

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

Herman T. den Dekker, MD,^{a,b,c} Agnes M. M. Sonnenschein-van der Voort, MSc, PhD,^{a,b,c} Johan C. de Jongste, MD, PhD,^a Isabella Annessi-Maesano, MD, PhD,^{d,e} S. Hasan Arshad, DM,^{f,g,h} Henrique Barros, MD, PhD,ⁱ Caroline S. Beardsmore, PhD,^j Hans Bisgaard, MD, DMSci,^{k,l} Sofia Correia Phar, MD, MSc,ⁱ Leone Craig, PhD, MSc, BSc,^{m,n} Graham Devereux, MD, PhD,ⁿ C. Kors van der Ent, MD, PhD,^o Ana Esplugues, PhD,^{p,q,r} Maria P. Fantini, MD,^s Claudia Flexeder, MSc,^t Urs Frey, MD, PhD,^u Francesco Forastiere, MD, PhD,^v Ulrike Gehring, PhD,^w Davide Gori, MD,^s Anne C. van der Gugten, MD, PhD,^o A. John Henderson, MD, PhD,^x Barbara Heude, PhD,^{y,z} Jesús Ibarluzea, PhD,^{r,aa} Hazel M. Inskip, MSc, PhD,^{bb} Thomas Keil, MD, MScPH,^{cc,dd} Manolis Kogevinas, MD, PhD,^{r,ee,ff,gg} Eskil Kreiner-Møller, MD,^{k,l} Claudia E. Kuehni, MD,^{hh} Susanne Lau, MD, PhD,ⁱⁱ Erik Melen, MD, PhD,^{jj} Monique Mommers, PhD,^{kk} Eva Morales, MD, PhD,^{r,ff,gg,ii} John Penders, PhD,^{kk} Katy C. Pike, MD, PhD,^g Daniela Porta, MSc,^v Irwin K. Reiss, MD, PhD,^{mm} Graham Roberts, DM,^{f,g,h} Anne Schmidt, MD,^{u,nn} Erica S. Schultz, MD,^{jj} Holger Schulz, MD,^t Jordi Sunyer, MD, PhD,^{r,ff,gg,ii} Matias Torrent, MD, PhD,^{oo} Maria Vassilaki, MD, MPH, PhD,^{pp} Alet H. Wijga, PhD,^{qq} Carlos Zabaleta, MD,^{rr} Vincent W. V. Jaddoe, MD, PhD,^{b,c,ss} and Liesbeth Duijts, MD, PhD^{a,b,mm}

Rotterdam, Utrecht, Maastricht, and Bilthoven, The Netherlands, Paris and Villejuif, France, Newport, Southampton, Leicester, Aberdeen, and Bristol, United Kingdom, Porto, Portugal, Copenhagen and Gentofte, Denmark, Valencia, Madrid, San Sebastian, Barcelona, and Balearic Islands, Spain, Bologna and Rome, Italy, Neuherberg, Berlin, and Wurzberg, Germany, Basel, Bern, and Stockholm, Switzerland, and Athens and Crete, Greece

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

Objective: We sought 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

From ^athe Department of Pediatrics, Division of Respiratory Medicine, ^bthe Department of Epidemiology, ^cthe Generation R Study Group, ^{mm}the Department of Pediatrics, Division of Neonatology, and ^{ss}the Department of Pediatrics, Erasmus University Medical Center, Rotterdam; ^dEPAR, UMR-S 707 INSERM Paris; ^eEPAR, UMR-S 707, Université Pierre et Marie Curie Paris; ^fthe David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight; ^gthe Faculty of Medicine, University of Southampton; ^hthe NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust; ⁱthe Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School; ^jthe Division of Child Health, Department of Infection, Immunity & Inflammation, University of Leicester and Institute for Lung Health, Leicester; ^kthe Copenhagen Prospective Studies on Asthma in Childhood (COPSAC2000), Faculty of Health Sciences, University of Copenhagen; ^lthe Danish Pediatric Asthma Center, Copenhagen University Hospital, Gentofte; ^mthe Public Health Nutrition Research Group and ⁿApplied Health Sciences, University of Aberdeen; ^othe Department of Pediatric Pulmonology, Wilhelmina Children's Hospital, University Medical Center Utrecht; ^pthe Faculty of Nursing and Chiropody, Valencia; ^qFISABIO, Valencia; ^rCIBER Epidemiología y Salud Pública (CIBERESP), Madrid; ^sthe Department of Biomedical and Neuromotor Sciences, University of Bologna; ^tHelmholtz Zentrum München, Institute of Epidemiology I, Neuherberg; ^uthe University Children's Hospital Basel (UKBB), University of Basel; ^vthe Department of Epidemiology, Lazio Regional Health Service, Rome; ^wthe Institute for Risk Assessment Sciences, Utrecht University; ^xthe School of Social and Community Medicine, University of Bristol; ^yCESP Inserm, UMR-S 1018, Team 10, Villejuif; ^zUniversité Paris-Sud, UMR-S 1018 Team 10, Villejuif; ^{aa}the Public Health Division of Gipuzkoa, San Sebastian; ^{bb}the MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital; ^{cc}the Institute of Social Medicine, Epidemiology and Health Economics, Charité University Medical Center, Berlin; ^{dd}the Institute for Clinical Epidemiology and Biometry, University of Würzburg; ^{ee}the National School of Public Health, Athens; ^{ff}the Centre for Research in Environmental Epidemiology (CREAL), Barcelona; ^{gg}Hospital del Mar Medical Research Institute (IMIM), Barcelona; ^{hh}the Institute of Social and Preventive Medicine (ISPM), University of Bern; ⁱⁱthe Department of Pediatric Pneumology and Immunology, Charité University Medical Centre, Berlin; ^{jj}the Institute of Environmental Medicine, Karolinska Institutet, Stockholm, and Sach's Children Hospital, Stockholm; ^{kk}the Department of Epidemiology, CAPHRI School for

