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

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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

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(age range, 3.9-19.1 years). Second, we explored whether these lung function outcomes mediated the associations of early growth characteristics with childhood asthma.
Results: Children born with a younger gestational age had a lower FEV_1, FEV_1/forced vital capacity (FVC) ratio, and forced expiratory volume after exhaling 75% of vital capacity (FEF_{75}), whereas those born with a smaller size for gestational age at birth had a lower FEV_1 but higher FEV_1/FVC ratio ($P < .05$). Greater infant weight gain was associated with higher FEV_1 but lower FEV_1/FVC ratio and FEF_{75} 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 FEV_1, FEV_1/FVC ratio, and FEF_{75} 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 2016;137:1026-35.)

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 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.

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

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.birthcohortsenrieco.net, www.ga2len.org, and www.birthcohorts.net; accessed until May 29, 2012). In total, 24 cohorts comprising data on 24,938 children fulfilled the criteria (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 ATS[22] or ERS and European Coal and Steel Community[23] (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), FEV_1, forced midexpiratory flow (FEF_{25-75}), and forced expiratory flow after exhaling 75% of vital capacity (FEF_{75}). We mainly focused on FEV_1, FEV_1/FVC ratio, and FEF_{75}, 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 FEV_1, FVC, FEV_1/FVC ratio, forced midexpiratory flow (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 multicolinearity 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 (FEV_1, FVC, FEV_1/FVC ratio, FEF_{25-75}, and FEF_{75}) as potential mediators (mediator model). The difference between the original effect estimates and the effect estimates after additional adjustment for potential mediators was expressed as percentage change. The percentage change was calculated by 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 I. 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 FEV_1, FEV_1/FVC ratio, and FEF_{75} 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 FEV_1 and higher FEV_1/FVC ratio (*P* for trend < .01; Fig 1, *D* and *E*). Small size for gestational age at birth was not associated with FEF_{75} (Fig 1, *F*). Greater infant weight gain was associated with a higher FEV_1 but a lower FEV_1/FVC ratio and FEF_{75} (*P* for trend < .01; Fig 1, *G-I*). Most associations showed a linear trend, except for the associations of birth weight with FEV_1/FVC ratio and infant weight gain with FEV_1 and FEV_1/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 FEV_1, FEV_1/FVC ratio, FEF_{25-75}, and FEF_{75} (*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 FEV_1 and FEV_1/FVC ratio among children born after 32 weeks only, whereas higher birth weight was associated with FEF_{75} 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 FEV_1, FEV_1/FVC ratio, and FEF_{75} (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 FEV_1, FEV_1/FVC ratio, and FEF_{75} (−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 FEF_{25-75}, 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 FEV_1, FEV_1/FVC ratio, and FEF_{75} might explain 7% (95% CI, 2% to 10%) to 45% (95% CI, 15% to 81%) of the

