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The effects of birthweight and growth on childhood wheezing disorders: findings from the Born in Bradford Cohort

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Abstract:

Background: the effect of birthweight on childhood wheezing disorders has been examined extensively with a consensus that there is a positive association between the two although with substantial heterogeneity in the results. The effect of childhood growth on childhood wheezing disorders has received less attention, however, and there has been limited application of the sophisticated statistical techniques required this issue.

Methods: We used data on children from the Born in Bradford birth cohort to analyse the effects of birthweight (N=13,734) and growth (N=1,598) on childhood wheezing disorders. We classified birthweight into three categories using World Health Organization (WHO) and Centres for Disease prevention and Control (CDC) guidelines. We derived driven weight Standardized Scores (SDS) using WHO growth standards.

Results: The adjusted RRs of wheezing disorders (diagnosed as asthma or had wheezing symptom) 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. According to age based weight SDS, 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” growers as compared to the “normal” growers group. According to visits based weight SDS, the adjusted RRs for wheezing disorders diagnosis was

1.38 (95% CI: 0.90 to 2.12; p=0.14) for the “inconsistent” growers as compared with the “consistent” growers group.

Conclusion: Low birthweight children have an increased risk of wheezing disorders whereas high birthweight children have a reduced risk in this birth cohort. Low birthweight coupled with a decelerated growth until 3 months and a sharp growth between 3 and 12 months has an increased risk of wheezing disorders.

INTRODUCTION

Asthma is defined as a chronic disease of the passage of airways, characterized by smooth muscle contraction, accumulation of mucous 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 pre-school 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 under-diagnosis 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 birthweight on wheezing disorders has been studied extensively with 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 birth weight 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 ≥2.5kg and 2.5–4.0kg birth weight children, respectively.[10] We also found a modest increased risk in high birth weight children (>4 kg) when compared with normal birth weight (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 risk estimates of the studies included 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[11-21] and others reporting reduced risk of wheezing disorders.[20 22-24] In addition to that, all of these studies, with the exception of one,[19] assumed homogenous growth among children, either used statistical techniques that can now be improved upon or a non-standard growth data

analysis that makes comparison and replication of results very difficult. For example, three [11 17 21] used data driven standardised scores (SDS), three [12 20 23 24] used country specific SDS and another one [15] used non-standardized weight measurements.

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

METHODS

Study participants

The Born in Bradford study is a prospective mainly bi-ethnic, cohort that examines the impact of environmental, genetic and social factors on health of the population of Bradford [25]. The methods of recruitment are explained in detail elsewhere. [25 26] 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 one 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 sub cohort (BiB1000) of 1,735 mothers and 1,763 babies were also recruited for follow-up examinations. After excluding multiple births, preterm births and death before the age of one week, a total of 1,598 children were included in growth pattern and wheezing disorder analyses.

Ethics statement

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

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; and, for weight at 1-5 visits from birth; (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 socio-economic status 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. By “asthma” diagnosis and “wheezing” symptoms, we refer to the presence of asthma and wheezing diagnosis codes in the record

respectively. By "wheezing disorder" based on diagnosis, we refer to the presence of "asthma" or "wheezing" diagnosis codes in the record and by "wheezing disorder" based on treatment, we refer to the existence of at least two drug prescriptions indicated for the treatment of asthma a minimum of one week and maximum of one year apart. Drug and disease terms and codes used to confirm "wheezing disorders" are listed in supplementary tables 1&2.

Variables for analysis

Primary variables:

Where regression modelling was carried out, exposure variables were birthweight and growth; outcome variables were wheezing disorders (i.e. "asthma", "wheezing" and "wheezing disorders").

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. In visit based, the visit number was used as a time score. 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 (i.e. intercept and slope) and weight status at every visit, respectively. In the age based approach, the age of the children at each time point were identical or weight values were constrained to be missing. 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.

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.[27-29] In order to minimise bias due to confounding and over-adjustment, Direct Acyclic Graphs (DAGs) were used [28 30] and models were tested using DAGitty software.[29] Drawing of a relationship between variables of interest (i.e. confounding and main variables) was guided by epidemiological, biologic and clinical knowledge. Figures S1 & 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 birthweight 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: birthweight, ethnicity, family asthma, 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, that is, after collection of data was already carried out by the BiB project. 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 was available for the variable "family asthma". Therefore, both birthweight and childhood growth models were not adjusted for family asthma.

Missing data estimation variables

Where imputations were carried out, missing data were estimated under 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).[31] The *auxiliary* variables included in the imputation process were: exposure variable, cofounding variables, and correlate 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 of imputations showed that birthweight, gestational age and outcome variables (i.e. 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 (i.e. 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.[32] 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.[31 32]

Statistical analysis and software

Birth weight was classified according to the CDC [33] and WHO methods [34] where <2.5kg=Low, 2.5-4.0kg=Normal and >4.0kg=High. Age-specific and sex-specific standardised scores (SDS) of weight were derived according to World Health Organisation (WHO) growth standards [35] in LMSgrowth Microsoft excel add-in software.[36] The WHO growth standards population that we used to derive the SDS scores was made up of singleton term births. Hence, multiple births and preterm births were excluded from the growth patterns and wheezing disorders analyses.

In identifying the best fitting growth patterns, growth mixture models (GMM) were fitted,[37 38] 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 less ≤1% of the total population. When comparing growth patterns of children in our GMM, we used WHO growth standards charts [35] 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 percentiles respectively.

Missing data on covariates were estimated using Multiple Imputations by Chained Equation (MICE) models under Missing data at Random (MAR) assumptions. [39 40] In deciding how many datasets to be imputed, we took the number of imputations (**n**) to be greater than the percentage or fraction of incomplete cases. [39 41] Missing growth data were estimated using a Full Information Maximum Likelihood (FIML) method in which parameters are estimated using all available observations in the dataset, under MAR assumption.[42 43]

GMM was carried out in Mplus version. 7.11, and covariates' missing data estimation and regression modelling were carried out in Stata version 12. 5% significance levels and 95% confidence intervals were adopted throughout.

RESULTS

Birthweight and wheezing disorders

The cohort was made up of 13,734 children that yielded 74,940 person years of follow-up. 37.3% and 32.8% were Pakistani and white British origin respectively; 12.6% were minority and 17.3% with missing ethnicity data. 50.4% and 47.3% were male and female respectively, and, 2.3% of children had missing information on sex. 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, 841 were diagnosed as asthmatic, 1994 had wheezing symptoms, 2347 were either diagnosed for asthma or had wheezing symptoms, and 3035 children were treated with asthma drugs based on primary care data available up to November 2014 (table 1).

Low birthweight

There was a significant increased risk of wheezing disorders in all four disease definitions. The adjusted 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 (1.10 to 1.42) respectively (table 2). The unadjusted RRs for "asthma" diagnosis, "wheezing" symptoms, "wheezing disorder" diagnosis and "wheezing disorder" treatment 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), see table 2.

High birthweight

There was a consistent but non-significant reduction of wheezing disorders risk for those children who were classified as being of high birthweight. 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 (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 birthweight 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), see table 2.

Table 1 **Characteristics of 13,734 children given wheezing disorders of complete cases on covariates**

	Wheezing disorder treatment		Asthma diagnosis		Wheezing symptoms		Wheezing disorder diagnosis	
	Yes/ No	Yes %	Yes/ No	Yes %	Yes/ No	Yes %	Yes/ No	Yes %
Birthweight								
Normal (2.5-4.0kg)	2,444/8,897	21.6%	668/10,673	5.9%	1,622/9,719	14.3%	1,907/9,434	16.8%
Low (<2.5kg)	311/828	27.3%	104/1,035	9.1%	209/930	18.3%	246/893	21.6%
High (>4.0kg)	280/974	22.3%	69/1,185	5.5%	163/1,091	13.0%	194/1,060	15.5%
Ethnicity								
White British	1,074/3,427	23.9%	217/4,284	4.8%	586/3,915	13.1%	706/3,795	15.7%
Pakistani	1,150/3,967	22.5%	382/4,735	7.5%	857/4,260	16.7%	985/4,132	19.2%
Others	308/1,425	17.8%	86/1,647	5.0%	207/1,526	11.9%	243/1,490	14.0%
Gender								
Male	1,775/5,142	25.7%	502/6,415	7.3%	1,220/5,697	17.6%	1,416/5,501	20.5%
Female	1,190/5,300	18.3%	318/6,172	4.9%	742/5,748	11.4%	890/5,600	13.7%
Gestational age								
Term	2,792/10,077	21.7%	769/12,100	6.0%	1,841/11,028	14.3%	2,166/10,703	16.8%
Pre-term	243/622	28.1%	72/793	8.3%	153/712	17.7%	181/684	20.9%
Number of births								
Singleton	2,911/10,173	22.2%	803/12,281	6.1%	1,923/11,161	14.7%	2,262/10,822	17.3%
Twins	52/262	16.6%	17/297	5.4%	38/276	12.1%	43/271	13.7%
Triplets	2/7	22.2%	0/9	0%	1/8	11.1%	1/8	11.1%
Maternal smoking								
No	1,710/6,181	21.7%	520/7,371	6.6%	1,162/6,729	14.7%	1,359/6,532	17.2%
Yes	823/2,639	23.8%	167/3,295	4.8%	490/2,972	14.2%	578/2,884	16.7%
Parity								
primiparous	1,128/3,987	22.1%	292/4,823	5.7%	686/4,429	13.4%	821/4,294	16.1%
multiparous	1,728/6,072	22.2%	489/7,311	6.3%	1,210/6,590	15.5%	1,401/6,399	18.0%
IMD 2010 Quintile score								
1	1,721/5,814	22.8%	487/7,048	6.5%	1,182/6,353	15.7%	1,372/6,163	18.2%
2	435/1,619	21.2%	115/1,939	5.6%	253/1,801	12.3%	304/1,750	14.8%
3	247/1,008	19.7%	59/1,196	4.7%	148/1,107	11.8%	177/1,078	14.1%
4	84/251	25.1%	18/317	5.4%	41/294	12.2%	53/282	15.8%
5	49/143	25.5%	8/184	4.2%	30/162	15.6%	33/159	17.2%

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% confidence intervals of covariates from multiple imputed data; 40 datasets**

	Asthma diagnosis	Wheezing symptoms	Wheezing disorder diagnosis	Wheezing disorder treatment
Birthweight				
Normal (2.5-4.0kg)	1	1	1	1
High (>4.0kg)	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 (<2.5kg)	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
Pre-term	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)

Growth and wheezing disorders

The BiB1000 follow-up cohort consisted of 1,598 children that contributed a total of 8,683 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% the BiB1000 children were diagnosed with or treated for wheezing disorders during the first three months and the first six months respectively (table S3).

Age based weight patterns

According to the optimal number of class determination results, a four class model was best (table S4). However, a three class model was preferred on an interpretability basis (table 3 & figure S3A). Class 1 (95.8%) was composed of children whose mean birthweight was at the 46th percentile and

were just over the 60th percentile at the age of 1 year and stayed around 60th percentile afterwards according to WHO growth standards.[35] Class 2 (2.2%) was composed of children whose mean weight at birth was on the 28th percentile then increased to the 96th percentile at one year of age and persisted to be overweight until the age of three. Class 3 (2.0%) were a group of children whose mean birthweight was on the 29th percentile, who subsequently showed very slow growth, their mean weight reaching the 3rd percentile at 1 year of age, followed by moderate acceleration to reach the 56th percentile by the age of three. Class 1, class 2 and class 3, could be characterised as "normal", "fast" and "slow" growers respectively. Table S5 gives estimated means of the growth model parameters.

Table 3 Estimated mean and percentiles of 1,598 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)	-

The associated adjusted RRs of the "fast" compared to the "normal" growers group for "asthma" diagnosis, "wheezing" symptoms, "wheezing disorder" diagnosis and "wheezing disorders" treatment 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 (table 4). The adjusted RRs of the "slow" as compared to the "normal" growers group for "wheezing" symptoms, "wheezing disorder" diagnosis and "wheezing

disorders" treatment were 0.72 (95% CI: 0.20 to 2.62), 0.60 (95% CI: 0.16 to 1.95) and 0.81 (95% CI: 0.29 to 2.25) respectively. The respective unadjusted relative risks 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 to 9.4, 10.7 to 18.3, 15.2 to 22.8, 23.4 to 28.5 and 35.4 to 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 (table S4). Class 1 (92.7%) comprised those children who were around the 46th percentile at birth and 52nd percentile during the first visit after birth and remained around the 60th percentile during the next four visits according to the WHO growth standards chart; [35] class 2 (7.3%) comprised children who were, on average, at the 29nd percentile at birth and 57th percentile during the first visit after birth then consistently accelerated to reach the 95th percentile during the last visit (figure S3B & table 3). Class 1 and class 2 could be characterised as "inconsistent" and "consistent" growers respectively.

