# Peak weight velocity in infancy is negatively associated with lung function in adolescence

**Running title: Growth and lung function**

**"take home" message:** Early weight gain is negatively associated with flow indices in adolescence, suggesting structural changes in the lung.

Claudia Flexeder[1], Elisabeth Thiering[1,2], Andrea von Berg[3], Dietrich Berdel[3], Barbara Hoffmann[4], Sibylle Koletzko[2], Carl-Peter Bauer[5], Berthold Koletzko[2], Joachim Heinrich[1,6], Holger Schulz[1]

[1] Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

[2] Dr von Hauner Children's Hospital, Ludwig Maximilians University of Munich, Munich, Germany

[3] Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany

[4] IUF Leibniz Research Institute for Environmental Medicine and Medical Faculty, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany

[5] Department of Pediatrics, Technical University of Munich, Munich, Germany

[6] Comprehensive Pneumology Center Munich (CPC-M), Member of the German Center for Lung Research

Corresponding author:

Dr. Joachim Heinrich

Institute of Epidemiology I

Helmholtz Zentrum München

German Research Center for Environmental Health

Ingolstädter Landstr. 1

85764 Neuherberg, Germany

Tel.: +49 89 3187 4150

Fax: +49 89 3187 3380

Email: heinrich@helmholtz-muenchen.de

# Abstract

**Background:** Rapid weight gain during infancy increases childhood asthma risk, which might be related to impaired lung function. This study investigated associations between peak weight velocity (PWV) during the first two years of life and spirometric lung function indices at 15 years of age.

**Methods:** Data from 1842 children participating in the GINIplus German birth cohort who underwent spirometry at age 15 were analysed. PWV was calculated from weight measurements obtained between birth and two years of age. Generalised additive models were fitted after adjustment for potential confounding factors (birth weight, height and age at lung function testing). Results are presented per interquartile range increase in PWV.

**Results:** PWV was negatively associated with pre-bronchodilation flow rates after extensive adjustment for potential confounders including asthma: forced expiratory flow at 50% of forced vital capacity ($FEF_{50}$) decreased by 129ml/s (95% CI=[-211;-46]), $FEF_{75}$ by 71ml/s [-130;-12] and $FEF_{25-75}$ by 103ml/s [-176;-30]. $FEV_1$/FVC was also negatively associated with PWV (-0.691% [-1.207;-0.174]) whereas forced expiratory volume in 1s ($FEV_1$) and forced vital capacity (FVC) were not. Similar results were found for measurements post-bronchodilation.

**Conclusion:** Early life weight gain was negatively associated with flow indices in adolescence, suggesting structural changes in peripheral lungs.



**Keywords:** lung function, growth, adolescence, asthma, weight gain, early life factor, spirometry

# Introduction

Many chronic diseases have their origin early in life ("concept of early programming") [1,2]. Environmental and nutritional factors resulting in a rapid weight gain early in life might increase the risk of being overweight or obese later on [3,4]. Furthermore, early weight gain is also associated with comorbidities of being overweight, such as asthma [5-7] and elevated blood pressure [8]. A study on eight European birth cohorts reported that children with a rapid increase in body mass index (BMI) during the first two years of life were at an increased risk of asthma up to the age of 6 years compared to children with a normative or persistent gain in BMI during the first 6 years of life [6]. Potential mechanisms regulating these associations might be a reduced lung and breathing volume as well as changes in hormones, such as leptin and adiponectin, which have pro- and anti-inflammatory effects [9]. Furthermore, a reduced lung volume is also associated with a lower birth weight and results in poorer lung function later in life [10-12] and newborns with a lower birth weight tend to have a higher weight gain after birth. This association might be explained by adjustment mechanisms during the foetal period and early infancy, which are reactions to adverse factors ("developmental plasticity hypothesis") [13,14]. Hence, early stage development might be important for lung function development and susceptibility to respiratory diseases. To date, only a few studies have investigated the influence of a rapid weight gain in early life on lung function during childhood [15,16] and adulthood [10,12]. For instance, a study in Dutch children reported that a rapid weight gain in the first 3 months of life was inversely associated with lung function indices measured at 5 years, including forced expiratory volume in 1 second ($FEV_1$) and forced expiratory flow at 25-75% of forced vital capacity ($FEF_{25-75}$) [16]. As in most studies, no longitudinal models were applied to derive early growth. Instead, weight gain was defined as the difference between weight measurements taken at two time points. To elucidate whether early growth has a permanent effect on later lung function and whether any observed association is due to reversible airway

narrowing, associations with all spirometric flow indices, pre- and post-bronchodilation, need to be considered. Accordingly, whether small or large airways are primarily affected should be assessed.

Therefore, we investigated associations between peak weight velocity in infancy and spirometric lung function indices measured before and after bronchodilation at age 15 years in a prospective German birth cohort of healthy full-term neonates born with normal birth weight.

# Materials and Methods

## *Study Population*

The German Infant Study on the Influence of Nutrition Intervention plus Air Pollution and Genetics on Allergy Development (GINIplus) is an ongoing birth cohort study initiated to prospectively investigate the influence of a nutrition intervention during infancy on allergy development. A total of 5991 healthy term born Caucasian neonates with birth weights greater than 2500 grams were recruited in the cities of Munich and Wesel between September 1995 and July 1998. Details of the study design have been described previously [17].

In total, 3198 adolescents participated in the 15 year follow-up of the GINIplus study, 2018 of which underwent a physical examination and 1842 of which had valid lung function measurements before and/or after bronchodilation. All analyses are based on this last subsample.

This study was approved by the respective local ethics committees: the Bavarian Medical Council (Bayerische Landesärztekammer, München) and the Medical Council of North-Rhine-Westphalia (Ärztekammer Nordrhein, Düsseldorf). Written informed consent was obtained from all participating families.

## *Assessment of Lung Function*

Spirometry before bronchodilation was performed in 1887 subjects during the physical examination at 15 years of age in line with the ATS/ERS recommendations [18]. Subjects were seated while wearing nose clips and a pneumotachograph-type spirometer (EasyOne Worldspirometer, ndd, Zurich,

Switzerland) was used to obtain flow-volume curves. The participants performed at least three, but not more than eight, trials per test. After completion of baseline spirometry, subjects inhaled the medication for the bronchodilator response according to ATS/ERS recommendations [18]. Spirometry was performed 15 minutes after salbutamol inhalation. Bronchodilation was performed in 1796 subjects.

All tests were visually inspected according to the acceptability criteria of the ATS/ERS [18]. Manoeuvres incorrectly performed or with artefacts were excluded. In total, 1842 subjects had valid lung function measurements before and/or after bronchodilation.

