Original Article

Early growth characteristics and the risk of reduced lung function and asthma: a meta-analysis of 25,000 children

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ABSTRACT

Background Children born preterm or with a small-size-for-gestational-age are at increased risk for childhood asthma.

Objective To assess the hypothesis that these associations are explained by reduced airway patency**.**

Methods We used individual participant data of 24,938 children from 24 birth cohorts to examine and meta-analyze the associations of gestational age, size-for-gestational-age, and infant weight gain with childhood lung function and asthma (age range 3.9 – 19.1 years). Second, we explored whether these lung function outcomes mediated the associations of early growth characteristics with childhood asthma.

Results Children born with a younger gestational age had a lower FEV_1 (forced expiratory volume in 1 second), FEV_1/FVC (FEV_1/forced vital capacity), and FEF_{75} (forced expiratory volume after exhaling 75% of vital capacity), whereas those born with a smaller size-for-gestational-age at birth had lower FEV_1 but higher FEV_1/FVC (p-values<0.05). Greater infant weight gain was associated with higher FEV_1, but lower FEV_1/FVC and FEF_{75} in childhood (p-values<0.05). All associations were present across the full range and independent of other early life growth characteristics. Preterm birth, low birth weight and greater infant weight gain were associated with an increased risk of childhood asthma (pooled odds ratio (95% CI): 1.34 (1.15, 1.57), 1.32 (1.07, 1.62) and 1.27 (1.21, 1.34), respectively). Mediation analyses suggested that FEV_1, FEV_1/FVC and FEF_{75} may explain 7 (2, 10)% to 45 (15, 81)% of the associations between early growth characteristics and lung function.

Conclusions Younger gestational age, smaller size-for-gestational-age, and greater infant weight gain were across the full ranges associated with childhood lung function. These associations explain to a substantial extent the risk of childhood asthma.

Capsule Summary

Younger gestational age, smaller size-for-gestational-age at birth, and greater infant weight gain are independently and across the full ranges associated with lung function adaptations, and might explain 7-45% of the risk of childhood asthma.

Clinical implications

Early growth characteristics may persistently affect lung function, and thereby contribute to the risk of obstructive respiratory diseases in later life.

Abbreviations

FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
FEF_{25-75}	Forced mid-expiratory flow
FEF_{75}	Forced expiratory flow after exhaling 75% of the vital capacity
SDS	Standard deviation scores
ATS/ERS	American Thoracic Society / European Respiratory Society
BMI	Body mass index

INTRODUCTION

Children born extremely preterm or with a low birth weight have high rates of neonatal respiratory diseases such as infant respiratory distress syndrome and bronchopulmonary dysplasia (1). An accumulating body of evidence suggests that these children also have an increased risk of chronic obstructive respiratory diseases in adulthood (2). More recent, prospective studies in children suggest that preterm birth and small size for gestational age at birth increase the risk of childhood asthma (3). Recent results of a meta-analysis of individual participant data of 147,000 children participating in prospective birth cohort studies showed consistent associations of younger gestational age at birth and greater infant weight gain with childhood asthma (4). The associations of lower birth weight with childhood asthma seem to be largely explained by gestational age at birth (4). The mechanisms underlying the associations of early growth characteristics with childhood asthma are not known yet. Airway caliber is a key determinant of total airway resistance. A reduced airway caliber could result in airway obstruction that predisposes to asthma and chronic obstructive pulmonary diseases (5-7). Therefore, we hypothesized that the associations of early growth characteristics with childhood asthma might be explained by developmental adaptations of the lungs and airways, leading to relatively small airways and, hence, a reduction in expiratory flows reflected by lower lung function values (8). Thus far, previous studies focused on the associations of birth weight and infant weight gain with childhood lung function have reported inconsistent results (9-16). These inconsistent results might be due to the different ages at which spirometry was performed, and not taking other early growth characteristics or potential confounders into account.

To test the hypothesis that the associations of early life growth characteristics with childhood asthma are explained by reduced airway patency, we performed an individual participant data meta-analysis of 24,938 children from 24 birth cohort studies. We examined the strength, consistency, and independence of the associations of gestational age at birth, birth weight and infant weight gain with lung function outcomes in childhood and whether

these lung function outcomes explain the previously reported associations of early growth characteristics with risk of childhood asthma.

METHODS

Sources of data

European population-based birth- and mother-child cohorts participated if they included children born between 1989 and 2011, had information available on at least gestational age and weight at birth and lung function measurements in childhood (until age 18 years), and were willing and able to exchange original data.(4) We identified 50 European cohorts selected from existing collaborations on childhood health or asthma-related outcomes (www.chicosproject.eu, www.birthcohortsenrieco.net, www.ga2len.org, and www.birthcohorts.net; accessed until May 29, 2012). In total, 24 cohorts, comprising data on 24,938 children, fulfilled the criteria (**S-figure 1**).

Information about gestational age and weight at birth and weight in the first year of life was obtained by measurements, medical registries or parental questionnaires (**S-table 1**). We created gestational age-adjusted birth weight standard deviation scores (birth weight SDS) based on European reference values (17). Infant weight gain in the first year was defined as the difference between weight at age 1 year (range 6-18 months) and weight at birth, divided by the number of months between these two measurements. Standard deviation scores (SDS) for age-specific infant weight gain were derived by intra-cohort means and standard deviations (18). Cohort specific growth characteristics are given in the **Supporting Information** (**S-table 2**).

All cohorts obtained lung function measurements by spirometry, of which 22 according to the recent guidelines of the American Thoracic Society / European Respiratory Society (ATS/ERS) (19-21), and 2 according to earlier guidelines of the ATS (22) or ERS and European Coal and Steel Community (23) (**S-table 1**). If cohorts had collected lung function data at multiple time points (n = 6 cohorts), we used the measurement closest to the

mean age of children (8.5 years) in the full meta-analysis. Variables for analyses were forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), forced mid-expiratory flow ($FEF_{25–75}$) and forced expiratory flow after exhaling 75% of the vital capacity (FEF_{75}). We mainly focused on FEV_1, FEV_1/FVC, and FEF_{75}, which reflect reduced airway patency in obstructive lung diseases such as asthma or bronchopulmonary dysplasia due to preterm birth or low birth weight (24, 25). All lung function variables were converted into sex-, height-, age-, and ethnicity (Caucasian versus non-Caucasian) -adjusted Z-scores based on the Global Lung Initiative reference values (26). Asthma (yes / no) was defined as ever physician diagnosed asthma, and was obtained by medical registries (2 cohorts) or parental questionnaires adapted from the International Study on Asthma and Allergy in Childhood (ISAAC) (27) (22 cohorts) at the age of spirometry (**S-table1**). Cohort specific characteristics of lung function measurements and asthma are given in the **Supporting Information** (**S-table 3**).

We included covariates based on known associations with childhood lung function from previous studies (28, 29). Information on covariates was mainly assessed by questionnaires (**S-table 1**). Potential confounders included maternal educational level, smoking during pregnancy, smoking during infancy of their offspring, history of asthma or atopy, child's sex, siblings, day care attendance in the first 2 years of life, breastfeeding, lower respiratory tract infections in the first 2 years of life, eczema, inhalant allergies, and body mass index (BMI) at the moment of lung function measurement. Cohort specific characteristics of all covariates are given in the **Supporting Information** (**S-tables 4-5**).

Statistical analysis

First, we conducted 1-stage random effect regression analyses to study the separate and combined associations of gestational age, birth weight and infant weight gain with FEV_1, FVC, FEV_1/FVC, FEF_{25-75} and FEF_{75}. For these analyses, individual participant data from all cohorts were combined and modeled simultaneously taking into account clustering of participants within studies (30). To prevent multicollinearity in our regression models, we

initially assessed the separate associations of gestational age and birth weight with lung function. Thereafter, we assessed whether the associations of birth weight with lung function was driven by gestational age by creating gestational age adjusted birth weight standard deviation scores. The models focused on the associations of infant weight gain with lung function outcomes were adjusted for gestational age and weight at birth. For these analyses, we used early growth characteristics as continuous variables in the models providing p-values for trend. To test non-linear and dose-response associations, we categorized gestational age, birth weight SDS and infant weight gain SDS. As a sensitivity analysis, we conducted a 2-stage random effect meta-analysis to study the associations of gestational age, birth weight, and infant weight gain, and dichotomized preterm birth and low birth weight with each lung function outcome. For this analysis, we used linear regression models per cohort, after which pooled regression coefficients (β's) from the per cohort effect estimates were calculated. We tested for heterogeneity between effect estimates using I^2 (31, 32). For all analyses, the first model was adjusted for child's sex (crude model), the second model was additionally adjusted for potential confounders (full model). To determine interactive effects between gestational age, birth weight and infant weight gain we added the corresponding multiplicative terms in the full model. Since we used Northern-European reference curves for birth weight SDS, we performed a sensitivity analysis to explore whether the associations were different in North-Western European subjects only. Numbers were too small to perform these analyses separately in other European regions. To assess differences in results related to pubertal growth changes, we repeated our analyses is strata of children aged < 11 years and ≥11 years (33). We also performed a complete-case sensitivity analysis to explore any differences between complete and non-complete-case analyses, and sensitivity analyses in which we excluded cohorts that used parental report of early growth characteristics or that did not perform spirometry measurements according to the ATS/ERS guidelines.

Second, we conducted a 1-stage random effect regression analysis to assess the associations of early growth characteristics with asthma, and observed whether changes in

the effect estimates occurred after additional adjustment for lung function measures (FEV_1, FVC, FEV_1/FVC, FEF_{25-75} and FEF_{75}) as potential mediators (mediator model). The difference between the original effect estimates and the effect estimates after additional adjustment for potential mediators was expressed as percentage change. The percentage change was calculated by the formula: 100 x (effect $estimate_{mediator}$ - effect $estimate_{original\ model}$)/(effect $estimate_{original\ model}$- 1). A 95% confidence interval for the percentage change of the effect estimate was calculated using a bootstrap method with 1,000 resamplings (34-36).

For all analyses, missing values in covariates were used as an additional group in the categorical variables to prevent exclusion of non-complete cases. Statistical analyses were performed with R version 3.0.0 (libraries rmeta and metafor; The R foundation for Statistical Computing), and Comprehensive Meta-Analysis (Biostat, US).

RESULTS

Subject characteristics

Information about the main characteristics of the cohorts are given in **Table 1**. Detailed information about determinants, outcomes and covariates is given in the **Supporting Information (S-tables 1-5)**. Of all participants, 8.2% (n = 2,053) was born preterm (<37 weeks of gestational age), and 4.8% (n = 1,191) was born with a low birth weight (<2,500 gram). The mean age at which spirometry assessments were performed was 8.5 (range 3.9 - 19.1) years. The proportion of children aged ≥11 years was 11.9% (n = 2,972).

Early growth measures and lung function outcomes

Results from the 1-stage random effect models showed that younger gestational age at birth was, across the full range, associated with lower FEV_1, FEV_1/FVC and FEF_{75} in childhood (p-values for trend <0.01) (**Figures 1A-C**). A smaller size-for-gestational-age at birth across the full range was associated with lower FEV_1 and higher FEV_1/FVC (p-values for trend <0.01) (**Figures 1D-E**). Small size-for-gestational-age at birth was not associated with FEF_{75}

(**Figure 1F**). Greater infant weight gain was associated with a higher FEV_1, but with a lower FEV_1/FVC and FEF_{75} (p-values for trend <0.01; **Figures 1G-I**). Most associations showed a linear trend, except for the associations of birth weight with FEV_1/FVC and infant weight gain with FEV_1 and FEV_1/FVC which were non-linear (**Figures 1E, G, H**).

To explore the combined effects of gestational age, birth weight SDS and infant weight gain SDS, we performed tests for interaction between these early growth characteristics. These tests for interaction were significant for gestational age and birth weight SDS in relation to FEV_1, FEV_1/FVC, FEF_{25-75} and FEF_{75} (p-values for interaction <0.01; **Figure 2, S-table 9**). Stratified analyses showed that a lower birth weight was associated with lower FEV_1 and FEV_1/FVC among children born after ≥ 32 weeks only, whereas higher birth weight was associated with FEF_{75} only among term born children (p-values for strata <0.05).

No differences in results were observed when we used 2-stage random effect models of combined effect estimates (**: S-tables 6-7**). Also, the results from the sensitivity analyses showed similar results when we used cohorts with North-Western European subjects only, when we excluded cohorts that did not perform spirometry measurements according to the recent ATS/ERS guidelines, when we performed stratified analyses for children aged < 11 years or ≥ 11 years (**S-table 8**), or when we excluded cohorts that used parental report of early growth characteristics (data not shown).

Figure 3 shows that compared to term born children, those born preterm had a lower FEV_1, FEV_1/FVC and FEF_{75}, (pooled Z-score (95% CI): -0.20 (-0.26, -0.14), -0.15 (-0.21, -0.09) and -0.19 (-0.27, -0.11), respectively). Also, compared to normal birth weight children, those with a low birth weight had lower FEV_1, FEV_1/FVC and FEF_{75} (-0.29 (-0.38, -0.21) and -0.16 (-0.25, -0.08) and -0.17 (-0.26, -0.08) respectively), independent of gestational age. Results of associations of growth characteristics with all lung function outcomes, including FVC and FEF_{25-75} are given in the **Supporting Information: S-tables 6-8**.

Early growth, lung function and asthma

Preterm birth, low birth weight and greater weight gain were all associated with an increased risk of childhood asthma (OR (95% CI): 1.34 (1.15, 1.57), 1.32 (1.07, 1.62) and 1.27 (1.21, 1.34), respectively. Mediation analyses suggested that FEV_1, FEV_1/FVC and FEF_{75} may explain 7 (2, 10)% to 45 (15, 81)%. Specifically, after additional adjustment for FEV_1, FEV_1/FVC or FEF_{75}, the associations of preterm birth with asthma attenuated with -7 (-19, -1)%, -14 (-40, -3)% and -39 (-69, -3)%, respectively. Similarly, the associations of low birth weight with asthma attenuated with -19 (-37, -12)%, -22 (-47, -11)% and -222 (-47, -11)%, respectively (**Table 2**). The strongest mediating effect was observed for FEF_{75} for the association between gestational age and asthma (-45 (-81, -15)%). Similar trends were observed for greater weight gain, although the associations did not attenuate into non-significant.

DISCUSSION

In this meta-analysis of individual participant data of 24,938 children from 24 birth cohorts, we observed that lower gestational age, smaller size at birth and greater infant weight gain were all associated with lower childhood FEV_1. The positive associations of birth weight and infant weight gain with FVC were larger than of the positive associations of birth weight and infant weight gain with FEV_1. This combination resulted in associations of higher birth weight and infant weight gain with lower FEV_1/FVC. Also, a lower gestational age at birth was associated with a lower FEF_{75} in childhood, suggesting persistent reduction of small airways patency. A greater infant weight gain was associated with lower FEF_{75}.. Remarkably, these associations were present across the full-range of early growth and not restricted to clinically diagnosed preterm- or low birth weight children. Also, the observed associations of the early life growth characteristics with lung function outcomes were independent of each other. Stratified analyses showed that children born very preterm with a relatively low birth weight had the lowest FEV_1 and FEV_1/FVC. The associations of early growth characteristics with childhood asthma were partly explained by lung function adaptations.

Whereas lung growth continues until the early adulthood, the most rapid development of airways and alveoli occurs in early life (37). Developmental adaptations in fetal life and infancy due to early life adverse exposures might result in impaired lung growth with smaller airways, decreased lung volume, and subsequently to an increased risk of bronchopulmonary dysplasia, asthma or COPD (9, 14, 38). Previous studies suggest that children with asthma already have a reduced lung function in the first months of life, and that this deficit progresses into childhood and early adulthood (39, 40). Airway caliber is a key determinant of total airway resistance and reduced caliber is a prominent feature of asthma and chronic obstructive pulmonary diseases (5-7). Lower lung function in early life is likely to lead to lower peak lung function in early adulthood, and the natural decline in FEV_1 from that point onwards will be accelerated by any additional adverse exposures (41). Thus, lung function during the lifecourse seems to be programmed at least partly in early life.

Children born preterm or with a very low birth weight are at increased risk of neonatal respiratory diseases (1). We observed that children born at a younger gestational age had a lower FEV_1, even after taking FVC into account, and a lower FEF_{75} in childhood. These associations were not only present among children born very preterm, but across the full range of gestational age at birth. Moreover, the associations of preterm birth with childhood asthma were partly explained by lung function. These findings are in line with previous studies showing persistent lung function adaptions in children and adults born preterm. A recent meta-analysis of 28 published studies showed that children born between 24 and 36 weeks had a lower FEV_1 at ages 5 up to 23 years (42). These and other studies suggest that preterm birth has adverse effects on lung function, persisting into adulthood (42-44).

