.52 to 0.97)	0.68 (0.51 to 0.90)	0.63 (0.49 to 0.81)
Triplets	–	0.57 (0.09 to 3.60)	0.48 (0.08 to 3.03)	0.75 (0.22 to 2.56)
Maternal smoking				
No	1	1	1	1
Yes	0.86 (0.70 to 1.05)	1.10 (0.98 to 1.24)	1.07 (0.97 to 1.19)	1.05 (0.97 to 1.15)
Parity				
Primiparous	1	1	1	1
Multiparous	1.04 (0.91 to 1.20)	1.14 (1.04 to 1.24)	1.10 (1.02 to 1.19)	1.02 (0.95 to 1.08)
IMD 2010 quintile score	0.96 (0.88 to 1.05)	0.95 (0.90 to 1.00)	0.95 (0.91 to 1.00)	0.97 (0.93 to 1.00)

Model adjusted for ethnicity, gender, gestational age, number of births, maternal smoking, parity and IMD score.
IMD, index of multiple deprivation.

(95% CI 0.77 to 1.04), 0.91 (95% CI 0.79 to 1.04) and 0.99 (95% CI 0.89 to1.11), respectively (table 2). The respective unadjusted RRs of high birth weight for 'asthma' diagnosis, 'wheezing' symptoms, 'wheezing disorder' diagnosis and 'wheezing disorder' treatment were 0.93 (95% CI 0.73 to 1.19), 0.91 (95% CI 0.78 to 1.06), 0.92 (95% CI 0.80 to 1.05) and 1.04 (95% CI 0.93 to 1.16).

Growth and wheezing disorders
The BiB1000 follow-up cohort consisted of 1598 children that contributed a total of 8683 person years of follow-up. The total number of children who had 'asthma' diagnosis, 'wheezing' symptoms, 'wheezing disorders' diagnosis and 'wheezing disorders' treatment were 113 (7.1%), 252 (15.8%), 300 (18.8%) and 369 (23.1%), respectively, slightly higher than the whole BiB cohort. Fewer than 2% and 10% of the BiB1000 children were diagnosed with or treated for wheezing disorders during the first 3 months and the first 6 months, respectively (see online supplementary table S3).

Age-based weight patterns
According to the optimal number of class determination results, a four class model was best (see online supplementary table S4). However, a three class model was preferred on an interpretability basis (table 3 and online

supplementary figure S3A). Class 1 (95.8%) was composed of children whose mean birth weight was at the 46th centile and were just over the 60th centile at the age of 1 year and stayed around 60th centile afterwards according to WHO growth standards.[34] Class 2 (2.2%) was composed of children whose mean weight at birth was on the 28th centile then increased to the 96th centile at 1 year of age and persisted to be overweight until the age of 3. Class 3 (2.0%) were a group of children whose mean birth weight was on the 29th centile, who subsequently showed very slow growth, their mean weight reaching the 3rd centile at 1 year of age, followed by moderate acceleration to reach the 56th centile by the age of 3. Class 1, class 2 and class 3 could be characterised as 'normal', 'fast' and 'slow' growth groups, respectively. Online supplementary table S5 gives estimated means of the growth model parameters.

The adjusted RRs for 'asthma' diagnosis, 'wheezing' symptoms, 'wheezing disorder' diagnosis and 'wheezing disorders' treatment for fast growth group were 0.81 (95% CI 0.12 to 5.46), 1.59 (95% CI 0.67 to 3.71), 1.30 (95% CI 0.56 to 3.06) and 0.77 (95% CI 0.20 to 2.51), respectively, when compared with the 'normal' growth group (table 4). The adjusted RRs of the 'slow' as compared with the 'normal' growth group for 'wheezing' symptoms, 'wheezing disorder' diagnosis and 'wheezing disorders' treatment were 0.72 (95% CI 0.20 to 2.62),

