Original Article

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

Herman T den Dekker, M.D.[1-3], Agnes MM Sonnenschein-van der Voort, MSc, Ph.D.[1-3], Johan C de Jongste, M.D., Ph.D.[1], Isabella Anessi–Maesano, M.D., Ph.D.[4,5], S Hasan Arshad, DM [6-8], Henrique Barros, M.D., Ph.D.[9], Caroline S Beardsmore, Ph.D.[10], Hans Bisgaard, M.D., DMSci [11,12], Sofia Correia, Phar., M.D., M.Sc [9], Leone Craig[13,14], Graham Devereux, M.D., Ph.D.[14], C Kors van der Ent, M.D., Ph.D.[15], Ana Esplugues, Ph.D.[16-18], Maria P Fantini, M.D.[19], Claudia Flexeder [20], Urs Frey, M.D., Ph.D.[21], Francesco Forastiere, M.D., Ph.D.[22], Ulrike Gehring, Ph.D.[23], Davide Gori, M.D.[19], Anne C van der Gugten, M.D., Ph.D.[15], A John Henderson, M.D., Ph.D.[24], Barbara Heude, Ph.D.[25,26], Jesús Ibarluzea, Ph.D.[18,27], Hazel M Inskip, M.Sc, Ph.D.[28], Thomas Keil, M.D., M.ScPH [29,30], Manolis Kogevinas, M.D., Ph.D.[18,31-33], Eskil Kreiner-Møller, M.D. [11,12], Claudia E Kuehni, M.D.[34], Susanne Lau, M.D., Ph.D.[35], Erik Mélen, M.D., Ph.D.[36], Monique Mommers, Ph.D.[37], Eva Morales, M.D., Ph.D.[18,32,33,38], John Penders, Ph.D.[37], Katy C Pike, M.D., Ph.D. [7], Daniela Porta, M.Sc[22], Irwin K. Reiss, M.D., Ph.D [39], Graham Roberts, DM [6-8], Anne Schmidt, M.D. [21,40], Erica S Schultz, M.D.[36], Holger Schulz, M.D. [20], Jordi Sunyer, M.D., Ph.D.[18,32,33,38], Matias Torrent, M.D., Ph.D.[41], Maria Vassilaki, M.D., MPH, Ph.D.[42], Alet H Wijga, Ph.D.[43], Carlos Zabaleta, M.D.[44], Vincent WV Jaddoe, M.D., Ph.D. [2,3,45], Liesbeth Duijts, M.D., Ph.D.[1,2,39]

1. Department of Pediatrics, Division of Respiratory Medicine, Erasmus Medical Center, Rotterdam, the Netherlands
2. Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands.
3. The Generation R Study Group, Erasmus Medical Center, Rotterdam, the Netherlands.
4. EPAR, UMR-S 707 INSERM Paris, Paris, France.
5. EPAR, UMR-S 707, Université Pierre et Marie Curie Paris 06, Paris, France.

6. The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK.
7. University of Southampton, Faculty of Medicine, Southampton, United Kingdom.
8. NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom.
9. Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, Porto, Portugal.
10. Division of Child Health, Department of Infection, Immunity & Inflammation, University of Leicester and Institute for Lung Health, Leicester, LE2 7LX, United Kingdom.
11. The Copenhagen Prospective Studies on Asthma in Childhood (COPSAC2000), Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.
12. The Danish Pediatric Asthma Center, Copenhagen University Hospital, Gentofte, Denmark.
13. Public Health Nutrition Research Group, University of Aberdeen, United Kingdom.
14. Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom.
15. Department of Paediatric Pulmonology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands.
16. Faculty of Nursing and Chiropody, Valencia, Spain
17. FISABIO, Valencia, Spain.
18. CIBER Epidemiología y Salud Pública (CIBERESP), Spain.
19. Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy.
20. Helmholtz Zentrum München, Institute of Epidemiology I, Neuherberg, Germany.
21. University Children's Hospital Basel (UKBB), University of Basel, Basel, Switzerland.
22. Department of Epidemiology, Lazio Regional Health Service, Rome, Italy.
23. Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands.
24. School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom.
25. CESP Inserm UMRS 1018 Team 10 Villejuif France.
26. Univ Paris Sud UMRS 1018 Team 10 Villejuif France.
27. Public Health Division of Gipuzkoa, San Sebastian, Spain
28. MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, United Kingdom.
29. Institute of Social Medicine, Epidemiology and Health Economics, Charité University Medical Center, Berlin, Germany.
30. Institute for Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany.
31. National School of Public Health, Athens, Greece.
32. Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Catalonia, Spain.