Public Health and Primary Care, Maastricht University; ^{ll}Universitat Pompeu Fabra (UPF), Barcelona; ⁿⁿthe Division of Respiratory Medicine, Department of Pediatrics, Inselspital, University of Bern; ^{oo}IB-SALUT, Area de Salut de Menorca, Balearic Islands; ^{pp}the Department of Social Medicine, School of Medicine, University of Crete; ^{qq}the Centre for Nutrition, Prevention and Health Services, National Institute for Public Health and the Environment (RIVM), Bilthoven; and ^{rr}Nuestra Señora de la Antigua Hospital, OSAKIDETZA Basque Health Service, San Sebastian.

Disclosure of potential conflict of interest: I. Annessi-Maesano has received a grant from the FP7 MeDALL project (Mechanisms of the Development of ALLergy, FP7 no. 261357) and has board memberships with the *European Respiratory Journal*, *Clinical and Experimental Allergy*, the *International Journal of Tuberculosis and Lung Disease*, *BMC Public Health*, the *European Respiratory Review*, *Multidisciplinary Respiratory Medicine*, *Therapeutic Advances in Respiratory Disease*, *Multidisciplinary Review Frontiers in Medicine*, and *La lettre du pneumologue*. S. H. Arshad has received grants from the National Institutes of Health (NIH) and the Medical Research Council and has consultant arrangements with Merck & Co. U. Frey and A. Schmidt have received grants from the Swiss National Science Foundation. A. J. Henderson has received grants from the Medical Research Council and the Wellcome Trust. H. M. Inskip has received grants from the UK Medical Research Council, the British Heart Foundation, Asthma Research UK, the British Lung Foundation, the Food Standards Agency, and the Dunhill Medical Trust; is deputy chair of a grant-funding board for the UK Medical Research Council; and has her employment funded by the Medical Research Council. S. Lau has received grants from the German Research Foundation, Allergopharma, and Symbiopharma and has consultant arrangements with Merck. K. C. Pike has received grants from the Food Standards Agency and the British Lung Foundation. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 19, 2015; revised August 11, 2015; accepted for publication August 15, 2015.

Corresponding author: Liesbeth Duijts, MD, PhD, Erasmus University Medical Center Rotterdam, Sp-3435, PO Box 2060, 3000 CB Rotterdam, The Netherlands. E-mail: l.duijts@erasmusmc.nl.

0091-6749/\$36.00

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2015.08.050>

(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 FEV₁, FEV₁/forced vital capacity (FVC) ratio, and forced expiratory volume after exhaling 75% of vital capacity (FEF₇₅), whereas those born with a smaller size for gestational age at birth had a lower FEV₁ but higher FEV₁/FVC ratio ($P < .05$). Greater infant weight gain was associated with higher FEV₁ but lower FEV₁/FVC ratio and FEF₇₅ in childhood ($P < .05$). 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, 1.34 [95% CI, 1.15-1.57], 1.32 [95% CI, 1.07-1.62], and 1.27 [95% CI, 1.21-1.34], respectively). Mediation analyses suggested that FEV₁, FEV₁/FVC ratio, and FEF₇₅ might explain 7% (95% CI, 2% to 10%) to 45% (95% CI, 15% to 81%) of the associations between early growth characteristics and asthma. **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 the risk of childhood asthma to a substantial extent. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: Preterm birth, low birth weight, infant growth, asthma, lung function, children, meta-analysis

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 Moreover, 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 taking part 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 seemed to be largely explained by gestational age at birth.⁴ The mechanisms underlying the associations of early growth characteristics with childhood asthma are not yet known.

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

Abbreviations used

ATS:	American Thoracic Society
ERS:	European Respiratory Society
FEF ₂₅₋₇₅ :	Forced midexpiratory flow
FEF ₇₅ :	Forced expiratory flow after exhaling 75% of the vital capacity
FVC:	Forced vital capacity
GLI:	Global Lung Initiative
SDS:	SD score

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 the risk of childhood asthma.

METHODS

Data sources

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.birthcohorts.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 (see supplemental information on [Methods](#) and [Fig E1](#) in this article's Online Repository at www.jacionline.org).

Information about gestational age and weight at birth and weight in the first year of life was obtained by means of measurements, medical registries, or parental questionnaires (see [Table E1](#) in this article's Online Repository at www.jacionline.org). We created gestational age-adjusted birth weight SD scores (SDSs) 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 2 measurements. SDSs for age-specific infant weight gain were derived by using intracohort means and SDs.¹⁸ Cohort-specific growth characteristics are provided in [Table E2](#) in this article's Online Repository at www.jacionline.org.