Table 4 **Characteristics of 1,598 children given wheezing disorders of complete cases on covariates**

	Wheezing disorder treatment		Asthma diagnosis		Wheezing symptoms		Wheezing disorder diagnosis	
	Yes/ No	Yes %	Yes/ No	Yes %	Yes/ No	Yes %	Yes/ No	Yes %
Birthweight								
Normal (2.5-4.0kg)	321/ 1,094	22.7%	101/1,314	7.1%	221/1,194	15.6%	264/1,151	18.7%
Low (<2.5kg)	20/50	28.6%	6/64	8.6%	14/56	20.0%	16/54	22.9%
High (>4.0kg)	28/85	24.8%	6/107	5.3%	17/96	15.0%	20/93	17.7%
Ethnicity								
White British	141/461	23.4%	24/578	4.0%	82/520	13.6%	95/507	15.8%
Pakistani	175/587	23.0%	73/689	9.6%	134/628	17.6%	164/598	21.5%
Others	53/179	22.8%	16/216	6.9%	36/196	15.5%	41/191	17.7%
Gender								
Male	212/566	27.2%	70/708	9.0%	159/619	20.4%	185/593	23.8%
Female	157/663	19.1%	43/777	5.2%	93/727	11.3%	115/705	14.0%
Maternal smoking								
No	256/885	22.4%	90/1,051	7.9%	177/964	15.5%	213/928	18.7%
Yes	112/344	24.6%	23/433	5.0%	74/382	16.2%	86/370	18.9%
Parity								
primiparous	144/468	23.5%	41/571	6.7%	87/ 525	14.2%	106/ 506	17.3%
multiparous	218/744	22.7%	70/ 892	7.3%	163/ 799	16.9%	191/ 771	19.9%
IMD 2010 Quintile score								
1	255/826	23.6%	83/ 998	7.7%	183/898	16.9%	217/864	20.1%
2	64/226	22.1%	19/ 271	6.6%	37/253	12.8%	45/ 245	15.5%
3	36/132	21.4%	10/ 158	6.0%	23/ 145	13.7%	28/140	16.7%
4	6/ 29	17.1%	1/34	2.9%	3/32	8.6%	4/31	11.4%
5	8/16	33.3%	0/24	0%	6/18	25.0%	6/18	25.0%

When two growth classes were compared in terms of wheezing disorders, the adjusted RRs of "asthma" diagnosis, "wheezing" symptoms, "wheezing disorder" diagnosis and "wheezing disorders" treatment for the "inconsistent" growers were 1.47 (95% CI: 0.71 to 3.01), 1.13 (0.66 to 1.95), 1.38 (0.90 to 2.12) and 1.17 (0.76 to 1.81) respectively, when compared to the "consistent" growers class. The respective unadjusted relative risks remained similar (table 4).

Table 5 adjusted and unadjusted relative risks and 95% CI for growth patterns and wheezing disorders

		Unadjusted RR (95% CI; p-value)	Adjusted RR (95% CI; p-value)
Age based weight SDS			
Class 2 (fast growers)	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 growers)	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 growers)	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 birthweight, ethnicity, gender, maternal smoking, parity and maternal SES; class 1 was a reference group in both models.

Complete cases versus imputed dataset results

The complete cases analysis for birthweight 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 1,572 of the 1,598 children. The results of complete cases 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 (tables S6 & S7).

Discussion

In this prospective cohort study, we found that low birthweight was strongly associated with wheezing disorders and there was consistent, albeit non-significant, evidence that high birthweight was associated with reduced risk of wheezing disorders during the pre-school period. Our findings for the effects of low birthweight 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 birthweight (OR=1.37; 95% CI: 1.05 to 1.79), [10] although the results here are slightly attenuated due to our use of relative risk as a measure of association. However, our finding of the effect of high birthweight on wheezing disorders is slightly different to that of the reported odds ratio 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" growers. While there was a non-significant increased risk of wheezing disorders according to diagnosis, there was a non-significant reduced risk of wheezing disorders treatment (table 5). However, the results showed that the "slow" growers group did have a non-significant reduction for both wheezing disorders diagnosis and treatment when compared to the "normal" growers group (table 5). Furthermore, in our attempt to further analyse the effects of visits based weight SDS on wheezing disorders, there was a non-significant increase of wheezing disorders diagnosis and treatment for the group of children who grew "inconsistently" and were seen to be obese by the last visit.

The findings of the effects of growth on wheezing disorders analyses may not be directly comparable with the previous studies [11 13-15 17 18 20-24] as they assumed a homogenous growth among the respective study population and investigated the effect of overall mean change on wheezing disorders. However, Rzehak et al [19] who used GMM reported hazard ratios of 1.22 (95% CI: 1.08 to 1.39) and 1.43 (95% CI: 0.90 to 2.27) for groups of children exhibiting rapid growth until 2 years (class 2) and persistent rapid growth (class 3), respectively. The authors' growth pattern and risk estimates were similar to the age based SDS class 2 and visits based class 2 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 growers' group's of the 'visits-based' growth patterns risk estimates.[12 16]

In our previous meta-analyses and systematic reviews we found that low birthweight and high BMI were associated with wheezing disorders. [10 44] 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 (table 3&5). We also noted that children with the lowest birthweight SDS were more likely to be obese and to have experienced wheezing disorder conditions (table 3&5). Given that a very small proportion of wheezing disorders or treatment cases were identified in the first three and six months (table S3), during which changes in growth occurred, it may strongly suggest that low birthweight coupled with rapid change in growth during the first six 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 Randomization study by Granell et al, it has been reported that obesity precedes childhood wheezing disorders. [45]

Our work has certain weakness so that the results need to be interpreted carefully. Firstly, although the sample size for birthweight 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 will have been excluded. Secondly, participation in the sub-cohort (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 maternal asthma was missing so our models were not adjusted for this potential confounding variable.

Nonetheless, there are particular strengths of our analysis. Firstly, in our birthweight and wheezing disorders analyses, our sample size was reasonably large. Secondly, 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. Thirdly, we were able to implement missing data techniques to minimize bias and presented both the complete cases and imputed datasets results to give more insight. Fourthly, although we had small size for growth patterns 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.[35] The standard scores are convertible to percentiles [36] 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 weak evidence to suggest "fast" or "inconsistent" growth predispose to wheezing disorders, and "slow" growth reduces the risk which needs further investigation using larger datasets. However, the results may indicate that maintaining optimal prenatal and postnatal growths reduce a risk of childhood wheezing disorders.

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Contributors: TFM, RGF and RCP conceived the idea. TFM performed all the statistical analyses, interpretation of results and drafted the manuscript. RGF and RCP revised and commented on the manuscript. All authors approved the final version of the manuscript.

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Data Sharing Statement ; This research has no additional unpublished data to share.

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Supplementary:

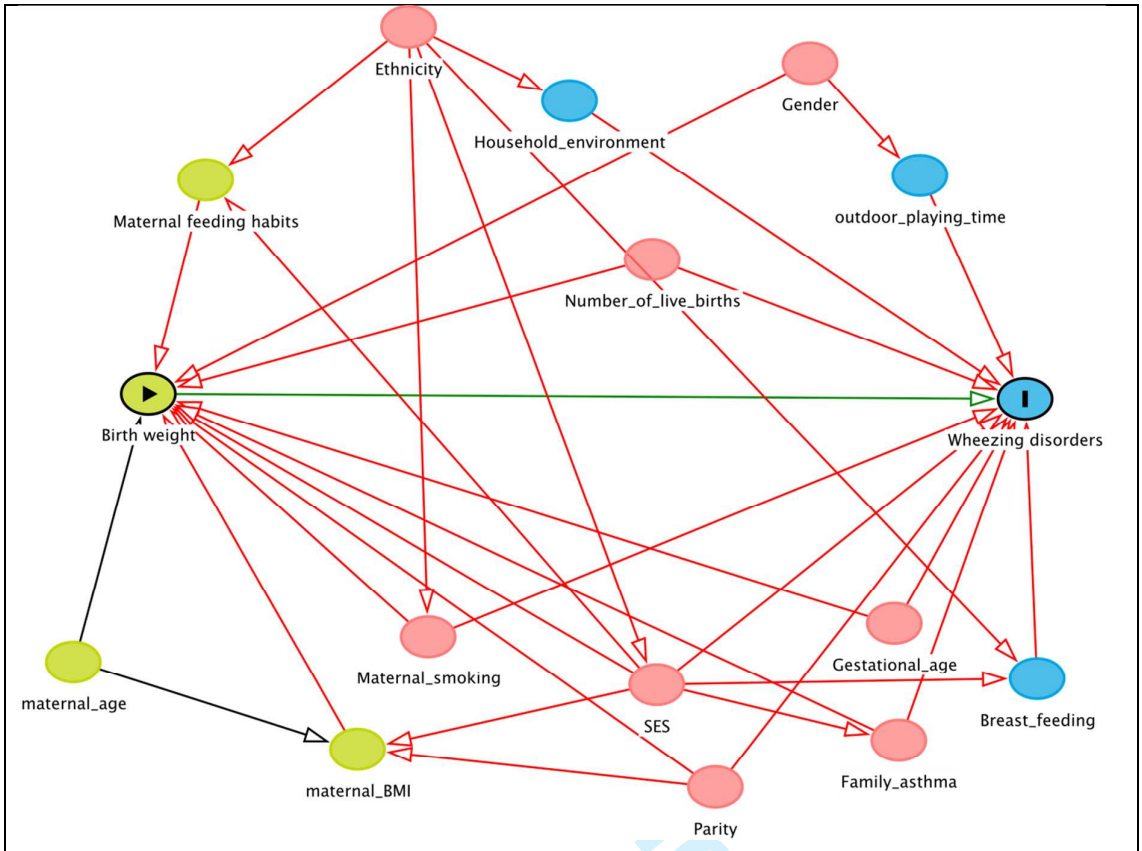
Table S1: list of drugs used to confirm diagnosis of wheezing disorders

Drug class names	Drug family names
Antimuscarinic bronchodilators	
	IPRATROPIUM BROMIDE
selective beta-2 agonists	
	FORMOTEROL FUMARATE
	SALBUTAMOL
	SALMETEROL
	TERBUTALINE SULPHATE
Leukotriene receptor antagonist	
	MONTELUKAST
	ZAFIRLUKAST
Nasal Corticosteroids	
	BECLOMETASONE DIPROPIONATE
	BUDESONIDE
	CICLESONIDE
	FLUTICASONE PROPIONATE
	MOMETASONE FURATE
	SODIUM CROMOGLICATE

Table S2: list of terms to confirm diagnosis of wheezing disorders

Name	List of terms	Read Code	Term ID
Wheezing			
	Expiratory polyphonic wheeze	Xa83N	YaVc1
	Expiratory wheeze	Xa7uu	YaVQZ
	Expiratory wheezing	Xa7vA	YaVQt
	Inspiratory wheeze	Xa7ut	YaVQY
	Inspiratory wheezing	Xa7v9	YaVQs
	Mild wheeze	XaX5K	Yaty9
	Moderate wheeze	XaX5L	YatyA
	Nocturnal wheeze/cough	173B.	YM1gs
	Severe wheeze	XaX5M	YatyC
	Very severe wheeze	XaX5N	YatyE
	Viral wheeze	XaMe7	YapfP
	Wheeze - rhonchi	X76If	Y7DxZ
	Wheezing	XE0qs	Y7DuF
	Wheezing symptom	XM0Ci	YM1is
	Wheezy	XE0qs	Y7DuF
Asthma			
	Acute asthma	Xa9zf	YaYk2
	Allergic asthma	XE0YT	Y108G
	Asthma	H33..	Y107p
	Asthma NOS	XE0YX	Y1080
	Asthma unspecified	H33z.	Y107y
	Asthmatic bronchitis	Xa0lZ	Y108e
	Brittle asthma	Ua1AX	YMFVN
	Childhood asthma	X101t	Y107w
	Chronic asthmatic bronchitis	H3120	Y108g
	Mild asthma	663V1	YaY1o
	Moderate asthma	663V2	YaY1p
	Nocturnal asthma	XaLPE	Y1084
	Non-allergic asthma	XE0YT	Y108G
	Occasional asthma	663V0	YaY1n

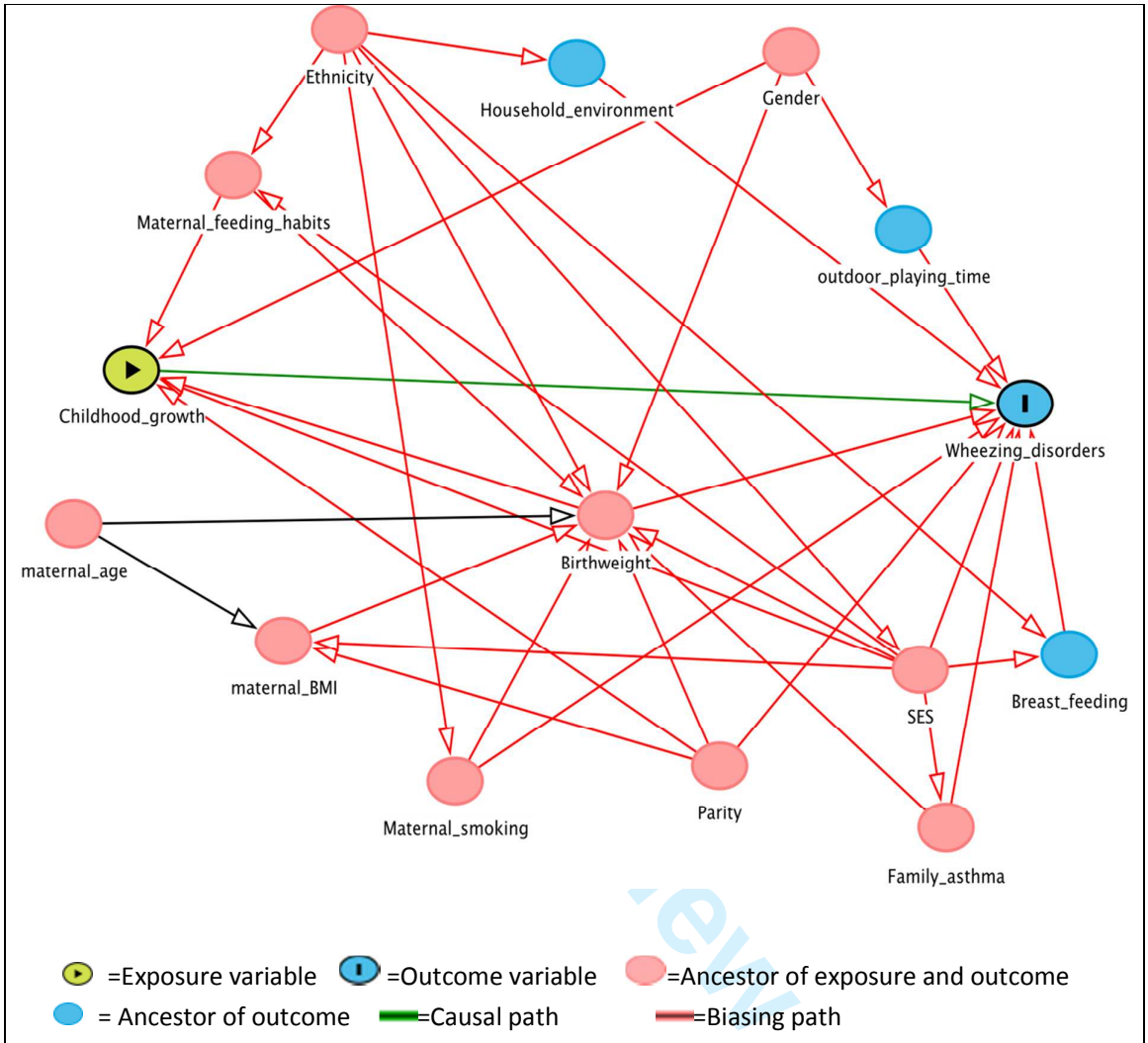
Figure S1 DAGitty schematic view of confounding adjustment for the effects of birthweight on wheezing disorders