Table 3 Estimated mean and percentiles of 1598 children by growth classes

	Growth classes		
	Class 1	Class 2	Class 3
Age-based weight SDS			
Birth	46th (–0.11 SDS)	28th (–0.59 SDS)	29th (–0.56 SDS)
1 month	43rd (–0.18 SDS)	19th (–0.89 SDS)	23rd (–0.75 SDS)
3 months	38th (–0.31 SDS)	7th (–1.48 SDS)	13th (–1.13 SDS)
6 months	45th (–0.12 SDS)	34th (–0.40 SDS)	8th (–1.39 SDS)
12 months	61st (0.27 SDS)	96th (1.75 SDS)	3rd (–1.91 SDS)
18 months	60th (0.25 SDS)	94th (1.57 SDS)	8th (–1.40 SDS)
24 months	59th (0.23 SDS)	92nd (1.39 SDS)	19th (–0.88 SDS)
36 months	58th (0.20 SDS)	85th (1.02 SDS)	56th (0.14 SDS)
Visits-based weight SDS			
Birth	47th (–0.08 SDS)	40th (–0.26 SDS)	–
1st visit	53rd (0.04 SDS)	56th (0.16 SDS)	–
2nd visit	55th (0.13 SDS)	71rd (0.54 SDS)	–
3rd visit	57th (0.18 SDS)	81st (0.89 SDS)	–
4th visit	57th (0.19 SDS)	88th (1.20 SDS)	–
5th visit	53rd (0.09 SDS)	96th (1.70 SDS)	–

SDS, standardised scores.

0.60 (95% CI 0.16 to 1.95) and 0.81 (95% CI 0.29 to 2.25), respectively. The respective unadjusted RRs for both growth groups remained similar (table 4).

Visits-based growth patterns

The age ranges of the children during their first, second, third, fourth and fifth visits after birth were 4.9–9.4, 10.7–18.3, 15.2–22.8, 23.4–28.5 and 35.4–40.6 months, respectively. Although the determination of the optimal number of classes favoured a model with four classes, the two class model was selected on a model interpretability basis (see online supplementary table S4). Class 1 (92.7%) comprised those children who were around the 46th centile at birth and 52nd centile during the first visit after birth and remained around the 60th centile during the next four visits according to the WHO growth standards chart[34]; class 2 (7.3%) comprised children who were, on average, at the 29th centile at birth and 57th centile during the first visit after birth then consistently accelerated to reach the 95th centile during the last visit (see online supplementary figure S3B and table 3). Class 1 and class 2 could be characterised as 'inconsistent' and 'consistent' growth groups, respectively.

The adjusted RRs for 'asthma' diagnosis, 'wheezing' symptoms, 'wheezing disorder' diagnosis and 'wheezing disorders' treatment for the 'inconsistent' growth group were 1.47 (95% CI 0.71 to 3.01), 1.13 (95% CI 0.66 to 1.95), 1.38 (95% CI 0.90 to 2.12) and 1.17 (95% CI 0.76 to 1.81), respectively, when compared with the 'consistent' growth group. The respective unadjusted RRs remained similar (table 5).

Complete cases versus imputed data set results

The complete cases analysis for birth weight and wheezing disorders retained 10 623 out of 13 734 children.

The complete case analyses for weight growth patterns based on age and visits retained 1572 of the 1598 children. The results of complete case analyses were very close to the imputed data analyses as expected given that all the outcome variables were completely observed and the missing indicator variables for the incomplete covariates did not have strong relationship with the outcome variables (see online supplementary tables S6 and S7).

DISCUSSION

In this prospective cohort study, we found that low birth weight was strongly associated with wheezing disorders and there was consistent, albeit weak, evidence that high birth weight was associated with reduced risk of wheezing disorders during the preschool period. Our findings for the effects of low birth weight on wheezing disorder diagnosis and treatment are in line with the findings of our recent meta-analysis and systematic review, showing a 37% increase in wheezing disorders risk for low birth weight (OR=1.37; 95% CI 1.05 to 1.79) compared with normal birth weight,[10] although the results here are slightly attenuated due to our use of RR as a measure of association. However, our finding of the effect of high birth weight on wheezing disorders is slightly different to that of the reported OR in the meta-analysis (OR=1.02; 95% CI 0.99 to 1.04) with both wheezing disorders diagnosis and treatment showing that there was a non-significant reduction of risk.

