Early life growth and associations with lung function and bronchial hyperresponsiveness at 11-years of age

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Key words:
The Norwegian Mother, Father and Child Cohort Study (MoBa); Medical Birth Registry of Norway (MBRN); growth; lung function; bronchial hyperresponsiveness; child.

Abstract

Low birthweight and being born small-for-gestational age (SGA) are linked to asthma and impaired lung function. Particularly, poor intrauterine growth followed by rapid catch-up growth during childhood may predispose for respiratory disease. Bronchial hyperresponsiveness (BHR) is an essential feature of asthma, but how foetal and early childhood growth are associated with BHR is less studied. Our hypothesis was that children born SGA or with accelerated early life growth have increased BHR and altered lung function at 11-years of age.

We studied the associations between SGA and early childhood growth with lung function and BHR at 11-years of age, in a subgroup of 468 children from the Norwegian Mother, Father and Child Cohort Study (MoBa), and included data from the Medical Birth Registry of Norway (MBRN).

Weight at 6 months of age was positively associated with forced vital capacity (adjusted Beta: 0.121; 95% Confidence interval: 0.023, 0.219) and negatively associated with the ratio of forced expiratory flow in first second/ forced vital capacity (-0.204; -0.317, -0.091) at 11-years of age. Similar patterns were found for weight at 36 months and for change in weight from birth to 6 months of age. SGA or other various variables of early childhood growth were not associated with BHR at 11-years of age.

Early life growth was associated with an obstructive lung function pattern, but not with BHR in 11-year old children. Foetal growth restriction or weight gain during early childhood do not seem to be important risk factors for subsequent BHR in children.

Introduction

Low birthweight and being born small-for-gestational age (SGA) have been linked to asthma and impaired lung function in several studies [1-3], supporting ideas originally put forward by Barker and colleagues [4]. Particularly, poor intrauterine growth followed by rapid catch-up growth in early childhood may predispose for later respiratory disease [2].

We and others have reported positive associations between various growth variables during childhood and forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) and negative associations with the FEV_1/FVC ratio [5-7]. A previous study from the Norwegian Mother, Father and Child Cohort study (MoBa) found a positive association between peak weight velocity from birth to 36 months of age and childhood asthma at 36 months of age [8]. Similar associations are reported by others, with an increased risk of asthma among children who are born SGA or experience a rapid infant weight gain [2].

Bronchial hyperresponsiveness (BHR), defined as excessive bronchoconstriction in response to an inhaled stimulus, is an essential feature of asthma [9], and is also observed after early respiratory insults such as preterm birth [10] and bronchiolitis in infancy [11]. Higher BHR was found in 11-year-old preterm children who were SGA, compared with preterm-born appropriate for gestational age (AGA) and term-born controls, indicating a long-term influence of early foetal growth restriction on later methacholine-induced airway smooth muscle response [12]. Similar associations have been found in experimental animal studies [13, 14]. Increased risk of asthma, but not BHR, is also reported in children with reduced foetal size during the first trimester [1]. Early rapid weight gain between 0 and 3 months of age was associated with both asthma and BHR in children at 8 years of age in another study [6]. These findings collectively underline that intrauterine environment and early childhood growth probably are related to essential aspects of the pathophysiology of asthma. However, the mechanisms behind these findings are poorly understood, and we particularly need more information on the associations of foetal and early childhood growth with subsequent BHR.

Children born SGA may also be constitutionally small with no history of intrauterine growth restriction, and foetuses may go through periods of growth restriction, but not necessarily end up being born SGA [15]. Most children born SGA experience catch-up growth before two years of age [15], and in a study from the Netherlands, infants with a smaller weight gain between the third trimester and birth had higher peak weight velocity [16]. Thus, SGA, catch-up growth, peak weight and height velocity may all serve as indirect variables of poor intrauterine growth.

Our hypothesis was that children born SGA or with accelerated early childhood growth have increased BHR and altered lung function at 11-years of age. The aim of this study was therefore to explore the relationship between SGA and early childhood growth with lung function and BHR in 11-year children.

Material and methods

Study population

We studied a subsample of children participating in the Norwegian Mother, Father and Child Cohort study (MoBa), a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health [17]. Participants were recruited from all over Norway from 1999-2008. The women consented to participation in 41% of the pregnancies. The cohort now includes 114.500 children, 95.200 mothers and 75.200 fathers. The current study is based on version seven of the quality-assured data files released for research in 2012 including 108.659 children. Data obtained through questionnaires from MoBa are linked to the Medical Birth Registry of Norway (MBRN), a national health registry containing information about all births in Norway, using national 11-digit person identification numbers.

We used information from questionnaires administered to mothers when they were 18 and 30 weeks pregnant and when the child was 6-, 18-, 36 months and 7 years. We also used information from a separate questionnaire completed by the father at 18 weeks pregnancy.

At 11-years of age, a sample of 1603 children from the MoBa cohort with maximum one hour travel to four different study sites in Norway (Haukeland University Hospital, Stavanger University Hospital, Østfold Hospital and Norwegian School of Sports Sciences), were invited to a clinical follow-up including spirometry for lung function, methacholine provocation test to assess BHR and skin prick test for atopic sensitisation. These children were recruited from a random sample of eligible children born between July 2002 and June 2004 with measures of different biomarkers available from maternal blood samples drawn during pregnancy (n=3542), extra asthma cases were added to the sample due to the asthma related research questions in this project. In the current study, we included 468 children with the necessary follow-up information available. Details regarding the selection process are described in Figure 1. The selection of the participants in this sub-sample of MoBa is also previously described elsewhere [18].

Exposures

Information on weight and length at birth were obtained from the Medical Birth Registry. Mothers transferred anthropometric measurements from their children's health report cards, recorded routinely by public health nurses according to guidelines from the Norwegian Directorate of Health, at 6 weeks and 3, 6, 8, 12, 15–18, 24 and 36 months. SGA was defined as birthweight below the 10^{th} percentile for gestational age (GA) according to Norwegian birthweight references by GA and sex [19]. Using the Norwegian growth reference data [20], we calculated standard deviation scores (SDS) according to sex and age. Changes in SDS for weight and length were calculated between birth and 6, 12 and 36 months of age. Catch-up growth was defined as a gain in SDS for weight and length greater than 0.67, which represent the width of each percentile band on standard growth charts [21]. We also examined peak weight and height velocity as a measure of the child's highest rate of growth up until 36 months of age. Growth curves were fitted by mixed effects linear regression using the Reed1 model separately for each gender: $Y = A + Bt + Cln(t+30) + D/(t+30)$ [22]. The Reed1 model fits growth during the first 36 months among children in MoBa better than other well-known growth models [23]. We calculated the peak weight and height velocity using the first derivative of the Reed1 model.