Minimal sufficient adjustment sets for estimating the total effect of birthweight on wheezing disorders:

- {Breast feeding, family asthma, gender, gestational age, household environment, maternal smoking, number of live births, parity, SES}
- {Breast feeding, family asthma, gestational age, household environment, maternal smoking, number of live births, parity, SES, outdoor playing time}
- {Ethnicity, family asthma, gender, gestational age, maternal smoking, number of live births, parity, SES}
- {Ethnicity, family asthma, gestational age, maternal smoking, number of live births, parity, SES, outdoor playing time}
- {Family asthma, gender, gestational age, maternal feeding habits, maternal smoking, number of live births, parity, SES}
- {Family asthma, gestational age, maternal feeding habits, maternal smoking, number of live births, parity, SES, outdoor playing time}

Figure S2 DAGitty schematic view of confounding adjustment for the effects of childhood growth on wheezing disorders



Minimal sufficient adjustment sets for estimating the total effect of childhood growth on wheezing disorders:

- {Birthweight, breast feeding, family asthma, gender, household environment, maternal smoking, parity, SES}
- {Birthweight, breast feeding, family asthma, household environment, maternal smoking, parity, SES, outdoor playing time}
- {Birthweight, ethnicity, family asthma, gender, maternal smoking, parity, SES}
- {Birthweight, ethnicity, family asthma, maternal smoking, parity, SES, outdoor playing time}
- {Birthweight, gender, maternal feeding habits, parity, SES}

Table S3: Period of diagnosis or treatment initiation for BiB1000 children

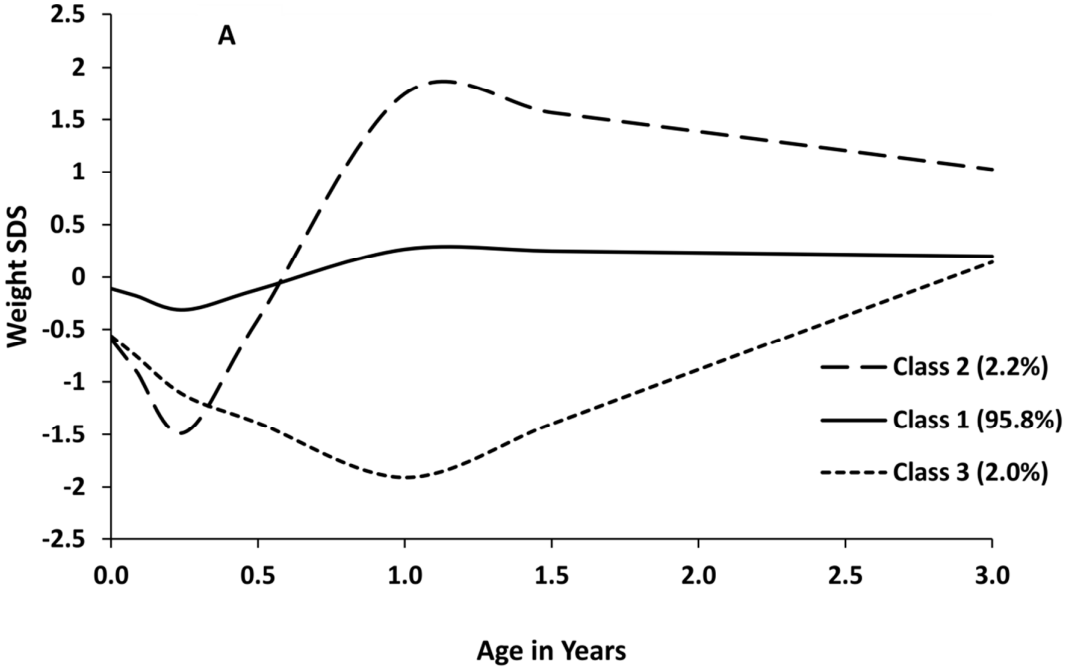
	Period in months			
	First 3 months	First 6 months	First 9 months	First 12 months
Wheezing disorders diagnosis	1.3%	8.3%	17.0%	27.7%
Wheezing disorders treatment	2.1%	16.8%	33.1%	46.1%
Asthma diagnosis	0%	1.8%	2.7%	4.4%
Wheezing symptoms	1.59	7.9%	19.8%	31.8%

Table S4: Model fit results for selection of optimal number of classes

Number of classes	Model fit Criterion				Classification quality	Likelihood ratio test
	-2LL	AIC	ABIC	df	Entropy	BLRT (-2LL diff; df diff; and P-values)
Age based weight SDS						
1 class	13,794	13,836	13,883	21	N/A	N/A
2 classes	13,752	13,805	13,862	26	0.94	42; 5; <0.01
3 classes	13,724	13,785	13,853	31	0.90	29; 5; <0.01
4 classes	13,698	13,770	13,849	36	0.88	24; 5; 0.02
5 classes	13,680	13,763	13,853	41	0.88	17; 5; 0.70
Visits based weight SDS						
1 class	14,100	14,129	14,159	14	N/A	N/A
2 classes	14,034	14, 069	14,109	18	0.79	67; 4; <0.01
3 classes	14,006	14,052	14,099	22	0.85	26; 4; <0.01
4 classes	13,992	14,044	14,102	26	0.79	15; 4; 0.03
5 classes	13,980	14,041	14,107	30	0.72	11; 4; 0.25

LL= Log-likelihood; AIC=Akaike Information Criterion; ABIC= sample size adjusted Bayesian Information Criterion; BLRT=Bootstrapped likelihood Ratio Test; -2LL diff=2 times the Log-likelihood difference, df=degrees of freedom (number of free parameters); df diff= difference in the degree of freedom or number of free parameters.

Figure S3: Estimated mean curves of weight SDS according to age (A) and visits (B)



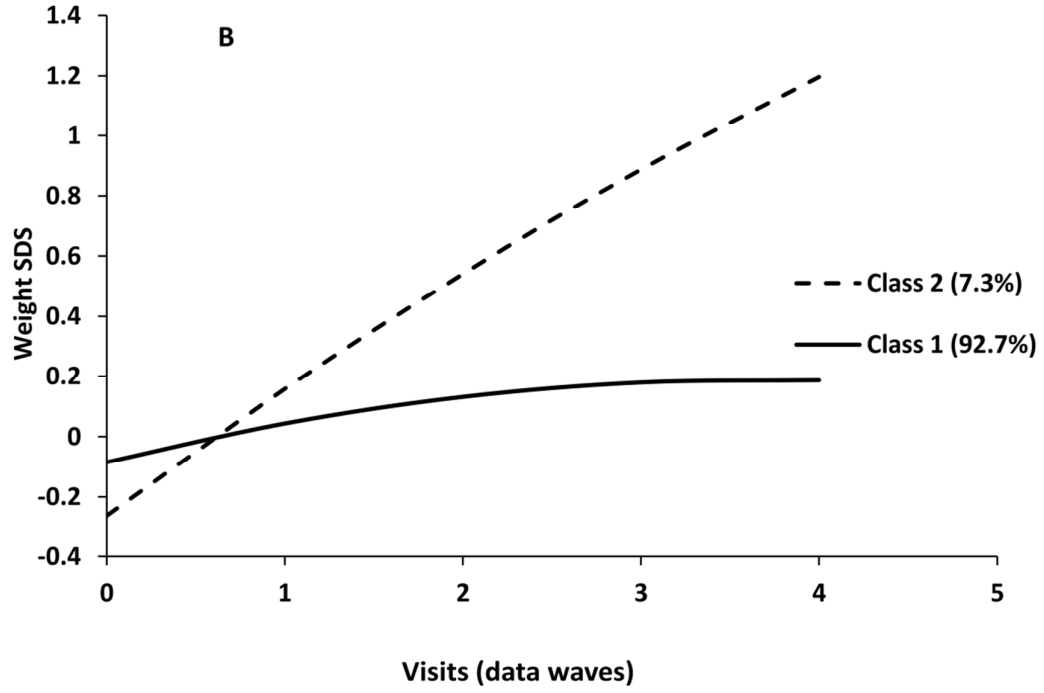


Table S5: Mean estimates of the latent classes of Growth Mixture Model parameters

	Parameter	Estimate and 95% CI	P-value
Age based GMM model			
Class 1 ('Normal growers')	Birthweight	–0.111 (–0.170 to –0.053)	<0.01
	$Velocity_{0-3}$	–0.671 (–0.903 to –0.439)	<0.01
	$Velocity_{3-12}$	0.645 (0.578 to 0.712)	<0.01
	$Velocity_{12-36}$	–0.028 (–0.053, –0.003)	0.03
Class 2('Fast growers')	Birthweight	–0.594 (–1.305 to 0.117)	0.10
	$Velocity_{0-3}$	–2.956 (–7.838 to 1.925)	0.24
	$Velocity_{3-12}$	3.588 (2.850 to 4.326)	<0.01
	$Velocity_{12-36}$	–0.302 (–0.993 to 0.390)	0.39
Class 3('Slow growers')	Birthweight	–0.564 (–1.146 to 0.018)	0.06
	$Velocity_{0-3}$	–1.878 (–3.980 to 0.225)	0.08
	$Velocity_{3-12}$	–0.871 (-1.950 to 0.208)	0.11
	$Velocity_{12-36}$	0.856 (0.266 to 1.446)	<0.01
Visits based GMM model			
Class 1 ('consistent growers')	Birthweight	–0.084 (–0.138 to –0.030)	<0.01
	Velocity	0.246 (0.196 to 0.297)	<0.01
	Acceleration	–0.056 (–0.067 to –0.045)	<0.01
Class 2 ('inconsistent growers')	Birthweight	–0.263 (–0.577 to 0.051)	0.10
	Velocity	0.732 (0.335 to 1.129)	<0.01
	Acceleration	–0.051 (–0.132 to 0.029)	0.21

Table S6: Adjusted relative risks and 95% confidence intervals of complete cases analysis (10,623 children)

	Wheezing disorders treatment	Asthma diagnosis	Wheezing symptoms	wheezing disorder diagnosis
Birthweight				
Normal (2.5-4.0kg)	1	1	1	1
High (>4.0kg)	1.03(0.90 to1.18)	0.88 (0.63 to 1.22)	1.01 (0.84 to 1.21)	0.97 (0.82 to 1.14)
Low (<2.5kg)	1.22 (1.06 to 1.41)	1.63 (1.24 to 2.14)	1.26 (1.05 to 1.51)	1.30 (1.10 to 1.53)
Ethnicity				
White British	1	1	1	1
Pakistani	0.96 (0.87 to 1.05)	1.39 (1.12 to 1.71)	1.26 (1.11 to 1.43)	1.22 (1.09 to 1.36)
Others	0.76 (0.68 to 0.86)	1.00 (0.76 to 1.30)	0.93 (0.79 to 1.09)	0.91 (0.78 to 1.05)
Gender				
Male	1	1	1	1
Female	0.73 (0.67 to 0.78)	0.64 (0.55 to 0.75)	0.64 (0.59to0.71)	0.65 (0.60 to 0.72)
Gestational age				
Term	1	1	1	1
Pre-term	1.21 (1.04 to 1.42)	1.13 (0.81 to 1.56)	1.10 (0.89 to 1.35)	1.11 (0.92 to 1.33)
Number of births				
Singleton	1	1	1	1
Twins	0.67 (0.51 to 0.88)	0.71 (0.43 to 1.19)	0.70 (0.50 to 0.99)	0.66 (0.48 to 0.91)
Triplets	1.18 (0.39 to 3.61)	-	0.83 (0.14 to 4.91)	0.69 (0.12 to 4.09)
Maternal smoking				
No	1	1	1	1
Yes	1.04 (0.96 to 1.14)	0.83 (0.68 to 1.03)	1.09 (0.96 to 1.22)	1.07 (0.96 to 1.19)
Parity				
primiparous	1	1	1	1
multiparous	1.01 (0.94 to 1.09)	1.06 (0.90 to 1.24)	1.12 (1.02 to 1.23)	1.09 (1.00 to 1.19)
IMD 2010 Quintile score	0.98 (0.94 to 1.02)	0.97 (0.88 to 1.07)	0.94 (0.89 to 1.00)	0.95 (0.91 to 1.01)

Table S7 Adjusted and unadjusted relative risks and 95% CI for growth patterns and wheezing disorders from complete cases analysis (1,572 children)