Spirometric indices were taken from the manoeuvre with the largest sum of $FEV_1$ and FVC. Further parameters evaluated were the ratio of $FEV_1$ and FVC ($FEV_1$/FVC), peak expiratory flow (PEF), forced expiratory flow rates at 25, 50 and 75% of exhaled FVC ($FEF_{25}$, $FEF_{50}$ and $FEF_{75}$) and the mean flow rate between 25 and 75% of FVC ($FEF_{25-75}$).

Reference equations for spirometry from the Global Lung Function Initiative (GLI – www.lungfunction.org/) [19] were applied to calculate standardised z-scores of the lung function parameters $FEV_1$, FVC, $FEV_1$/FVC, $FEF_{75}$ and $FEF_{25-75}$.

## *Weight Velocity and Confounding Variables*

Weight measurements during infancy were obtained from “baby books” created during the children’s preventive medical check-ups conducted by a paediatrician at birth, day 3-10, week 4-6, and months 3-4, 6-7, 10-12 and 21-24, to monitor growth.

Individual weight gain curves up to age two years were calculated from the anthropometric measurements using the modified Reed1 model, as previously described [5,20-22]. Peak weight velocity (PWV) was defined as the maximum of the first derivative of the individual weight gain curves, computed separately for males and females, using nonlinear random effects models.

Potential confounders examined were sex, study centre (Munich and Wesel), cohort (intervention vs. observation group), age, weight and height at lung function testing, maternal smoking during pregnancy, birth weight, exclusive breastfeeding (>4 months, 1-4 months and no exclusive breastfeeding), parental history of atopy and exposure to tobacco smoke at home up to the age of 6 years. Additionally, parental education levels were defined using the highest number of years of education achieved by either parent (low for less than 10 years, intermediate for 10 years, and high for more than 10 years). A positive bronchodilation response was defined as an increase of more than 12% and more than 200ml in $FEV_1$ and/or FVC measured after bronchodilation compared to before bronchodilation, according to ATS/ERS standards [23]. An adolescent was defined as asthmatic if a doctor diagnosis of asthma was reported at the $11^{th}$, $12^{th}$, $13^{th}$, $14^{th}$ or $15^{th}$ year of age or if the adolescent took asthma medication during the past 12 months, based on information obtained at the 15 year follow-up.

## *Statistical Analyses*

Linear associations between PWV and spirometric lung function indices were analysed using generalised additive models, which account for potential nonlinear effects of continuous covariates on the outcome variable [24].

Three sets of confounder adjustments were considered for all outcomes examined: Model 1 (crude) was adjusted for sex; Model 2 (minimal) was additionally adjusted for study centre, cohort, age, weight and

height at lung function measurement; and Model 3 (main) was further adjusted for parental education, parental atopy, birth weight, exclusive breastfeeding during the first 4 months, maternal smoking during pregnancy, exposure to tobacco smoke at home up to age six and doctor diagnosed asthma and/or a positive bronchodilation response. Asthmatics and those with a positive bronchodilation response were excluded in a sensitivity analysis to investigate the stability of associations among non-asthmatics.

Differences between males and females were tested using Pearson's chi-squared test or Wilcoxon rank sum test. All association results are presented as regression coefficients (β) per interquartile range (IQR) increase in PWV with corresponding 95% confidence intervals (CI). P-values below 0.05 are used to indicate statistical significance. All analyses were performed using the statistical software package R, version 3.0.2 [25].

# Results

Study characteristics stratified by sex and for the combined population are presented in Table 1. The median of the PWV was 12.5kg/year and the IQR was 3.5kg/year. Males tended to have a higher PWV (median: 13.7kg/year; IQR: 3.3kg/year) compared to females (median: 11.5kg/year; IQR: 3.0kg/year). In the total population, 9.0% of adolescents were asthmatic and 4.0% had a positive bronchodilation response. Males had a higher prevalence of asthma (10.8% vs 7.3%) and positive bronchodilation (5.1% vs 3.0%) compared to females.

Table 2 shows the median and first and third quartiles of the spirometric lung function parameters measured before and after bronchodilation, as well as of the z-scores calculated according to GLI. With the exception of $FEV_1$/FVC, the measured lung function indices had higher median values before and after bronchodilation among males compared to females. However, the medians of the z-scores were higher among females than males. The medians of all baseline z-scores were slightly negative.

The results for the associations between PWV and the spirometric lung function parameters before bronchodilation measured at 15 years of age are presented in Table 3. In the crude model, PWV was positively associated with $FEV_1$, FVC and PEF, whereas $FEV_1$/FVC was negatively associated with early weight gain. No statistically significant associations were found with flow indices (Model 1). However, the flow rates were negatively associated with PWV in the minimally and main adjusted models. In the main models (Model 3), $FEF_{50}$ decreased by 129ml/s (β=-0.129 [-0.211;-0.046]), $FEF_{75}$ decreased by 71ml/s (β=-0.071 [-0.130;-0.012]) and $FEF_{25-75}$ decreased by 103ml/s (β=-0.103 [-0.176;-0.030]) per IQR increase in PWV. $FEV_1$/FVC was also significantly negatively associated with PWV in the main model (Model 3: β=-0.691 [-1.207;-0.174]). Although $FEV_1$, PEF and $FEF_{25}$ were negatively associated with early weight gain in the minimally adjusted model (Model 2: $FEV_1$ β=-0.034 [-0.065;-0.004]; PEF β=-0.092

179 [-0.170;-0.014]; $FEF_{25}$ β=-0.115 [-0.195;-0.035]), the effect sizes were attenuated and no longer
180 statistically significant after adjustment for further covariates (Model 3: $FEV_1$ β=-0.013 [-0.047;0.022];
181 PEF β=-0.054 [-0.143;0.034]; $FEF_{25}$ β=-0.068 [-0.158;0.021]). FVC was not associated with PWV in the
182 minimally adjusted (β=0.002 [-0.031;0.035]) or main models (β=0.013 [-0.025;0.051]).

183 Associations between PWV and the lung function parameters measured after bronchodilation were
184 similar to those for the lung function parameters measured at baseline (Table 4). Small decreases in the
185 effect estimates for $FEV_1$/FVC (β=-0.473 [-0.930;-0.015]) as well as for the flow rates $FEF_{50}$ (β=-0.083
186 [-0.165;-0.001]), $FEF_{75}$ (β=-0.089 [-0.153;-0.024]) and $FEF_{25-75}$ (β=-0.093 [-0.166;-0.020]) were observed in
187 the main models (Model 3).

188 Table 5 summarises the results for the associations between PWV and the standardised z-scores of the
189 lung function parameters, calculated according to GLI. Early weight gain was negatively associated with
190 $FEV_1$/FVC, $FEF_{75}$ and $FEF_{25-75}$, which is in accordance with the results obtained using the non-transformed
191 spirometric values.

192 Restricting the analyses to non-asthmatics and those with no positive bronchodilation response did not
193 yield any differences in the associations (Supplement Tables S1 and S2).