33. Hospital del Mar Medical Research Institute (IMIM), Barcelona, Catalonia,Spain.
34. Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland.
35. Department of Paediatric Pneumology and Immunology, Charité University Medical Centre, Berlin, Germany.
36. Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, and Sach's Children Hospital, Stockholm, Sweden.
37. Department of Epidemiology, CAPHRI School for Public Health and Primary Care, Maastricht University, Maastricht, The Netherlands.
38. Universitat Pompeu Fabra (UPF), Barcelona, Catalonia, Spain.
39. Department of Pediatrics, Division of Neonatology, Erasmus Medical Center, Rotterdam, the Netherlands.
40. Division of Respiratory Medicine, Department of Pediatrics, Inselspital, University of Bern, Bern, Switzerland.
41. IB-SALUT, Area de Salut de Menorca, Balearic Islands, Spain.
42. Department of Social Medicine, School of Medicine, University of Crete, Greece.
43. Centre for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands.
44. Nuestra Señora de la Antigua Hospital, OSAKIDETZA Basque Health Service, San Sebastian, Spain.
45. Department of Pediatrics, Erasmus Medical Center, Rotterdam, the Netherlands.

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Correspondence: Dr. Liesbeth Duijts, M.D., Ph.D., Erasmus MC, University Medical Center Rotterdam, Sp-3435, PO box 2060, 3000 CB Rotterdam, The Netherlands. Tel: +31 10 7036263; Fax: +31 10 7036811; E-mail: l.duijts@erasmusmc.nl.

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ABSTRACT

Background Children born preterm or with a small-size-for-gestational-age are at increased risk for childhood asthma. We tested the hypothesis that these associations are explained by reduced airway patency**.**

Methods and Materials We used individual participant data of 24,938 children from 24 birth cohorts to examine the associations of gestational age, size-for-gestational-age, and infant weight gain with childhood lung function (forced expiratory volume in 1 second (FEV_1), FEV_1/forced vital capacity (FEV_1/FVC), forced expiratory flow after exhaling 75% of the vital capacity (FEF_{75})) and risk of doctor-diagnosed asthma (age range 3.9 – 19.1 years). Second, we used similar models to explore whether these lung function outcomes mediated the associations of early growth characteristics with the risk of childhood asthma.

Results Children born with a younger gestational age had a lower FEV_1, FEV_1/FVC, and FEF_{75}, 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~~s~~ and independent of other early life growth characteristics. In line with these observations, preterm birth, low birth weight and greater infant weight gain were associated with an increased risk of childhood asthma (pooled odds ratio (95% CI): 1.50 (1.2, 1.57), 1.40 (1.18, 1.65) and 1.23 (1.17, 1.28), respectively). ~~These associations were mediated up to 45% by lung function characteristics.~~Mediation analyses suggested that FEV_1, FEV_1/FVC and FEF_{75} may explain 6.3 (2.5, 9.9)% to 44.6 (14.6, 81.1)% of the associations between early growth characteristics and lung function.

Conclusions Results from this individual participant meta-analysis suggest that younger gestational age at birth, smaller size-for-gestational-age at birth, and greater infant weight gain across the full ranges were associated with adaptations in childhood lung function, and that these associations explain to a substantial extent the risk of childhood asthma.

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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 ~~, but might include~~ 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 52 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; assessed until May 29, 2012). In total, 24 cohorts, comprising data on 24,938 children, fulfilled the criteria (~~**Supporting Information:** **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 (~~**Supporting Information:** **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, ~~most of them (n = 21)~~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) (~~**Supporting Information:** **S-table 1**~~) ~~(21-23)~~. If cohorts had collected lung function data at multiple time

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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 (~~**Supporting Information:**~~ **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 started to assess the associations of gestational age and birth weight with lung function separately. 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. 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 these terms multiplicative 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 ~~of the effect estimate~~ was calculated by the formula: 100 x (effect $estimate_{mediator}$ - effect $estimate_{~~model 1~~original model}$)/(effect $estimate_{~~model 1~~original model}$- 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 ~~only~~ significant for gestational age and birth weight SDS in relation to ~~lung function outcomes~~FEV_1, FEV_1/FVC, FEF_{25-75} and FEF_{75} (p-values for interaction <0.01; **Figure 2**, **S-table 9**). ~~Specifically,~~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 (~~**Supporting Information**~~**: 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). ~~Also, the results were similar when we used cohorts with North-Western European subjects only, complete-cases, or when we excluded cohorts that used parental report of early growth characteristics (**Supporting Information: S-table 8)** or did not perform spirometry measurements according to the ATS/ERS guidelines (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): 1.50 (1.2, 1.57), 1.40 (1.18, 1.65) and 1.23 (1.17, 1.28), respectively. ~~The associations of preterm birth and low birth weight attenuated after additional adjustment for FEV_1, FEV_1/FVC or FEF_{75}.~~ Mediation analyses suggested that FEV_1, FEV_1/FVC and FEF_{75} may explain 6.3 (2.5, 9.9)% to 44.6 (14.6, 81.1)%. Specifically, after additional adjustment for FEV_1, FEV_1/FVC or FEF_{75}, the associations of preterm birth with asthma attenuated with -7.3 (-18.8, -0.9)%, -14.4 (-39.6, -2.8)% and -39.0 (-69.3, -3.4)%, respectively. Similarly, the associations of low birth weight with asthma attenuated with -19.0 (-37.3, -11.8)%, -21.6 (-47.3, -11.4)% and -21.6 (-47.3, -11.4)%, respectively (**Table 2**). The strongest mediating effect was observed for FEF_{75} for the association between gestational age and asthma (44.6 (81.1, 14.6)%). ~~Overall, the strongest attenuations towards non-significant were observed after adjustment for FEF_{75} with an up to 45% reduction of the effect estimate (**Table 2**). A similar trend~~Similar trends were ~~was~~ 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 FEF_{25-75} in young adults aged 21 and 31 years (9, 11). The effect of birth weight was independent of preterm birth in both studies. However, studies among children showed conflicting results (12, 13). We observed an association of lower birth weight with lower FEV_1, independent of gestational age at birth. We previously reported that the effect of lower birth weight on asthma was largely explained by gestational age (4). Therefore, although gestational age-adjusted birth weight is associated with lower lung function this seems not related to the risk of clinically manifest childhood asthma.