All cohorts obtained lung function measurements by using spirometry, of which 22 were according to the recent guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS)¹⁹⁻²¹ and 2 were according to earlier guidelines of the ATS²² or ERS and European Coal and Steel Community²³ (see [Table E1](#)). 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), FEV₁, forced midexpiratory flow (FEF₂₅₋₇₅), and forced expiratory flow after exhaling 75% of vital capacity (FEF₇₅). We mainly focused on FEV₁, FEV₁/FVC ratio, and FEF₇₅, which reflect reduced airway patency in patients with obstructive lung diseases, such as asthma or bronchopulmonary dysplasia, associated with preterm birth or low birth weight.^{24,25} All lung function variables were converted into sex-, height-, age-, and ethnicity (white vs nonwhite)-adjusted z scores based on Global Lung Initiative (GLI) reference values.²⁶ Asthma (yes/no) was defined as ever having 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 (22 cohorts)²⁷ at the age of spirometry (see [Table E1](#)). Cohort-specific

characteristics of lung function measurements and asthma are provided in Table E3 in this article's Online Repository at www.jacionline.org.

We included covariates based on known associations with childhood lung function from previous studies.^{28,29} Information on covariates was mainly assessed by using questionnaires (see Table E1). 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, breast-feeding, lower respiratory tract infections in the first 2 years of life, eczema, inhalant allergies, and body mass index at the moment of lung function measurement. Cohort-specific characteristics of all covariates are given in Tables E4 and E5 in this article's Online Repository at www.jacionline.org. More detailed information on the Methods is given in this article's Online Repository.

Statistical analysis

First, we conducted 1-stage random effects regression analyses to study the separate and combined associations of gestational age, birth weight, and infant weight gain with FEV₁, FVC, FEV₁/FVC ratio, forced midexpiratory flow (FEF₂₅₋₇₅), and FEF₇₅. 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 SDSs. 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 nonlinear 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 effects 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 values) from the per-cohort effect estimates were calculated. We tested for heterogeneity between effect estimates by using *I*² values.^{31,32} For all analyses, the first model was adjusted for child's sex (crude model), and 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. Because we used Northern European reference curves for birth weight SDSs, we performed a sensitivity analysis to explore whether the associations were different in Northwestern 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 in strata of children aged less than 11 years and 11 years or older.³³ We also performed a complete case sensitivity analysis to explore any differences between complete and noncomplete 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 effects 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 (FEV₁, FVC, FEV₁/FVC ratio, FEF₂₅₋₇₅, and FEF₇₅) 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 using the following formula:

$$100 \times (\text{Effect estimate}_{\text{mediator}} - \text{Effect estimate}_{\text{original model}}) / (\text{Effect estimate}_{\text{original model}} - 1).$$

A 95% CI for the percentage change of the effect estimate was calculated by using a bootstrap method with 1000 resamplings.³⁴⁻³⁶

For all analyses, missing values in covariates were used as an additional group in the categorical variables to prevent exclusion of noncomplete cases.

Statistical analyses were performed with R version 3.0.0 (libraries *rmeta* and *metafor*, R Foundation for Statistical Computing) and Comprehensive Meta-Analysis (Biostat, Englewood, NJ) software.

RESULTS

Subjects' characteristics

Information about the main characteristics of the cohorts are given in Table 1. Detailed information about determinants, outcomes, and covariates is given in Tables E1 to E5. Of all participants, 8.2% (*n* = 2053) were born preterm (<37 weeks of gestational age), and 4.8% (*n* = 1191) were born with a low birth weight (<2500 g). The mean age at which spirometric assessments were performed was 8.5 years (range, 3.9-19.1 years). The proportion of children aged 11 years or older was 11.9% (*n* = 2972).

Early growth measures and lung function outcomes

Results from the 1-stage random effects models showed that younger gestational age at birth was, across the full range, associated with lower FEV₁, FEV₁/FVC ratio, and FEF₇₅ in childhood (*P* for trend < .01; Fig 1, A-C). A smaller size for gestational age at birth across the full range was associated with lower FEV₁ and higher FEV₁/FVC ratio (*P* for trend < .01; Fig 1, D and E). Small size for gestational age at birth was not associated with FEF₇₅ (Fig 1, F). Greater infant weight gain was associated with a higher FEV₁ but a lower FEV₁/FVC ratio and FEF₇₅ (*P* for trend < .01; Fig 1, G-I). Most associations showed a linear trend, except for the associations of birth weight with FEV₁/FVC ratio and infant weight gain with FEV₁ and FEV₁/FVC ratio, which were nonlinear (Fig 1, E, G, and 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 SDSs in relation to FEV₁, FEV₁/FVC ratio, FEF₂₅₋₇₅, and FEF₇₅ (*P* for interaction < .01; Fig 2 and see Table E9 in this article's Online Repository at www.jacionline.org). Stratified analyses showed that a lower birth weight was associated with lower FEV₁ and FEV₁/FVC ratio among children born after 32 weeks only, whereas higher birth weight was associated with FEF₇₅ only among term-born children (*P* for strata < .05).

No differences in results were observed when we used 2-stage random effects models of combined effect estimates (see Tables E6 and E7 in this article's Online Repository at www.jacionline.org). Also, the results from the sensitivity analyses showed similar results when we used cohorts with Northwestern European subjects only, when we excluded cohorts that did not perform spirometric measurements according to the recent ATS/ERS guidelines, when we performed stratified analyses for children aged less than 11 years or 11 years or greater (see Table E8 in this article's Online Repository at www.jacionline.org), or when we excluded cohorts that used parental report of early growth characteristics (data not shown).

