

Growth velocity during infancy and onset of asthma in school-aged children

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Abstract

Background: Growth velocities during infancy might affect the risk of asthma in childhood. This study examines the association between peak height and weight velocities during the first 2 years of life and onset of asthma and wheeze up to 10 years of age.

Methods: Data from 9086 children who participated in the GINIplus and LISAplus birth cohorts were analyzed. Information on asthma was requested annually from 1 to 10 years and information on wheeze at 1, 2, 4, 6, and 10 years. Peak height and weight velocities were calculated using height and weight measurements obtained between birth and 2 years of age. Cox proportional hazards models and generalized linear mixed models were calculated after adjustment for potential confounding factors including birth weight and body mass index at 10 years of age.

Results: Per interquartile range increase in peak weight velocity (PWV), the risk of asthma increased significantly (adjHR: 1.22; CI: 1.02–1.47). The relationship between peak height velocity (PHV) and onset of asthma was nonsignificant (adjHR: 1.08; CI: 0.88–1.31). Wheeze was not significantly associated with PHV or with PWV (adjOR: 1.07; CI: 0.64–1.77 and adjOR: 1.11; CI: 0.68–1.79, respectively).

Conclusions: Weight gain during infancy is positively associated with physician-diagnosed asthma in school-aged children.

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Several studies in adults have reported an association between asthma and obesity (1, 2). Compared to these studies, the results of cross-sectional studies in children and adolescents also show a positive association between body mass index and asthma, but results are less consistent (2). Because in cross-sectional studies body mass index and asthma are assessed at the same time, it cannot be differentiated

whether obesity affects asthma or vice versa (3). However, in some prospective studies, obesity was suggested to increase the risk of asthma later in life in childhood and adolescents as well as in adults, with inconsistent findings also for men and women (2, 4, 5). For instance, in a study of children aged 6–14 years, an increased risk of asthma was determined only in obese boys (6) whereas in a study of

7- to 18-year-old children, such an association was found among girls (7).

The results for the association between weight gain in infancy and asthma later in life are even less clear. Besides these inconsistencies, no longitudinal models were applied in any study so far. Therefore, we aimed to examine the relationship between growth velocity in infancy and onset of asthma or wheeze later in life prospectively and longitudinally. Two German birth cohorts followed children from birth to 10 years of age. We used modelled height and weight velocities during the first 2 years of life as measures for growth in infancy. These growth velocities were derived from growth models that depict the different periods of growth in infancy.

Materials and methods

Study population

Data from two ongoing German birth cohorts of healthy full-term neonates (gestational age ≥ 37 weeks) born between 1995 and 1999 in Munich, Wesel, Bad Honnef, and Leipzig with very similar study design were combined for longitudinal analyses of asthma and wheeze. The GINIplus (German Infant Nutritional Intervention plus environmental and genetic influences on allergy development) study is an ongoing birth cohort study, initiated to prospectively investigate the influence of nutrition intervention during infancy plus air pollution and genetics on allergy development. Between September 1995 and July 1998, a total of 5991 newborns were recruited in obstetric clinics in Munich and Wesel whereby parental atopy was not an inclusion criterion for the study. The cohort is composed of an intervention ($n = 2252$) and a nonintervention group ($n = 3739$) whereby group assignment has been based on family history of allergy. The intervention comprised a randomized controlled trial to compare the effect of hydrolyzed formulas vs conventional cow's milk formula on development of allergic diseases. Mothers were encouraged to breastfeed for at least 4 months and were advised to feed the randomly allocated formula in case of insufficient breastfeeding. Details on the study design have been described elsewhere (8–10). The LISAplus study is an ongoing population-based birth cohort study, designed to assess 'Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics'. In total, 3097¹ healthy full-term neonates were recruited from 14 obstetrical clinics in Munich, Leipzig, Wesel, and Bad Honnef between November 1997 and January 1999, and the participants were not preselected based on family history of allergic disease. A detailed description of screening and recruitment has been described previously (11, 12). Children were followed at 1, 2, 3, 4, 6, and 10 years of age in the GINIplus study, whereas at the age of 6, 12, and 18 months and 2, 4, 6, and 10 years in the LISAplus study.

¹After the 6-year follow-up, two participants dropped out of the LISAplus study. Thus, only 3095 children of the LISAplus study were included in our analyses.

For both studies, approval by the respective local ethics committees (Bavarian General Medical Council, University of Leipzig, Medical Council of North-Rhine-Westphalia) and written consent from all participating families were obtained.

Growth velocities

Height and weight measurements during infancy were obtained by using information of the preventive medical checkups ('U-Untersuchungen'), noted in the baby books and reported by the parents at follow-up. These are repeated physical examinations of a child conducted by a pediatrician at birth, at days 3–10, at weeks 4–6, months 3–4, 6–7, 10–12 and at the 21–24th months of life to monitor physical growth. