

Original Article

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

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ABSTRACT

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

Methods and Materials We used individual participant data of 24,938 children from 24 birth cohorts to examine the associations of gestational age, size-for-gestational-age, and infant weight gain with childhood lung function (forced expiratory volume in 1 second (FEV₁), FEV₁/forced vital capacity (FEV₁/FVC), forced expiratory flow after exhaling 75% of the vital capacity (FEF₇₅)) and risk of doctor-diagnosed asthma (age range 3.9 – 19.1 years).

Second, we used similar models to explore whether these lung function outcomes mediated the associations of early growth characteristics with the risk of childhood asthma.

Results Children born with a younger gestational age had a lower FEV₁, FEV₁/FVC, and FEF₇₅, whereas those born with a smaller size-for-gestational-age at birth had lower FEV₁ but higher FEV₁/FVC (p-values<0.05). Greater infant weight gain was associated with higher FEV₁, but lower FEV₁/FVC and FEF₇₅ in childhood (p-values<0.05). All associations were present across the full ranges and independent of other early life growth characteristics. In line with these observations, preterm birth, low birth weight and greater infant weight gain were associated with an increased risk of childhood asthma (pooled odds ratio (95% CI):

1.50 (1.2, 1.57), 1.40 (1.18, 1.65) and 1.23 (1.17, 1.28), respectively). ~~These associations were mediated up to 45% by lung function characteristics. Mediation analyses suggested that FEV₁, FEV₁/FVC and FEF₇₅ may explain 6.3 (2.5, 9.9)% to 44.6 (14.6, 81.1)% of the associations between early growth characteristics and lung function.~~

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

29 **INTRODUCTION**

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

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

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

58

59 **METHODS**

60

61 **Sources of data**

62 European population-based birth- and mother-child cohorts participated if they included
63 children born between 1989 and 2011, had information available on at least gestational age
64 and weight at birth and lung function measurements in childhood (until age 18 years), and
65 were willing and able to exchange original data.(4) We identified 52 European cohorts
66 selected from existing collaborations on childhood health or asthma-related outcomes
67 (www.chicosproject.eu, www.birthcohortsenrieco.net, www.ga2len.org,
68 and www.birthcohorts.net; assessed until May 29, 2012). In total, 24 cohorts, comprising
69 data on 24,938 children, fulfilled the criteria (**Supporting Information: S-figure 1**).

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

79 All cohorts obtained lung function measurements by spirometry, ~~most of them (n =~~
80 ~~24)of which 22~~ according to the recent guidelines of the American Thoracic Society /
81 European Respiratory Society (ATS/ERS) (19-21), and 2 according to earlier guidelines of
82 the ATS (22) or ERS and European Coal and Steel Community (23), (**Supporting**
83 **Information: S-table 1**) ~~(24-23)~~. If cohorts had collected lung function data at multiple time

Field Code Changed

84 points (n = 6 cohorts), we used the measurement closest to the mean age of children (8.5
85 years) in the full meta-analysis. Variables for analyses were forced vital capacity (FVC),
86 forced expiratory volume in 1 second (FEV₁), forced mid-expiratory flow (FEF₂₅₋₇₅) and
87 forced expiratory flow after exhaling 75% of the vital capacity (FEF₇₅). We mainly focused on
88 FEV₁, FEV₁/FVC, and FEF₇₅, which reflect reduced airway patency in obstructive lung
89 diseases such as asthma or bronchopulmonary dysplasia due to preterm birth or low birth
90 weight (24, 25). All lung function variables were converted into sex-, height-, age-, and
91 ethnicity (Caucasian versus non-Caucasian) -adjusted Z-scores based on the Global Lung
92 Initiative reference values (26). Asthma (yes / no) was defined as ever physician diagnosed
93 asthma, and was obtained by medical registries ([2 cohorts](#)) or parental questionnaires
94 [adapted from the International Study on Asthma and Allergy in Childhood \(ISAAC\)](#) (27) ([22](#)
95 [cohorts](#)) at the age of spirometry ([S-table1](#)). Cohort specific characteristics of lung function
96 measurements and asthma are given in the **Supporting Information (S-table 3)**.

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

106

107 **Statistical analysis**

108 First, we conducted 1-stage random effect regression analyses to study the separate and
109 combined associations of gestational age, birth weight and infant weight gain with FEV₁,
110 FVC, FEV₁/FVC, FEF₂₅₋₇₅ and FEF₇₅. For these analyses, individual participant data from all
111 cohorts were combined and modeled simultaneously taking into account clustering of

112 participants within studies (30). To prevent multicollinearity in our regression models, we
113 started to assess the associations of gestational age and birth weight with lung function
114 separately. Thereafter, we assessed whether the associations of birth weight with lung
115 function was driven by gestational age by creating gestational age adjusted birth weight
116 standard deviation scores. The models focused on the associations of infant weight gain
117 with lung function outcomes were adjusted for gestational age and weight at birth. To test
118 non-linear and dose-response associations, we categorized gestational age, birth weight
119 SDS and infant weight gain SDS. As a sensitivity analysis, we conducted a 2-stage random
120 effect meta-analysis to study the associations of gestational age, birth weight, and infant
121 weight gain, and dichotomized preterm birth and low birth weight with each lung function
122 outcome. For this analysis, we used linear regression models per cohort, after which pooled
123 regression coefficients (β 's) from the per cohort effect estimates were calculated. We tested
124 for heterogeneity between effect estimates using I^2 (31, 32). For all analyses, the first model
125 was adjusted for child's sex (crude model), the second model was additionally adjusted for
126 potential confounders (full model). To determine interactive effects between gestational age,
127 birth weight and infant weight gain we added these terms multiplicative in the full model.
128 Since we used Northern-European reference curves for birth weight SDS, we performed a
129 sensitivity analysis to explore whether the associations were different in North-Western
130 European subjects only. Numbers were too small to perform these analyses separately in
131 other European regions. To assess differences in results related to pubertal growth changes,
132 we repeated our analyses in strata of children aged < 11 years and ≥ 11 years (33). We also
133 performed a complete-case sensitivity analysis to explore any differences between complete
134 and non-complete-case analyses, and sensitivity analyses in which we excluded cohorts that
135 used parental report of early growth characteristics or that did not perform spirometry
136 measurements according to the ATS/ERS guidelines.

137 Second, we conducted a 1-stage random effect regression analysis to assess the
138 associations of early growth characteristics with asthma, and observed whether changes in
139 the effect estimates occurred after additional adjustment for lung function measures (FEV_1 ,

140 FVC, FEV₁/FVC, FEF₂₅₋₇₅ and FEF₇₅) as potential mediators (mediator model). [The](#)
141 [difference between the original effect estimates and the effect estimates after additional](#)
142 [adjustment for potential mediators was expressed as percentage change.](#) The percentage
143 change ~~of the effect estimate~~ was calculated by the formula: $100 \times (\text{effect estimate}_{\text{mediator}} -$
144 $\text{effect estimate}_{\text{model+original model}}) / (\text{effect estimate}_{\text{model+original model}} - 1)$. A 95% confidence interval
145 for the percentage change of the effect estimate was calculated using a bootstrap method
146 with 1,000 resamplings (34-36).

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

151

152 RESULTS

153

154 Subject characteristics

155 Information about the main characteristics of the cohorts are given in **Table 1**. Detailed
156 information about determinants, outcomes and covariates is given in the **Supporting**
157 **Information (S-tables 1-5)**. Of all participants, 8.2% (n = 2,053) was born preterm (<37
158 weeks of gestational age), and 4.8% (n = 1,191) was born with a low birth weight (<2,500
159 gram). The mean age at which spirometry assessments were performed was 8.5 (range 3.9
160 - 19.1) years. [The proportion of children aged ≥11 years was 11.9% \(n = 2,972\).](#)

161

162 Early growth measures and lung function outcomes

163 Results from the 1-stage random effect models showed that younger gestational age at birth
164 was, across the full range, associated with lower FEV₁, FEV₁/FVC and FEF₇₅ in childhood
165 (p-values for trend <0.01) (**Figures 1A-C**). A smaller size-for-gestational-age at birth across
166 the full range was associated with lower FEV₁ and higher FEV₁/FVC (p-values for trend
167 <0.01) (**Figures 1D-E**). Small size-for-gestational-age at birth was not associated with FEF₇₅

168 **(Figure 1F)**. Greater infant weight gain was associated with a higher FEV₁, but with a lower
169 FEV₁/FVC and FEF₇₅ (p-values for trend <0.01; **Figures 1G-I**). Most associations showed a
170 linear trend, except for the associations of birth weight with FEV₁/FVC and infant weight gain
171 with FEV₁ and FEV₁/FVC which were non-linear (Figures 1E, G, H).

172 To explore the combined effects of gestational age, birth weight SDS and infant
173 weight gain SDS, we performed tests for interaction between these early growth
174 characteristics. These tests for interaction were ~~only~~ significant for gestational age and birth
175 weight SDS in relation to ~~lung function outcomes~~ FEV₁, FEV₁/FVC, FEF₂₅₋₇₅ and FEF₇₅ (p-
176 values for interaction <0.01; **Figure 2, S-table 9**). Specifically, Stratified analyses showed
177 that a lower birth weight was associated with lower FEV₁ and FEV₁/FVC among children
178 born after ≥ 32 weeks only, whereas higher birth weight was associated with FEF₇₅ only
179 among term born children (p-values for strata <0.05).

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

191 **Figure 3** shows that compared to term born children, those born preterm had a lower
192 FEV₁, FEV₁/FVC and FEF₇₅, (pooled Z-score (95% CI): -0.20 (-0.26, -0.14), -0.15 (-0.21, -
193 0.09) and -0.19 (-0.27, -0.11), respectively). Also, compared to normal birth weight children,
194 those with a low birth weight had lower FEV₁, FEV₁/FVC and FEF₇₅ (-0.29 (-0.38, -0.21) and
195 -0.16 (-0.25, -0.08) and -0.17 (-0.26, -0.08) respectively), independent of gestational age.

196 Results of associations of growth characteristics with all lung function outcomes, including
197 FVC and FEF₂₅₋₇₅ are given in the **Supporting Information: S-tables 6-8**.

198

199 **Early growth, lung function and asthma**

200 Preterm birth, low birth weight and greater weight gain were all associated with an increased
201 risk of childhood asthma (OR (95% CI): 1.50 (1.2, 1.57), 1.40 (1.18, 1.65) and 1.23 (1.17,
202 1.28), respectively. ~~The associations of preterm birth and low birth weight attenuated after
203 additional adjustment for FEV₁, FEV₁/FVC or FEF₇₅. Mediation analyses suggested that
204 FEV₁, FEV₁/FVC and FEF₇₅ may explain 6.3 (2.5, 9.9)% to 44.6 (14.6, 81.1)%. Specifically,
205 after additional adjustment for FEV₁, FEV₁/FVC or FEF₇₅, the associations of preterm birth
206 with asthma attenuated with -7.3 (-18.8, -0.9)%, -14.4 (-39.6, -2.8)% and -39.0 (-69.3, -
207 3.4)%, respectively. Similarly, the associations of low birth weight with asthma attenuated
208 with -19.0 (-37.3, -11.8)%, -21.6 (-47.3, -11.4)% and -21.6 (-47.3, -11.4)%, respectively
209 (Table 2). The strongest mediating effect was observed for FEF₇₅ for the association
210 between gestational age and asthma (44.6 (81.1, 14.6)%). Overall, the strongest
211 attenuations towards non-significant were observed after adjustment for FEF₇₅ with an up to
212 45% reduction of the effect estimate (Table 2). A similar trend Similar trends were was
213 observed for greater weight gain, although the associations did not attenuate into non-
214 significant.~~

215

216 **DISCUSSION**

217 In this meta-analysis of individual participant data of 24,938 children from 24 birth cohorts,
218 we observed that lower gestational age, smaller size at birth and greater infant weight gain
219 were all associated with lower childhood FEV₁. The positive associations of birth weight and
220 infant weight gain with FVC were larger than of the positive associations of birth weight and
221 infant weight gain with FEV₁. This combination resulted in associations of higher birth weight
222 and infant weight gain with lower FEV₁/FVC. Also, a lower gestational age at birth was
223 associated with a lower FEF₇₅ in childhood, suggesting persistent reduction of small airways

224 patency. A greater infant weight gain was associated with lower FEF_{75} . Remarkably, these
225 associations were present across the full-range of early growth and not restricted to clinically
226 diagnosed preterm- or low birth weight children. Also, the observed associations of the early
227 life growth characteristics with lung function outcomes were independent of each other.
228 Stratified analyses showed that children born very preterm with a relatively low birth weight
229 had the lowest FEV_1 and FEV_1/FVC . The associations of early growth characteristics with
230 childhood asthma were partly explained by lung function adaptations.

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

243 Children born preterm or with a very low birth weight are at increased risk of neonatal
244 respiratory diseases (1). We observed that children born at a younger gestational age had a
245 lower FEV_1 , even after taking FVC into account, and a lower FEF_{75} in childhood. These
246 associations were not only present among children born very preterm, but across the full
247 range of gestational age at birth. Moreover, the associations of preterm birth with childhood
248 asthma were partly explained by lung function. These findings are in line with previous
249 studies showing persistent lung function adaptations in children and adults born preterm. A
250 recent meta-analysis of 28 published studies showed that children born between 24 and 36

251 weeks had a lower FEV₁ at ages 5 up to 23 years (42). These and other studies suggest that
252 preterm birth has adverse effects on lung function, persisting into adulthood (42-44).

253 In the present study, a lower birth weight was associated with lower FEV₁ in
254 childhood. This suggests that a lower birth weight leads to a persistent reduction of airway
255 patency. A previous study analyzed 10 studies examining the associations of birth weight
256 with FEV₁ in adults (range 19 – 70 years) (10). The authors reported a modest positive
257 association between FEV₁ and birth weight. Two recent studies from longitudinal birth
258 cohorts among adults reported strong positive associations of birth weight with FEV₁ and
259 FEF₂₅₋₇₅ in young adults aged 21 and 31 years (9, 11). The effect of birth weight was
260 independent of preterm birth in both studies. However, studies among children showed
261 conflicting results (12, 13). We observed an association of lower birth weight with lower
262 FEV₁, independent of gestational age at birth. We previously reported that the effect of lower
263 birth weight on asthma was largely explained by gestational age (4). Therefore, although
264 gestational age-adjusted birth weight is associated with lower lung function this seems not
265 related to the risk of clinically manifest childhood asthma.

266 Previous studies examining associations between infant weight gain and childhood
267 lung function have reported inconsistent results (14-16). Differences might be due to
268 different ages at which spirometry was performed, not taking other weight characteristics
269 into account, such as birth weight or current body mass index, and possible hidden bias due
270 to the use of mL instead of Z-scores for lung function (45). In line with the findings for birth
271 weight, we observed that lower infant weight gain was associated with a lower childhood
272 FEV₁. This association was fully explained by FVC. These results suggest dysanapsis, in
273 which airways remained small in relation to total lung volume as a result of a mismatch
274 between airway and alveolar growth (46). Hence, a lower FEV₁ due to lower birth weight or
275 infant weight can be explained by a lower lung volume. Greater infant weight gain was also
276 associated with a lower FEF₇₅, which is in line with previous studies reporting associations of
277 body mass index or adiposity with reduced expiratory flows and asthma (47, 48). A
278 suggested mechanism is leptin release from adipose tissue, which might have pro-

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

283 To the best of our knowledge this is the first study that examines the individual and
284 combined associations of the main early growth characteristics with childhood lung function
285 outcomes, and whether lung function adaptations explain the previously reported
286 associations of early growth characteristics with childhood asthma. ~~showing associations of~~
287 all early growth characteristics with lung function and subsequent risk of childhood asthma.

288 Our results suggest that respiratory consequences of preterm birth and a low birth weight
289 present across the full range. This observation might have important population effects,
290 since the largest majority of children are in the less extreme ranges of gestational age and
291 weight at birth. Furthermore, our results suggest that the associations of gestational age,
292 birth weight and infant weight gain with childhood asthma are at least partly explained by
293 adaptions in airway caliber. We observed strong effect estimates with wide confidence
294 intervals. Therefore, these mediation effects should be interpreted carefully. The effect
295 estimates for the observed associations could be considered as small and without clinical
296 relevance for individuals. However, the associations may be important from an etiological
297 respiratory developmental perspective and may be important on a population-level. The
298 associations of early growth characteristics with lung function outcomes seemed already
299 established before the pubertal growth spurt. The largest lung and airway growth occurs
300 before pubertal growth spurt (37, 51), with FVC increasing proportionately more than the
301 FEV₁ (33). Lung and airway growth is proportionally less after start of the pubertal growth
302 spurt (33), which might explain the similar effect estimates before and after the pubertal
303 growth spurt. Further studies are needed to identify the developmental adaptations of the
304 lungs and immune system that might explain the mediating effect of lung function on the
305 associations of early growth characteristics with childhood asthma. ~~More information is~~
306 needed on the specific maternal and childhood exposures, which lead to the specific early

307 ~~growth patterns and affect the risk of later life respiratory diseases.~~ Identification of
308 modifiable exposures may lead to development of future preventive strategies.

309 Some methodological limitations need to be discussed. We used data from 24
310 ongoing cohort studies. Missing values always occur in these studies. Since we did not have
311 additional data on patterns of missing values in all 24 cohorts, we were not able to perform
312 multiple imputation. Data on childhood asthma was mainly obtained by parental
313 questionnaires adapted from the International Study on Asthma and Allergy in Childhood
314 (ISAAC) (27). This questionnaire has been validated in various age groups in many
315 countries against measurements of bronchial hyperresponsiveness and doctor-diagnosed
316 asthma, and is widely accepted in epidemiological studies. We did not have information on
317 use of asthma medication, which might have influenced the lung function values in asthmatic
318 patients. This missing information on asthma medication may have influenced our effect
319 estimates. We would expect that asthmatic children who use asthma medication would in
320 general have had a higher lung function values in case of good adherence and inhaler
321 technique. We used GLI reference data to convert lung function values into Z-scores. These
322 prediction equations were based on 74,187 individuals including 31,840 individuals aged
323 <20 years, of whom 58% were assessed before, and 42% were assessed during pubertal
324 growth spurt (26). To date, the GLI normal values are considered the most accurate
325 reference values for all age ranges, and have been adopted by both the ATS and ERS. For
326 the covariates, we imputed missing values as additional category to prevent exclusion of
327 non-complete cases. No differences in results were observed in complete case analyses. No
328 direct clinical and laboratory information about pubertal growth was available. Also,
329 although we took major potential confounders into account, residual confounding may still be
330 an issue. No information was available about e.g. exposure to environmental micro-
331 organisms or asthma severity. Exploring mediation of lung function for the association of
332 early growth characteristics with asthma using the method proposed by Baron and Kenny
333 might have been limited by misclassification of lung function measurements or asthma
334 diagnosis although we aimed to reduce this issue by multi-level modelling (52). Most of the

335 participating studies had measured childhood lung function and asthma at the same age.
336 Therefore, further follow-up studies with longitudinally measured detailed data on lung
337 function and asthma or related symptoms from birth onwards are needed to disentangle the
338 direction of causality.

339 In conclusion, younger gestational age, lower birth weight and lower infant weight
340 gain were independently associated with persistent changes in childhood lung function.
341 These associations were present across the full spectrum of these early growth
342 characteristics. Stratified analyses showed that children born very preterm with a relatively
343 low birth weight had the lowest FEV₁ and FEV₁/FVC. Our results suggest that associations
344 of early growth with the risk of childhood asthma were partly explained by lung function
345 adaptations. Thus, fetal and infant growth patterns may persistently affect lung function, and
346 thereby contribute to the risk of respiratory diseases in later life.

347

348 **Author's contributions**

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

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Figure 1. Associations of gestational age, birth weight and infant weight gain with FEV₁, FEV₁/FVC ratio and FEF₇₅.

Legend:

Values represent Z-scores differences (95% confidence interval) from multi-level random effect models for the associations of gestational age at birth (A, B, C), gestational age adjusted birth weight (birth weight SDS) (D, E, F), and infant weight gain (SDS) (G, H, I) with lung function outcomes, compared with reference groups. Reference groups were 40-42.9 weeks of gestational age, 0-0.99 birth weight SDS and 0.00 – 0.99 infant weight gain (SDS) (largest groups), and represented by an open bullet. Lung function outcomes are forced expiratory volume in 1 second (FEV₁), FEV₁/forced vital capacity (FVC) ratio, and forced expiratory flow at 75% of the exhaled FVC (FEF₇₅). Models are adjusted for maternal education, smoking during pregnancy, smoking during childhood, atopy, asthma and child's sex, number of siblings, daycare attendance, breastfeeding, respiratory tract infections, childhood eczema, inhalant allergies and body mass index. Infant weight gain SDS was additionally adjusted for birth weight and gestational age at birth.

Figure 2. Combined associations of gestational age and birth weight with FEV₁, FEV₁/FVC ratio and FEF₇₅.

Legend:

Values are Z-score differences (95% confidence interval) from multi-level models for the combined associations of gestational age at birth and birth weight SDS (A, B, C) with lung function outcomes, compared with reference groups. Reference groups were >37 weeks of gestational age with -1.00 to 0.99 birth weight SDS (largest group), and represented by a bullet. Lung function outcomes are forced expiratory volume in 1 second (FEV₁), FEV₁/forced vital capacity (FVC) ratio, and forced expiratory flow at 75% of the exhaled FVC (FEF₇₅). Models are adjusted for maternal education, smoking during pregnancy, smoking

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

Figure 3. Forest plots of the associations between preterm birth and low birth weight with FEV₁, FEV₁/FVC ratio and FEF₇₅.

Legend:

Values are pooled Z-score differences (95% confidence interval) from random effect meta-analysis for the associations of preterm birth vs. term birth (A, B, C) and low birth weight vs. normal birth weight (D, E, F) with lung function outcomes. Lung function outcomes are forced expiratory volume in 1 second (FEV₁), FEV₁/forced vital capacity (FVC) ratio, and forced expiratory flow at 75% of the exhaled FVC (FEF₇₅). Models are adjusted for maternal education, smoking during pregnancy, smoking during childhood, atopy, asthma and child's sex, number of siblings, daycare attendance, breastfeeding, respiratory tract infections, childhood eczema, inhalant allergies and body mass index. Low birth weight was adjusted for gestational age.

Table 1. Characteristics of participating cohorts.

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

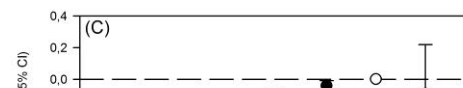
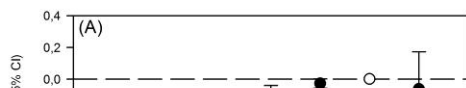


Table 1 (continued). Characteristics of participating cohorts.

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

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

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

	Risk of childhood asthma						
	Odds ratio (95% Confidence Interval)						
	Full model	Full model + FEV₁	% change (95% CI)	Full model + FEV₁/FVC	% change (95% CI)	Full model + FEF₇₅	% change (95% CI)
<u>Gestational age (weeks)</u>	0.94 (0.92, 0.97)** n = 15,019	0.95 (0.93, 0.97)** n = 14,832	-9.8% (-16.4, -5.3)**	0.95 (0.93, 0.97)** n = 14,017	-13.5% (-21.0, -7.3)**	0.97 (0.94, 1.00) n = 9,177	-44.6% (-81.1, -14.6)**
<u>Preterm birth (<37 weeks)</u>	1.34 (1.15, 1.57)** n = 15,019	1.30 (1.11, 1.53)** n = 14,832	-7.3% (-18.8, -0.9)*	1.27 (1.08, 1.49)** n = 14,017	-14.4% (-39.6, -2.8)*	1.20 (0.99, 1.47) n = 9,177	-39.0% (-69.3, -3.4)*
<u>Birth weight (500 grams)</u>	0.94 (0.90, 0.97)** n = 15,547	0.95 (0.91, 0.99)* n = 15,360	-18.9% (-37.0, -11.2)**	0.94 (0.90, 0.98)** n = 13,985	-10.5% (-21.9, -3.4)**	0.96 (0.92, 1.02) n = 9,135	-17.8 (-50.6, -9.0)**
<u>Low birth weight (<2,500 grams)</u>	1.32 (1.07, 1.62)** n = 15,547	1.25 (1.02, 1.54)* n = 15,360	-19.0% (-37.3, -11.8)**	1.23 (0.99, 1.52) n = 13,985	-21.6% (-47.3, -11.4)**	1.05 (0.81, 1.36) n = 9,135	-82.5% (-149, 10.3)
<u>Birth weight (SDS)</u>	0.98 (0.94, 1.03) n = 14,947	1.00 (0.96, 1.05) n = 14,760	-83.8% (-950, 825)	0.98 (0.94, 1.03) n = 13,946	-14.0% (-247, 281)	0.99 (0.93, 1.04) n = 9,122	-15.8% (-158, 169)
<u>Small for gestational age (<10th percentile)</u>	1.18 (1.01, 1.37)* n = 14,947	1.13 (0.97, 1.32) n = 14,760	-28.9% (-253, 108)	1.16 (0.99, 1.36) n = 13,946	-18.8% (-123, 164)	1.20 (1.00, 1.44) n = 9,122	10.2% (-8.3, 26.2)
<u>Infant weight gain in first year (SDS), adjusted for gestational age and weight at birth</u>	1.27 (1.21, 1.34)** n = 12,511	1.28 (1.22, 1.35)** n = 12,511	6.5% (2.3, 9.9)**	1.25 (1.18, 1.31)** n = 11,780	-8.4% (-16.1, -3.2)**	1.13 (1.06, 1.20)** n = 7,969	-60.8 (-115, 39.5)

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

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

	Risk of childhood asthma Odds ratio (95% Confidence Interval)						
	Full model	Full model + FEV ₁	% change (95% CI)	Full model + FEV ₁ /FVC	% change (95% CI)	Full model + FEF ₇₅	% change (95% CI)
Gestational age (weeks)	0.94 (0.92, 0.97)**	0.95 (0.93, 0.97)**	-0.8% (-16.4, -5.3)**	0.95 (0.93, 0.97)**	-13.5% (-21.0, -7.3)**	0.97 (0.94, 1.00)	-44.6% (-81.1, -14.6)**
Preterm birth (<37 weeks)	1.34 (1.15, 1.57)**	1.30 (1.11, 1.53)**	-7.3% (-18.8, -0.9)*	1.27 (1.08, 1.49)**	-14.4% (-30.6, -2.8)*	1.20 (0.99, 1.47)	-39.0% (-69.3, -3.4)*
Birth weight (500 grams)	0.94 (0.90, 0.97)**	0.95 (0.91, 0.99)*	-18.0% (-37.0, -11.2)**	0.94 (0.90, 0.98)**	-10.5% (-21.9, -3.4)**	0.96 (0.92, 1.02)	-47.8 (-50.6, -9.0)**
Low birth weight (<2,500 grams)	1.32 (1.07, 1.62)**	1.25 (1.02, 1.54)*	-19.0% (-37.3, -11.8)**	1.23 (0.99, 1.52)	-21.6% (-47.3, -11.4)**	1.05 (0.81, 1.36)	-82.5% (-149, 10.3)
Birth weight (SDS)	0.98 (0.94, 1.03)	1.00 (0.96, 1.05)	-83.8% (-95.0, 82.5)	0.98 (0.94, 1.03)	-14.0% (-24.7, 28.1)	0.99 (0.93, 1.04)	-15.8% (-158, 169)
Small for gestational age (<10th percentile)	1.18 (1.01, 1.37)*	1.13 (0.97, 1.32)	-28.9% (-25.3, 108)	1.16 (0.99, 1.36)	-18.8% (-12.3, 16.4)	1.20 (1.00, 1.44)	10.2% (-8.3, 26.2)
Infant weight gain in first year (SDS), adjusted for gestational age and weight at birth	1.27 (1.21, 1.34)**	1.28 (1.22, 1.35)**	6.5% (2.3, 9.9)**	1.25 (1.18, 1.31)**	-8.4% (-16.1, -3.2)**	1.13 (1.06, 1.20)**	-60.8 (-115, 39.5)

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

daycare attendance, breastfeeding, respiratory tract infections, childhood eczema, inhalant allergies and body mass index (full model), and additionally for lung function outcomes (mediator model).