Fig 3 shows that compared with term-born children, those born preterm had a lower FEV₁, FEV₁/FVC ratio, and FEF₇₅ (pooled *z* score, -0.20 [95% CI, -0.26 to -0.14], -0.15 [95% CI, -0.21 to -0.09], and -0.19 [95% CI, -0.27 to -0.11], respectively). Also, compared with children of normal birth

TABLE I. Characteristics of participating cohorts

Cohort name (country)	No.	Birth years	Gestational age at birth (wk), median (5% to 95% range)	Birth weight (g), mean (SD)	FVC, mean z score (SD)	FEV ₁ , mean z score (SD)	FEV ₁ /FVC ratio, mean z score (SD)	FEF ₂₅₋₇₅ , mean z score (SD)	FEF ₇₅ , mean z score (SD)	Childhood asthma (yes)
ALSPAC (United Kingdom)	6873	1991-1992	39.5 (1.9)	3424 (543)	0.49 (1.28)	0.44 (1.17)	-0.07 (1.15)	0.04 (1.08)	0.30 (1.06)	17.9 (1231)
BAMSE (Sweden)	2042	1994-1996	39.9 (1.8)	3537 (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)	3367 (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)	3335 (457)	-1.76 (0.82)	-1.04 (0.90)	0.51 (1.65)	0.45 (1.00)	—	6.0 (13)
COPSAC ₂₀₀₀ (Denmark)	314	1998-2001	40.0 (1.6)	3529 (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)	3284 (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)	3314 (530)	0.06 (0.76)	-0.01 (0.88)	-0.15 (0.97)	-0.30 (0.90)	—	6.6 (30)
Generation R (The Netherlands)	1927	2002-2006	39.7 (1.9)	3392 (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)	1562	2005-2006	38.4 (2.1)	3152 (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	—	3493 (479)	—	0.02 (0.92)	—	—	—	5.9 (49)
INMA Gipuzkoa (Spain)	277	2006-2008	39.7 (1.4)	3284 (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)	3200 (493)	0.01 (1.13)	-0.16 (1.07)	-0.24 (1.19)	-0.42 (1.29)	-0.06 (1.32)	4.9 (18)
INMA Sabadell (Spain)	408	2004-2007	39.8 (1.3)	3261 (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)	3227 (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)	1030	1989-1990	39.9 (1.5)	3411 (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)	3552 (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)	3373 (599)	-0.33 (1.11)	-0.38 (1.12)	-0.76 (0.90)	-0.62 (1.01)	—	37.2 (108)
Leicester 1998 (United Kingdom)	1476	1993-1997	39.2 (2.0)	3314 (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)	3414 (460)	-0.06 (0.97)	0.24 (1.00)	0.41 (1.00)	1.15 (0.14)	—	5.0 (32)
PIAMA (The Netherlands)	1767	1996-1997	39.9 (1.7)	3526 (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)	3175 (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)	3488 (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)	3447 (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)	3553 (499)	0.16 (1.11)	0.46 (1.14)	0.31 (0.93)	-0.04 (1.23)	0.12 (1.07)	9.3 (55)

Values are means (SDs) and percentages (absolute numbers) for information on asthma. Additional information on data collection (see [Table E1](#)), determinants (see [Table E2](#)), outcomes (see [Table E3](#)), and maternal and child-related covariates (see [Tables E4 and E5](#)) is provided in this article's Online Repository.

No., Number of participants with information on at least gestational age or birth weight and a lung function outcome.

weight, those with low birth weight had lower FEV₁, FEV₁/FVC ratio, and FEF₇₅ (-0.29 [95% CI, -0.38 to -0.21] and -0.16 [95% CI, -0.25 to -0.08], and -0.17 [95% CI, -0.26 to -0.08], respectively) independent of gestational age. Results of associations of growth characteristics with all lung function outcomes, including FVC and FEF₂₅₋₇₅, are provided in [Tables E6 to E8](#).

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 (odds ratio, 1.34 [95% CI, 1.15-1.57], 1.32 [95% CI, 1.07-1.62], and 1.27 [95% CI, 1.21-1.34], respectively). Mediation analyses suggested that FEV₁, FEV₁/FVC ratio, and FEF₇₅ might explain 7% (95% CI, 2% to 10%) to 45% (95% CI, 15% to 81%) of the