		Unadjusted RR (95% CI; p-value)	Adjusted RR (95% CI; p-value)
Age based weight SDS			
Class 2	Asthma diagnosis	0.82 (0.12 to 5.56; 0.84)	0.81 (0.12 to 5.46; 0.83)
(fast growers)	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	Asthma diagnosis	1	1
(slow growers)	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	Asthma diagnosis	1.66 (0.81 to 3.42; 0.17)	1.47 (0.71 to 3.01; 0.30)
(inconsistent	Wheezing symptom	1.15 (0.66 to 1.99; 0.62)	1.13 (0.66 to 1.95; 0.65)
growers)	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 birthweight, ethnicity, gender, maternal smoking, parity and maternal SES; class 1 was a reference group in both models.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract [**Methods section of the abstract page 1**]
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found [**Results section of abstract page 1**]
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported [**Page 3**]
Objectives	3	State specific objectives, including any prespecified hypotheses [**Page 4**]
Methods		
Study design	4	Present key elements of study design early in the paper [**Methodology page 5**]
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Pages 5-6]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Pages 5-6]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[N/A]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Page 6]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Pages 5-6]**
Bias	9	Describe any efforts to address potential sources of bias **[Page 6-7]**
Study size	10	Explain how the study size was arrived at **[Page 5]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Pages 5-6]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Pages 6-7]**
		(*b*) Describe any methods used to examine subgroups and interactions **[N/A]**
		(*c*) Explain how missing data were addressed **[Page 7]**
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **[N/A]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Page 5]**
		(b) Give reasons for non-participation at each stage **[Page 5]**
		(c) Consider use of a flow diagram **[N/A]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Page 8**
		(b) Indicate number of participants with missing data for each variable of interest **[Page 9]**
		(c) Summarise follow-up time (eg, average and total amount) **[Page 8]**
Outcome data	15*	Report numbers of outcome events or summary measures over time **[Page 8]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included **[Pages 10 &13]**
		(*b*) Report category boundaries when continuous variables were categorized **[Page 6]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[N/A]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 14]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Page 15]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Pages 14-15]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Page 14-15]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[within acknowledgments and funding]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The effects of birthweight and growth on childhood wheezing disorders: findings from the Born in Bradford Cohort

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The effects of birthweight and growth on childhood wheezing disorders: findings from the Born in Bradford Cohort

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Abstract:

Objectives: To examine the effects of birthweight and childhood growth on childhood wheezing disorders. We hypothesised that low birthweight 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 1,598 children participated in the analyses of the effects of birthweight and growth on wheezing disorders, respectively.

Primary and secondary outcome measures: wheezing disorders diagnosis (diagnosed as asthma or had wheezing symptom) and treatment during the ages of 0 to 7 years were the primary outcome measures. Diagnosis of asthma and occurrence of wheezing during the same period were secondary outcome measures.

Results: The adjusted 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 respective RRs of wheezing disorders treatment were 1.27 (95% CI: 1.15 to 1.40) and 0.99 (95% CI: 0.89 to1.11). 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 to the "normal" growth. The respective RRs of wheezing disorders treatment were 0.77 (95% CI: 0.28 to 2.17; p=0.63) and 0.81 (95% CI: 0.29 to 2.25; p=0.69).

Conclusion: Low birthweight children have an increased risk of wheezing disorders whereas high birthweight children have a reduced risk in this birth cohort. Low birthweight coupled with a decelerated growth until 3 months and a sharp growth between 3 and 12 months has an increased risk of wheezing disorders diagnosis, but not wheezing disorders treatment.

Key study strengths:

- A large sample, contemporary birth cohort data was used
- DAGs were used to minimize bias potential bias due to confounding
- Multiple Imputation by chained equations was used to minimize bias due to missing data
- Age and sex specific standardised scores and growth percentiles were used to illustrate the growth of cohort children in reference to standard growth charts

Key study weaknesses:

- 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 (i.e. family asthma and breast feeding) was missing

INTRODUCTION

Asthma is defined as a chronic disease of the passage of airways, characterized by smooth muscle contraction, accumulation of mucous 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 pre-school 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 under-diagnosis 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 birthweight on wheezing disorders has been studied extensively with 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 birth weight 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 ≥2.5kg and 2.5–4.0kg birth weight children, respectively.[10] We also found a modest increased risk in high birth weight children (>4 kg) when compared with normal birth weight (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 risk estimates of the studies included 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[11-21] and others reporting reduced risk of wheezing disorders.[20 22-24] In addition to that, all of these studies, with the exception of one,[19] assumed homogenous growth among children, either used statistical techniques that can now be improved upon or a non-standard growth data

analysis that makes comparison and replication of results very difficult. For example, three [11 17 21] used data driven standardised scores (SDS), three [12 20 23 24] used country specific SDS and another one [15] used non-standardized weight measurements.

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

METHODS

Study participants

The Born in Bradford study is a prospective mainly bi-ethnic, cohort that examines the impact of environmental, genetic and social factors on health of the population of Bradford [25]. The methods of recruitment are explained in detail elsewhere. [25 26] 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 one 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 sub cohort (BiB1000) of 1,735 mothers and 1,763 babies were also recruited for follow-up examinations. After excluding multiple births, preterm births and death before the age of one week, a total of 1,598 children were included in growth pattern and wheezing disorder analyses.

Ethics statement

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

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 socio-economic status 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 asthma and 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 one week and maximum of one year 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 supplementary tables 1&2.

Variables for analysis

Primary variables:

Where regression modelling was carried out, exposure variables were birthweight and growth; outcome variables were wheezing disorders (i.e. *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 was 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 visit 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 birthweight was measured (i.e. birth), and 1, 2, 3, 4, and 5 represent for 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 (i.e. intercept and slope) and weight status (i.e. 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.[27-29] In order to minimise bias due to confounding and over-adjustment, Direct Acyclic Graphs (DAGs) were used [28 30] and models were tested using DAGitty software.[29] Drawing of a relationship between variables of interest (i.e. confounding and main variables) was guided by epidemiological, biologic and clinical knowledge. Figures S1 & 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 birthweight 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: birthweight, 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, that is, after collection of data was already carried out by the BiB project. 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 was available for the variable "family asthma" and "breast feeding".

Missing data estimation variables

Where imputations were carried out, missing data were estimated under 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).[31] The *auxiliary* variables included in the imputation process were: exposure variable, 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 of imputations showed that birthweight, gestational age and outcome variables (i.e. 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 (i.e. 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.[32] 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.[31 32]

Statistical analysis and software

Birth weight was classified according to the Centre of Diseases prevention and Control (CDC) [33] and World Health Organisation (WHO) methods [34] where <2.5kg=Low, 2.5-4.0kg=Normal and >4.0kg=High. Age-specific and sex-specific standardised scores (SDS) of weight were derived

according to World Health Organisation (WHO) growth standards [35] in LMSgrowth Microsoft excel add-in software.[36] The WHO growth standards population that we used to derive the SDS scores was made up of singleton term births. Hence, multiple births and preterm births were excluded from the growth patterns and wheezing disorders analyses.

In identifying the best fitting growth patterns, growth mixture models (GMM) were fitted,[37 38] 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 less ≤1% of the total population. When comparing growth patterns of children in our GMM, we used WHO growth standards charts [35] 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 percentiles respectively.

Missing data on covariates were estimated using Multiple Imputations by Chained Equation (MICE) models under Missing data at Random (MAR) assumptions. [39 40] In deciding how many datasets to be imputed, we took the number of imputations (**n**) to be greater than the percentage or fraction of incomplete cases. [39 41] Missing growth data were estimated using a Full Information Maximum Likelihood (FIML) method in which parameters are estimated using all available observations in the dataset, under MAR assumption.[42 43]

GMM was carried out in Mplus version. 7.11, and covariates' missing data estimation and regression modelling were carried out in Stata version 12. 5% significance levels and 95% confidence intervals were adopted throughout.

RESULTS

Birthweight and wheezing disorders

The cohort was made up of 13,734 children that yielded 74,940 person years of follow-up. 37.3% and 32.8% were Pakistani and white British origin respectively; 12.6% were minority and 17.3% with missing ethnicity data. 50.4% and 47.3% were male and female respectively, and, 2.3% of children had missing information on sex. 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 birthweight

Low birthweight was associated with all four disease definitions. The adjusted 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 (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 birthweight

There was a consistent but weak evidence for a reduction of wheezing disorders risk for those children who were classified as being of high birthweight. 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 (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 birthweight 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).

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 %
Birthweight								
Normal (2.5-4.0kg)	668/10,673	5.9%	1,622/9,719	14.3%	1,907/9,434	16.8%	2,444/8,897	21.6%
Low (<2.5kg)	104/1,035	9.1%	209/930	18.3%	246/893	21.6%	311/828	27.3%
High (>4.0kg)	69/1,185	5.5%	163/1,091	13.0%	194/1,060	15.5%	280/974	22.3%
Ethnicity								
White British	217/4,284	4.8%	586/3,915	13.1%	706/3,795	15.7%	1,074/3,427	23.9%
Pakistani	382/4,735	7.5%	857/4,260	16.7%	985/4,132	19.2%	1,150/3,967	22.5%
Others	86/1,647	5.0%	207/1,526	11.9%	243/1,490	14.0%	308/1,425	17.8%
Gender								
Male	502/6,415	7.3%	1,220/5,697	17.6%	1,416/5,501	20.5%	1,775/5,142	25.7%
Female	318/6,172	4.9%	742/5,748	11.4%	890/5,600	13.7%	1,190/5,300	18.3%
Gestational age								
Term	769/12,100	6.0%	1,841/11,028	14.3%	2,166/10,703	16.8%	2,792/10,077	21.7%
Pre-term	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%	1,923/11,161	14.7%	2,262/10,822	17.3%	2,911/10,173	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	520/7,371	6.6%	1,162/6,729	14.7%	1,359/6,532	17.2%	1,710/6,181	21.7%
Yes	167/3,295	4.8%	490/2,972	14.2%	578/2,884	16.7%	823/2,639	23.8%
Parity								
primiparous	292/4,823	5.7%	686/4,429	13.4%	821/4,294	16.1%	1,128/3,987	22.1%
multiparous	489/7,311	6.3%	1,210/6,590	15.5%	1,401/6,399	18.0%	1,728/6,072	22.2%
IMD 2010 Quintile score								
1	487/7,048	6.5%	1,182/6,353	15.7%	1,372/6,163	18.2%	1,721/5,814	22.8%
2	115/1,939	5.6%	253/1,801	12.3%	304/1,750	14.8%	435/1,619	21.2%
3	59/1,196	4.7%	148/1,107	11.8%	177/1,078	14.1%	247/1,008	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% confidence intervals of covariates using 40 imputed datasets**

	Asthma diagnosis	Wheezing symptoms	Wheezing disorder diagnosis	Wheezing disorder treatment
Birthweight				
Normal (2.5-4.0kg)	1	1	1	1
High (>4.0kg)	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 (<2.5kg)	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
Pre-term	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)

Note: model adjusted for ethnicity, gender, gestational age, number of births, maternal smoking, parity and IMD score.

Growth and wheezing disorders

The BiB1000 follow-up cohort consisted of 1,598 children that contributed a total of 8,683 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 three months and the first six months respectively (supplementary table S3).

Age based weight patterns

According to the optimal number of class determination results, a four class model was best (supplementary table S4). However, a three class model was preferred on an interpretability basis

(table 3 & figure S3A). Class 1 (95.8%) was composed of children whose mean birthweight was at the 46th percentile and were just over the 60th percentile at the age of 1 year and stayed around 60th percentile afterwards according to WHO growth standards.[35] Class 2 (2.2%) was composed of children whose mean weight at birth was on the 28th percentile then increased to the 96th percentile at one year of age and persisted to be overweight until the age of three. Class 3 (2.0%) were a group of children whose mean birthweight was on the 29th percentile, who subsequently showed very slow growth, their mean weight reaching the 3rd percentile at 1 year of age, followed by moderate acceleration to reach the 56th percentile by the age of three. Class 1, class 2 and class 3, could be characterised as "normal", "fast" and "slow" growth groups respectively. Supplementary Table S5 gives estimated means of the growth model parameters.

Table 3 Estimated mean and percentiles of 1,598 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)	-

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 the "normal" growth group (table 4). The adjusted RRs of the "slow" as compared to the "normal" growth group for "wheezing" symptoms, "wheezing disorder" diagnosis and "wheezing disorders" treatment were 0.72 (95% CI: 0.20 to 2.62), 0.60 (95% CI: 0.16 to 1.95) and 0.81 (95% CI: 0.29 to 2.25) respectively. The respective unadjusted relative risks 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 to 9.4, 10.7 to 18.3, 15.2 to 22.8, 23.4 to 28.5 and 35.4 to 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 (supplementary table S4). Class 1 (92.7%) comprised those children who were around the 46th percentile at birth and 52nd percentile during the first visit after birth and remained around the 60th percentile during the next four visits according to the WHO growth standards chart; [35] class 2 (7.3%) comprised children who were, on average, at the 29nd percentile at birth and 57th percentile during the first visit after birth then consistently accelerated to reach the 95th percentile during the last visit (figure S3B & table 3). Class 1 and class 2 could be characterised as "inconsistent" and "consistent" growth groups respectively.

Table 4 **Characteristics of 1,598 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 %
Birthweight								
Normal (2.5-4.0kg)	101/1,314	7.1%	221/1,194	15.6%	264/1,151	18.7%	321/ 1,094	22.7%
Low (<2.5kg)	6/64	8.6%	14/56	20.0%	16/54	22.9%	20/50	28.6%
High (>4.0kg)	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	90/1,051	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%

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 (0.66 to 1.95), 1.38 (0.90 to 2.12) and 1.17 (0.76 to 1.81) respectively, when compared to the "consistent" growth group. The respective unadjusted relative risks remained similar (table 5).

Table 5 adjusted and unadjusted relative risks 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 birthweight, ethnicity, gender, maternal smoking, parity and maternal SES; class 1 was a reference group in both models.