194

# Discussion

PWV during the first two years of life was negatively associated with lung function parameters, primarily with flow indices ($FEV_1$/FVC, $FEF_{50}$, $FEF_{75}$ and $FEF_{25-75}$), in adolescence. These associations were present for lung function indices measured before and after bronchodilation. Analyses restricted to non-asthmatics and those with no positive bronchodilation showed similar results. These associations were independent from a number of other early life factors, such as birth weight, which might have an influence on lung function later in life.

## *Comparison with results from other studies*

A few studies have analysed the relationship between early growth and lung function later in life, but results for only a few lung function parameters were presented [10,12,15,16,26]. Van der Gugten et al. [16] reported that a rapid weight gain, defined as a difference between z-scores of weight at birth and at age 3 months greater than 0.67, was associated with a decrease in $FEV_1$ by 34ml and in $FEF_{25-75}$ by 82ml/s at 5 years of age after adjustment for birth weight. These effects are comparable to the results of our study, although we did not identify a significant association with $FEV_1$ before or after bronchodilation. However, in a study in the Northern Finland Birth Cohort [10] in which spirometry was performed at age 31 years, a positive relationship was found between lung function with birth weight and weight gain in the first 12 months of life. $FEV_1$ increased by 20.1ml in men and by 19.0ml in women per 1kg increase in weight gain. For FVC, increases of 50.6ml and 29.8ml were reported for men and women, respectively. The results for FVC in our study also tended to show a positive association with PWV, but they were not statistically significant. Whether wheezing modifies the relationship between early growth and lung function in adolescence and young adulthood has been investigated by Sherrill et al. in a small study sample (127 participants) [26]. A positive association between weight gain from 3 to

6 years of age with $FEV_1$ and FVC at 16 and 22 years of age was only found in children who had not wheezed during the first years of life. In summary, previous studies which have examined associations between early weight gain and lung function had yielded inconsistent results and none have considered lung function measurements taken after bronchodilation. The present study thereby represents an important contribution to the literature as we identified several consistent associations between early weight gain and lung function parameters, primarily with flow indices, and demonstrated that these associations remained similar post bronchodilation.

## *Potential biological mechanisms*

The biological mechanisms regulating the associations between early weight gain and lung function in childhood, adolescence and adulthood remain to be elucidated. However, a potential association seems biologically plausible as the lung undergoes a substantial growth and development, particularly with regard to the structure of the peripheral lung, during fetal life and the first years after birth [27,28]. A rapid increase in the number and size of the alveoli and growth of the airway diameter can be seen between birth and around 18 months of age [27,29].

Several studies have shown that the origins of asthma and chronic diseases could occur early in life [1,5,13,30,31]. Adverse factors early in life, such as maternal smoking and restricted growth in utero, are associated with restricted lung development, which in turn, is related to impaired lung function and increased susceptibility to respiratory diseases during childhood and adulthood [13,27,31]. These changes in lung growth and development could result from adaptation mechanisms which occurred during the foetal period and early infancy as a response to different environmental and lifestyle factors [13,31]. Therefore, pre- and postnatal factors might affect lung growth and maturation as well as alveolaristaion, resulting in poorer lung function later in life [27]. There are other hypotheses to explain

239 the influence of early life risk factors on the development of diseases later in life [6,32]. For instance, the
240 "mismatch hypothesis" suggests that an imbalance between the pre- or postnatal environment and the
241 childhood environment might result in long-lasting health effects. For example, foetal undernutrition
242 and a subsequent obesogenic childhood environment may increase the risk for obesity and other
243 diseases later in life [32]. In our study, we adjusted for several environmental and lifestyle factors.
244 Accelerated growth in infancy and its adverse effects on factors in childhood and adolescence could also
245 be explained by a high protein supply leading to an increased secretion of insulin and insulin-like growth
246 factor 1 and hence to higher weight gain in infancy and adipogenic activity [3,32,33]. Insulin-like growth
247 factors also play a role in alveogenesis and lung growth [34].

248 The hypothesis that peripheral airways are especially susceptible early in life is supported by our results
249 which demonstrate an association between early weight gain and spirometric indices indicative of small
250 airway function, measured both before and after bronchodilation. If reduced lung function in
251 adolescence would be caused by functional and not structural changes, for instance, because of an
252 effect of rapid weight gain on the function of the airway musculature, the airway narrowing would be
253 reversible and the effect of PWV on spirometric lung function indices would disappear after
254 bronchodilation. As the results of our study were consistent for lung function parameters measured
255 before and after bronchodilation, we assume that structural changes in the lung might underlie the
256 observed association with PWV.

## 257 *Strengths and limitations*

258 An important strength of the current study was the availability of a broad range of spirometric lung
259 function indices, measured before and after bronchodilation. We had parameters indicative of airway
260 obstruction ($FEV_1$ and $FEV_1$/FVC), lung volume and size (FVC), as well as more rarely investigated

parameters of small airways and airway narrowing (forced expiratory flow rates ($FEF_{25}$, $FEF_{50}$ and $FEF_{75}$) and mean flow rate ($FEF_{25-75}$)). We were also able to investigate whether the associations observed between weight gain in infancy and lung function in adolescence were reversible by comparing pre- and post-bronchodilation measurements. Another major strength of this study was the longitudinal study design and longitudinal modelling of early weight gain. Individual growth curves could be fitted based on up to seven weight measurements available from birth to the age of two years. A further strength of this study is the cautious consideration of the impact of a low birth weight on later lung function. Newborns with birth weights <2500 grams were not included in this analysis and an adjustment for birth weight was included in the main models.

A limitation of the current study was that the standardised z-scores for lung function calculated based on reference equations from GLI did not fit very well to our study population. The regression models fitted for the association between early weight gain and lung function z-scores still required adjustments for sex, as well as age and height at lung function testing, as these variables were significant in the model. However, the results for the GLI z-scores were similar to those for the non-transformed lung function parameters.

## *Conclusion*

The results of our study indicate that an increased weight gain velocity in infancy is associated with lower lung function values, primarily with flow indices, in adolescence, measured both before and after bronchodilation. These results suggest structural rather than functional changes in lung function.

# Acknowledgements

We thank the families for their participation in the study, the obstetric units for allowing recruitment and the GINI study team for its excellent work.

**GINIplus study group**

The GINI Study Team: Institute of Epidemiology I, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg (J. Heinrich, I. Brüske, H. Schulz, C. Flexeder, C. Zeller, M. Standl, M. Schnappinger, M. Sußmann, E. Thiering, C. Tiesler); Department of Pediatrics, Marien-Hospital, Wesel (D. Berdel, A. von Berg); Ludwig-Maximilians-University of Munich, Dr von Hauner Children's Hospital (S. Koletzko); Child and Adolescent Medicine, University Hospital rechts der Isar of the Technical University Munich (C.P. Bauer, U. Hoffmann); IUF- Environmental Health Research Institute, Düsseldorf (B. Hoffmann, E. Link, C. Klümper).