Outcomes

The outcome variables were lung function measured by spirometry and BHR measured by methacholine provocation test.

Spirometry was performed according to guidelines from the American Thoracic Society and European Respiratory Society [24]. The Norwegian School of Sports Sciences used Jaeger Master Screen PFT, Sentry Suite® version 3.0 (*CareFusion Germany 234 GmbH, Hoechberg, Germany*) while the other study sites used Vmax 22© spirometer (*SensorMedics, Yorba Linda, CA, USA*). The lung function variables included were FVC, FEV_1, FEV_1/FVC ratio and forced expiratory flow at 25-75 of FVC (FEF_{25-75}), all standardized for age, height, and sex and reported as percentages of predicted (%) and SDS [25].

Methacholine provocation was performed with an inhalation-synchronized dosimetric nebulizer, providing baseline FEV_1 was >65% predicted [26]. The test continued until a fall in FEV_1 of >20% compared with baseline occurred (positive test), or until the maximal cumulative dose of 24.5 µmol was reached. The dose–response slope (DRS) from the methacholine challenge was calculated as the ratio of maximal percentage decline in FEV_1 from baseline to cumulative administered dose of methacholine (%/µmol) [27].

Covariates/confounders

Factors that could influence both the exposures and outcomes were identified as potential confounders, as illustrated in a directed acyclic graph (Supplementary Figure S1).

Child characteristics included GA, child gender, breastfeeding during the first 6 months of life and child`s age and body mass index (BMI) at the 11-year examination. Ever use of asthma medications from 18-36 months and 3-7 years of age was reported by the mothers at the 36 months and 7-year questionnaire. Asthma medications were categorized into no use, inhaled short acting beta-2 agonist only or inhaled corticosteroids (ICS) with or without inhaled short acting beta-2 agonist.

Parental characteristics included maternal age, parity, education and smoking during pregnancy, in addition to parental (maternal and paternal) height, BMI and history of asthma. Covariates were categorized as shown in Table 1.

We obtained information of gender, parity and GA in weeks from the Medical Birth Registry, while self-reported information of other measures were obtained from questionnaires.

Atopy

Atopic sensitisation at 11-years of age was defined by a positive skin prick test (SPT) for at least one allergen (wheal diameter ≥ 3mm larger than the negative control), and included the following allergens: *Dermatophagoides pteronyssinus*, dog, horse and cat dander, *Cladosporium herbarium*, birch, timothy, mugwort, egg white, milk, peanut, hazelnut, soya and codfish. The SPT was performed with Soluprick® allergens (ALK Albello, Hørsholm, Denmark). Histamine (10 mg/ml) was used as a positive control and 0.9% saline solution as a negative control.

Statistical analysis

The amount of missing information on individual values was 14.5%. Due to lack of data particular for height measurements during early childhood, peak height velocity was missing for 50% of the children, for the other exposures the amount of missing varied from 15-35% (Supplemental tables S1 and S2). The missing covariate information was imputed using multiple imputations by chained equations including exposures, covariates and outcomes. We imputed 100 data sets.

Continuous variables are presented as group means with 95% confidence intervals (CI) and compared by Student’s t test, or as medians and interquartile ranges (IQR) compared

by Mann–Whitney U-test, as appropriate. Categorical variables are presented as counts and percentages, and differences tested by Pearson chi-square test. Six children had slightly higher FEV_1 after inhaling methacholine compared to their baseline value and therefore negative values of DRS. Negative values were set to zero and 0.1 was added to all DRS values to allow for logarithmic transformations, which was necessary due to a skewed distribution of DRS to methacholine. BHR was included both as a continuous variable using the natural logarithm of DRS (LnDRS) and as a dichotomized variable with children in the upper tertile (> 66 percentile for DRS) as responders and the rest as non-responders. Multivariable linear and logistic regressions were used to study associations of various growth variables with lung function and BHR for the listed potential confounders. To examine whether the associations between postnatal growth and BHR was mediated by being born SGA or by BMI at 11-years of age, we adjusted for these covariates in separate multivariable models. In addition, we performed a sensitivity analysis excluding children reporting use of ICS at 7-years of age to assess if use of ICS influences the relationship between growth and BHR.

Analyses were carried out using SPSS version 26.0 (IBM Corp. Armonk, N.Y., USA). Generally, two-sided p-values ≤ 0.05 were considered statistically significant.

Power

We performed power calculations for two dichotomous exposures (SGA and catch-up weight) prior to study start. We estimated that 10% of the children (n=47) were born SGA [8]. To detect a 120% absolute difference in DRS to methacholine with 80% power, a total sample size of 470 children should be included (45 children born SGA and 425 not born SGA). An absolute difference of 120% in DRS seems clinically relevant, a previous follow-up study of preterm children reported a 200% absolute difference in DRS in children born SGA vs not born SGA [10]. In addition, at 11-years of age an absolute difference of 112% in DRS was found between children with a previous history of bronchiolitis compared to controls [11].

Further, we estimated that 30% of children in the present study would have experienced catch-up weight gain [21]. A total sample size of 470 including 30% with catch-up weight (n=140), would make us able to detect a 65% difference in DRS to methacholine. As discussed above, such a difference will be of clinical relevance.