Analysis of our age-based weight growth patterns have shown inconsistent results for the group classified as 'fast' growth group. While there was a weak evidence for an increased risk of wheezing disorders according to diagnosis, there was a weak evidence for a reduced risk of wheezing disorders treatment (table 5). However, the

Table 4 Characteristics of 1598 children with complete data on wheezing disorders and covariates

	Asthma diagnosis		Wheezing symptoms		Wheezing disorder diagnosis		Wheezing disorder treatment	
	Yes/no	Yes (%)	Yes/no	Yes (%)	Yes/no	Yes (%)	Yes/no	Yes (%)
Birth weight (kg)								
Normal (2.5–4.0)	101/1314	7.1	221/1194	15.6	264/1151	18.7	321/1094	22.7
Low (<2.5)	6/64	8.6	14/56	20.0	16/54	22.9	20/50	28.6
High (>4.0)	6/107	5.3	17/96	15.0	20/93	17.7	28/85	24.8
Ethnicity								
White British	24/578	4.0	82/520	13.6	95/507	15.8	141/461	23.4
Pakistani	73/689	9.6	134/628	17.6	164/598	21.5	175/587	23.0
Others	16/216	6.9	36/196	15.5	41/191	17.7	53/179	22.8
Gender								
Male	70/708	9.0	159/619	20.4	185/593	23.8	212/566	27.2
Female	43/777	5.2	93/727	11.3	115/705	14.0	157/663	19.1
Maternal smoking								
No	90/1051	7.9	177/964	15.5	213/928	18.7	256/885	22.4
Yes	23/433	5.0	74/382	16.2	86/370	18.9	112/344	24.6
Parity								
Primiparous	41/571	6.7	87/525	14.2	106/506	17.3	144/468	23.5
Multiparous	70/892	7.3	163/799	16.9	191/771	19.9	218/744	22.7
IMD 2010 quintile score								
1	83/998	7.7	183/898	16.9	217/864	20.1	255/826	23.6
2	19/271	6.6	37/253	12.8	45/ 245	15.5	64/226	22.1
3	10/158	6.0	23/ 145	13.7	28/140	16.7	36/132	21.4
4	1/34	2.9	3/32	8.6	4/31	11.4	6/ 29	17.1
5	0/24	0	6/18	25.0	6/18	25.0	8/16	33.3

IMD, index of multiple deprivation.

results showed that the 'slow' growth group did have a reduced risk for both wheezing disorders diagnosis and treatment, albeit weak evidence, when compared with the 'normal' growth group (table 5). Furthermore, in our attempt to further analyse the effects of visits-based weight SDS on wheezing disorders, there was a weak evidence for an increase risk of wheezing disorders diagnosis and treatment for the group of children who grew 'inconsistently' and were seen to be obese by the last visit.

Table 5 Adjusted and unadjusted RRs and 95% CI for growth patterns and wheezing disorders in the BiB1000 cohort

	Unadjusted RR (95% CI; p Value)	Adjusted RR (95% CI; p Value)
Age-based weight SDS		
Class 2 (fast growth)		
Asthma diagnosis	0.82 (0.12 to 5.56; 0.84)	0.81 (0.12 to 5.46; 0.83)
Wheezing symptom	1.50 (0.62 to 3.56; 0.36)	1.59 (0.68 to 3.71; 0.29)
Wheezing disorder diagnosis	1.25 (0.53 to 2.97; 0.61)	1.30 (0.56 to 3.06; 0.54)
Wheezing disorder treatment	0.76 (0.27 to 2.14; 0.60)	0.77 (0.28 to 2.17; 0.63)
Class 3 (slow growth)		
Asthma diagnosis	1	1
Wheezing symptom	0.80 (0.21 to 2.93; 0.73)	0.72 (0.20 to 2.63; 0.29)
Wheezing disorder diagnosis	0.67 (0.18 to 2.45; 0.54)	0.60 (0.16 to 2.18; 0.44)
Wheezing disorder treatment	0.81 (0.29 to 2.25; 0.68)	0.81 (0.29 to 2.25; 0.69)
Visits-based weight SDS		
Class 2 (inconsistent growth)		
Asthma diagnosis	1.66 (0.81 to 3.42; 0.17)	1.47 (0.71 to 3.01; 0.30)
Wheezing symptom	1.15 (0.66 to 1.99; 0.62)	1.13 (0.66 to 1.95; 0.65)
Wheezing disorder diagnosis	1.42 (0.92 to 2.19; 0.11)	1.38 (0.90 to 2.12; 0.14)
Wheezing disorder treatment	1.14 (0.74 to 1.76; 0.55)	1.17 (0.76 to 1.81; 0.47)

Both models were adjusted for birth weight, ethnicity, gender, maternal smoking, parity and maternal SES; class 1 was a reference group in both models.
BiB, Born in Bradford; RR, relative risk; SDS, standardised scores; SES, socioeconomic status.