We thank Elaine Fuertes for editing the manuscript.

**Funding**

The GINIplus study was mainly supported for the first 3 years of the Federal Ministry for Education, Science, Research and Technology (interventional arm) and Helmholtz Zentrum Munich (former GSF) (observational arm). The 4 year, 6 year, and 10 year follow-up examinations of the GINIplus study were covered from the respective budgets of the 5 study centres (Helmholtz Zentrum Munich (former GSF),

Research Institute at Marien-Hospital Wesel, LMU Munich, TU Munich and from 6 years onwards also from IUF - Leibniz Research-Institute for Environmental Medicine at the University of Düsseldorf) and a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). The 15 year follow-up examination of the GINIplus study was partially supported by the Commission of the European Communities, the 7th Framework Programme, MeDALL project as well as by the companies Mead Johnson and Nestlé.

This work was supported by the Kompetenznetz Adipositas (Competence Network Obesity) funded by the Federal Ministry of Education and Research (FKZ 01GI1121A) and the Comprehensive Pneumology Center Munich (CPC-M) as member of the German Center for Lung Research. Work reported herein is carried out with partial financial support from the Commission of the European Communities, the 7th Framework Programme, contract FP7-289346-EARLY NUTRITION and the European Research Council Advanced Grant ERC-2012-AdG – no.322605 META-GROWTH. This manuscript does not necessarily reflect the views of the Commission and in no way anticipates the future policy in this area.

# References


[1] Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. BMJ. 1991 Sep;303(6804):671–675.

[2] Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease-the hypothesis revisited. BMJ. 1999 Jul;319(7204):245–249.

[3] Koletzko B, Symonds ME, Olsen SF for The Early Nutrition Programming Project and The Early Nutrition Academy. Programming research: where are we and where do we go from here? Am J Clin Nutr. 2011 Dec;94(6 Suppl):2036S–2043S.

[4] Oddy WH, Mori TA, Huang RC, Marsh JA, Pennell CE, Chivers PT, Hands BP, Jacoby P, Rzehak P, Koletzko BV, Beilin LJ. Early infant feeding and adiposity risk: from infancy to adulthood. Ann Nutr Metab. 2014;64:262-270.

[5] Flexeder C, Thiering E, Brüske I, Koletzko S, Bauer CP, Wichmann HE, Mansmann U, von Berg A, Berdel D, Krämer U, Schaaf B, Lehmann I, Herbarth O, Heinrich J for the GINIplus and LISAplus Study Group. Growth velocity during infancy and onset of asthma in school-aged children. Allergy. 2012 Feb;67(2):257–264.

[6] Rzehak P, Wijga AH, Keil T, Eller E, Bindslev-Jensen C, Smit HA, Weyler J, Dom S, Sunyer J, Mendez M, Torrent M, Vall O, Bauer CP, Bderdel D, Schaaf B, Chen CM, Bergström A, Fantini MP, Mommers M, Wahn U, Lau S, Heinrich J for the working group of GA$^2$LEN-WP 1.5 Birth Cohorts. Body mass index trajectory classes and incident asthma in childhood: results from 8 European Birth Cohorts–a

337 Global Allergy and Asthma European Network initiative. J Allergy Clin Immunol. 2013 Jun;131(6):1528–
338 1536.

339 [7] Scholtens S, Wijga AH, Seidell JC, Brunekreef B, de Jongste JC, Gehring U, Postma DS, Kerkhof M,
340 Smit HA. Overweight and changes in weight status during childhood in relation to asthma symptoms at 8
341 years of age. J Allergy Clin Immunol. 2009 Jun;123(6):1312–8.e2.

342 [8] Thiering E, Brüske I, Kratzsch J, Hoffmann B, Herbarth O, von Berg A, Schaaf B, Wichmann HE,
343 Heinrich J, the LISAplus Study Group. Peak growth velocity in infancy is positively associated with blood
344 pressure in school-aged children. J Hypertens. 2012 Jun;30(6):1114–1121.

345 [9] Shore SA. Obesity and asthma: possible mechanisms. J Allergy Clin Immunol. 2008
346 May;121(5):1087–93; quiz 1094–5.

347 [10] Canoy D, Pekkanen J, Elliott P, Pouta A, Laitinen J, Hartikainen AL, Zitting P, Patel S, Little MP,
348 Järvelin MR. Early growth and adult respiratory function in men and women followed from the fetal
349 period to adulthood. Thorax. 2007 May;62(5):396–402.

350 [11] Dezateux C, Lum S, Hoo AF, Hawdon J, Costeloe K, Stocks J. Low birth weight for gestation and
351 airway function in infancy: exploring the fetal origins hypothesis. Thorax. 2004 Jan;59(1):60–66.

352 [12] Hancox RJ, Poulton R, Greene JM, McLachlan CR, Pearce MS, Sears MR. Associations between
353 birth weight, early childhood weight gain and adult lung function. Thorax. 2009 Mar;64(3):228–232.

354 [13] Duijts L. Fetal and infant origins of asthma. Eur J Epidemiol. 2012 Jan;27(1):5–14.

355 [14] Koletzko B, Brands B, Chourdakis M, Cramer S, Grote V, Hellmuth C, Kirchberg F, Prell C, Rzehak
356 P, Uhl O, Weber M. The Power of Programming and The Early Nutrition Project: opportunities for health

357 promotion by nutrition during the first thousand days of life and beyond. Ann Nutr Metab. 2014;64:141–
358 150.

359 [15] Turner S, Zhang G, Young S, Cox M, Goldblatt J, Landau L, Le Souëf P. Associations between
360 postnatal weight gain, change in postnatal pulmonary function, formula feeding and early asthma.
361 Thorax. 2008 Mar;63(3):234–239.

362 [16] van der Gugten AC, Koopman M, Evelein AMV, Verheij TJM, Uiterwaal CSPM, van der Ent CK.
363 Rapid early weight gain is associated with wheeze and reduced lung function in childhood. Eur Respir J.
364 2012 Feb;39(2):403–410.

365 [17] von Berg A, Krämer U, Link E, Bollrath C, Heinrich J, Brockow I, Koletzko S, Grübl A, Filipiak-
366 Pittroff B, Wichmann HE, Bauer CP, Reinhardt D, Berdel D, the GINIplus study group. Impact of early
367 feeding on childhood eczema: development after nutritional intervention compared with the natural
368 course - the GINIplus study up to the age of 6 years. Clin Exp Allergy. 2010 Apr;40(4):627–636.

369 [18] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der
370 Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF,
371 Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. Eur Respir J. 2005 Aug;26(2):319–338.

372 [19] Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MSM,
373 Zheng J, Stocks J on behalf of the ERS Global Lung function Initiative. Multi-ethnic reference values for
374 spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012
375 Dec;40(6):1324–1343.