Ethics

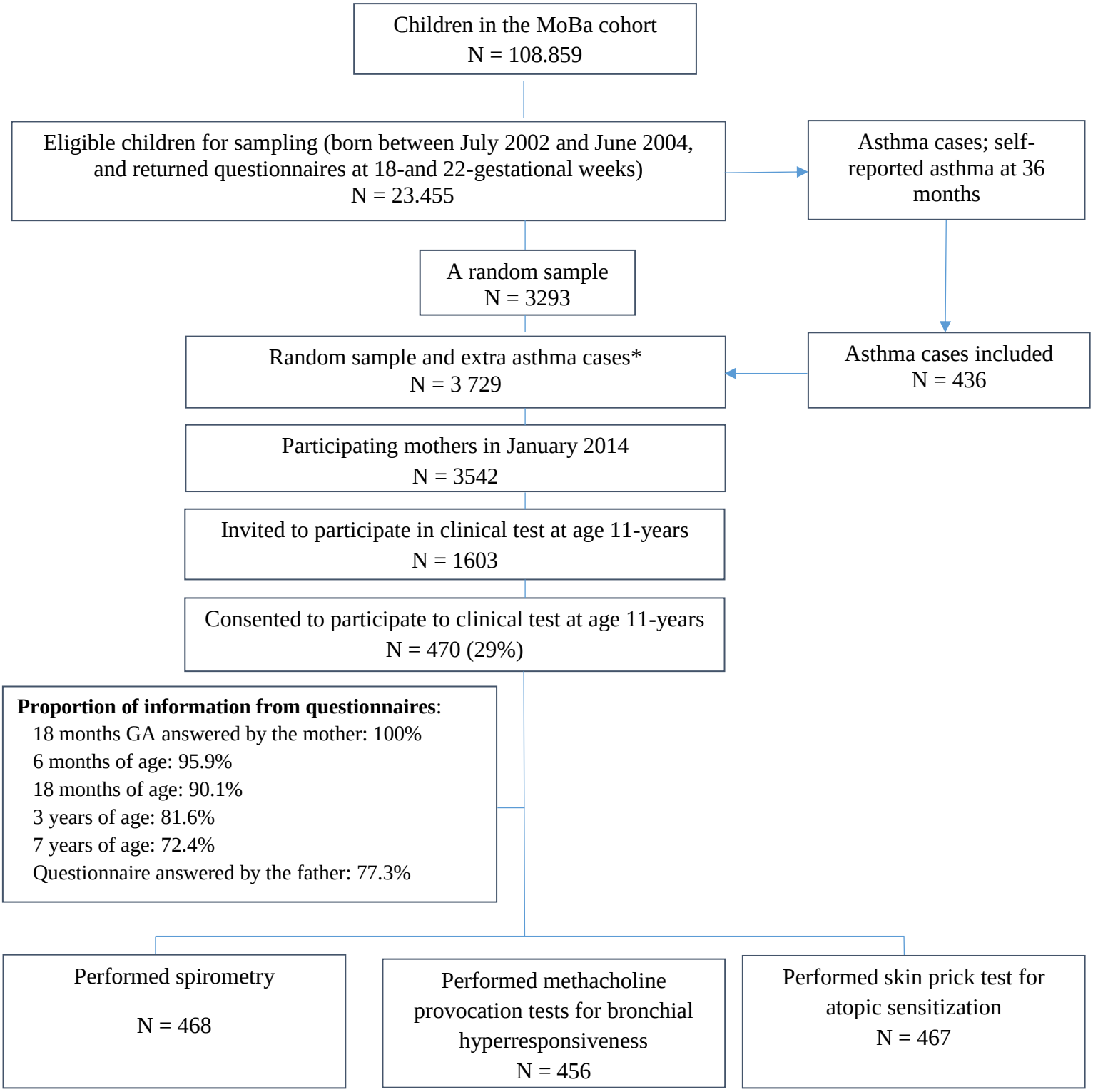
The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical

and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act. The study was approved by the Norwegian Data Inspectorate (01/4325) and the Regional Ethics Committee for Medical Research South/East Norway (S-97045, S-95113). The current study also had a separate approval from The Regional Committee for Medical Research Ethics (2011/2313) and the Norwegian Data Inspectorate (08/00854- 2/IUR).

Results

Of 1603 invited children, 470 (29%) consented to participate in the follow-up study at 11-years of age. The background characteristics of all children are shown in Table 1. Two children failed to complete spirometry according to standard quality criteria, leaving 468 participants (Figure 1). Furthermore, 12 children had no results from methacholine provocation, due to technical problems, leaving 456 children with valid results from the BHR test (Figure 1 and Table 2). Of these, 24% had negative methacholine provocation test.

Figure 1. Flow-chart for the study population included in the present study.



Abbreviations: MoBa: Norwegian Mother, Father and Child Cohort; GA: gestational age.

*Among the eligible children (n = 23.455) a random sample were drawn (n = 3293), and thereafter extra asthma cases were sampled (n = 608).

Table 1. Basic characteristics of all 468 children included in the study. Data from the Norwegian Mother, Father and Child Cohort (MoBa), results from complete case analysis.

Variable	**N**	
Boys, n (%)	468	256 (55.1)
Gestational age, weeks, *mean (SD)*	464	39.5 (1.86)
Birth weight, grams, *mean (SD)*	465	3633 (595)
SGA, n (%)	464	29 (6.3)
Catch-up weight birth-12months, n (%)	355	106 (29.9)
Catch-up length birth-12 months, n (%)	351	95 (27.1)
Hospitalized with LRTI before 18 months of age, n (%)	420	37 (8.8)
Ever use of asthma medication 6-36 months of age, n (%)	382	
No medication		251 (65.7)
Beta-2 agonist only		23 (6.0)
ICS with or without beta-2		108 (28.3)
Ever use of asthma medication 3-7 years, n (%)	338	
No medication		278 (82.2)
Beta-2 agonist only		5 (1.5)
ICS with or without beta-2		55 (16.3)
Maternal parity, n (%)	465	
Primiparous		180 (38.7)
1		188 (40.4)
2		76 (16.3)
≥3		21 (4.5)
Maternal asthma, n (%)	468	59 (12.6)
Maternal atopy, n (%)	457	154 (33.7)
Paternal asthma, n (%)	361	35 (9.7)
Paternal atopy, n (%)	361	89 (24.7)

Maternal education, n (%)	466	
<12 y		37 (7.9)
12 y		131 (28.1)
13-16 y		200 (42.9)
≥17 y		98 (21.0)
Paternal education, n (%)	462	
<12 y		57 (12.3)
12 y		183 (39.6)
13-16 y		127 (27.5)
≥17 y		95 (20.6)
Maternal pre-pregnancy BMI, kg/m^2, n (%)	456	
Underweight (<18.5)		15 (3.3)
Normal weight (18.5-24.9)		313 (68.6)
Overweight (≥25)		128 (28.1)
Paternal BMI, kg/m^2, n (%)	440	
Underweight (<18.5)		1 (0.2)
Normal weight (18.5-24.9)		212 (48.2)
Overweight (≥25)		227 (51.6)
Maternal smoking after 18 weeks pregnancy, n (%)	456	51 (11.2)

Abbreviations: SD: standard deviation. SGA: small for gestational age. BMI: body mass index. LRTI: lower respiratory tract infection. Beta -2 agonist only: inhaled short acting beta-2 agonist without inhaled corticosteroid (ICS).