In the present study, a lower birth weight was associated with lower FEV_1 in childhood. This suggests that a lower birth weight leads to a persistent reduction of airway patency. A previous study analyzed 10 studies examining the associations of birth weight with FEV_1 in adults (range 19 – 70 years) (10). The authors reported a modest positive association between FEV_1 and birth weight. Two recent studies from longitudinal birth cohorts among adults reported strong positive associations of birth weight with FEV_1 and

265 FEF_{25-75} in young adults aged 21 and 31 years (9, 11). The effect of birth weight was
266 independent of preterm birth in both studies. However, studies among children showed
267 conflicting results (12, 13). We observed an association of lower birth weight with lower
268 FEV_1, independent of gestational age at birth. We previously reported that the effect of lower
269 birth weight on asthma was largely explained by gestational age (4). Therefore, although
270 gestational age-adjusted birth weight is associated with lower lung function this seems not
271 related to the risk of clinically manifest childhood asthma.
272 Previous studies examining associations between infant weight gain and childhood
273 lung function have reported inconsistent results (14-16). Differences might be due to
274 different ages at which spirometry was performed, not taking other weight characteristics
275 into account, such as birth weight or current body mass index, and possible hidden bias due
276 to the use of mL instead of Z-scores for lung function (45). In line with the findings for birth
277 weight, we observed that lower infant weight gain was associated with a lower childhood
278 FEV_1 and FVC (p-value for continuous variables <0.001) Lower infant weight gain was
279 associated with a less lower FEV_1 than lower FVC which resulted in a higher FEV_1/FVC.
280 These results suggest dysanapsis, in which airways reflected by FEV_1 remain relatively
281 small in relation to total lung volume reflected by FVC, as a result of a mismatch between
282 airway and alveolar growth (46). Greater infant weight gain was also associated with a lower
283 FEF_{75}, which is in line with previous studies reporting associations of body mass index or
284 adiposity with reduced expiratory flows and asthma (47, 48). A suggested mechanism is
285 leptin release from adipose tissue, which might have pro-inflammatory effects in the airways
286 (49), or a direct effect of increased body weight on lung function (50). However, our analyses
287 were adjusted for childhood body mass index. Further studies are needed to explore
288 whether the associations of infant weight gain with end-expiratory flows are explained by
289 specific adiposity-related measures or biomarkers.
290 To the best of our knowledge this is the first study that examines the individual and
291 combined associations of the main early growth characteristics with childhood lung function
292 outcomes, and whether lung function adaptations explain the previously reported

associations of early growth characteristics with childhood asthma. Our results suggest that respiratory consequences of preterm birth and a low birth weight present across the full range. This observation might have important population effects, since the largest majority of children are in the less extreme ranges of gestational age and weight at birth. Furthermore, our results suggest that the associations of gestational age, birth weight and infant weight gain with childhood asthma are at least partly explained by adaptions in airway caliber. We observed strong effect estimates with wide confidence intervals which limits the precision. Therefore, these mediation effects should be interpreted carefully. The effect estimates for the observed associations could be considered as small and without clinical relevance for individuals. However, the associations may be important from an etiological respiratory developmental perspective and may be important on a population-level. The associations of early growth characteristics with lung function outcomes seemed already established before the pubertal growth spurt. The largest lung and airway growth occurs before pubertal growth spurt (37, 51), with FVC increasing proportionately more than the FEV_1 (33). Lung and airway growth is proportionally less after start of the pubertal growth spurt (33), which might explain the similar effect estimates before and after the pubertal growth spurt. Further studies are needed to identify the developmental adaptations of the lungs and immune system that might explain the mediating effect of lung function on the associations of early growth characteristics with childhood asthma. Identification of modifiable exposures may lead to development of future preventive strategies.

Some methodological limitations need to be discussed. We used data from 24 ongoing cohort studies. Missing values always occur in these studies. Since we did not have additional data on patterns of missing values in all 24 cohorts, we were not able to perform multiple imputation. Data on childhood asthma was mainly obtained by parental questionnaires adapted from the International Study on Asthma and Allergy in Childhood (ISAAC) (27). This questionnaire has been validated in various age groups in many countries against measurements of bronchial hyperresponsiveness and doctor-diagnosed asthma, and is widely accepted in epidemiological studies. We did not have information on

use of asthma medication, which might have influenced the lung function values in asthmatic patients. This missing information on asthma medication may have influenced our effect estimates. We would expect that asthmatic children who use asthma medication would in general have had a higher lung function values in case of good adherence and inhaler technique. We used GLI reference data to convert lung function values into Z-scores. These prediction equations were based on 74,187 individuals including 31,840 individuals aged <20 years, of whom 58% were assessed before, and 42% were assessed during pubertal growth spurt (26). To date, the GLI normal values are considered the most accurate reference values for all age ranges, and have been adopted by both the ATS and ERS. For the covariates, we imputed missing values as additional category to prevent exclusion of non-complete cases. No differences in results were observed in complete case analyses. No direct clinical and laboratory information about pubertal growth was available. Also, although we took major potential confounders into account, residual confounding may still be an issue. No information was available about e.g. exposure to environmental micro-organisms or asthma severity. Exploring mediation of lung function for the association of early growth characteristics with asthma using the method proposed by Baron and Kenny might have been limited by misclassification of lung function measurements or asthma diagnosis although we aimed to reduce this issue by multi-level modelling (52). Most of the participating studies had measured childhood lung function and asthma at the same age. Therefore, further follow-up studies with longitudinally measured detailed data on lung function and asthma or related symptoms from birth onwards are needed to disentangle the direction of causality.

In conclusion, younger gestational age, lower birth weight and lower infant weight gain were independently associated with persistent changes in childhood lung function. These associations were present across the full spectrum of these early growth characteristics. Stratified analyses showed that children born very preterm with a relatively low birth weight had the lowest FEV_1 and FEV_1/FVC. Our results suggest that associations of early growth with the risk of childhood asthma were partly explained by lung function

adaptations. Thus, fetal and infant growth patterns may persistently affect lung function, and thereby contribute to the risk of respiratory diseases in later life.

Author's contributions

HD, AS, JJ, VJ, and LD contributed to the study design, data analysis plan, data collection, data analysis, data interpretation, writing, reviewing the manuscript critically and gave consent for submission. All other authors contributed equally to study design, data analysis plan, data collection, reviewing the manuscript critically and gave consent for submission.

REFERENCES

1. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ. 2012;345:e7976.

2. Brostrom EB, Akre O, Katz-Salamon M, Jaraj D, Kaijser M. Obstructive pulmonary disease in old age among individuals born preterm. Eur J Epidemiol. 2013 Jan;28(1):79-85.

3. Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. PLoS Med. 2014 Jan;11(1):e1001596.

4. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, Annesi-Maesano I, Arshad SH, Barros H, et al. Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 European children. J Allergy Clin Immunol. 2014 May;133(5):1317-29.

5. van der Gugten A, Korte K, van der Ent K, Uiterwaal C, Verheij T. Small airway caliber is the most important contributor of wheezing in healthy unselected newborns. Am J Respir Crit Care Med. 2011 Feb 15;183(4):553; author reply -4.

6. Rasmussen F, Taylor DR, Flannery EM, Cowan JO, Greene JM, Herbison GP, et al. Risk factors for hospital admission for asthma from childhood to young adulthood: a longitudinal population study. J Allergy Clin Immunol. 2002 Aug;110(2):220-7.

7. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet. 2004 Aug 21-27;364(9435):709-21.

8. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008 Jul 3;359(1):61-73.

9. Canoy D, Pekkanen J, Elliott P, Pouta A, Laitinen J, Hartikainen AL, et al. Early growth and adult respiratory function in men and women followed from the fetal period to adulthood. Thorax. 2007 May;62(5):396-402.

10. Lawlor DA, Ebrahim S, Davey Smith G. Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. Thorax. 2005 Oct;60(10):851-8.

11. Suresh S, Mamun AA, O'Callaghan M, Sly PD. The impact of birth weight on peak lung function in young adults. Chest. 2012 Dec;142(6):1603-10.

12. Lima Rda C, Victora CG, Menezes AM, Barros FC. Respiratory function in adolescence in relation to low birth weight, preterm delivery, and intrauterine growth restriction. Chest. 2005 Oct;128(4):2400-7.

13. Lum S, Hoo AF, Dezateux C, Goetz I, Wade A, DeRooy L, et al. The association between birthweight, sex, and airway function in infants of nonsmoking mothers. Am J Respir Crit Care Med. 2001 Dec 1;164(11):2078-84.

14. Hancox RJ, Poulton R, Greene JM, McLachlan CR, Pearce MS, Sears MR. Associations between birth weight, early childhood weight gain and adult lung function. Thorax. 2009 Mar;64(3):228-32.

15. Sherrill DL, Guerra S, Wright AL, Morgan WJ, Martinez FD. Relation of early childhood growth and wheezing phenotypes to adult lung function. Pediatr Pulmonol. 2011 Oct;46(10):956-63.

16. van der Gugten AC, Koopman M, Evelein AM, Verheij TJ, Uiterwaal CS, van der Ent CK. Rapid early weight gain is associated with wheeze and reduced lung function in childhood. Eur Respir J. 2012 Feb;39(2):403-10.

17. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand. 1991 Aug-Sep;80(8-9):756-62.

18. Bland JM, Altman DG. Measurement error. BMJ. 1996 Jun 29;312(7047):1654.

19. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Respir J. 2005 Jul;26(1):153-61.

20. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005 Aug;26(2):319-38.

21. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005 Sep;26(3):511-22.

22. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med. 1995 Sep;152(3):1107-36.

23. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl. 1993 Mar;16:5-40.

24. Bjermer L. The role of small airway disease in asthma. Curr Opin Pulm Med. 2014 Jan;20(1):23-30.

25. Lipworth B, Manoharan A, Anderson W. Unlocking the quiet zone: the small airway asthma phenotype. Lancet Respir Med. 2014 Jun;2(6):497-506.

26. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012 Dec;40(6):1324-43.

27. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J. 1995 Mar;8(3):483-91.

28. Boezen HM, Vonk JM, van Aalderen WM, Brand PL, Gerritsen J, Schouten JP, et al. Perinatal predictors of respiratory symptoms and lung function at a young adult age. Eur Respir J. 2002 Aug;20(2):383-90.

29. Kotecha SJ, Watkins WJ, Paranjothy S, Dunstan FD, Henderson AJ, Kotecha S. Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents. Thorax. 2012 Jan;67(1):54-61.

30. Debray TP, Moons KG, Abo-Zaid GM, Koffijberg H, Riley RD. Individual participant data meta-analysis for a binary outcome: one-stage or two-stage? PloS one. 2013;8(4):e60650.

31. Normand SL. Meta-analysis: formulating, evaluating, combining, and reporting. Statistics in medicine. 1999 Feb 15;18(3):321-59.

32. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Statistics in medicine. 2002 Feb 28;21(4):589-624.

33. Quanjer PH, Stanojevic S, Stocks J, Hall GL, Prasad KV, Cole TJ, et al. Changes in the FEV(1)/FVC ratio during childhood and adolescence: an intercontinental study. Eur Respir J. 2010 Dec;36(6):1391-9.

34. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986 Dec;51(6):1173-82.

35. Cerin E, MacKinnon DP. A commentary on current practice in mediating variable analyses in behavioural nutrition and physical activity. Public Health Nutr. 2009 Aug;12(8):1182-8.

36. MacKinnon DP, Fairchild AJ. Current Directions in Mediation Analysis. Curr Dir Psychol Sci. 2009 Feb;18(1):16-20.

37. Narayanan M, Owers-Bradley J, Beardsmore CS, Mada M, Ball I, Garipov R, et al. Alveolarization continues during childhood and adolescence: new evidence from helium-3 magnetic resonance. Am J Respir Crit Care Med. 2012 Jan 15;185(2):186-91.

38. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. BMJ. 1991 Sep 21;303(6804):671-5.

39. Bisgaard H, Jensen SM, Bonnelykke K. Interaction between asthma and lung function growth in early life. Am J Respir Crit Care Med. 2012 Jun 1;185(11):1183-9.

40. Haland G, Carlsen KC, Sandvik L, Devulapalli CS, Munthe-Kaas MC, Pettersen M, et al. Reduced lung function at birth and the risk of asthma at 10 years of age. N Engl J Med. 2006 Oct 19;355(16):1682-9.

41. Stocks J, Sonnappa S. Early life influences on the development of chronic obstructive pulmonary disease. Ther Adv Respir Dis. 2013 Jun;7(3):161-73.

42. Kotecha SJ, Edwards MO, Watkins WJ, Henderson AJ, Paranjothy S, Dunstan FD, et al. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. Thorax. 2013 Aug;68(8):760-6.

43. Narang I, Rosenthal M, Cremonesini D, Silverman M, Bush A. Longitudinal evaluation of airway function 21 years after preterm birth. Am J Respir Crit Care Med. 2008 Jul 1;178(1):74-80.

44. Vollsaeter M, Roksund OD, Eide GE, Markestad T, Halvorsen T. Lung function after preterm birth: development from mid-childhood to adulthood. Thorax. 2013 Aug;68(8):767-76.

45. Miller MR, Pincock AC. Predicted values: how should we use them? Thorax. 1988 Apr;43(4):265-7.

46. ad hoc Statement Committee ATS. Mechanisms and limits of induced postnatal lung growth. Am J Respir Crit Care Med. 2004 Aug 1;170(3):319-43.

47. Scholtens S, Wijga AH, Seidell JC, Brunekreef B, de Jongste JC, Gehring U, et al. Overweight and changes in weight status during childhood in relation to asthma symptoms at 8 years of age. J Allergy Clin Immunol. 2009 Jun;123(6):1312-8 e2.

48. Rzehak P, Wijga AH, Keil T, Eller E, Bindslev-Jensen C, Smit HA, et al. Body mass index trajectory classes and incident asthma in childhood: results from 8 European Birth Cohorts--a Global Allergy and Asthma European Network initiative. J Allergy Clin Immunol. 2013 Jun;131(6):1528-36.

49. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab. 2004 Jun;89(6):2548-56.

50. Dixon AE, Holguin F, Sood A, Salome CM, Pratley RE, Beuther DA, et al. An official American Thoracic Society Workshop report: obesity and asthma. Proc Am Thorac Soc. 2010 Sep;7(5):325-35.

51. Kotecha S. Lung growth for beginners. Paediatr Respir Rev. 2000 Dec;1(4):308-13.

52. Cole DA, Preacher KJ. Manifest variable path analysis: potentially serious and misleading consequences due to uncorrected measurement error. Psychol Methods. 2014 Jun;19(2):300-15.

Figure 1. Associations of gestational age, birth weight and infant weight gain with FEV_1, FEV_1/FVC ratio and FEF_{75}.

Legend:

Values represent Z-scores differences (95% confidence interval) from multi-level random effect models for the associations of gestational age at birth (A, B, C), gestational age adjusted birth weight (birth weight SDS) (D, E, F), and infant weight gain (SDS) (G, H, I) with lung function outcomes, compared with reference groups. Reference groups were 40-42.9 weeks of gestational age, 0-0.99 birth weight SDS and 0.00 – 0.99 infant weight gain (SDS) (largest groups), and represented by an open bullet. Lung function outcomes are forced expiratory volume in 1 second (FEV_1), FEV_1/forced vital capacity (FVC) ratio, and forced expiratory flow at 75% of the exhaled FVC (FEF_{75}). Models are adjusted for maternal education, smoking during pregnancy, smoking during childhood, atopy, asthma and child's sex, number of siblings, daycare attendance, breastfeeding, respiratory tract infections, childhood eczema, inhalant allergies and body mass index. Infant weight gain SDS was additionally adjusted for birth weight and gestational age at birth.

Figure 2. Combined associations of gestational age and birth weight with FEV_1, FEV_1/FVC ratio and FEF_{75}.

Legend:

Values are Z-score differences (95% confidence interval) from multi-level models for the combined associations of gestational age at birth and birth weight SDS (A, B, C) with lung function outcomes, compared with reference groups. Reference groups were >37 weeks of gestational age with -1.00 to 0.99 birth weight SDS (largest group), and represented by a bullet. Lung function outcomes are forced expiratory volume in 1 second (FEV_1), FEV_1/forced vital capacity (FVC) ratio, and forced expiratory flow at 75% of the exhaled FVC (FEF_{75}). Models are adjusted for maternal education, smoking during pregnancy, smoking

during childhood, atopy, asthma and child's sex, number of siblings, daycare attendance, breastfeeding, respiratory tract infections, childhood eczema, inhalant allergies and body mass index. *P-value < 0.05. **P-value < 0.01. Given p-values reflect differences between birth weight SDS groups (A, B, C) within strata of gestational age using -1.00 to 0.99 birth weight SDS as reference group. P_{int}: p-values of multiplicative interaction terms.

Figure 3. Forest plots of the associations between preterm birth and low birth weight with FEV_1, FEV_1/FVC ratio and FEF_{75}.

Legend:

Values are pooled Z-score differences (95% confidence interval) from random effect meta-analysis for the associations of preterm birth vs. term birth (A, B, C) and low birth weight vs. normal birth weight (D, E, F) with lung function outcomes. Lung function outcomes are forced expiratory volume in 1 second (FEV_1), FEV_1/forced vital capacity (FVC) ratio, and forced expiratory flow at 75% of the exhaled FVC (FEF_{75}). Models are adjusted for maternal education, smoking during pregnancy, smoking during childhood, atopy, asthma and child's sex, number of siblings, daycare attendance, breastfeeding, respiratory tract infections, childhood eczema, inhalant allergies and body mass index. Low birth weight was adjusted for gestational age.