Complete cases versus imputed dataset results

The complete cases analysis for birthweight 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 1,572 of the 1,598 children. The results of complete cases 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 (supplementary tables S6 & S7).

Discussion

In this prospective cohort study, we found that low birthweight was strongly associated with wheezing disorders and there was consistent, albeit weak, evidence that high birthweight was associated with reduced risk of wheezing disorders during the pre-school period. Our findings for the effects of low birthweight 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 birthweight (OR=1.37; 95% CI: 1.05 to 1.79) compared to normal birthweight, [10] although the results here are slightly attenuated due to our use of relative risk as a measure of association. However, our finding of the effect of high birthweight on wheezing disorders is slightly different to that of the reported odds ratio 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 results showed that the "slow" growth group did have a reduced risk for both wheezing disorders diagnosis and treatment, albeit weak evidence, when compared to 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.

The findings of the effects of growth on wheezing disorders analyses may not be directly comparable with the previous studies [11 13-15 17 18 20-24] as they assumed a homogenous growth among the respective study population and investigated the effect of overall mean change on wheezing disorders. However, Rzehak et al [19] who used GMM reported hazard ratios 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' group's of the 'visits-based' growth patterns risk estimates.[12 16]

In our previous meta-analyses and systematic reviews we found that low birthweight and high BMI were associated with wheezing disorders. [10 44] 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 (table 3&5). We also noted that children with the lowest birthweight SDS were more likely to be obese and to have experienced wheezing disorder conditions (table 3&5). Given that a very small proportion of wheezing disorders or treatment cases were identified in the first three and six months (table S3), during which changes in growth occurred, it may strongly suggest that low birthweight coupled with rapid change in growth during the first six 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 Randomization study by Granell et al, it has been reported that obesity precedes childhood wheezing disorders.[45]

Our work has certain weakness so that the results need to be interpreted carefully. Firstly, although the sample size for birthweight 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. Secondly, participation in the sub-cohort (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 [19] also reported that there was no significant difference between adjusted and unadjusted (i.e. for breast feeding and family asthma) model results which may show that lack of adjustment for only two potential confounding variables may have minimal effect into our growth and wheezing disorders model results.

Nonetheless, there are particular strengths of our analysis. Firstly, in our birthweight and wheezing disorders analyses, our sample size was reasonably large. Secondly, 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. Thirdly, we were able to implement missing data techniques to minimize bias and presented both the complete cases and imputed datasets results to give more insight. Fourthly, although we had small size for growth patterns 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.[35] The standard scores are convertible to percentiles [36] 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 weak evidence to suggest “fast” or “inconsistent” growth predispose to wheezing disorders, and “slow” growth reduces the risk which needs further investigation using larger datasets. However, the results may indicate that maintaining optimal prenatal and postnatal growths reduce a risk of childhood wheezing disorders.

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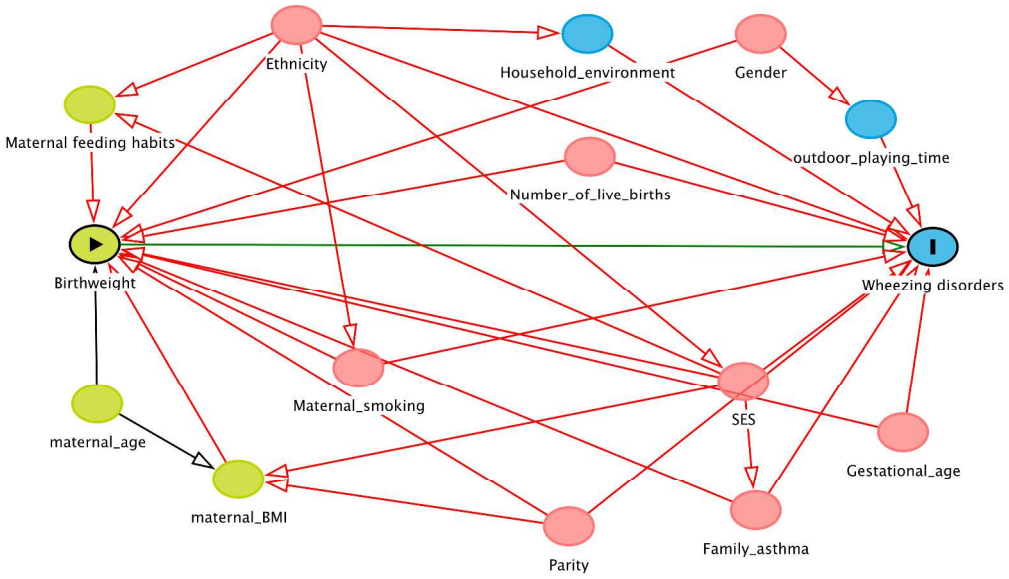

Figure S1: DAGitty schematic view of confounding adjustment for the effects of birthweight on wheezing disorders.

Minimal sufficient adjustment sets for estimating the total effect of birthweight on wheezing disorders:
•Ethnicity, family asthma, gender, gestational age, maternal smoking, number of live births, parity, SES
•Ethnicity, family asthma, gestational age, maternal smoking, number of live births, parity, SES, outdoor playing time

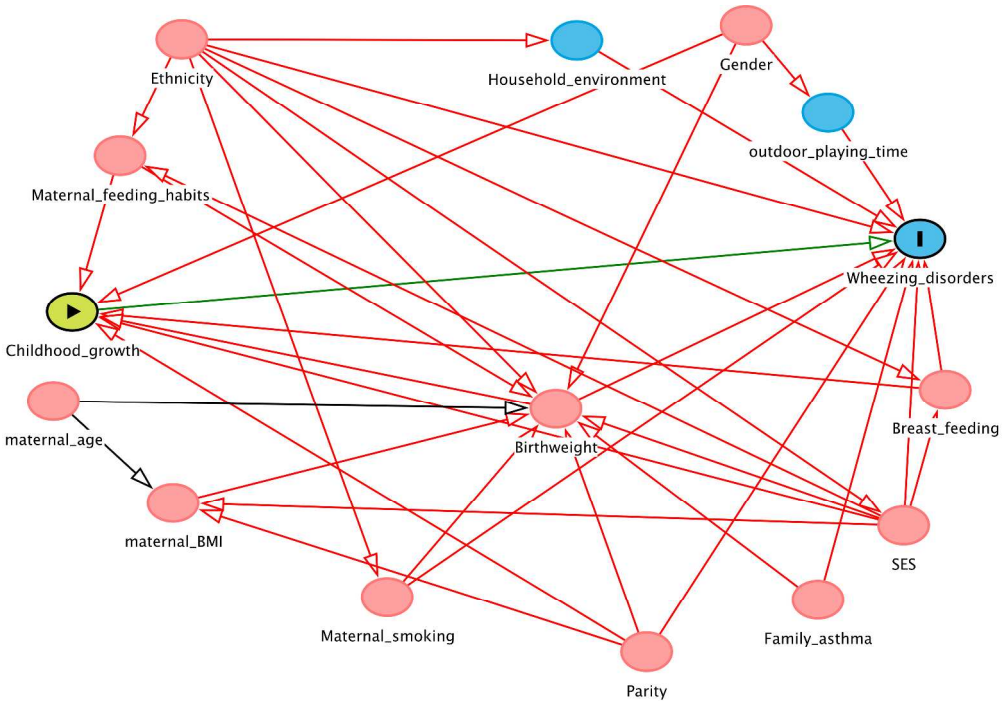

Figure S2: DAGitty schematic view of confounding adjustment for the effects of childhood growth on wheezing disorders.

Minimal sufficient adjustment sets for estimating the total effect of childhood growth on wheezing disorders:
•Birthweight, breast feeding, ethnicity, family asthma, gender, maternal smoking, parity, SES
•Birthweight, breast feeding, ethnicity, family asthma, maternal smoking, parity, SES, outdoor playing time
•Birthweight, breast feeding, gender, maternal feeding habits, parity, SES

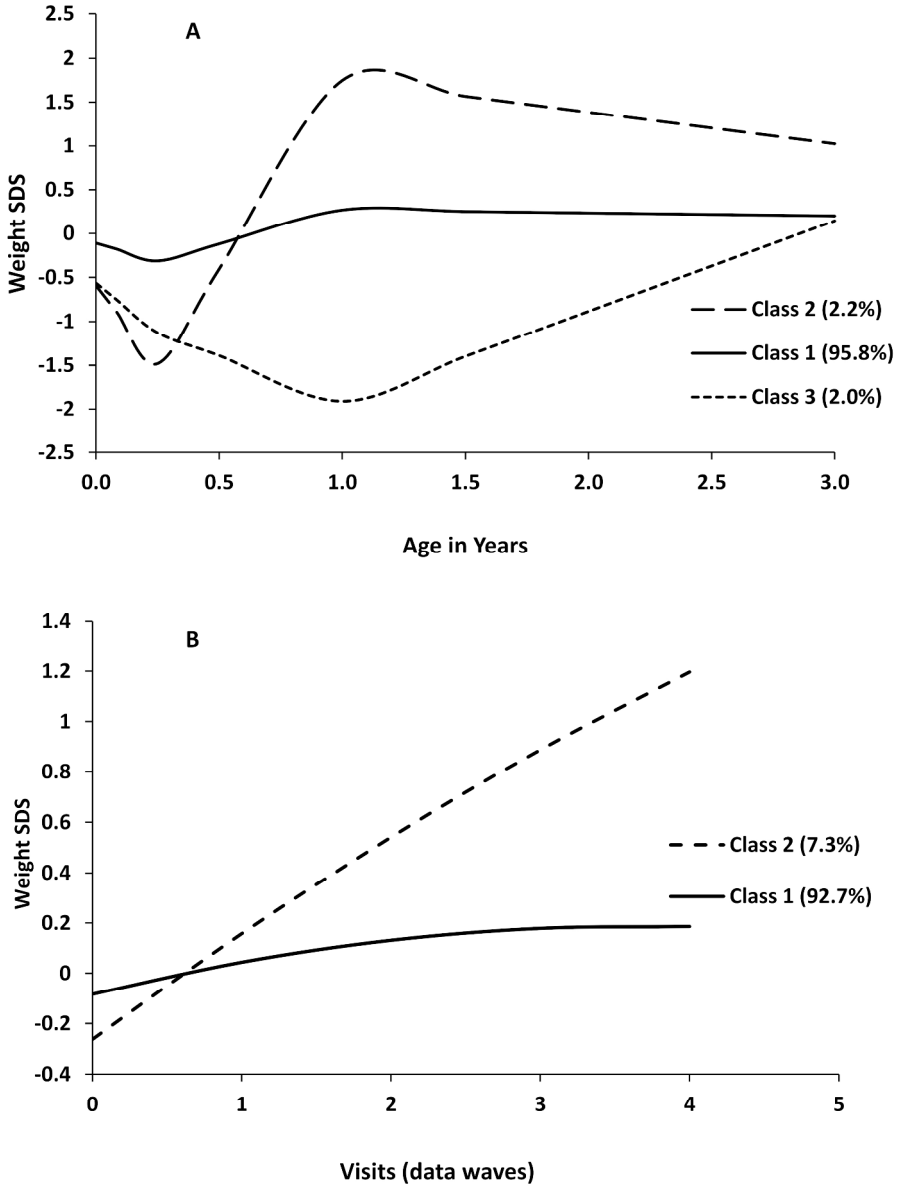

Figure S3 Estimated mean curves of weight SDS according to age (A) and visits (B)

Supplementary:

Table S1: list of drugs used to confirm diagnosis of wheezing disorders

Drug class names	Drug family names
Antimuscarinic bronchodilators	
	IPRATROPIUM BROMIDE
selective beta-2 agonists	
	FORMOTEROL FUMARATE
	SALBUTAMOL
	SALMETEROL
	TERBUTALINE SULPHATE
Leukotriene receptor antagonist	
	MONTELUKAST
	ZAFIRLUKAST
Nasal Corticosteroids	
	BECLOMETASONE DIPROPIONATE
	BUDESONIDE
	CICLESONIDE
	FLUTICASONE PROPIONATE
	MOMETASONE FURATE
	SODIUM CROMOGLICATE

Table S2: list of terms to confirm diagnosis of wheezing disorders

Name	List of terms	Read Code	Term ID
Wheezing			
	Expiratory polyphonic wheeze	Xa83N	YaVc1
	Expiratory wheeze	Xa7uu	YaVQZ
	Expiratory wheezing	Xa7vA	YaVQt
	Inspiratory wheeze	Xa7ut	YaVQY
	Inspiratory wheezing	Xa7v9	YaVQs
	Mild wheeze	XaX5K	Yaty9
	Moderate wheeze	XaX5L	YatyA
	Nocturnal wheeze/cough	173B.	YM1gs
	Severe wheeze	XaX5M	YatyC
	Very severe wheeze	XaX5N	YatyE
	Viral wheeze	XaMe7	YapfP
	Wheeze - rhonchi	X76If	Y7DxZ
	Wheezing	XE0qs	Y7DuF
	Wheezing symptom	XM0Ci	YM1is
	Wheezy	XE0qs	Y7DuF
Asthma			
	Acute asthma	Xa9zf	YaYk2
	Allergic asthma	XE0YT	Y108G
	Asthma	H33..	Y107p
	Asthma NOS	XE0YX	Y1080
	Asthma unspecified	H33z.	Y107y
	Asthmatic bronchitis	Xa0lZ	Y108e
	Brittle asthma	Ua1AX	YMFVN
	Childhood asthma	X101t	Y107w
	Chronic asthmatic bronchitis	H3120	Y108g
	Mild asthma	663V1	YaY1o
	Moderate asthma	663V2	YaY1p
	Nocturnal asthma	XaLPE	Y1084
	Non-allergic asthma	XE0YT	Y108G
	Occasional asthma	663V0	YaY1n

Table S3 **Period of diagnosis or treatment initiation for BiB1000 children**

	Period in months			
	First 3 months	First 6 months	First 9 months	First 12 months
Wheezing disorders diagnosis	1.3%	8.3%	17.0%	27.7%
Wheezing disorders treatment	2.1%	16.8%	33.1%	46.1%
Asthma diagnosis	0%	1.8%	2.7%	4.4%
Wheezing symptoms	1.59	7.9%	19.8%	31.8%

Table S4 Model fit results for selection of optimal number of classes

Number of classes	Model fit Criterion				Classification quality	Likelihood ratio test
	-2LL	AIC	ABIC	df	Entropy	BLRT (-2LL diff; df diff; and P-values)
Age based weight SDS						
1 class	13,794	13,836	13,883	21	N/A	N/A
2 classes	13,752	13,805	13,862	26	0.94	42; 5; <0.01
3 classes	13,724	13,785	13,853	31	0.90	29; 5; <0.01
4 classes	13,698	13,770	13,849	36	0.88	24; 5; 0.02
5 classes	13,680	13,763	13,853	41	0.88	17; 5; 0.70
Visits based weight SDS						
1 class	14,100	14,129	14,159	14	N/A	N/A
2 classes	14,034	14, 069	14,109	18	0.79	67; 4; <0.01
3 classes	14,006	14,052	14,099	22	0.85	26; 4; <0.01
4 classes	13,992	14,044	14,102	26	0.79	15; 4; 0.03
5 classes	13,980	14,041	14,107	30	0.72	11; 4; 0.25

LL= Log-likelihood; AIC=Akaike Information Criterion; ABIC= sample size adjusted Bayesian Information Criterion; BLRT=Bootstrapped likelihood Ratio Test; -2LL diff=2 times the Log-likelihood difference, df=degrees of freedom (number of free parameters); df diff= difference in the degree of freedom or number of free parameters.