[20] Simondon K, Simondon F, Delpeuch F, Cornu A. Comparative study of five growth models applied to weight data from Congolese infants between birth and 14 months of age. Am J Hum Biol. 1992;4:327–335.

[21] Tzoulaki I, Sovio U, Pillas D, Hartikainen AL, Pouta A, Laitinen J, Tammelin TH, Jarvelin MR, Elliott P. Relation of immediate postnatal growth with obesity and related metabolic risk factors in adulthood: the northern Finland birth cohort 1966 study. Am J Epidemiol. 2010 May;171(9):989–998.

[22] Berkey CS, Reed RB. A model for describing normal and abnormal growth in early childhood. Hum Biol. 1987 Dec;59(6):973–987.

[23] Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CPM, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. Eur Respir J. 2005 Nov;26(5):948–968.

[24] Hastie T, Tibshirani R. Generalized Additive Models. Statistical Science. 1986;1(3):297–310.

[25] R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria; 2013. Available from: http://www.R-project.org/.

[26] Sherrill DL, Guerra S, Wright AL, Morgan WJ, Martinez FD. Relation of early childhood growth and wheezing phenotypes to adult lung function. Pediatr Pulmonol. 2011 Oct;46(10):956–963.

[27] Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. Lancet Respir Med. 2013 Nov;1(9):728–742.

[28] Burri PH. Structural aspects of postnatal lung development - alveolar formation and growth. Biol Neonate. 2006;89(4):313–322.

[29] Lucas JS, Inskip HM, Godfrey KM, Foreman CT, Warner JO, Gregson RK, Clough JB. Small size at birth and greater postnatal weight gain: relationships to diminished infant lung function. Am J Respir Crit Care Med. 2004 Sep;170(5):534–540.

[30] Bisgaard H, Jensen SM, Bønnelykke K. Interaction between asthma and lung function growth in early life. Am J Respir Crit Care Med. 2012 Jun;185(11):1183–1189.

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

[32] Koletzko B, Brands B, Poston L, Godfrey K, Demmelmair H, for the Early Nutrition Project. Early nutrition programming of long-term health. Proc Nutr Soc. 2012 Aug;71(3):371–378.

[33] Weber M, Grote V, Closa-Monasterolo R, Escribano J, Langhendries JP, Dain E, Giovannini M, Verduci E, Gruszfeld D, Socha P, Koletzko B for The European Childhood Obesity Trial Study Group. Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial. Am J Clin Nutr. 2014 May;99(5):1041-1051.

[34] Green CJ, Holly JM, Bolton CE, Bayer A, Ebrahim S, Gallacher J, Ben-Shlomo Y. Role of IGF-I, IGF-II and IGFBP-3 in lung function of males: the Caerphilly Prospective Study. Int J Mol Epidemiol Genet. 2014;5(2):112–119.

# Tables

**Table 1. Study characteristics of participants at the 15 year follow-up [with valid lung function data]**

| | % (n/N) or median (25th, 75th percentile) | | |
|---|---|---|---|
| | Male (n=884) | Female (n=958) | Total (n=1842) |
| Study centre | | | |
| Munich, % | 50.7 (448/884) | 50.2 (481/958) | 50.4 (929/1842) |
| Wesel, % | 49.3 (436/884) | 49.8 (477/958) | 49.6 (913/1842) |
| Study | | | |
| GINI observation, % | 48.3 (427/884) | 50.7 (486/958) | 49.6 (913/1842) |
| GINI intervention, % | 51.7 (457/884) | 49.3 (472/958) | 50.4 (929/1842) |
| Sex | | | |
| Male, % | 100 (884/884) | -- | 48 (884/1842) |
| Female, % | -- | 100 (958/958) | 52 (958/1842) |
| Age, years | 15.2 (15.1,15.4) | 15.2 (15.1,15.4) | 15.2 (15.1,15.4) |
| Weight at 15 years, kg * | 64 (57,73) | 58 (53,64) | 60 (54,67.5) |
| Height at 15 years, cm * | 177 (172,182) | 167 (163,171) | 171 (166,177) |
| Peak weight velocity, kg/year * | 13.7 (12.3,15.5) | 11.5 (10.1,13.1) | 12.5 (10.9,14.4) |
| Birth weight, g * | 3520 (3180,3860) | 3400 (3110,3690) | 3470 (3150,3760) |
| Parental education[a] | | | |
| Low, % | 7.6 (67/884) | 6.3 (60/956) | 6.9 (127/1840) |
| Medium, % | 30.1 (266/884) | 26.3 (251/956) | 28.1 (517/1840) |
| High, % | 62.3 (551/884) | 67.5 (645/956) | 65 (1196/1840) |
| Exclusive breastfeeding | | | |
| No, % | 24.7 (204/827) | 23.5 (212/904) | 24 (416/1731) |
| 1-4 months, % | 28.4 (235/827) | 27.5 (249/904) | 28 (484/1731) |
| >4 months, % | 46.9 (388/827) | 49 (443/904) | 48 (831/1731) |
| Smoking during pregnancy | | | |
| No, % | 88.3 (709/803) | 87.6 (735/839) | 87.9 (1444/1642) |
| Yes, % | 11.7 (94/803) | 12.4 (104/839) | 12.1 (198/1642) |
| Parental atopy[b] | | | |
| No, % | 40.9 (358/876) | 41.5 (394/949) | 41.2 (752/1825) |
| Yes, % | 59.1 (518/876) | 58.5 (555/949) | 58.8 (1073/1825) |
| Exposure to tobacco smoke at home up to age 6 | | | |
| No, % | 56.7 (468/825) | 57.9 (520/898) | 57.3 (988/1723) |
| Yes, % | 43.3 (357/825) | 42.1 (378/898) | 42.7 (735/1723) |
| Asthma at age 15 * | | | |
| No, % | 89.2 (767/860) | 92.7 (855/922) | 91 (1622/1782) |
| Yes, % | 10.8 (93/860) | 7.3 (67/922) | 9 (160/1782) |
| Positive bronchodilation at age 15 * | | | |
| No, % | 94.9 (774/816) | 97 (869/896) | 96 (1643/1712) |
| Yes, % | 5.1 (42/816) | 3 (27/896) | 4 (69/1712) |
| Asthma and/or positive bronchodilation * | | | |
| No, % | 84.2 (669/795) | 89.7 (781/871) | 87 (1450/1666) |
| Yes, % | 15.8 (126/795) | 10.3 (90/871) | 13 (216/1666) |

[a] low for less than 10, medium for 10 and high for more than 10 years of school

[b] either mother or father reported having physician-diagnosed asthma, hay fever, allergic rhinitis, allergic conjunctivitis or atopic eczema at one point in time

* significant difference between males and females

**Table 2. Characteristics of spirometric lung function parameters measured before and after bronchodilation**

| | Median (25th, 75th percentile) | | |
|---|---|---|---|
| | Male (n=884) | Female (n=958) | Total (n=1842) |
| **before bronchodilation** | | | |
| $FEV_1$, l * | 3.82 (3.41,4.25) | 3.2 (2.93,3.46) | 3.43 (3.05,3.89) |
| FVC, l * | 4.54 (3.99,5.03) | 3.62 (3.3,3.96) | 3.95 (3.5,4.56) |
| $FEV_1$/FVC, % * | 85.37 (80.74,89.3) | 88.77 (84.49,92.56) | 87.12 (82.46,91.21) |
| PEF, l/s * | 7.66 (6.89,8.57) | 6.48 (5.9,7.12) | 6.98 (6.16,7.91) |
| $FEF_{25}$, l/s * | 6.48 (5.64,7.34) | 5.83 (5.31,6.48) | 6.08 (5.42,6.9) |
| $FEF_{50}$, l/s * | 4.59 (3.81,5.43) | 4.23 (3.56,4.82) | 4.36 (3.68,5.08) |
| $FEF_{75}$, l/s * | 2.21 (1.71,2.76) | 2.08 (1.65,2.52) | 2.15 (1.67,2.62) |
| $FEF_{25-75}$, l/s * | 4.03 (3.33,4.75) | 3.71 (3.17,4.28) | 3.84 (3.24,4.5) |
| | | | |
| z-score $FEV_1$ GLI | -0.66 (-1.27,0) | -0.59 (-1.15,0.02) | -0.63 (-1.2,0.01) |
| z-score FVC GLI * | -0.63 (-1.24,0.05) | -0.51 (-1.06,0.1) | -0.55 (-1.13,0.08) |
| z-score $FEV_1$/FVC GLI | -0.12 (-0.81,0.55) | -0.09 (-0.79,0.59) | -0.11 (-0.8,0.57) |
| z-score $FEF_{75}$ GLI | -0.13 (-0.82,0.52) | -0.13 (-0.75,0.5) | -0.13 (-0.78,0.51) |
| z-score $FEF_{25-75}$ GLI * | -0.46 (-1.22,0.19) | -0.37 (-0.97,0.31) | -0.41 (-1.09,0.26) |
| | | | |
| **after bronchodilation** | | | |
| $FEV_1$, l * | 3.95 (3.51,4.36) | 3.27 (3.01,3.55) | 3.52 (3.14,4) |
| FVC, l * | 4.51 (4.02,5) | 3.61 (3.31,3.96) | 3.96 (3.49,4.55) |
| $FEV_1$/FVC, % * | 88.09 (84.2,91.57) | 91.53 (87.51,94.3) | 89.85 (85.65,93.19) |
| PEF, l/s * | 7.79 (6.93,8.77) | 6.66 (6.05,7.31) | 7.13 (6.32,8.07) |
| $FEF_{25}$, l/s * | 6.79 (5.92,7.67) | 6.08 (5.49,6.75) | 6.38 (5.63,7.15) |
| $FEF_{50}$, l/s * | 5.07 (4.28,5.75) | 4.62 (4.08,5.22) | 4.79 (4.16,5.52) |
| $FEF_{75}$, l/s * | 2.55 (1.99,3.14) | 2.42 (1.96,2.91) | 2.47 (1.98,3.04) |
| $FEF_{25-75}$, l/s * | 4.51 (3.74,5.16) | 4.12 (3.57,4.69) | 4.26 (3.65,4.9) |
| | | | |
| z-score $FEV_1$ GLI | -0.4 (-1.06,0.24) | -0.37 (-0.95,0.23) | -0.38 (-0.99,0.23) |
| z-score FVC GLI * | -0.62 (-1.22,-0.01) | -0.53 (-1.08,0.09) | -0.57 (-1.15,0.04) |
| z-score $FEV_1$/FVC GLI | 0.34 (-0.3,0.94) | 0.37 (-0.31,0.99) | 0.35 (-0.31,0.96) |
| z-score $FEF_{75}$ GLI | 0.27 (-0.35,0.91) | 0.34 (-0.23,0.98) | 0.32 (-0.29,0.95) |
| z-score $FEF_{25-75}$ GLI * | -0.03 (-0.7,0.55) | 0.14 (-0.45,0.74) | 0.06 (-0.56,0.67) |

Abbreviations: $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; $FEF_{25}$, $FEF_{50}$, $FEF_{75}$, forced expiratory flow rates at 25, 50 and 75% of exhaled FVC; $FEF_{25-75}$, mean flow rate between 25 and 75 % of FVC; GLI, z-scores according to the Global Lung Function Initiative [19]

* significant difference between males and females

**Table 3. Results for the association between peak weight velocity per interquartile range increase and lung function parameters measured before bronchodilation**

| | Model 1[a] | | | Model 2[b] | | | Model 3[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | p-value | β | 95% CI | p-value | β | 95% CI | p-value |
| $FEV_1$ | **0.137** | 0.099, 0.174 | <0.001 | **-0.034** | -0.065, -0.004 | 0.029 | -0.013 | -0.047, 0.022 | 0.469 |
| FVC | **0.225** | 0.182, 0.268 | <0.001 | 0.002 | -0.031, 0.035 | 0.904 | 0.013 | -0.025, 0.051 | 0.498 |
| $FEV_1$/FVC | **-1.416** | -1.854, -0.978 | <0.001 | **-0.905** | -1.366, -0.445 | <0.001 | **-0.691** | -1.207, -0.174 | 0.009 |
| PEF | **0.150** | 0.069, 0.230 | <0.001 | **-0.092** | -0.170, -0.014 | 0.021 | -0.054 | -0.143, 0.034 | 0.228 |
| $FEF_{25}$ | 0.078 | -0.002, 0.158 | 0.055 | **-0.115** | -0.195, -0.035 | 0.005 | -0.068 | -0.158, 0.021 | 0.136 |
| $FEF_{50}$ | -0.018 | -0.091, 0.055 | 0.628 | **-0.183** | -0.256, -0.109 | <0.001 | **-0.129** | -0.211, -0.046 | 0.002 |
| $FEF_{75}$ | -0.023 | -0.074, 0.028 | 0.374 | **-0.096** | -0.148, -0.045 | <0.001 | **-0.071** | -0.130, -0.012 | 0.018 |
| $FEF_{25-75}$ | -0.007 | -0.072, 0.058 | 0.829 | **-0.151** | -0.215, -0.086 | <0.001 | **-0.103** | -0.176, -0.030 | 0.006 |

Abbreviations: CI, confidence interval, $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; $FEF_{25}$, $FEF_{50}$, $FEF_{75}$, forced expiratory flow rates at 25, 50 and 75% of exhaled FVC; $FEF_{25-75}$, mean flow rate between 25 and 75 % of FVC