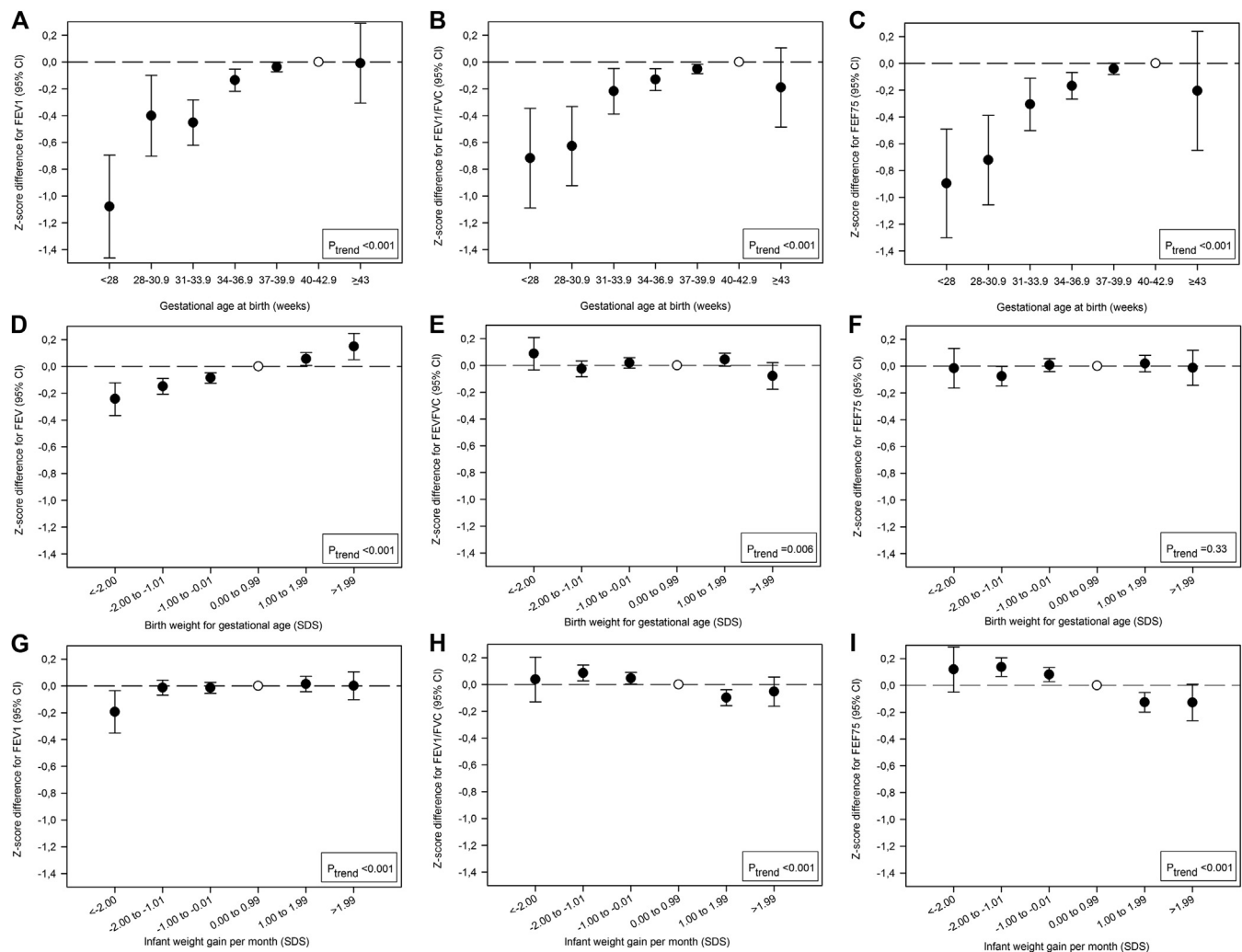


FIG 1. Associations of gestational age, birth weight, and infant weight gain with FEV₁, FEV₁/FVC ratio, and FEF₇₅. Values represent z score differences (95% CIs) from multilevel random effects models for the associations of gestational age at birth (A-C), gestational age-adjusted birth weight (SDS; D-F), and infant weight gain (SDS; G-I) with lung function outcomes compared with reference groups. Reference groups were 40 to 42.9 weeks of gestational age, 0 to 0.99 birth weight SDS, and 0.00 to 0.99 infant weight gain SDS (largest groups) and represented by an *open bullet*. Models are adjusted for maternal education, smoking during pregnancy, smoking during childhood, atopy, asthma, child's sex, number of siblings, day care attendance, breast-feeding, 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.

associations between early growth characteristics and lung function. Specifically, after additional adjustment for FEV₁, FEV₁/FVC ratio, or FEF₇₅, the associations of preterm birth with asthma attenuated, with -7% (95% CI, -19% to -1%), -14% (95% CI, -40% to -3%), and -39% (95% CI, -69% to -3%), respectively. Similarly, the associations of low birth weight with asthma attenuated, with -19% (95% CI, -37% to -12%), -22% (95% CI, -47% to -11%), and -22% (95% CI, -47% to -11%), respectively (Table II). The strongest mediating effect was observed for FEF₇₅ for the association between gestational age and asthma (-45% [95% CI, -81% to -15%]). Similar trends were observed for greater weight gain, although the associations did not attenuate into nonsignificance.

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 FEV₁. The positive associations of birth weight and infant weight gain with FVC were larger than the positive associations of birth weight and infant weight gain with FEV₁. This combination resulted in associations of higher birth weight and infant weight gain with lower FEV₁/FVC ratio. Also, a lower gestational age at birth was associated with a lower FEF₇₅ in childhood, suggesting persistent reduction in small-airways patency. A greater infant weight gain was associated with lower FEF₇₅. Remarkably, these associations were present across the full range of early growth and not restricted to clinically