Table 2. Clinical characteristics of all 468 children at the 11-year follow-up, results from complete case analysis.

Variable	**N**	
Age at follow-up, year, *mean (SD)*	468	10.9 (0.66)
Weight, kg, *mean (SD)*	468	39.1 (7.39)
Length, cm, *mean (SD)*	468	147.6 (7.09)
BMI, kg/m^2, *mean (SD)*	468	17.8 (2.38)
FVC	468	
z- score, *mean (SD)*		-0.03 (0.93)
% of predicted, *mean (SD)*		99.77 (10.91)
FEV_1	468	
z- score, *mean (SD)*		-0.20 (0.97)
% of predicted, *mean (SD)*		97.61 (11.11)
FEV_1/FVC	468	
z- score, *mean (SD)*		-0.29 (1.06)
% of predicted, *mean (SD)*		97.41 (7.37)
FEF_{25-75}%	468	
z- score, *mean (SD)*		-0.55 (1.00)
% of predicted, *mean (SD)*		88.87 (21.29)
DRS, %/µmol, *median (quartiles)*	456	6.88 (1.10, 22.27)
Atopic sensitization, n (%)	468	185 (39.5)

Abbreviations: FVC: Forced vital capacity. FEV_1: Forced expiratory volume in first second. FEV_1/FVC: Ratio of FEV_1 over FVC. FEF_{25-75}: Forced expiratory flow between 25-75% FVC. DRS: Methacholine dose response slope. DRS (%/µmol) is the ratio of maximum percentage decline in FEV_1 from baseline to cumulative administered dose (µmol) of methacholine.

SD: Standard deviation.

The mean birthweight in the population was 3633.3 gram (SD 594.2), the mean weight was 8.05 kg (0.95) at 6 months, 9.86 kg (1.39) at 12 months, and 15.0 kg (1.67) at 36 months. The associations between weight SDS and change in weight SDS at various ages with lung function variables and Ln DRS are shown in Table 3 (multiple imputation), the corresponding results for the complete case analysis (non-imputed data) are given in supplementary Table S1.

Table 3. Summary of unadjusted and adjusted linear regression analyses of lung function and bronchial hyperresponsiveness (Ln DRS) in 11-year-old Norwegian children according to weight and BMI SDS at various ages, results from Multiple imputation, N=468 for lung function variables and N=456 for Ln DRS.

	Outcome variable														
	FVC SDS			**FEV_1 SDS**			**FEV_1/FVC SDS**			**FEF_{25-75} SDS**			**Ln DRS**		
Exposure	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**
Birth weight SDS															
Unadjusted	0.057	-0.007, 0.122	0.083	0.068	0.001, 0.136	**0.048**	0.017	-0.057, 0.092	0.645	0.055	-0.015, 0.125	0.122	-0.042	-0.167, 0.83	0.510
Adjusted [a]	0.049	-0.041, 0.140	0.285	0.058	-0.037, 0.153	0.230	0.005	-0.102, 0.111	0.927	0.057	-0.042, 0.156	0.261	-0.004	-0.180, 0.172	0.966
Weight 6 months SDS															
Unadjusted	0.117	0.027, 0.206	**0.010**	0.018	-0.075, 0.111	0.707	-0.159	-0.261, -0.057	**0.002**	-0.104	-0.201, -0.007	**0.035**	0.036	-0.138, 0.211	0.683
Adjusted [a]	0.121	0.023, 0.219	**0.015**	-0.005	-0.107, 0.096	0.916	-0.204	-0.317, -0.091	**<0.001**	-0.143	-0.250, -0.036	**0.009**	0.079	-0.114, 0.272	0.420
Weight 12 months SDS															
Unadjusted	0.033	-0.033, 0.099	0.326	0.015	-0.058, 0.088	0.681	-0.026	-0.113, 0.061	0.552	0.001	-0.082, 0.083	0.987	-0.009	-0.138, 0.119	0.886

Adjusted [a]	0.045	-0.025, 0.116	0.210	0.022	-0.054, 0.198	0.566	-0.035	-0.128, 0.058	0.458	-0.002	-0.087, 0.083	0.964	0.009	-0.128, 0.147	0.893
Weight 36 months SDS															
Unadjusted	0.131	0.030, 0.231	**0.011**	0.075	-0.035, 0.185	0.181	-0.089	-0.204, 0.027	0.131	-0.006	-0.117, 0.105	0.920	-0.017	-0.208, 0.173	0.859
Adjusted [a]	0.145	0.038, 0.253	**0.008**	0.087	-0.029, 0.204	0.141	-0.097	-0.221 0.026	0.123	-0.010	-0.127, 0.107	0.869	-0.023	-0.228, 0.182	0.826
Change in weight SDS															
Birth to 6 months of age															
Unadjusted	-0.002	-0.108, 0.103	0.967	-0.112	-0.222, -0.001	**0.047**	-0.190	-0.309, -0.071	**0.002**	-0.164	-0.277, -0.051	**0.005**	0.118	-0.082, 0.318	0.248
Adjusted [a]	0.024	-0.086, 0.133	0.672	-0.097	-0.212, 0.017	0.095	-0.201	-0.328, -0.074	**0.002**	-0.151	-0.270, -0.031	**0.014**	0.111	-0.101, 0.323	0.303
Birth to 12 months of age															
Unadjusted	-0.013	-0.071, 0.045	0.661	-0.034	-0.101, 0.033	0.317	-0.032	-0.106, 0.042	0.400	-0.036	-0.110, 0.037	0.334	0.021	-0.091, 0.133	0.708
Adjusted [a]	0.020	-0.047, 0.086	0.563	-0.005	-0.078, 0.068	0.894	-0.034	-0.121, 0.053	0.446	-0.027	-0.109, 0.056	0.529	0.011	-0.122, 0.144	0.872

Birth to 36 months of age															
Unadjusted	0.012	-0.052, 0.076	0.711	-0.023	-0.092, 0.046	0.509	-0.058	-0.129, 0.017	0.130	-0.050	-0.120, 0.020	0.162	0.028	-0.096, 0.151	0.662
Adjusted [a]	0.054	-0.022, 0.131	0.161	0.016	-0.066, 0.098	0.704	-0.059	-0.147, 0.029	0.190	-0.039	-0.123, 0.044	0.354	-0.011	-0.160, 0.138	0.885

Abbreviations: FVC: Forced vital capacity. FEV_1: Forced expiratory volume in first second. FEV_1/FVC: Ratio of FEV_1 over FVC. FEF_{25-75}: Forced expiratory flow between 25-75% of FVC. DRS: Methacholine dose response slope. DRS (%/µmol) is the ratio of maximum percentage decline in FEV_1 from baseline to cumulative administered dose (µmol) of methacholine CI: confidence interval, SDS: standard deviation score.