[a] adjusted for sex

[b] adjusted for sex, study centre, cohort, age, weight and height at lung function measurement

[c] adjusted for all variables in Model 2 plus parental education, birth weight, maternal smoking during pregnancy, breastfeeding, parental atopy, exposure to tobacco smoke at home up to age 6 and doctor diagnosed asthma and/or positive bronchodilation response

**Table 4. Results for the association between peak weight velocity per interquartile range increase and lung function parameters measured after bronchodilation**

| | Model 1[a] | | | Model 2[b] | | | Model 3[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | p-value | β | 95% CI | p-value | β | 95% CI | p-value |
| $FEV_1$ | **0.159** | 0.120, 0.198 | <0.001 | -0.016 | -0.047, 0.015 | 0.310 | 0.003 | -0.031, 0.037 | 0.859 |
| FVC | **0.230** | 0.186, 0.274 | <0.001 | 0.013 | -0.021, 0.047 | 0.451 | 0.022 | -0.016, 0.059 | 0.256 |
| $FEV_1$/FVC | **-1.107** | -1.504, -0.710 | <0.001 | **-0.723** | -1.139, -0.308 | 0.001 | **-0.473** | -0.930, -0.015 | 0.043 |
| PEF | **0.178** | 0.096, 0.261 | <0.001 | -0.043 | -0.123, 0.037 | 0.288 | -0.015 | -0.103, 0.073 | 0.737 |
| $FEF_{25}$ | **0.110** | 0.028, 0.192 | 0.008 | -0.075 | -0.155, 0.006 | 0.069 | -0.036 | -0.125, 0.052 | 0.425 |
| $FEF_{50}$ | 0.052 | -0.023, 0.126 | 0.173 | **-0.131** | -0.204, -0.058 | <0.001 | **-0.083** | -0.165, -0.001 | 0.048 |
| $FEF_{75}$ | -0.011 | -0.069, 0.047 | 0.707 | **-0.113** | -0.170, -0.055 | <0.001 | **-0.089** | -0.153, -0.024 | 0.007 |
| $FEF_{25-75}$ | 0.028 | -0.040, 0.095 | 0.423 | **-0.137** | -0.203, -0.071 | <0.001 | **-0.093** | -0.166, -0.020 | 0.013 |

Abbreviations: CI, confidence interval, $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; $FEF_{25}$, $FEF_{50}$, $FEF_{75}$, forced expiratory flow rates at 25, 50 and 75% of exhaled FVC; $FEF_{25-75}$, mean flow rate between 25 and 75 % of FVC

[a] adjusted for sex

[b] adjusted for sex, study centre, cohort, age, weight and height at lung function measurement

[c] adjusted for all variables in Model 2 plus parental education, birth weight, maternal smoking during pregnancy, breastfeeding, parental atopy, exposure to tobacco smoke at home up to age 6 and doctor diagnosed asthma and/or positive bronchodilation response

**Table 5. Results for the association between peak weight velocity per interquartile range increase and GLI z-scores for lung function parameters (before and after bronchodilation)**

| | Model 1[a] | | | Model 2[b] | | | Model 3[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | p-value | β | 95% CI | p-value | β | 95% CI | p-value |
| **before bronchodilation** | | | | | | | | | |
| z-score $FEV_1$ GLI | -0.007 | -0.072, 0.058 | 0.827 | **-0.081** | -0.148, -0.015 | 0.016 | -0.036 | -0.112, 0.039 | 0.341 |
| z-score FVC GLI | **0.102** | 0.038, 0.167 | 0.002 | 0.000 | -0.063, 0.064 | 0.994 | 0.024 | -0.049, 0.096 | 0.522 |
| z-score $FEV_1$/FVC GLI | **-0.198** | -0.268, -0.127 | <0.001 | **-0.147** | -0.221, -0.073 | <0.001 | **-0.122** | -0.204, -0.039 | 0.004 |
| z-score $FEF_{75}$ GLI | **-0.144** | -0.211, -0.078 | <0.001 | **-0.136** | -0.207, -0.066 | <0.001 | **-0.097** | -0.177, -0.017 | 0.017 |
| z-score $FEF_{25-75}$ GLI | **-0.132** | -0.199, -0.064 | <0.001 | **-0.167** | -0.238, -0.095 | <0.001 | **-0.116** | -0.197, -0.036 | 0.005 |
| **after bronchodilation** | | | | | | | | | |
| z-score $FEV_1$ GLI | 0.046 | -0.020, 0.112 | 0.172 | -0.040 | -0.107, 0.027 | 0.241 | 0.001 | -0.074, 0.076 | 0.976 |
| z-score FVC GLI | **0.125** | 0.059, 0.190 | <0.001 | 0.022 | -0.043, 0.087 | 0.506 | 0.042 | -0.030, 0.114 | 0.253 |
| z-score $FEV_1$/FVC GLI | **-0.154** | -0.221, -0.086 | <0.001 | **-0.124** | -0.194, -0.054 | 0.001 | **-0.088** | -0.166, -0.011 | 0.026 |
| z-score $FEF_{75}$ GLI | **-0.131** | -0.199, -0.063 | <0.001 | **-0.144** | -0.216, -0.072 | <0.001 | **-0.107** | -0.187, -0.028 | 0.008 |
| z-score $FEF_{25-75}$ GLI | **-0.102** | -0.169, -0.036 | 0.003 | **-0.150** | -0.220, -0.080 | <0.001 | **-0.101** | -0.179, -0.023 | 0.011 |

Abbreviations: CI, confidence interval, $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEF_{75}$, forced expiratory flow rates at 75% of exhaled FVC; $FEF_{25-75}$, mean flow rate between 25 and 75 % of FVC; GLI, z-scores according to the Global Lung Function Initiative [19]

[a] adjusted for sex

[b] adjusted for sex, study centre, cohort, age, weight and height at lung function measurement

[c] adjusted for all variables in Model 2 plus parental education, birth weight, maternal smoking during pregnancy, breastfeeding, parental atopy, exposure to tobacco smoke at home up to age 6 and doctor diagnosed asthma and/or positive bronchodilation response