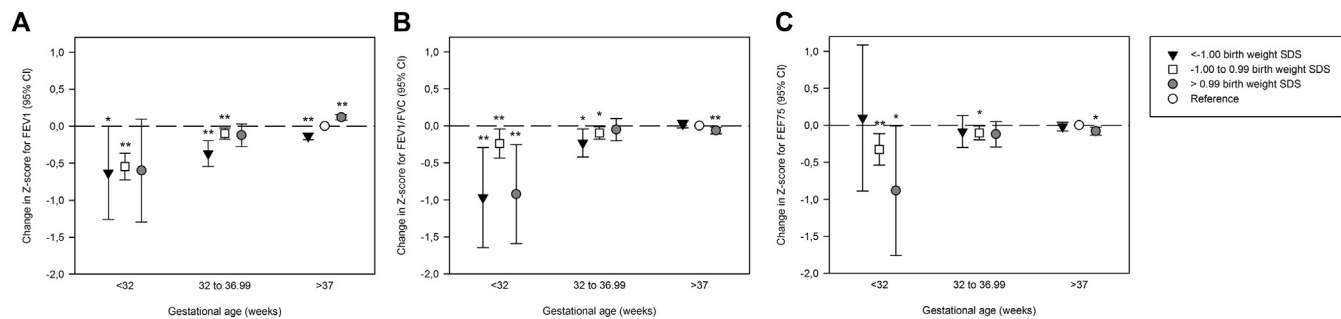


FIG 2. Combined associations of gestational age and birth weight with FEV₁ (A), FEV₁/FVC (B), and FEF₇₅ (C). Values are z score differences (95% CI) from multilevel models for the combined associations of gestational age at birth and birth weight SDS with lung function outcomes compared with reference groups. Strata of gestational age (<32, 32-36.99, >37 weeks) and birth weight (<-1.00, -1.00-0.99, >0.99) were combined. Reference groups were greater than 37 weeks of gestational age with -1.00 to 0.99 birth weight SDS (largest group) and represented by a bullet. Models are adjusted for maternal education, smoking during pregnancy, smoking during childhood, atopy, asthma, child's sex, number of siblings, day care attendance, breast-feeding, respiratory tract infections, childhood eczema, inhalant allergies, and body mass index. **P* < .05 and ***P* < .01.

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 FEV₁ and FEV₁/FVC ratio. The associations of early growth characteristics with childhood asthma were partly explained by lung function adaptations.

Whereas lung growth continues until early adulthood, the most rapid development of the airways and alveoli occurs in early life.³⁷ Developmental adaptations in fetal life and infancy caused by early-life adverse exposures might result in impaired lung growth, with smaller airways, decreased lung volume, and subsequently an increased risk of bronchopulmonary dysplasia, asthma, or chronic obstructive pulmonary disease.^{9,14,38} Previous studies suggest that children with asthma already have 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 decrease in FEV₁ from that point onward will be accelerated by any additional adverse exposures.⁴¹ Thus lung function during the life course 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 FEV₁, even after taking FVC into account, and a lower FEF₇₅ 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 adaptations 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 FEV₁ at ages 5 up to 23 years.⁴² These and other studies suggest that preterm birth has adverse effects on lung function that persist into adulthood.⁴²⁻⁴⁴

In the present study a lower birth weight was associated with lower FEV₁ 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 FEV₁ in adults (range, 19-70 years).¹⁰ The authors reported a modest positive association between FEV₁ and birth weight. Two recent studies from longitudinal birth cohorts among adults reported strong positive associations of birth weight with FEV₁ and FEF₂₅₋₇₅ 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 FEV₁ 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 caused by the use of milliliters 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 FEV₁ (*P* for trend < .01). Alternatively, greater infant weight gain was associated with a higher childhood FEV₁. This association was fully explained by FVC. These results suggest dysanapsis, in which FVC is higher relative to FEV₁ as a result of possible disproportional growth of lung volume and airways. Dysanapsis is commonly used to indicate relatively narrow airways for lung volume, but here a relatively higher lung volume for airways applies.⁴⁶ Greater infant weight gain was also associated with a lower FEF₇₅, 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 proinflammatory 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