[a] Adjusted for: Gestational age, child gender, breastfeeding first 6 months of life (not for birth weight SDS), maternal age, maternal parity, maternal education, maternal height, maternal pre-pregnancy BMI, paternal height, paternal BMI, maternal smoking during pregnancy, maternal asthma, paternal asthma.

In the adjusted analyses using the imputed dataset, weight SDS at 6 months of age was positively associated with FVC SDS (Beta: 0.121; 95% Confidence interval: 0.023, 0.219) and negatively associated with FEV_1/FVC SDS (-0.204; -0.317, -0.091) ratio and FEF_{25-75} SDS (-0.143; -0.250, -0.036). Weight at 36 months was positively associated with FVC SDS (0.145; 0.038, 0.253). The change in weight SDS from birth to 6 months was negatively associated with FEV_1/FVC SDS (Beta -0.201; 95% CI: -0.328, -0.074) and FEF_{25-75} SDS (-0.151; -0.270, -0.031) (Table 3). The same patterns were found in the complete case analysis (Table S1). Birth length SDS, length SDS at 6, 12 and 36 and change in length SDS from birth to 6, 12 or 36 months of age were not associated with any lung function variables (data not shown). Neither weight/length SDS nor change in weight/length SDS at various ages were associated with Ln DRS (Table 3).

A total of 6.3% of children were classified as SGA and 29.9% had catch-up weight gain from birth to 12 months of age (Table 1). Neither SGA, catch-up weight/height nor peak height/weight velocity were associated with lung function variables (data not shown) nor Ln DRS (Table 4). The corresponding results for complete case are shown in Table S2 and did not substantially differ compared to the multiple imputation analysis. Separate sensitivity analyses did not change the associations for BHR significantly, these included SGA, BMI and restricting the analysis to children not reporting use of ICS at 7-years of age (Table 4).

No growth variables were associated with the dichotomized DRS variable > 66 percentile (data not shown).

Table 4. Unadjusted and adjusted regression analyses for bronchial hyperresponsiveness measured as dose response slope to methacholine (Ln DRS) in 11-year-old children, results from Multiple imputation N=456

Exposure	Beta	95% CI interval	P-value
SGA			
Unadjusted	-0.307	-0.968, 0.353	0.362
Adjusted [a]	-0.334	-1.02, 0.349	0.338
Adjusted [b]	-0.361	-1.05, 0.329	0.305
Adjusted [c]	-0.390	-1.20, 0.421	0.346
Peak weight velocity			
Unadjusted	3.06	-6.27, 12.39	0.521
Adjusted [a]	1.51	-8.54, 11.56	0.768
Adjusted [b]	1.81	-8.33, 11.95	0.726
Adjusted [c]	2.84	-9.24, 14.93	0.645
Adjusted [d]	1.20	-8.88. 11.28	0.816
Peak height velocity			
Unadjusted	0.700	-1.47, 2.87	0.527
Adjusted [a]	0.489	-1.78. 2.76	0.673
Adjusted [b]	0.487	-1.78, 2.76	0.674
Adjusted [c]	1.11	-1.86, 4.09	0.462
Adjusted [d]	0.496	-1.78, 2.78	0.669
Catch-up weight 0-6 months			
Unadjusted	0.112	-0.248, 0.472	0.543
Adjusted [a]	0.093	-0.285, 0.471	0.631
Adjusted [b]	0.094	-0.284, 0.472	0.627
Adjusted [c]	0.145	-0.294, 0.585	0.517
Adjusted [d]	0.138	-0.252, 0.527	0.489
Catch-up length 0-6 months			
Unadjusted	0.173	-0.214, 0.561	0.381
Adjusted [a]	0.154	-0.262, 0.571	0.468
Adjusted [b]	0.151	-0.266, 0.568	0.479

Adjusted [c]	0.190	-0.283, 0.664	0.430
Adjusted [d]	0.174	-0.247, 0.595	0.418
Catch-up weight 0-12 months			
Unadjusted	0.121	-0.269, 0.512	0.543
Adjusted [a]	0.115	-0.304, 0.534	0.589
Adjusted [b]	0.115	-0.305, 0.534	0.592
Adjusted [c]	0.116	-0.348, 0.580	0.624
Adjusted [d]	0.148	-0.281, 0.577	0.498
Catch-up length 0-12 months			
Unadjusted	0.231	-0.179, 0.641	0.269
Adjusted [a]	0.198	-0.248, 0.644	0.384
Adjusted [b]	0.195	-0.251, 0.642	0.391
Adjusted [c]	0.108	-0.405, 0.621	0.679
Adjusted [d]	0.222	-0.230, 0.675	0.335

Abbreviations: SGA: small for gestational age. CI: confidence interval.

[a] Adjusted for: gestational age, child gender, breastfeeding first 6 months of life (not for SGA), maternal age, maternal parity, maternal education, maternal height, maternal pre-pregnancy body mass index (BMI), maternal asthma, paternal asthma, paternal height, paternal BMI, maternal smoking during pregnancy.

[b] Also adjusted for child's BMI at 11 year examination.

[c] Only children without use of inhaled corticosteroids (ICS) reported at 7 years of age.

[d] Also adjusted for SGA.

Discussion

In this study of children from a general population, SGA or early childhood growth were not associated with BHR at 11-years of age. However, we found positive associations between weight at 6 months of age and measures of lung volume, and negative associations between weight gain and measures of obstructive lung function.