# Supplementary Material

**Supplement Table S1. Results for the association between peak weight velocity per interquartile range increase and lung function parameters measured before bronchodilation for the study population restricted to non-asthmatics and subjects with no positive bronchodilation response**

| | Model1[a] | | | Model 2[b] | | | Model 3[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | p-value | β | 95% CI | p-value | β | 95% CI | p-value |
| $FEV_1$ | **0.150** | 0.109, 0.192 | <0.001 | -0.016 | -0.050, 0.017 | 0.331 | -0.007 | -0.043, 0.030 | 0.722 |
| FVC | **0.239** | 0.190, 0.287 | <0.001 | 0.020 | -0.017, 0.057 | 0.295 | 0.023 | -0.018, 0.064 | 0.265 |
| $FEV_1$/FVC | **-1.407** | -1.865, -0.950 | <0.001 | **-0.886** | -1.367, -0.405 | <0.001 | **-0.743** | -1.270, -0.217 | 0.006 |
| PEF | **0.188** | 0.100, 0.277 | <0.001 | -0.053 | -0.138, 0.032 | 0.221 | -0.026 | -0.119, 0.067 | 0.581 |
| $FEF_{25}$ | **0.117** | 0.031, 0.202 | 0.008 | -0.076 | -0.162, 0.010 | 0.082 | -0.051 | -0.145, 0.043 | 0.284 |
| $FEF_{50}$ | 0.005 | -0.074, 0.085 | 0.894 | **-0.156** | -0.235, -0.077 | <0.001 | **-0.124** | -0.211, -0.037 | 0.005 |
| $FEF_{75}$ | -0.014 | -0.070, 0.042 | 0.622 | **-0.0**80 | -0.137, -0.023 | 0.006 | **-0.067** | -0.130, -0.003 | 0.040 |
| $FEF_{25-75}$ | 0.014 | -0.056, 0.084 | 0.702 | **-0.123** | -0.193, -0.054 | 0.001 | **-0.097** | -0.174, -0.020 | 0.014 |
| | | | | | | | | | |
| z-score $FEV_1$ GLI | 0.025 | -0.046, 0.096 | 0.495 | -0.044 | -0.117, 0.029 | 0.237 | -0.023 | -0.103, 0.058 | 0.582 |
| z-score FVC GLI | **0.135** | 0.063, 0.207 | <0.001 | 0.035 | -0.037, 0.107 | 0.337 | 0.043 | -0.036, 0.122 | 0.284 |
| z-score $FEV_1$/FVC GLI | **-0.200** | -0.275, -0.125 | <0.001 | **-0.147** | -0.226, -0.068 | <0.001 | **-0.129** | -0.215, -0.042 | 0.004 |
| z-score $FEF_{75}$ GLI | **-0.134** | -0.205, -0.062 | <0.001 | **-0.114** | -0.190, -0.038 | 0.003 | **-0.093** | -0.178, -0.009 | 0.031 |
| z-score $FEF_{25-75}$ GLI | **-0.111** | -0.183, -0.039 | 0.003 | **-0.139** | -0.215, -0.063 | <0.001 | **-0.109** | -0.193, -0.025 | 0.011 |

Abbreviations: CI, confidence interval, $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; $FEF_{25}$, $FEF_{50}$, $FEF_{75}$, forced expiratory flow rates at 25, 50 and 75% of exhaled FVC; $FEF_{25-75}$, mean flow rate between 25 and 75 % of FVC; GLI, z-scores according to the Global Lung Function Initiative [19]

[a] adjusted for sex

[b] adjusted for sex, study centre, cohort, age, weight and height at lung function measurement

[c] adjusted for all variables in Model 2 plus parental education, birth weight, maternal smoking during pregnancy, breastfeeding, parental atopy and exposure to tobacco smoke at home up to age 6

**Supplement Table S2. Results for the association between peak weight velocity per interquartile range increase and lung function parameters measured after bronchodilation for the study population restricted to non-asthmatics and subjects with no positive bronchodilation response**

| | Model1[a] | | | Model 2[b] | | | Model 3[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | β | 95% CI | p-value | β | 95% CI | p-value | β | 95% CI | p-value |
| $FEV_1$ | **0.166** | 0.124, 0.208 | <0.001 | -0.011 | -0.044, 0.022 | 0.515 | 0.002 | -0.034, 0.039 | 0.897 |
| FVC | **0.238** | 0.191, 0.286 | <0.001 | 0.020 | -0.017, 0.057 | 0.278 | 0.028 | -0.013, 0.069 | 0.178 |
| $FEV_1$/FVC | **-1.133** | -1.550, -0.716 | <0.001 | **-0.766** | -1.201, -0.331 | 0.001 | **-0.615** | -1.087, -0.142 | 0.011 |
| PEF | **0.201** | 0.112, 0.290 | <0.001 | -0.014 | -0.101, 0.073 | 0.748 | 0.023 | -0.070, 0.117 | 0.624 |
| $FEF_{25}$ | **0.122** | 0.034, 0.210 | 0.006 | -0.060 | -0.147, 0.027 | 0.177 | -0.021 | -0.115, 0.073 | 0.659 |
| $FEF_{50}$ | 0.060 | -0.018, 0.139 | 0.134 | **-0.112** | -0.189, -0.034 | 0.005 | -0.085 | -0.170, 0.001 | 0.054 |
| $FEF_{75}$ | -0.018 | -0.080, 0.045 | 0.585 | **-0.114** | -0.177, -0.052 | <0.001 | **-0.102** | -0.171, -0.033 | 0.004 |
| $FEF_{25-75}$ | 0.028 | -0.043, 0.100 | 0.440 | **-0.128** | -0.197, -0.058 | <0.001 | **-0.103** | -0.180, -0.027 | 0.008 |
| | | | | | | | | | |
| z-score $FEV_1$ GLI | 0.054 | -0.018, 0.126 | 0.142 | -0.031 | -0.105, 0.042 | 0.400 | -0.002 | -0.082, 0.079 | 0.970 |
| z-score FVC GLI | **0.136** | 0.065, 0.208 | <0.001 | 0.036 | -0.035, 0.108 | 0.320 | 0.053 | -0.026, 0.131 | 0.191 |
| z-score $FEV_1$/FVC GLI | **-0.157** | -0.229, -0.085 | <0.001 | **-0.129** | -0.203, -0.055 | 0.001 | **-0.109** | -0.190, -0.028 | 0.008 |
| z-score $FEF_{75}$ GLI | **-0.140** | -0.213, -0.067 | <0.001 | **-0.147** | -0.224, -0.070 | <0.001 | **-0.126** | -0.211, -0.042 | 0.004 |
| z-score $FEF_{25-75}$ GLI | **-0.103** | -0.174, -0.033 | 0.004 | **-0.140** | -0.214, -0.065 | <0.001 | **-0.113** | -0.195, -0.031 | 0.007 |

Abbreviations: CI, confidence interval, $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; $FEF_{25}$, $FEF_{50}$, $FEF_{75}$, forced expiratory flow rates at 25, 50 and 75% of exhaled FVC; $FEF_{25-75}$, mean flow rate between 25 and 75 % of FVC; GLI, z-scores according to the Global Lung Function Initiative [19]

[a] adjusted for sex

[b] adjusted for sex, study centre, cohort, age, weight and height at lung function measurement

[c] adjusted for all variables in Model 2 plus parental education, birth weight, maternal smoking during pregnancy, breastfeeding, parental atopy and exposure to tobacco smoke at home up to age 6