Table 1. Characteristics of participating cohorts.

Cohort name (country)	**N**	**Birth years**	**Gestational age at birth (weeks)**	**Birth weight (gram)**	**FVC**	**FEV_1**	**FEV_1/ FVC**	**FEF_{25-75}**	**FEF_{75}**	**Childhood asthma**
			Median (5-95% range)	Mean (SD)	Mean Z-score (SD)	Mean Z-score (SD)	Mean Z-score (SD)	Mean Z-score (SD)	Mean Z-score (SD)	Yes
ALSPAC (United Kingdom)	6,873	1991-1992	39.5 (1.9)	3,424 (543)	0.49 (1.28)	0.44 (1.17)	-0.07 (1.15)	0.04 (1.08)	0.30 (1.06)	17.9 (1,231)
BAMSE (Sweden	2,042	1994-1996	39.9 (1.8)	3,537 (551)	0.65 (0.93)	0.45 (0.96)	-0.37 (0.89)	-	-	14.8 (303)
BILD (Switzerland)	159	1999-ongoing	39.7 (1.3)	3,367 (441)	-0.23 (0.98)	0.02 (0.89)	0.33 (0.95)	-0.06 (0.87)	-	-
CONER (Italy)	217	2004-2005	39.2 (1.4)	3,335 (457)	-1.76 (0.82)	-1.04 (0.90)	0.51 (1.65)	0.45 (1.00)	-	6.0 (13)
COPSAC2000 (Denmark)	314	1998-2001	40.0 (1.6)	3,529 (531)	-0.53 (0.98)	-0.11 (1.03)	0.47 (0.95)	-	-	18.8 (59)
EDEN (France)	897	2003-2005	39.3 (1.7)	3,284 (514)	-1.08 (1.05)	-0.77 (1.03)	0.21 (0.97)	-0.39 (1.01)	0.16 (0.88)	18.1 (162)
GASPII (Italy)	453	2003-2004	39.2 (1.8)	3,314 (530)	0.06 (0.76)	-0.01 (0.88)	-0.15 (0.97)	-0.30 (0.90)	-	6.6 (30)
GENERATION R (The Netherlands)	1,927	2002-2006	39.7 (1.9)	3,392 (576)	0.23 (0.92)	0.15 (0.95)	-0.19 (0.92)	0.15 (1.05)	-0.09 (0.89)	5.5 (106)
GENERATION XXI (Portugal)	1,562	2005-2006	38.4 (2.1)	3,152 (551)	0.41 (0.95)	0.59 (0.98)	0.21 (0.82)	0.12 (0.85)	0.44 (0.80)	6.5 (102)
GINI (Germany)	707	1995-1998	-	3,493 (479)	-	0.02 (0.92)	-	-	-	5.9 (49)
INMA Gipuzkoa (Spain)	277	2006-2008	39.7 (1.4)	3,284 (436)	-0.54 (1.16)	-0.59 (1.17)	-0.05 (0.91)	-0.45 (0.99)	-0.16 (1.00)	5.4 (15)
INMA Menorca (Spain)	367	1997-1998	39.2 (1.8)	3,200 (493)	0.01 (1.13)	-0.16 (1.07)	-0.24 (1.19)	-0.42 (1.29)	-0.06 (1.32)	4.9 (18)

Table 1 (continued). Characteristics of participating cohorts.

Cohort name (country)	N	Birth years	Gestational age at birth (weeks)	Birth weight (gram)	FVC	FEV_1	FEV_1/ FVC	FEF_{25-75}	FEF_{75}	Childhood asthma
			Median (5-95% range)	Mean (SD)	Mean Z-score (SD)	Mean Z-score (SD)	Mean Z-score (SD)	Mean Z-score (SD)	Mean Z-score (SD)	Yes
INMA Sabadell (Spain)	408	2004-2007	39.8 (1.3)	3,261 (404)	-0.47 (1.38)	-0.57 (1.30)	-0.08 (1.03)	-0.61 (1.00)	-0.25 (1.12)	0.7 (3)
INMA Valencia (Spain)	455	2003-2005	39.6 (1.7)	3,227 (491)	0.30 (1.10)	0.30 (1.08)	-0.04 (0.95)	-0.13 (0.91)	-0.04 (0.90)	-
ISLE OF WIGHT (United Kingdom)	1,030	1989-1990	39.9 (1.5)	3,411 (510)	0.24 (0.91)	0.39 (1.01)	0.22 (1.03)	0.04 (0.99)	-	21.5 (221)
KOALA (The Netherlands)	438	2000-2003	40.0 (1.2)	3,552 (467)	0.15 (0.94)	-0.13 (0.95)	-0.55 (0.84)	-	-	8.0 (35)
LEICESTER 1990 (United Kingdom)	290	1985-1990	39.0 (2.2)	3,373 (599)	-0.33 (1.11)	-0.38 (1.12)	-0.76 (0.90)	-0.62 (1.01)	-	37.2 (108)
LEICESTER 1998 (United Kingdom)	1,476	1993-1997	39.2 (2.0)	3,314 (592)	-0.41 (1.04)	-0.39 (1.05)	0.01 (1.03)	-	0.05 (0.94)	36.4 (538)
MAS (Germany)	641	1990	40.0 (1.4)	3,414 (460)	-0.06 (0.97)	0.24 (1.00)	0.41 (1.00)	1.15 (0.14)	-	5.0 (32)
PIAMA (The Netherlands)	1,767	1996-1997	39.9 (1.7)	3,526 (540)	0.04 (0.95)	0.07 (1.04)	-0.04 (1.01)	-1.67 (1.21)	-0.21 (0.95)	10.0 (176)
RHEA (Greece)	666	2007-2008	38.1 (1.7)	3,175 (506)	-0.25 (1.09)	-0.33 (1.14)	-0.10 (0.94)	-0.38 (0.96)	-0.17 (1.05)	5.9 (39)
SEATON (United Kingdom)	578	1997	39.5 (1.8)	3,488 (563)	-0.12 (1.08)	-0.06 (1.08)	-0.04 (0.96)	-0.27 (0.98)	-	20.1 (116)
SWS (United Kingdom)	803	1998-2007	39.7 (1.9)	3,447 (548)	0.13 (1.01)	0.03 (0.95)	-0.18 (1.05)	-0.28 (0.94)	-	15.1 (121)
WHISTLER (The Netherlands)	591	2001-2012	40.0 (1.3)	3,553 (499)	0.16 (1.11)	0.46 (1.14)	0.31 (0.93)	-0.04 (1.23)	0.12 (1.07)	9.3 (55)