The associations between anthropometric measures and later respiratory outcomes such as asthma and lung function have been examined by many. The results vary between study populations and both positive, negative and no associations have been reported, which may be due to different ages of follow-up and different definitions of exposures and outcomes [2, 7] . In this study, we found positive associations between weight SDS at 6 months of age and FVC and negative associations of both weight SDS at 6 months and change in weight SDS from birth to 6 months with FEV_1/FVC ratio and FEF_{25-75}. These results are in line with several other studies reporting positive associations between postnatal growth variables and lung volumes, but negative associations with variables related to obstructive lung function [5-7, 28]. There are several suggestions behind these findings. Within a normal BMI range, accelerated weight gain through childhood seem to be associated with both increased lung volumes (FVC) and airway size (FEV_1), but more so for lung volumes [5, 6]. This disproportionate growth between lung size and airway caliber during childhood has been called 'dysanapsis', by many considered a physiological phenomenon [29]. However, the lower FEV_1/FVC ratio related to BMI and weight gain in childhood has also been interpreted as a flow limitation [29]. Unfortunately, we had no data regarding asthma symptoms at 11-years of age, but a previous study from the MoBA cohort reported positive associations between peak weight velocity and childhood asthma at 3 and 7 years of age [8], consistent with findings from other studies reporting positive associations between early weight gain and asthma [2, 6].

BHR is an essential feature of asthma, and previous literature provide an obvious reason to particularly study the association between early life growth and subsequent BHR, contributing to a better overall understanding of the mechanisms between growth in early life and various respiratory outcomes. However, only a few studies have addressed the relationships between early life characteristics and methacholine BHR. One study reported higher BHR in pre-term children born SGA children than pre-term children born AGA and term-born controls [12]. In a large study of 9723 children aged 8-15 years, Sonnenschein-van der Voort et al. found positive associations between higher weight gain from 0-3 months of age (OR: 1.11; 95% CI 1.03-1.20) and from 3-12 months of age (1.09; 1.00-1.19) with

methacholine responsiveness at 8 years of age. In that study, methacholine responsiveness was dichotomized, and the results reported as ORs for being in the highest tertile versus lower tertiles [6].

In contrast, we found no associations between SGA or any other postnatal growth variables with BHR at 11-years. The conflicting results may have several reasons. Some suggest that associations between early growth and respiratory outcomes weaken with time [2], a notion that fits Sonnenschein-van der Voort's positive findings at 8 years of age and our negative findings obtained at 11-years of age [6]. In their study, encompassing a high number of participants, they found a 10% higher odds for being in the upper tertile of BHR, whereas our study was powered to detect differences we considered clinically relevant.

SGA, catch-up growth, and peak weight/height growth velocity may all be indirect markers of poor intrauterine growth [15, 16, 30]. Pike et al. examined how direct measures of foetal growth were associated with BHR in both rats and humans and found higher BHR in rats fed with protein-restricted diets during pregnancy than in controls [13]. They also reported higher BHR in 6-year-old children with a smaller change in abdominal circumference growth between 11 and 19 weeks' gestation compared to those with more rapid abdominal growth, but found no association between birthweight and BHR [13]. In contrast, Turner et al. showed no associations between infants with reduced foetal size during the first trimester and BHR at 10-years of age [1]. In addition, they reported an increased risk of asthma and reduced FVC and FEV_1 at age 10 years in those with persistent low foetal growth compared to those with persistent high foetal growth [1]. Turner et al. suggest that risk factors related to development of asthma versus atopy and airway inflammation may occur at different ages, explaining the inconsistent findings between foetal growth and asthma/lung function versus BHR [1]. It is possible that risk factor for asthma leading to reduced airway diameter is present during early life, whereas risk factors related to atopy, airway inflammation and remodelling may occur later in life [1, 31].

One previous study reported inverse associations between peak weight velocity during the first two years of life and lung function at 15 years of age, both before and after bronchodilation, suggesting that weight gain primarily cause structural changes of the airways and not functional changes of the airway musculature [28]. The results from these studies could support the findings from our study, indicating that the associations between growth in early life and subsequent asthma and lung function may be mediated through other mechanisms than BHR.

Previous studies from our group have shown increased BHR in late childhood in subjects with a previous history of severe bronchiolitis and prematurity, underlining that these early life respiratory insults certainly are risk factors for subsequent lung disease [10, 11, 32]. The results from the present study do not suggest that risk factors related to being born SGA or having catch-up growth have the same impact on subsequent lung disease in otherwise healthy individuals. It seems clear that we need considerably more information on these issues to build a robust explanatory model.

Strengths and limitations

The main strengths of the study are the prospective design and the inclusion of various measures that reflect poor intrauterine growth. The main limitation of the study is the modest participation rate with a risk of selection bias, which may influence the generalizability of the results. However, adding asthma cases to the study population could increase the possibility to detect relevant associations with BHR if present. There are also some missing data, but similar results from the multiple imputation and complete case analysis strengthen the reliability of the results. Moreover, the associations between weight and change in weight at 6 months of age with lung function are in line with findings from other studies. Also the number of children with atopic sensitization are in line with data presented by others [33]. Our study was only powered to detect relatively large and clinically relevant associations between growth variables and BHR, but there were no tendency for associations between the growth variables and BHR, underlining the consistence of our findings.

Conclusion

In 11 year-old children, weight and weight gain were positively associated with lung volumes and negatively associated with variables related to obstructive lung function at follow-up. However, neither being born SGA, catch-up growth nor velocity of weight gain during early childhood were associated with BHR. Although we studied only indirect measures of foetal growth in a relatively small group of children, the findings from our study do not support that foetal growth restriction or weight gain during early childhood are important risk factors for subsequent BHR later in childhood. Larger prospective studies with repeated measurements of growth during foetal life and early childhood in relation to BHR are necessary before firm conclusions can be made.

Acknowledgement:

The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this on-going cohort study. The Norwegian Research Council (grant number 221097 to Wenche Nystad) also supported this study.

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Highlights

Poor intrauterine growth and increased early weight gain predispose for lung disease.

Bronchial hyperresponsiveness is an essential feature of asthma.

How early life growth is associated with bronchial hyperresponsiveness is not known.

Increased early weight gain is associated with obstructive lung function in children.

Early weight gain is not related to bronchial hyperresponsiveness in children.

Table S1. Summary of unadjusted and adjusted linear regression analyses of lung function and bronchial hyperresponsiveness (Ln DRS) in 11-year-old Norwegian children according to weight and BMI SDS at various ages, results from complete case analysis.