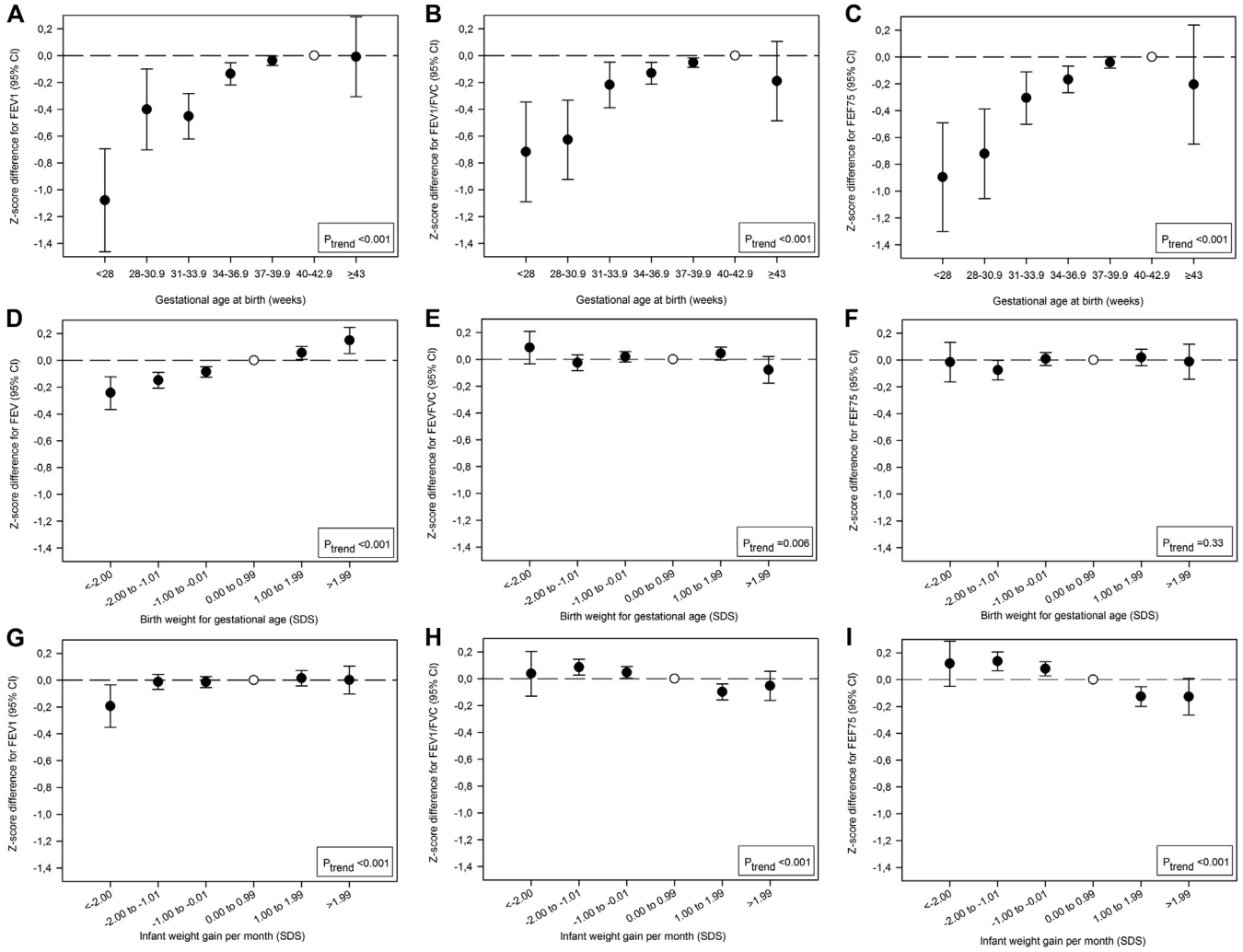

FIG 1. Associations of gestational age, birth weight, and infant weight gain with FEV_1, FEV_1/FVC ratio, and FEF_{75}. Values represent *z* score differences (95% CIs) from multilevel random effects models for the associations of gestational age at birth **(A-C)**, gestational age–adjusted birth weight (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 FEV_1, FEV_1/FVC ratio, or FEF_{75}, 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 −222% (95% CI, −47% to −11%), respectively (Table II). The strongest mediating effect was observed for FEF_{75} 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 FEV_1. 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 FEV_1. This combination resulted in associations of higher birth weight and infant weight gain with lower FEV_1/FVC ratio. Also, a lower gestational age at birth was associated with a lower FEF_{75} in childhood, suggesting persistent reduction in 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

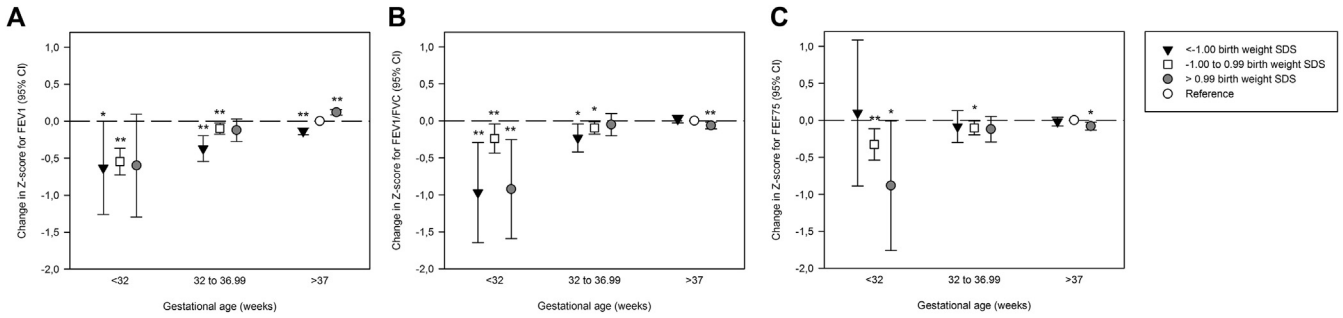

FIG 2. Combined associations of gestational age and birth weight with FEV_1 **(A)**, FEV_1/FVC **(B)**, and FEF_{75} **(C)**. Values are *z* score differences (95% CI) from multilevel models for the combined associations of gestational age at birth and birth weight SDS with lung function outcomes compared 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 FEV_1 and FEV_1/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 FEV_1 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 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 that persist 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 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 FEV_1 (P for trend < .01). Alternatively, greater infant weight gain was associated with a higher childhood FEV_1. This association was fully explained by FVC. These results suggest dysanapsis, in which FVC is higher relative to FEV_1 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 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 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