Table S5 **Mean estimates of the latent classes of Growth Mixture Model parameters**

	Parameter	Estimate and 95% CI	P-value
Age based GMM model			
Class 1 ('Normal growers')	Birthweight	–0.111 (–0.170 to –0.053)	<0.01
	$Velocity_{0-3}$	–0.671 (–0.903 to –0.439)	<0.01
	$Velocity_{3-12}$	0.645 (0.578 to 0.712)	<0.01
	$Velocity_{12-36}$	–0.028 (–0.053, –0.003)	0.03
Class 2('Fast growers')	Birthweight	–0.594 (–1.305 to 0.117)	0.10
	$Velocity_{0-3}$	–2.956 (–7.838 to 1.925)	0.24
	$Velocity_{3-12}$	3.588 (2.850 to 4.326)	<0.01
	$Velocity_{12-36}$	–0.302 (–0.993 to 0.390)	0.39
Class 3('Slow growers')	Birthweight	–0.564 (–1.146 to 0.018)	0.06
	$Velocity_{0-3}$	–1.878 (–3.980 to 0.225)	0.08
	$Velocity_{3-12}$	–0.871 (-1.950 to 0.208)	0.11
	$Velocity_{12-36}$	0.856 (0.266 to 1.446)	<0.01
Visits based GMM model			
Class 1 ('consistent growers')	Birthweight	–0.084 (–0.138 to –0.030)	<0.01
	Velocity	0.246 (0.196 to 0.297)	<0.01
	Acceleration	–0.056 (–0.067 to –0.045)	<0.01
Class 2 ('inconsistent growers')	Birthweight	–0.263 (–0.577 to 0.051)	0.10
	Velocity	0.732 (0.335 to 1.129)	<0.01
	Acceleration	–0.051 (–0.132 to 0.029)	0.21

Table S6 Adjusted relative risks and 95% confidence intervals of complete cases analysis (10,623 children)

	Wheezing disorders treatment	Asthma diagnosis	Wheezing symptoms	wheezing disorder diagnosis
Birthweight				
Normal (2.5-4.0kg)	1	1	1	1
High (>4.0kg)	1.03(0.90 to1.18)	0.88 (0.63 to 1.22)	1.01 (0.84 to 1.21)	0.97 (0.82 to 1.14)
Low (<2.5kg)	1.22 (1.06 to 1.41)	1.63 (1.24 to 2.14)	1.26 (1.05 to 1.51)	1.30 (1.10 to 1.53)
Ethnicity				
White British	1	1	1	1
Pakistani	0.96 (0.87 to 1.05)	1.39 (1.12 to 1.71)	1.26 (1.11 to 1.43)	1.22 (1.09 to 1.36)
Others	0.76 (0.68 to 0.86)	1.00 (0.76 to 1.30)	0.93 (0.79 to 1.09)	0.91 (0.78 to 1.05)
Gender				
Male	1	1	1	1
Female	0.73 (0.67 to 0.78)	0.64 (0.55 to 0.75)	0.64 (0.59to0.71)	0.65 (0.60 to 0.72)
Gestational age				
Term	1	1	1	1
Pre-term	1.21 (1.04 to 1.42)	1.13 (0.81 to 1.56)	1.10 (0.89 to 1.35)	1.11 (0.92 to 1.33)
Number of births				
Singleton	1	1	1	1
Twins	0.67 (0.51 to 0.88)	0.71 (0.43 to 1.19)	0.70 (0.50 to 0.99)	0.66 (0.48 to 0.91)
Triplets	1.18 (0.39 to 3.61)	-	0.83 (0.14 to 4.91)	0.69 (0.12 to 4.09)
Maternal smoking				
No	1	1	1	1
Yes	1.04 (0.96 to 1.14)	0.83 (0.68 to 1.03)	1.09 (0.96 to 1.22)	1.07 (0.96 to 1.19)
Parity				
primiparous	1	1	1	1
multiparous	1.01 (0.94 to 1.09)	1.06 (0.90 to 1.24)	1.12 (1.02 to 1.23)	1.09 (1.00 to 1.19)
IMD 2010 Quintile score	0.98 (0.94 to 1.02)	0.97 (0.88 to 1.07)	0.94 (0.89 to 1.00)	0.95 (0.91 to 1.01)

Table S7 **Adjusted and unadjusted relative risks and 95% CI for growth patterns and wheezing disorders from complete cases analysis (1,572 children)**

		Unadjusted RR (95% CI; p-value)	Adjusted RR (95% CI; p-value)
Age based weight SDS			
Class 2	Asthma diagnosis	0.82 (0.12 to 5.56; 0.84)	0.81 (0.12 to 5.46; 0.83)
(fast growers)	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	Asthma diagnosis	1	1
(slow growers)	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	Asthma diagnosis	1.66 (0.81 to 3.42; 0.17)	1.47 (0.71 to 3.01; 0.30)
(inconsistent	Wheezing symptom	1.15 (0.66 to 1.99; 0.62)	1.13 (0.66 to 1.95; 0.65)
growers)	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 birthweight, ethnicity, gender, maternal smoking, parity and maternal SES; class 1 was a reference group in both models.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract [**Methods section of the abstract page 1**]
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found [**Results section of abstract page 1**]
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported [**Page 3**]
Objectives	3	State specific objectives, including any prespecified hypotheses [**Page 4**]
Methods		
Study design	4	Present key elements of study design early in the paper [**Methodology page 5**]
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Pages 5-6]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Pages 5-6]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[N/A]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Page 6]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Pages 5-6]**
Bias	9	Describe any efforts to address potential sources of bias **[Page 6-7]**
Study size	10	Explain how the study size was arrived at **[Page 5]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Pages 5-6]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Pages 6-7]**
		(*b*) Describe any methods used to examine subgroups and interactions **[N/A]**
		(*c*) Explain how missing data were addressed **[Page 7]**
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **[N/A]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Page 5]**
		(b) Give reasons for non-participation at each stage **[Page 5]**
		(c) Consider use of a flow diagram **[N/A]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Page 8**
		(b) Indicate number of participants with missing data for each variable of interest **[Page 9]**
		(c) Summarise follow-up time (eg, average and total amount) **[Page 8]**
Outcome data	15*	Report numbers of outcome events or summary measures over time **[Page 8]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included **[Pages 10 &13]**
		(*b*) Report category boundaries when continuous variables were categorized **[Page 6]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[N/A]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 14]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Page 15]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Pages 14-15]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Page 14-15]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[within acknowledgments and funding]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The effects of birthweight and growth on childhood wheezing disorders: findings from the Born in Bradford Cohort

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The effects of birthweight and growth on childhood wheezing disorders: findings from the Born in Bradford Cohort

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Abstract:

Objectives: To examine the effects of birthweight and childhood growth on childhood wheezing disorders. We hypothesised that low birthweight 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 1,598 children participated in the analyses of the effects of birthweight 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 to 7 years were the primary outcome measures. Diagnosis of asthma and occurrence of wheezing during the same period were secondary outcome measures. Birthweight was classified as normal (2.5-4.0kg), low (<2.5kg) and high (>4.0kg). 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 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 to the "normal" growth.

Conclusion: Low birthweight 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 birthweight 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.

Key study strengths:

- A large sample, contemporary birth cohort data was used
- DAGs were used to minimize bias potential bias due to confounding
- Multiple Imputation by chained equations was used to minimize bias due to missing data
- Age and sex specific standardised scores and growth percentiles were used to illustrate the growth of cohort children in reference to standard growth charts

Key study weaknesses:

- 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 (i.e. family asthma and breast feeding) was missing

INTRODUCTION

Asthma is defined as a chronic disease of the passage of airways, characterized by smooth muscle contraction, accumulation of mucous 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 pre-school 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 under-diagnosis 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 birthweight on wheezing disorders has been studied extensively with 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 birth weight 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 ≥2.5kg and 2.5–4.0kg birth weight children, respectively.[10] We also found a modest increased risk in high birth weight children (>4 kg) when compared with normal birth weight (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[11-21] and others reporting reduced risk of wheezing disorders.[20 22-24] In addition to that, all of these studies, with the exception of one,[19] assumed homogenous growth among children, either used statistical techniques that can now be improved upon or a non-standard growth data

analysis that makes comparison and replication of results very difficult. For example, three [11 17 21] used data driven standardised scores (SDS), three [12 20 23 24] used country specific SDS and another one [15] used non-standardized weight measurements.

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

METHODS

Study participants

The Born in Bradford study is a prospective mainly bi-ethnic, cohort that examines the impact of environmental, genetic and social factors on health of the population of Bradford [25]. The methods of recruitment are explained in detail elsewhere. [25 26] 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 one 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 sub cohort (BiB1000) of 1,735 mothers and 1,763 babies were also recruited for follow-up examinations. After excluding multiple births, preterm births and death before the age of one week, a total of 1,598 children were included in growth pattern and wheezing disorder analyses.

Ethics statement

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

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 socio-economic status 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 one 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 supplementary tables 1&2.

Variables for analysis

Primary variables:

Where regression modelling was carried out, exposure variables were birthweight and growth; outcome variables were wheezing disorders (i.e. *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 was 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 visit 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 birthweight was measured (i.e. birth), and 1, 2, 3, 4, and 5 represent for 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 (i.e. intercept and slope) and weight status (i.e. 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.[27-29] In order to minimise bias due to confounding and over-adjustment, Direct Acyclic Graphs (DAGs) were used [28 30] and models were tested using DAGitty software.[29] Drawing of a relationship between variables of interest (i.e. confounding and main variables) was guided by epidemiological, biologic and clinical knowledge. Figures S1 & 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 birthweight 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: birthweight, 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 was available for the variables "family asthma" and "breast feeding".

Missing data estimation variables

Where imputations were carried out, missing data were estimated under 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).[31] The *auxiliary* variables included in the imputation process were: exposure variable, 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 of imputations showed that birthweight, gestational age and outcome variables (i.e. 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 (i.e. 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.[32] 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.[31 32]

Statistical analysis and software

Birth weight was classified according to the Centre of Diseases prevention and Control (CDC) [33] and World Health Organisation (WHO) methods [34] where <2.5kg=Low, 2.5-4.0kg=Normal and >4.0kg=High. Age-specific and sex-specific standardised scores (SDS) of weight were derived according to World Health Organisation (WHO) growth standards [35] in LMSgrowth Microsoft excel add-in software.[36] The WHO growth standards population that we used to derive the SDS scores was made up of singleton term births. Hence, multiple births and preterm births were excluded from the growth patterns and wheezing disorders analyses.

In identifying the best fitting growth patterns, growth mixture models (GMM) were fitted,[37 38] 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 less ≤1% of the total population. When comparing growth patterns of children in our GMM, we used WHO growth standards charts [35] 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 percentiles respectively.

Missing data on covariates were estimated using Multiple Imputations by Chained Equation (MICE) models under Missing data at Random (MAR) assumptions. [39 40] In deciding how many datasets to be imputed, we took the number of imputations (**n**) to be greater than the percentage or fraction of incomplete cases. [39 41] Missing growth data were estimated using a Full Information Maximum Likelihood (FIML) method in which parameters are estimated using all available observations in the dataset, under MAR assumption.[42 43]

GMM was carried out in Mplus version. 7.11, and covariates' missing data estimation and regression modelling were carried out in Stata version 12. 5% significance levels and 95% confidence intervals were adopted throughout.

RESULTS

Birthweight and wheezing disorders

The cohort was made up of 13,734 children that yielded 74,940 person years of follow-up. 37.3% and 32.8% were Pakistani and white British origin respectively; 12.6% were minority and 17.3% with missing ethnicity data. 50.4% and 47.3% were male and female respectively, and, 2.3% of children had missing information on sex. 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 birthweight

Low birthweight was associated with all four disease definitions. The adjusted 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 (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 birthweight

There was a consistent but weak evidence for a reduction of wheezing disorders risk for those children who were classified as being of high birthweight. 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 (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 birthweight 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).