	Outcome variable																
	FVC SDS				FEV_1 SDS			FEV_1/FVC SDS			FEF_{25-75} SDS			Ln DRS			
Exposure	**n**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**	**n**	**Beta**	**95% CI**	**P-value**
Birth weight SDS																	
Unadjusted	434	0.023	-0.057, 0.103	0.573	0.040	-0.042, 0.122	0.340	0.025	-0.064, 0.113	0.582	0.054	-0.029, 0.138	0.198	423	-0.067	-0.219, 0.085	0.387
Adjusted [a]	305	0.024	-0.091, 0.140	0.677	0.029	-0.091, 0.148	0.636	0.006	-0.122, 0.133	0.930	0.030	-0.092, 0.152	0.627	299	0.039	-0.183, 0.260	0.731
Weight 6 months SDS																	
Unadjusted	428	0.121	0.029, 0.212	**0.010**	0.018	-0.079, 0.114	0.718	-0.163	-0.266, -0.060	**0.002**	-0.108	-0.206, -0.010	**0.032**	416	0.050	-0.127, 0.227	0.580
Adjusted [a]	305	0.135	0.012, 0.258	**0.032**	0.028	-0.103, 0.159	0.676	-0.181	-0.317, -0.044	**0.010**	-0.117	-0.250, 0.016	0.084	299	-0.070	-0.308, 0.168	0.565
Weight 12 months SDS																	
Unadjusted	379	0.101	-0.007, 0.209	0.066	-0.004	-0.116, 0.107	0.939	-0.163	-0.281, -0.045	**0.007**	-0.093	-0.205, 0.019	0.104	371	0.099	-0.105, 0.303	0.342
Adjusted [a]	278	0.179	0.046, 0.312	**0.009**	0.113	-0.026, 0.253	0.111	-0.105	-0.254 0.045	0.171	-0.025	-0.167, 0.118	0.735	275	-0.075	-0.303, 0.153	0.516
Weight 36 months SDS																	
Unadjusted	311	0.163	0.053, 0.274	**0.004**	0.091	-0.018, 0.201	0.102	-0.111	-0.227, 0.006	0.063	-0.002	-0.113, 0.109	0.970	302	0.004	-0.196, 0.204	0.965
Adjusted [a]	228	0.224	0.084, 0.363	**0.002**	0.149	0.006, 0.292	**0.041**	-0.134	-0.281, 0.013	0.073	-0.038	-0.179, 0.103	0.598	223	-0.098	-0.347, 0.151	0.437

Change in weight SDS																
Birth to 6 months of age																
Unadjusted	399	0.019	-0.094, 0.131	0.747	-0.098	-0.213, 0.017	0.095	-0.205	-0.326, -0.083	**0.001**	-0.164	-0.279, -0.048	**0.005**	388	0.100	-0.114, 0.315	0.359
Adjusted [a]	290	0.044	-0.094, 0.181	0.533	-0.050	-0.193, 0.093	0.493	-0.171	-0.322, -0.020	**0.027**	-0.093	-0.237, 0.051	0.203	284	-0.097	-0.365, 0.170	0.475
Birth to 12 months of age																
Unadjusted	355	0.048	-0.044, 0.141	0.304	0.004	-0.091, 0.098	0.941	-0.074	-0.173, 0.025	0.143	-0.041	-0.134, 0.052	0.389	348	0.093	-0.081, 0.268	0.293
Adjusted [a]	263	0.104	-0.016, 0.224	0.088	0.106	-0.018, 0.231	0.095	0.000	-0.133, 0.133	0.999	0.045	-0.081, 0.171	0.485	260	-0.075	-0.303, 0.153	0.516
Birth to 36 months of age																
Unadjusted	291	0.094	0.003, 0.184	**0.044**	0.042	-0.047, 0.130	0.353	-0.085	-0.176, 0.007	0.070	-0.032	-0.119, 0.054	0.462	283	0.081	-0.082, 0.244	0.329
Adjusted [a]	217	0.134	0.024, 0.245	**0.018**	0.071	-0.042, 0.183	0.218	-0.112	-0.226, 0.002	0.054	-0.059	-0.168, 0.050	0.284	212	-0.044	-0.241, 0.154	0.664

Abbreviations: FVC: Forced vital capacity. FEV_1: Forced expiratory volume in first second. FEV_1/FVC: Ratio of FEV_1 over FVC. FEF_{25-75}: Forced expiratory flow between 25-75% of FVC. DRS: Methacholine dose response slope. DRS (%/µmol) is the ratio of maximum percentage decline in FEV_1 from baseline to cumulative administered dose (µmol) of methacholine CI: confidence interval. SDS: standard deviation score.

[a] Adjusted for: Gestational age, child gender, breastfeeding first 6 months of life (not for birth weight SDS), maternal age, maternal parity, maternal education, maternal height, maternal pre-pregnancy BMI, paternal height, paternal BMI, maternal smoking during pregnancy, maternal asthma, paternal asthma.