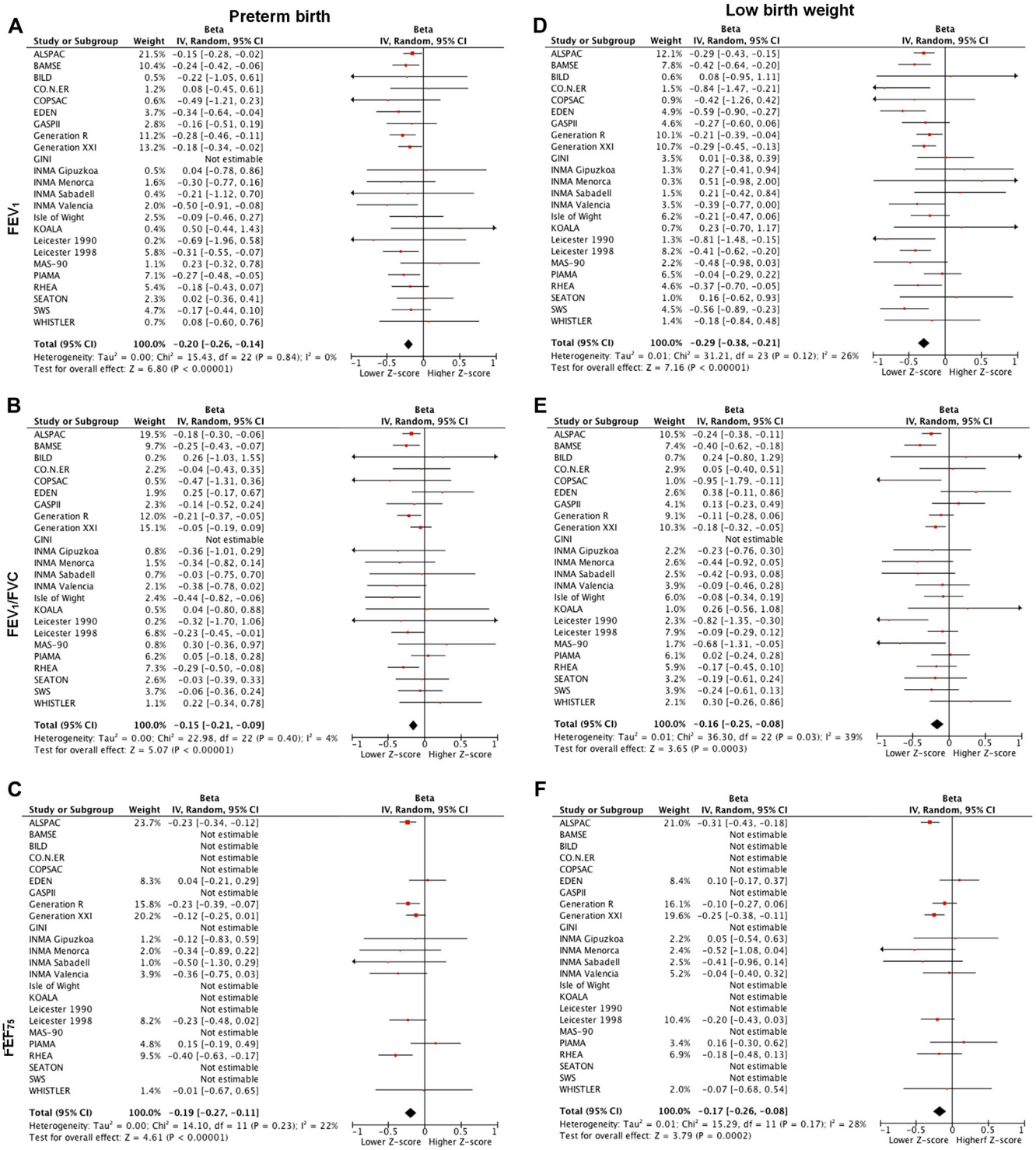

FIG 3. Forest plots of associations between preterm birth and low birth weight with FEV_1, FEV_1/FVC ratio, and FEF_{75}. Values are pooled *z* score differences (95% CI) from a random effects meta-analysis for associations of preterm birth versus term birth **(A-C)** and low birth weight versus normal birth weight **(D-F)** with lung function outcomes. Lung function outcomes are FEV_1, FEV_1/FVC ratio, and FEF_{75}. 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 $(100 \times [OR_{mediator} - OR_{model\ 1}]/[OR_{model\ 1} - 1])$, 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 adaptions 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 FEV_1.[33] Lung and airway growth is proportionally less after start of the pubertal growth spurt,[33] which might explain the similar effect estimates before and after the pubertal growth spurt. Further studies are needed to identify the developmental adaptations of the lungs and immune system that might explain the mediating effect of lung function on the associations of early growth characteristics with childhood asthma. Identification of modifiable exposures 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 FEV_1 and FEV_1/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.

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