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 %
Birthweight								
Normal (2.5-4.0kg)	668/10,673	5.9%	1,622/9,719	14.3%	1,907/9,434	16.8%	2,444/8,897	21.6%
Low (<2.5kg)	104/1,035	9.1%	209/930	18.3%	246/893	21.6%	311/828	27.3%
High (>4.0kg)	69/1,185	5.5%	163/1,091	13.0%	194/1,060	15.5%	280/974	22.3%
Ethnicity								
White British	217/4,284	4.8%	586/3,915	13.1%	706/3,795	15.7%	1,074/3,427	23.9%
Pakistani	382/4,735	7.5%	857/4,260	16.7%	985/4,132	19.2%	1,150/3,967	22.5%
Others	86/1,647	5.0%	207/1,526	11.9%	243/1,490	14.0%	308/1,425	17.8%
Gender								
Male	502/6,415	7.3%	1,220/5,697	17.6%	1,416/5,501	20.5%	1,775/5,142	25.7%
Female	318/6,172	4.9%	742/5,748	11.4%	890/5,600	13.7%	1,190/5,300	18.3%
Gestational age								
Term	769/12,100	6.0%	1,841/11,028	14.3%	2,166/10,703	16.8%	2,792/10,077	21.7%
Pre-term	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%	1,923/11,161	14.7%	2,262/10,822	17.3%	2,911/10,173	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	520/7,371	6.6%	1,162/6,729	14.7%	1,359/6,532	17.2%	1,710/6,181	21.7%
Yes	167/3,295	4.8%	490/2,972	14.2%	578/2,884	16.7%	823/2,639	23.8%
Parity								
primiparous	292/4,823	5.7%	686/4,429	13.4%	821/4,294	16.1%	1,128/3,987	22.1%
multiparous	489/7,311	6.3%	1,210/6,590	15.5%	1,401/6,399	18.0%	1,728/6,072	22.2%
IMD 2010 Quintile score								
1	487/7,048	6.5%	1,182/6,353	15.7%	1,372/6,163	18.2%	1,721/5,814	22.8%
2	115/1,939	5.6%	253/1,801	12.3%	304/1,750	14.8%	435/1,619	21.2%
3	59/1,196	4.7%	148/1,107	11.8%	177/1,078	14.1%	247/1,008	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% confidence intervals of covariates using 40 imputed datasets**

	Asthma diagnosis	Wheezing symptoms	Wheezing disorder diagnosis	Wheezing disorder treatment
Birthweight				
Normal (2.5-4.0kg)	1	1	1	1
High (>4.0kg)	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 (<2.5kg)	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
Pre-term	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)

Note: model adjusted for ethnicity, gender, gestational age, number of births, maternal smoking, parity and IMD score.

Growth and wheezing disorders

The BiB1000 follow-up cohort consisted of 1,598 children that contributed a total of 8,683 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 three months and the first six months respectively (table S3).

Age based weight patterns

According to the optimal number of class determination results, a four class model was best (table S4). However, a three class model was preferred on an interpretability basis (table 3 & figure S3A).

Class 1 (95.8%) was composed of children whose mean birthweight was at the 46th percentile and were just over the 60th percentile at the age of 1 year and stayed around 60th percentile afterwards according to WHO growth standards.[35] Class 2 (2.2%) was composed of children whose mean weight at birth was on the 28th percentile then increased to the 96th percentile at one year of age and persisted to be overweight until the age of three. Class 3 (2.0%) were a group of children whose mean birthweight was on the 29th percentile, who subsequently showed very slow growth, their mean weight reaching the 3rd percentile at 1 year of age, followed by moderate acceleration to reach the 56th percentile by the age of three. Class 1, class 2 and class 3, could be characterised as "normal", "fast" and "slow" growth groups respectively. Table S5 gives estimated means of the growth model parameters.

Table 3 Estimated mean and percentiles of 1,598 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)	-

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 the "normal" growth group (table 4). The adjusted RRs of the "slow" as compared to the "normal" growth group for "wheezing" symptoms, "wheezing disorder" diagnosis and "wheezing disorders" treatment were 0.72 (95% CI: 0.20 to 2.62), 0.60 (95% CI: 0.16 to 1.95) and 0.81 (95% CI: 0.29 to 2.25) respectively. The respective unadjusted relative risks 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 to 9.4, 10.7 to 18.3, 15.2 to 22.8, 23.4 to 28.5 and 35.4 to 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 (table S4). Class 1 (92.7%) comprised those children who were around the 46th percentile at birth and 52nd percentile during the first visit after birth and remained around the 60th percentile during the next four visits according to the WHO growth standards chart; [35] class 2 (7.3%) comprised children who were, on average, at the 29nd percentile at birth and 57th percentile during the first visit after birth then consistently accelerated to reach the 95th percentile during the last visit (figure S3B & table 3). Class 1 and class 2 could be characterised as "inconsistent" and "consistent" growth groups respectively.

Table 4 **Characteristics of 1,598 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 %
Birthweight								
Normal (2.5-4.0kg)	101/1,314	7.1%	221/1,194	15.6%	264/1,151	18.7%	321/ 1,094	22.7%
Low (<2.5kg)	6/64	8.6%	14/56	20.0%	16/54	22.9%	20/50	28.6%
High (>4.0kg)	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	90/1,051	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%

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 (0.66 to 1.95), 1.38 (0.90 to 2.12) and 1.17 (0.76 to 1.81) respectively, when compared to the "consistent" growth group. The respective unadjusted relative risks remained similar (table 5).

Table 5 adjusted and unadjusted relative risks 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 birthweight, ethnicity, gender, maternal smoking, parity and maternal SES; class 1 was a reference group in both models.

Complete cases versus imputed dataset results

The complete cases analysis for birthweight 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 1,572 of the 1,598 children. The results of complete cases 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 (tables S6 & S7).

Discussion

In this prospective cohort study, we found that low birthweight was strongly associated with wheezing disorders and there was consistent, albeit weak, evidence that high birthweight was associated with reduced risk of wheezing disorders during the pre-school period. Our findings for the effects of low birthweight 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 birthweight (OR=1.37; 95% CI: 1.05 to 1.79) compared to normal birthweight, [10] although the results here are slightly attenuated due to our use of relative risk as a measure of association. However, our finding of the effect of high birthweight on wheezing disorders is slightly different to that of the reported odds ratio 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 results showed that the "slow" growth group did have a reduced risk for both wheezing disorders diagnosis and treatment, albeit weak evidence, when compared to 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.

The findings of the effects of growth on wheezing disorders analyses may not be directly comparable with the previous studies [11 13-15 17 18 20-24] as they assumed a homogenous growth among the respective study population and investigated the effect of overall mean change on wheezing disorders. However, Rzehak et al [19] who used GMM reported hazard ratios 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' group's of the 'visits-based' growth patterns risk estimates.[12 16]

In our previous meta-analyses and systematic reviews we found that low birthweight and high BMI were associated with wheezing disorders. [10 44] 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 (table 3&5). We also noted that children with the lowest birthweight SDS were more likely to be obese and to have experienced wheezing disorder conditions (table 3&5). Given that a very small proportion of wheezing disorders or treatment cases were identified in the first three and six months (table S3), during which changes in growth occurred, it may strongly suggest that low birthweight coupled with rapid change in growth during the first six 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 Randomization study by Granell et al, it has been reported that obesity precedes childhood wheezing disorders.[45]

Our work has certain weakness so that the results need to be interpreted carefully. Firstly, although the sample size for birthweight 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. Secondly, participation in the sub-cohort (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 [19] also reported that there was no significant difference between unadjusted and adjusted (i.e. for breast feeding and family asthma) model results.

Nonetheless, there are particular strengths of our analysis. Firstly, in our birthweight and wheezing disorders analyses, our sample size was reasonably large. Secondly, 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. Thirdly, we were able to implement missing data techniques to minimize bias and presented both the complete cases and imputed datasets results to give more insight. Fourthly, although we had small size for growth patterns 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.[35] The standard scores are convertible to percentiles [36] 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 datasets. However, the results may indicate that maintaining optimal prenatal and postnatal growths reduce a risk of childhood wheezing disorders.

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Contributors: TFM, RGF and RCP conceived the idea. TFM performed all the statistical analyses, interpretation of results and drafted the manuscript. RGF and RCP revised and commented on the manuscript. All authors approved the final version of the manuscript.

Competing interests: No, there are no competing interests.

Data sharing: No additional data available.

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Supplementary:

Table S1: list of drugs used to confirm diagnosis of wheezing disorders

Drug class names	Drug family names
Antimuscarinic bronchodilators	
	IPRATROPIUM BROMIDE
selective beta-2 agonists	
	FORMOTEROL FUMARATE
	SALBUTAMOL
	SALMETEROL
	TERBUTALINE SULPHATE
Leukotriene receptor antagonist	
	MONTELUKAST
	ZAFIRLUKAST
Nasal Corticosteroids	
	BECLOMETASONE DIPROPIONATE
	BUDESONIDE
	CICLESONIDE
	FLUTICASONE PROPIONATE
	MOMETASONE FURATE
	SODIUM CROMOGLICATE

Table S2: list of terms to confirm diagnosis of wheezing disorders

Name	List of terms	Read Code	Term ID
Wheezing			
	Expiratory polyphonic wheeze	Xa83N	YaVc1
	Expiratory wheeze	Xa7uu	YaVQZ
	Expiratory wheezing	Xa7vA	YaVQt
	Inspiratory wheeze	Xa7ut	YaVQY
	Inspiratory wheezing	Xa7v9	YaVQs
	Mild wheeze	XaX5K	Yaty9
	Moderate wheeze	XaX5L	YatyA
	Nocturnal wheeze/cough	173B.	YM1gs
	Severe wheeze	XaX5M	YatyC
	Very severe wheeze	XaX5N	YatyE
	Viral wheeze	XaMe7	YapfP
	Wheeze - rhonchi	X76If	Y7DxZ
	Wheezing	XE0qs	Y7DuF
	Wheezing symptom	XM0Ci	YM1is
	Wheezy	XE0qs	Y7DuF
Asthma			
	Acute asthma	Xa9zf	YaYk2
	Allergic asthma	XE0YT	Y108G
	Asthma	H33..	Y107p
	Asthma NOS	XE0YX	Y1080
	Asthma unspecified	H33z.	Y107y
	Asthmatic bronchitis	Xa0lZ	Y108e
	Brittle asthma	Ua1AX	YMFVN
	Childhood asthma	X101t	Y107w
	Chronic asthmatic bronchitis	H3120	Y108g
	Mild asthma	663V1	YaY1o
	Moderate asthma	663V2	YaY1p
	Nocturnal asthma	XaLPE	Y1084
	Non-allergic asthma	XE0YT	Y108G
	Occasional asthma	663V0	YaY1n

Table S3 Period of diagnosis or treatment initiation for BiB1000 children

	Period in months			
	First 3 months	First 6 months	First 9 months	First 12 months
Wheezing disorders diagnosis	1.3%	8.3%	17.0%	27.7%
Wheezing disorders treatment	2.1%	16.8%	33.1%	46.1%
Asthma diagnosis	0%	1.8%	2.7%	4.4%
Wheezing symptoms	1.59	7.9%	19.8%	31.8%

Table S4 Model fit results for selection of optimal number of classes

Number of classes	Model fit Criterion				Classification quality	Likelihood ratio test
	-2LL	AIC	ABIC	df	Entropy	BLRT (-2LL diff; df diff; and P-values)
Age based weight SDS						
1 class	13,794	13,836	13,883	21	N/A	N/A
2 classes	13,752	13,805	13,862	26	0.94	42; 5; <0.01
3 classes	13,724	13,785	13,853	31	0.90	29; 5; <0.01
4 classes	13,698	13,770	13,849	36	0.88	24; 5; 0.02
5 classes	13,680	13,763	13,853	41	0.88	17; 5; 0.70
Visits based weight SDS						
1 class	14,100	14,129	14,159	14	N/A	N/A
2 classes	14,034	14, 069	14,109	18	0.79	67; 4; <0.01
3 classes	14,006	14,052	14,099	22	0.85	26; 4; <0.01
4 classes	13,992	14,044	14,102	26	0.79	15; 4; 0.03
5 classes	13,980	14,041	14,107	30	0.72	11; 4; 0.25

LL= Log-likelihood; AIC=Akaike Information Criterion; ABIC= sample size adjusted Bayesian Information Criterion; BLRT=Bootstrapped likelihood Ratio Test; -2LL diff=2 times the Log-likelihood difference, df=degrees of freedom (number of free parameters); df diff= difference in the degree of freedom or number of free parameters.