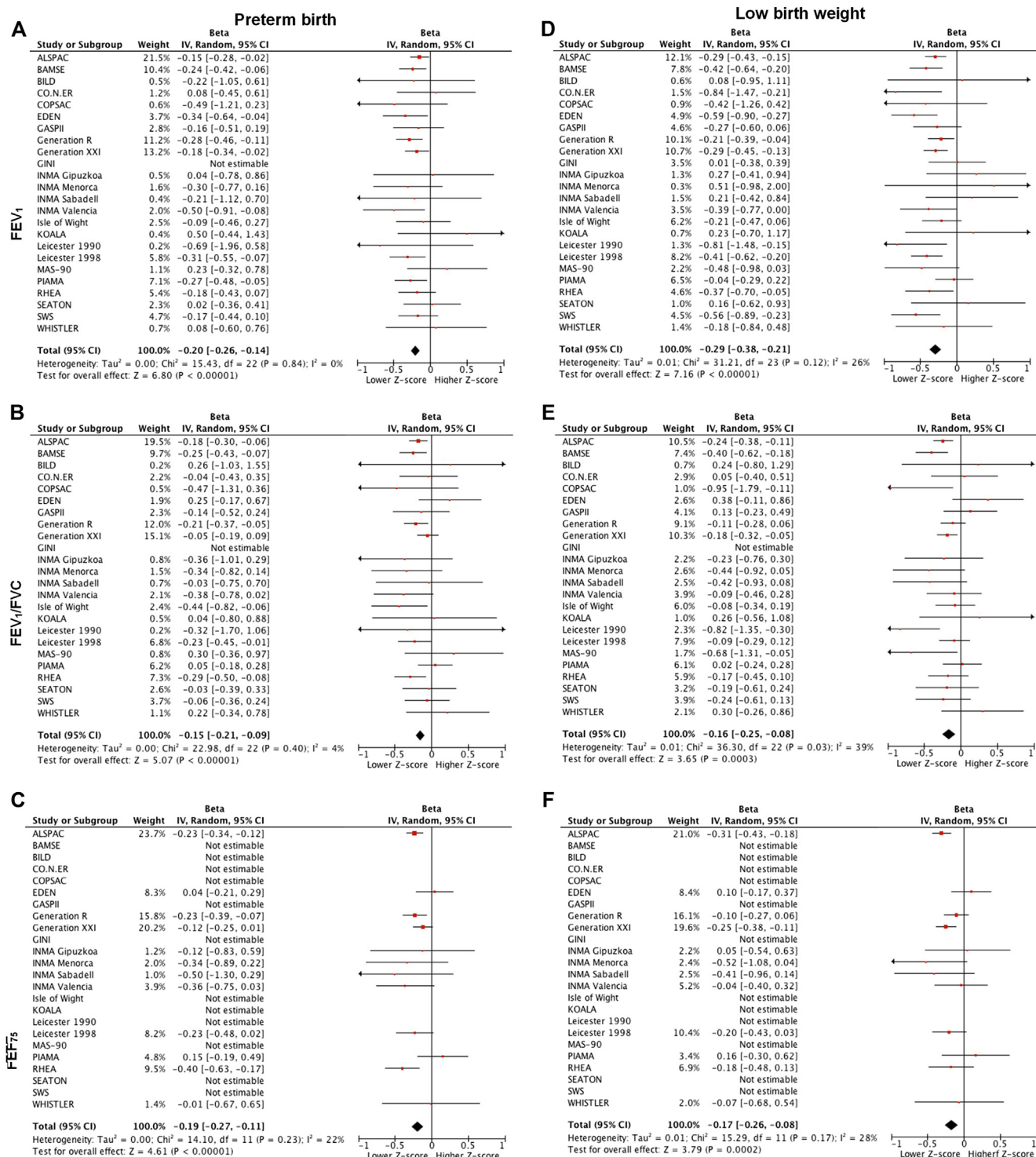


FIG 3. Forest plots of associations between preterm birth and low birth weight with FEV₁, FEV₁/FVC ratio, and FEF₇₅. Values are pooled z score differences (95% CI) from a random effects meta-analysis for associations of preterm birth versus term birth (A-C) and low birth weight versus normal birth weight (D-F) with lung function outcomes. Lung function outcomes are FEV₁, FEV₁/FVC ratio, and FEF₇₅. Models are adjusted for maternal education, smoking during pregnancy, smoking during childhood, atopy, asthma, child's sex, number of siblings, day care attendance, breast-feeding, respiratory tract infections, childhood eczema, inhalant allergies, and body mass index. Low birth weight was adjusted for gestational age.

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 examining the individual and combined associations of the main early growth characteristics with childhood lung function outcomes

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

	Risk of childhood asthma						
	Full model, odds ratio (95% CI)	Full model + FEV ₁ , odds ratio (95% CI)	Percentage change in odds ratio (95% CI)	Full model + FEV ₁ /FVC ratio, odds ratio (95% CI)	Percentage change in odds ratio (95% CI)	Full model + FEF ₇₅ , odds ratio (95% CI)	Percentage change in odds ratio (95% CI)
Gestational age (wk)	0.94 (0.92 to 0.97), [†] n = 15,019	0.95 (0.93 to 0.97), [†] n = 14,832	−9.8% (−16.4% to −5.3%), [†]	0.95 (0.93 to 0.97), [†] n = 14,017	−13.5% (−21.0% to −7.3%), [†]	0.97 (0.94 to 1.00), n = 9,177	−44.6% (−81.1% to −14.6%), [†]
Preterm birth (<37 wk)	1.34 (1.15 to 1.57), [†] n = 15,019	1.30 (1.11 to 1.53), [†] n = 14,832	−7.3% (−18.8% to −0.9%), [*]	1.27 (1.08 to 1.49), [†] n = 14,017	−14.4% (−39.6% to −2.8%), [*]	1.20 (0.99 to 1.47), n = 9,177	−39.0% (−69.3% to −3.4%), [*]
Birth weight (500 g)	0.94 (0.90 to 0.97), [†] n = 15,547	0.95 (0.91 to 0.99), [*] n = 15,360	−18.9% (−37.0% to −11.2%), [†]	0.94 (0.90 to 0.98), [†] n = 13,985	−10.5% (−21.9% to −3.4%), [†]	0.96 (0.92 to 1.02), n = 9,135	−17.8% (−50.6% to −9.0%), [†]
Low birth weight (<2,500 g)	1.32 (1.07 to 1.62), [†] n = 15,547	1.25 (1.02 to 1.54), [*] n = 15,360	−19.0% (−37.3% to −11.8%), [†]	1.23 (0.99 to 1.52), n = 13,985	−21.6% (−47.3% to −11.4%), [†]	1.05 (0.81 to 1.36), n = 9,135	−82.5% (−149% to 10.3%)
Birth weight (SDS)	0.98 (0.94 to 1.03), n = 14,947	1.00 (0.96 to 1.05), n = 14,760	−83.8% (−950% to 825%)	0.98 (0.94 to 1.03), n = 13,946	−14.0% (−247% to 281%)	0.99 (0.93 to 1.04), n = 9,122	−15.8% (−158% to 169%)
Small for gestational age (<10th percentile)	1.18 (1.01 to 1.37), [*] n = 14,947	1.13 (0.97 to 1.32), n = 14,760	−28.9% (−253% to 108%)	1.16 (0.99 to 1.36), n = 13,946	−18.8% (−123% to 164%)	1.20 (1.00 to 1.44), n = 9,122	10.2% (−8.3% to 26.2%)
Infant weight gain in first year (SDS) adjusted for gestational age and weight at birth	1.27 (1.21 to 1.34), [†] n = 12,511	1.28 (1.22 to 1.35), [†] n = 12,511	6.5% (2.3% to 9.9%), [†]	1.25 (1.18 to 1.31), [†] n = 11,780	−8.4% (−16.1% to −3.2%), [†]	1.13 (1.06 to 1.20), [†] n = 7,969	−60.8% (−115% to 39.5%)

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

* $P < .05$.