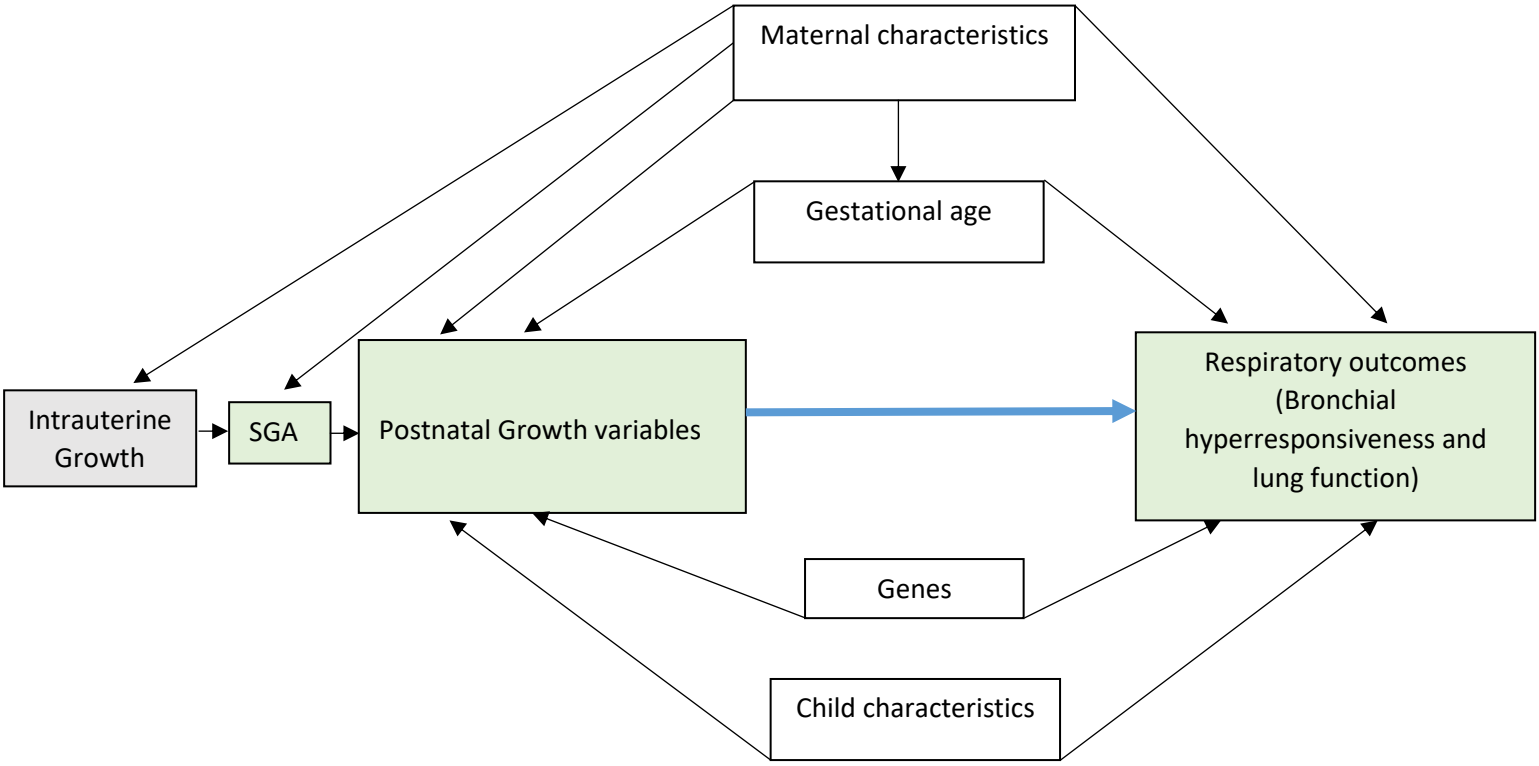
Table S2. Unadjusted and adjusted regression analyses for bronchial hyperresponsiveness measured as dose response slope to methacholine (Ln DRS) in 11-year-old children, results from complete case analysis.

Exposure	N	Beta	95% CI interval	P-value
SGA				
Unadjusted	452	-0.335	-1.01, 0.341	0.330
Adjusted [a]	317	-0.472	-1.30, 0.357	0.263
Adjusted [b]	317	-0.524	-1.36, 0.311	0.218
Adjusted [c]	200	-0.791	-1.81, 0.228	0.127
Peak weight velocity				
Unadjusted	328	3.46	-7.75, 14.67	0.544
Adjusted [a]	249	-7.87	-21.29, 5.56	0.249
Adjusted [b]	249	-7.61	-21.27, 6.06	0.274
Adjusted [c]	164	-9.15	-26.01, 7.72	0.286
Adjusted [d]	249	-8.13	-21.58, 5.32	0.235
Peak height velocity				
Unadjusted	219	-3.01	-9.79, 3.77	0.383
Adjusted [a]	163	-6.61	-15.48, 2.26	0.143
Adjusted [b]	163	-6.53	-15.44. 2.38	0.150
Adjusted [c]	108	-4.29	-40.14, 31.57	0.807
Adjusted [d]	163	-6.71	-15.59, 2.17	0.138
Catch-up weight 0-6 months				
Unadjusted	386	0.132	-0.247, 0.511	0.494
Adjusted [a]	281	-0.221	-0.681, 0.238	0.344
Adjusted [b]	281	-0.225	-0.686, 0.235	0.336
Adjusted [c]	180	-0.225	-0.790, 0.339	0.432
Adjusted [d]	281	-0.152	-0.276, 0.075	0.527
Catch-up length 0-6 months				
Unadjusted	376	0.238	-0.181, 0.658	0.264
Adjusted [a]	276	0.092	-0.418, 0.601	0.723
Adjusted [b]	276	0.078	-0.437, 0.592	0.767
Adjusted [c]	177	0.227	-0.406, 0.861	0.480
Adjusted [d]	276	0.143	-0.368, 0.655	0.581
Catch-up weight 0-12 months				
Unadjusted	348	0.162	-0.250, 0.574	0.439
Adjusted [a]	260	-0.108	-0.610, 0.394	0.672
Adjusted [b]	260	-0.113	-0.617, 0.391	0.659
Adjusted [c]	170	0.023	-0.619, 0.664	0.945
Adjusted [d]	260	-0.004	-0.520, 0.513	0.989
Catch-up length 0-12 months				
Unadjusted	344	0.339	-0.09, 0.767	0.120
Adjusted [a]	256	0.076	-0.472, 0.623	0.785
Adjusted [b]	256	0.063	-0.488, 0.614	0.822
Adjusted [c]	169	0.124	-0.599, 0.846	0.736
Adjusted [d]	256	0.148	-0.406, 0.702	0.600

Abbreviations: SGA: small for gestational age. CI: confidence interval.

[a] Adjusted for: gestational age, child gender, breastfeeding first 6 months of life (not for SGA), maternal age, maternal parity, maternal education, maternal height, maternal pre-pregnancy body mass index (BMI), maternal asthma, paternal asthma, paternal height, paternal BMI, maternal smoking during pregnancy.
[b] Also adjusted for child's BMI at 11 year examination.
[c] Only children without use of inhaled corticosteroids (ICS) reported at 7 years of age.
[d] Also adjusted for SGA.

Figure S1: Directed acyclic graph (DAG)



Child characteristics:

Gender and breastfeeding during first 6 months.

Genes: Genetic predisposition for growth;

Maternal height, maternal BMI, paternal height, paternal BMI, maternal asthma, paternal asthma.

Maternal characteristics:
Maternal age, maternal education, parity, maternal smoking during pregnancy.

Abbreviations: SGA: small for gestational age, BMI: Body mass index.