N = number of participants with information on at least gestational age or birth weight, and a lung function outcome. Lung function outcomes are forced vital capacity (FVC), force expiratory volume in 1 second (FEV_1), mid forced expiratory flow (FEF_{25-75}) and force expiratory flow at 75% of the exhaled FVC (FEF_{75}). Values are means (standard deviations) and percentages (absolute numbers) for the information on asthma. Additional information on data collection (Table S1), determinants (Table S2), outcomes (Table S3), and maternal and child related covariates (Tables S4, S5) is provided in the Supporting Information.

Table 2. Associations of birth weight, gestational age and infant weight gain with childhood asthma, additionally adjusted for lung function.

	Risk of childhood asthma Odds ratio (95% Confidence Interval)						
	Full model	**Full model + FEV_1**	**% change (95% CI)**	**Full model + FEV_1/FVC**	**% change (95% CI)**	**Full model + FEF_{75}**	**% change (95% CI)**
Gestational age (weeks)	0.94 (0.92, 0.97)** n = 15,019	0.95 (0.93, 0.97)** n = 14,832	-9.8% (- 16.4, - 5.3)**	0.95 (0.93, 0.97)** n = 14,017	-13.5% (-21.0, -7.3)**	0.97 (0.94, 1.00) n = 9,177	-44.6% (-81.1, -14.6)**
Preterm birth (<37 weeks)	1.34 (1.15, 1.57)** n = 15,019	1.30 (1.11, 1.53)** n = 14,832	-7.3% (-18.8, -0.9)*	1.27 (1.08, 1.49)** n = 14,017	-14.4% (-39.6, -2.8)*	1.20 (0.99, 1.47) n = 9,177	-39.0% (-69.3, -3.4)*
Birth weight (500 grams)	0.94 (0.90, 0.97)** n = 15,547	0.95 (0.91, 0.99)* n = 15,360	-18.9% (-37.0, -11.2)**	0.94 (0.90, 0.98)** n = 13,985	-10.5% (-21.9, -3.4)**	0.96 (0.92, 1.02) n = 9,135	-17.8 (-50.6, -9.0)**
Low birth weight (<2,500 grams)	1.32 (1.07, 1.62)** n = 15,547	1.25 (1.02, 1.54)* n = 15,360	-19.0% (-37.3, -11.8)**	1.23 (0.99, 1.52) n = 13,985	-21.6% (-47.3, -11.4)**	1.05 (0.81, 1.36) n = 9,135	-82.5% (-149, 10.3)
Birth weight (SDS)	0.98 (0.94, 1.03) n = 14,947	1.00 (0.96, 1.05) n = 14,760	-83.8% (-950, 825)	0.98 (0.94, 1.03) n =13,946	-14.0% (-247, 281)	0.99 (0.93, 1.04) n = 9,122	-15.8% (-158, 169)
Small for gestational age (<10th percentile)	1.18 (1.01, 1.37)* n = 14,947	1.13 (0.97, 1.32) n = 14,760	-28.9% (-253, 108)	1.16 (0.99, 1.36) n = 13,946	-18.8% (-123, 164)	1.20 (1.00, 1.44) n = 9,122	10.2% (-8.3, 26.2)
Infant weight gain in first year (SDS), adjusted for gestational age and weight at birth	1.27 (1.21, 1.34)** n = 12,511	1.28 (1.22, 1.35)** n = 12,511	6.5% (2.3, 9.9)**	1.25 (1.18, 1.31)** n = 11,780	-8.4% (-16.1, -3.2)**	1.13 (1.06, 1.20)** n = 7,969	-60.8 (-115, 39.5)

*p<0.05 **p<0.01. Values are odds ratios or percentage change in odds ratios (95% confidence interval) from random effect models and represent the risk of asthma per week, 500 grams or SDS increase in gestational age, birth weight, gestational age adjusted birth weight (birth weight SDS), or infant weight gain (SDS), respectively, or represent odds ratios or percentage change in odds ratios (95% confidence interval) in risk of asthma for preterm birth vs. term birth, low birth weight vs. normal birth weight or small for gestational age vs. normal and large for gestational age ($<10^{th}$ percentile vs $>10^{th}$ percentile). Percentage change in odds ratio (OR) is calculated using the formula (100 x ($OR_{mediator}$ - $OR_{model\ 1}$)/($OR_{model\ 1}$ - 1)), with corresponding 95% confidence interval obtained by bootstrap procedures. To enable comparison of effect estimates, results for gestational age adjusted birth weight and infant weight gain are presented as per SDS. Models are adjusted for maternal education, smoking during pregnancy, smoking during childhood, atopy, asthma and child's sex, number of siblings, daycare attendance, breastfeeding, respiratory tract infections, childhood eczema, inhalant allergies and body mass index (full model), and additionally for lung function outcomes (mediator model).