[†] $P < .01$.

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 low birth weight present across the full range. This observation might have important population effects because 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 adaptations in airway caliber. We observed strong effect estimates with wide CIs, which limit precision. Therefore these mediation effects should be interpreted carefully. The effect estimates for the observed associations could be considered small and without clinical relevance for subjects. However, the associations might be important from an etiologic respiratory developmental perspective and might 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 FEV₁.³³ 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 might 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. Because 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 using parental questionnaires adapted from the International Study on Asthma and Allergy in Childhood questionnaire.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 epidemiologic 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 might have influenced our effect estimates. We would expect that asthmatic children who use asthma medication would in general have had 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 subjects, including 31,840 subjects aged less than 20 years, of whom 58% were assessed before and 42% were assessed during a 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 an additional category to prevent exclusion of noncomplete 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 might still be an issue. No information was available about, for example, exposure to environmental microorganisms or asthma severity. Exploring mediation of lung function for the association of early growth characteristics with asthma by 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 using multilevel modeling.⁵² Most of the participating studies 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 onward 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 FEV₁ and FEV₁/FVC ratio. 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 might persistently affect lung function and thereby contribute to the risk of respiratory diseases in later life.

Clinical implications: Early growth characteristics might persistently affect lung function and thereby contribute to the risk of obstructive respiratory diseases in later life.

REFERENCES

- 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.
- 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;28:79-85.
- 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;11:e1001596.
- 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;133:1317-29.
- 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;183:553, author reply 554.
- 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;110:220-7.
- Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* 2004;364:709-21.
- 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;359:61-73.
- 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;62:396-402.
- 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;60:851-8.
- Suresh S, Mamun AA, O'Callaghan M, Sly PD. The impact of birth weight on peak lung function in young adults. *Chest* 2012;142:1603-10.
- 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;128:2400-7.
- Lum S, Hoo AF, Dezateux C, Goetz L, 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;164:2078-84.
- 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;64:228-32.
- 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;46:956-63.
- 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;39:403-10.
- 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;80:756-62.
- Bland JM, Altman DG. Measurement error. *BMJ* 1996;312:1654.
- Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. *Eur Respir J* 2005;26:153-61.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
- 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;26:511-22.
- Standardization of spirometry, 1994 update. American Thoracic Society. *Am J Respir Crit Care Med* 1995;152:1107-36.
- 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;16:5-40.
- Bjerner L. The role of small airway disease in asthma. *Curr Opin Pulm Med* 2014;20:23-30.
- Lipworth B, Manoharan A, Anderson W. Unlocking the quiet zone: the small airway asthma phenotype. *Lancet Respir Med* 2014;2:497-506.
- 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;40:1324-43.
- 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;8:483-91.
- 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;20:383-90.
- 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;67:54-61.
- 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:e60650.
- Normand SL. Meta-analysis: formulating, evaluating, combining, and reporting. *Stat Med* 1999;18:321-59.
- van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002;21:589-624.
- Quanjer PH, Stanojevic S, Stocks J, Hall GL, Prasad KV, Cole TJ, et al. Changes in the FEV₁/FVC ratio during childhood and adolescence: an intercontinental study. *Eur Respir J* 2010;36:1391-9.
- Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;51:1173-82.

35. Cerin E, MacKinnon DP. A commentary on current practice in mediating variable analyses in behavioural nutrition and physical activity. *Public Health Nutr* 2009;12:1182-8.
36. MacKinnon DP, Fairchild AJ. Current directions in mediation analysis. *Curr Dir Psychol Sci* 2009;18:16-20.
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;185:186-91.
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;303:671-5.
39. Bisgaard H, Jensen SM, Bonnelykke K. Interaction between asthma and lung function growth in early life. *Am J Respir Crit Care Med* 2012;185:1183-9.
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;355:1682-9.
41. Stocks J, Sonnappa S. Early life influences on the development of chronic obstructive pulmonary disease. *Ther Adv Respir Dis* 2013;7:161-73.
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;68:760-6.
43. Narang I, Rosenthal M, Cremonesi D, Silverman M, Bush A. Longitudinal evaluation of airway function 21 years after preterm birth. *Am J Respir Crit Care Med* 2008;178:74-80.
44. Vollaeter M, Roksund OD, Eide GE, Markestad T, Halvorsen T. Lung function after preterm birth: development from mid-childhood to adulthood. *Thorax* 2013;68:767-76.
45. Miller MR, Pincock AC. Predicted values: how should we use them? *Thorax* 1988;43:265-7.
46. Ad Hoc Statement Committee ATS. Mechanisms and limits of induced postnatal lung growth. *Am J Respir Crit Care Med* 2004;170:319-43.
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;123:1312-8.e2.
48. Rzehak P, Wijga AH, Keil T, Eller E, Bindeslev-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;131:1528-36.
49. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 2004;89:2548-56.
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;7:325-35.
51. Kotecha S. Lung growth for beginners. *Paediatr Respir Rev* 2000;1:308-13.
52. Cole DA, Preacher KJ. Manifest variable path analysis: potentially serious and misleading consequences due to uncorrected measurement error. *Psychol Methods* 2014;19:300-15.