Table S5 Mean estimates of the latent classes of Growth Mixture Model parameters

	Parameter	Estimate and 95% CI	P-value
Age based GMM model			
Class 1 ('Normal growers')	Birthweight	–0.111 (–0.170 to –0.053)	<0.01
	$Velocity_{0-3}$	–0.671 (–0.903 to –0.439)	<0.01
	$Velocity_{3-12}$	0.645 (0.578 to 0.712)	<0.01
	$Velocity_{12-36}$	–0.028 (–0.053, –0.003)	0.03
Class 2('Fast growers')	Birthweight	–0.594 (–1.305 to 0.117)	0.10
	$Velocity_{0-3}$	–2.956 (–7.838 to 1.925)	0.24
	$Velocity_{3-12}$	3.588 (2.850 to 4.326)	<0.01
	$Velocity_{12-36}$	–0.302 (–0.993 to 0.390)	0.39
Class 3('Slow growers')	Birthweight	–0.564 (–1.146 to 0.018)	0.06
	$Velocity_{0-3}$	–1.878 (–3.980 to 0.225)	0.08
	$Velocity_{3-12}$	–0.871 (-1.950 to 0.208)	0.11
	$Velocity_{12-36}$	0.856 (0.266 to 1.446)	<0.01
Visits based GMM model			
Class 1 ('consistent growers')	Birthweight	–0.084 (–0.138 to –0.030)	<0.01
	Velocity	0.246 (0.196 to 0.297)	<0.01
	Acceleration	–0.056 (–0.067 to –0.045)	<0.01
Class 2 ('inconsistent growers')	Birthweight	–0.263 (–0.577 to 0.051)	0.10
	Velocity	0.732 (0.335 to 1.129)	<0.01
	Acceleration	–0.051 (–0.132 to 0.029)	0.21

Table S6 Adjusted relative risks and 95% confidence intervals of complete cases analysis (10,623 children)

	Wheezing disorders treatment	Asthma diagnosis	Wheezing symptoms	wheezing disorder diagnosis
Birthweight				
Normal (2.5-4.0kg)	1	1	1	1
High (>4.0kg)	1.03(0.90 to1.18)	0.88 (0.63 to 1.22)	1.01 (0.84 to 1.21)	0.97 (0.82 to 1.14)
Low (<2.5kg)	1.22 (1.06 to 1.41)	1.63 (1.24 to 2.14)	1.26 (1.05 to 1.51)	1.30 (1.10 to 1.53)
Ethnicity				
White British	1	1	1	1
Pakistani	0.96 (0.87 to 1.05)	1.39 (1.12 to 1.71)	1.26 (1.11 to 1.43)	1.22 (1.09 to 1.36)
Others	0.76 (0.68 to 0.86)	1.00 (0.76 to 1.30)	0.93 (0.79 to 1.09)	0.91 (0.78 to 1.05)
Gender				
Male	1	1	1	1
Female	0.73 (0.67 to 0.78)	0.64 (0.55 to 0.75)	0.64 (0.59to0.71)	0.65 (0.60 to 0.72)
Gestational age				
Term	1	1	1	1
Pre-term	1.21 (1.04 to 1.42)	1.13 (0.81 to 1.56)	1.10 (0.89 to 1.35)	1.11 (0.92 to 1.33)
Number of births				
Singleton	1	1	1	1
Twins	0.67 (0.51 to 0.88)	0.71 (0.43 to 1.19)	0.70 (0.50 to 0.99)	0.66 (0.48 to 0.91)
Triplets	1.18 (0.39 to 3.61)	-	0.83 (0.14 to 4.91)	0.69 (0.12 to 4.09)
Maternal smoking				
No	1	1	1	1
Yes	1.04 (0.96 to 1.14)	0.83 (0.68 to 1.03)	1.09 (0.96 to 1.22)	1.07 (0.96 to 1.19)
Parity				
primiparous	1	1	1	1
multiparous	1.01 (0.94 to 1.09)	1.06 (0.90 to 1.24)	1.12 (1.02 to 1.23)	1.09 (1.00 to 1.19)
IMD 2010 Quintile score	0.98 (0.94 to 1.02)	0.97 (0.88 to 1.07)	0.94 (0.89 to 1.00)	0.95 (0.91 to 1.01)

Table S7 Adjusted and unadjusted relative risks and 95% CI for growth patterns and wheezing disorders from complete cases analysis (1,572 children)

		Unadjusted RR (95% CI; p-value)	Adjusted RR (95% CI; p-value)
Age based weight SDS			
Class 2	Asthma diagnosis	0.82 (0.12 to 5.56; 0.84)	0.81 (0.12 to 5.46; 0.83)
(fast growers)	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	Asthma diagnosis	1	1
(slow growers)	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	Asthma diagnosis	1.66 (0.81 to 3.42; 0.17)	1.47 (0.71 to 3.01; 0.30)
(inconsistent	Wheezing symptom	1.15 (0.66 to 1.99; 0.62)	1.13 (0.66 to 1.95; 0.65)
growers)	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 birthweight, ethnicity, gender, maternal smoking, parity and maternal SES; class 1 was a reference group in both models.

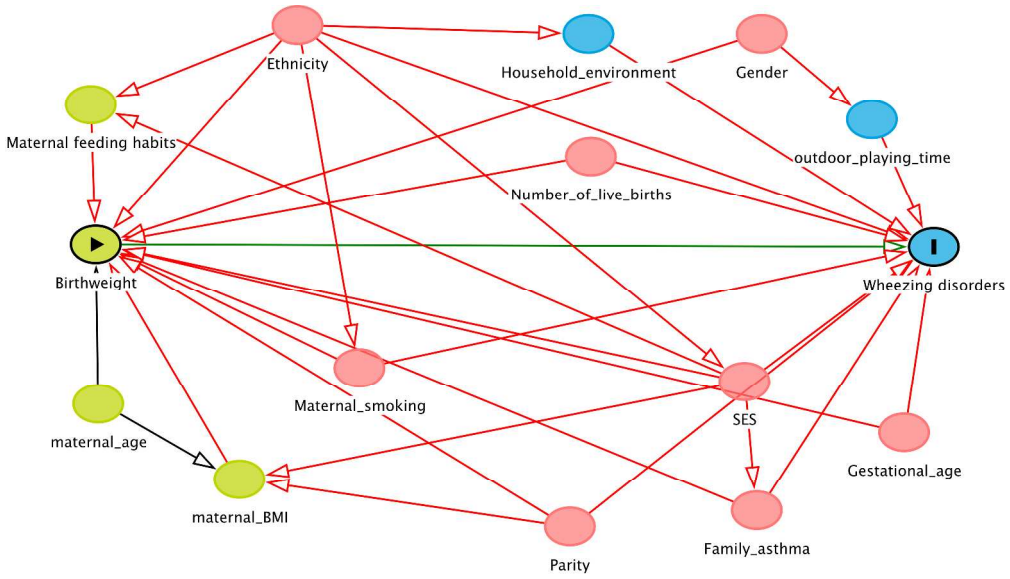


Figure S1: DAGitty schematic view of confounding adjustment for the effects of birthweight on wheezing disorders.

Minimal sufficient adjustment sets for estimating the total effect of birthweight on wheezing disorders:
•Ethnicity, family asthma, gender, gestational age, maternal smoking, number of live births, parity, SES
•Ethnicity, family asthma, gestational age, maternal smoking, number of live births, parity, SES, outdoor playing time

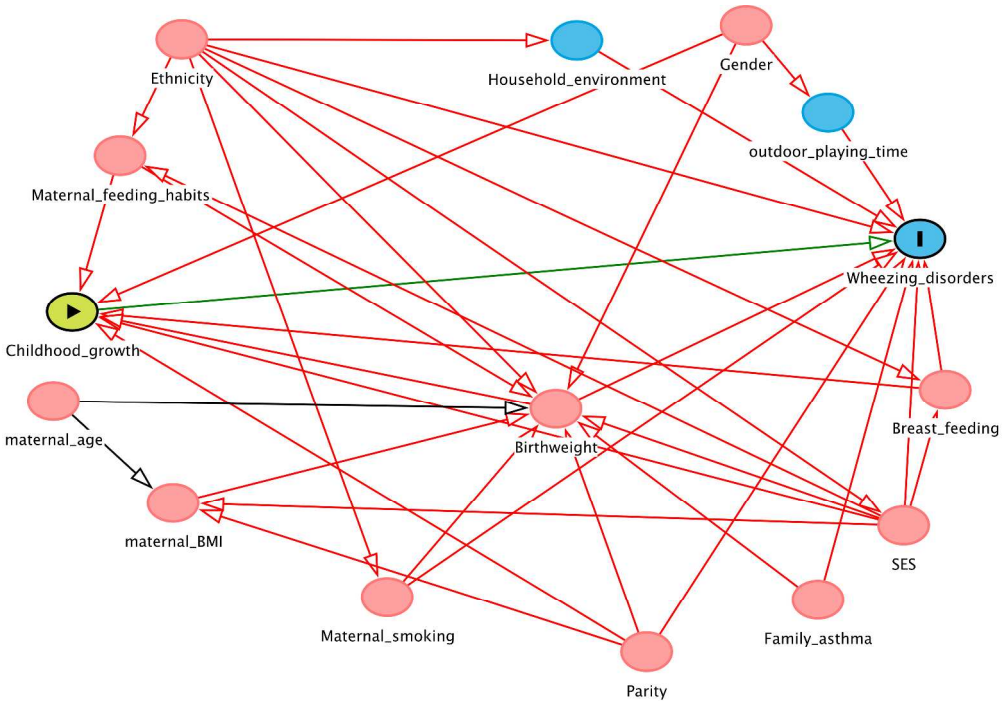
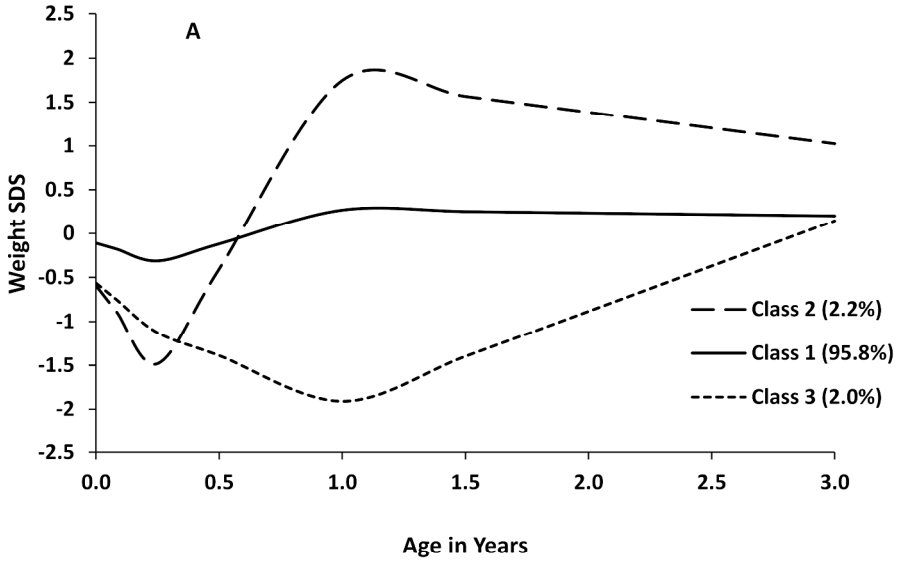


Figure S2: DAGitty schematic view of confounding adjustment for the effects of childhood growth on wheezing disorders.

Minimal sufficient adjustment sets for estimating the total effect of childhood growth on wheezing disorders:
•Birthweight, breast feeding, ethnicity, family asthma, gender, maternal smoking, parity, SES
•Birthweight, breast feeding, ethnicity, family asthma, maternal smoking, parity, SES, outdoor playing time
•Birthweight, breast feeding, gender, maternal feeding habits, parity, SES



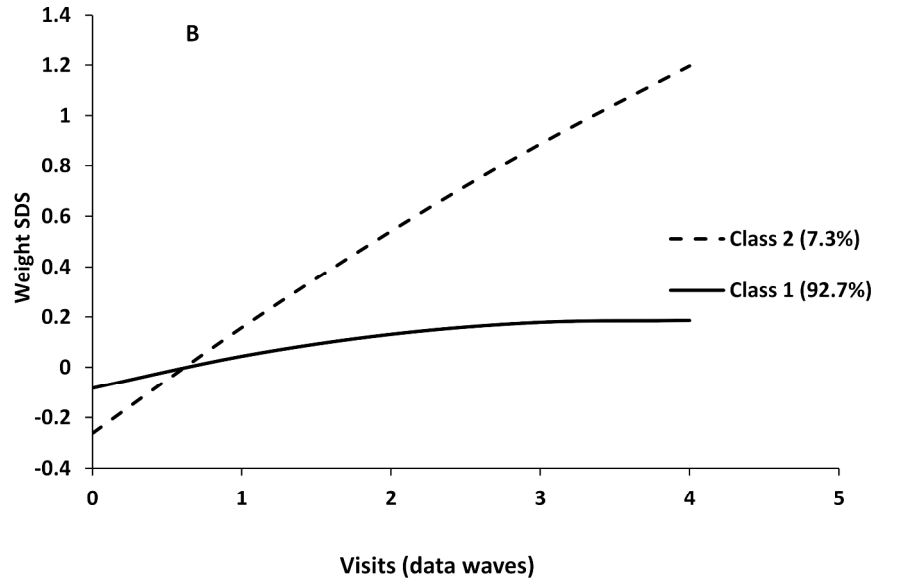


Figure S3 Estimated mean curves of weight SDS according to age (A) and visits (B)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract [**Methods section of the abstract page 1**]
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found [**Results section of abstract page 1**]
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported [**Page 3**]
Objectives	3	State specific objectives, including any prespecified hypotheses [**Page 4**]
Methods		
Study design	4	Present key elements of study design early in the paper [**Methodology page 5**]
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Pages 5-6]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[Pages 5-6]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[N/A]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Page 6]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Pages 5-6]**
Bias	9	Describe any efforts to address potential sources of bias **[Page 6-7]**
Study size	10	Explain how the study size was arrived at **[Page 5]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Pages 5-6]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Pages 6-7]**
		(*b*) Describe any methods used to examine subgroups and interactions **[N/A]**
		(*c*) Explain how missing data were addressed **[Page 7]**
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **[N/A]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Page 5]**
		(b) Give reasons for non-participation at each stage **[Page 5]**
		(c) Consider use of a flow diagram **[N/A]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Page 8**
		(b) Indicate number of participants with missing data for each variable of interest **[Page 9]**
		(c) Summarise follow-up time (eg, average and total amount) **[Page 8]**
Outcome data	15*	Report numbers of outcome events or summary measures over time **[Page 8]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included **[Pages 10 &13]**
		(*b*) Report category boundaries when continuous variables were categorized **[Page 6]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[N/A]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 14]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Page 15]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Pages 14-15]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Page 14-15]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[within acknowledgments and funding]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.