Previous studies examining associations between infant weight gain and childhood lung function have reported inconsistent results (14-16). Differences might be due to different ages at which spirometry was performed, not taking other weight characteristics into account, such as birth weight or current body mass index, and possible hidden bias due to the use of mL instead of Z-scores for lung function (45). In line with the findings for birth weight, we observed that lower infant weight gain was associated with a lower childhood FEV_1. This association was fully explained by FVC. These results suggest dysanapsis, in which airways remained small in relation to total lung volume as a result of a mismatch between airway and alveolar growth (46). ~~Hence, a lower FEV_1 due to lower birth weight or infant weight can be explained by a lower lung volume.~~ Greater infant weight gain was also associated with a lower FEF_{75}, which is in line with previous studies reporting associations of body mass index or adiposity with reduced expiratory flows and asthma (47, 48). A suggested mechanism is leptin release from adipose tissue, which might have pro-

inflammatory effects in the airways (49), or a direct effect of increased body weight on lung function (50). However, our analyses were adjusted for childhood body mass index. Further studies are needed to explore whether the associations of infant weight gain with end-expiratory flows are explained by specific adiposity-related measures or biomarkers.

To the best of our knowledge this is the first study that examines the individual and combined associations of the main early growth characteristics with childhood lung function outcomes, and whether lung function adaptations explain the previously reported associations of early growth characteristics with childhood asthma. ~~showing associations of all early growth characteristics with lung function and subsequent risk of 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. 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. ~~More information is needed on the specific maternal and childhood exposures, which lead to the specific early~~

~~growth patterns and affect the risk of later life respiratory diseases.~~ 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.

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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).

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)**	0.95 (0.93, 0.97)**	*-9.8% (-16.4, -5.3)***	0.95 (0.93, 0.97)**	*-13.5% (-21.0, -7.3)***	0.97 (0.94, 1.00)	*-44.6% (-81.1, -14.6)***
Preterm birth (<37 weeks)	1.34 (1.15, 1.57)**	1.30 (1.11, 1.53)**	*-7.3% (-18.8, 0.9)**	1.27 (1.08, 1.49)**	*-14.4% (-39.6, 2.8)**	1.20 (0.99, 1.47)	*-39.0% (-69.3, 3.4)**
Birth weight (500 grams)	0.94 (0.90, 0.97)**	0.95 (0.91, 0.99)*	*-18.9% (-37.0, -11.2)***	0.94 (0.90, 0.98)**	*-10.5% (-21.9, -3.4)***	0.96 (0.92, 1.02)	*-17.8 (-50.6, -9.0)***
Low birth weight (<2,500 grams)	1.32 (1.07, 1.62)**	1.25 (1.02, 1.54)*	*-19.0% (-37.3, -11.8)***	1.23 (0.99, 1.52)	*-21.6% (-47.3, -11.4)***	1.05 (0.81, 1.36)	*-82.5% (-149, 10.3)*
Birth weight (SDS)	0.98 (0.94, 1.03)	1.00 (0.96, 1.05)	*-83.8% (-950, 825)*	0.98 (0.94, 1.03)	*-14.0% (-247, 281)*	0.99 (0.93, 1.04)	*-15.8% (-158, 169)*
Small for gestational age (<10th percentile)	1.18 (1.01, 1.37)*	1.13 (0.97, 1.32)	*-28.9% (-253, 108)*	1.16 (0.99, 1.36)	*-18.8% (-123, 164)*	1.20 (1.00, 1.44)	*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)**	1.28 (1.22, 1.35)**	*6.5% (2.3, 9.9)***	1.25 (1.18, 1.31)**	*-8.4% (-16.1, -3.2)***	1.13 (1.06, 1.20)**	*-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 $(100 \times (OR_{mediator} - OR_{model\ 1})/(OR_{model\ 1} - 1))$, 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).~~