The findings of the effects of growth on wheezing disorders analyses may not be directly comparable with the previous studies[7 11 13 14 16 17 19–23] as they assumed a homogeneous growth among the respective study population and investigated the effect of overall mean change on wheezing disorders. However, Rzehak et al[18] who used GMM reported HRs of 1.22 (95% CI 1.08 to 1.39) and 1.43 (95% CI 0.90 to 2.27) for groups of children exhibited rapid growth only until 2 years and persistent rapid growth, respectively. The authors' growth pattern and risk estimates were similar to our age-based fast growth group and visits-based inconsistent growth group, respectively. Another two studies that investigated the effects of weight status changes at different age points reported an insignificant increase in wheezing disorders risk which are similar to our 'inconsistent growth' groups of the 'visits-based' growth pattern risk estimates.[12 15]

In our previous meta-analyses and systematic reviews, we found that low birth weight and high body mass index (BMI) were associated with wheezing disorders.[10 43] However, we also acknowledged that it may not be apparent whether high BMI is causing wheezing disorders or otherwise from the findings. This is because children with wheezing disorders may become less active which can lead to obesity or obese children may experience wheezing symptoms due to narrowing of airways. In our growth patterns and wheezing disorders analyses, we noted that, on average, the children with lower birthweight SDS showed significant growth changes during the first 6 months and were more likely to have experienced wheezing disorder conditions (tables 3 and 5). We also noted that children with the lowest birthweight SDS were more likely to be obese and to have experienced wheezing disorder conditions (tables 3 and 5). Given that a very small proportion of wheezing disorders or treatment cases were identified in the first 3 and 6 months (see online supplementary table S3), during which changes in growth occurred, it may strongly suggest that low birth weight coupled with rapid change in growth during the first 6 months is a risk factor for wheezing disorders. The temporal relationship between obesity and wheezing disorders in this study remains difficult to disentangle; however, in a recent Mendelian randomisation study by Granell et al,[44] it has been reported that obesity precedes childhood wheezing disorders.

Our work has certain weakness, so that the results need to be interpreted carefully. First, although the sample size for birth weight and wheezing disorders was sufficiently large, study participants were those who were born at a single centre: the Bradford Royal Infirmary (BRI) maternity hospital. Births in the regional tertiary centre, home births and births in smaller hospitals outside Bradford would have been excluded. Second, participation in the subcohort (BiB1000) of growth patterns was mainly driven by the mothers' willingness to participate, and so there is likely to be selection bias. Third, some of the classes identified by our GMM

contained a small proportion of children that resulted in having less precise risk estimates. Fourth, missing levels of growth data at some ages and visits was substantial, although we applied missing data handling techniques to address this limitation. Fifth, information on family asthma and breast feeding was missing, so our models were not adjusted for these potential confounding variables. However, the lack of adjustment may not have had a drastic effect on our birthweight risk estimates as there was no difference between the studies that adjusted for family asthma and those did not.[10] Likewise, Rzehak et al[18] also reported that there was no significant difference between unadjusted and adjusted (ie, for breast feeding and family asthma) model results.

Nonetheless, there are particular strengths of our analysis. First, in our birthweight and wheezing disorders analyses, our sample size was reasonably large. Second, we were able to implement techniques to reduce potential bias due to confounding variables such as the use of DAGs to inform the modelling process. Third, we were able to implement missing data techniques to minimise bias and presented both the complete cases and imputed data sets results to give more insight. Fourth, although we had small size for growth pattern analysis, we are able to implement advanced statistical techniques to account for potential heterogeneity of growth between and within groups. Finally, we were also able to use age-specific and sex-specific standardised weight scores which have the advantage of clearly depicting the growth patterns of children in comparison to the standard growth reference.[34] The standard scores are convertible to percentiles[35] which can then be compared with the growth charts used by clinicians or growth monitoring workers in their daily practice.

In conclusion, in this large prospective cohort data analysis, we have confirmed that low birthweight children have a moderate associated risk of wheezing disorders whereas high birthweight children have a non-significant reduced risk. There is a weak evidence that suggests 'fast' or 'inconsistent' growth predispose to wheezing disorders, and 'slow' growth reduces the risk which needs further investigation using larger data sets. However, the results may indicate that maintaining optimal prenatal and postnatal growths reduce a risk of childhood wheezing disorders.

Competing interests None declared.

Ethics approval Ethics approval was granted to the Born in Bradford project by Bradford Research Ethics Committee (Ref 07/H1302/112).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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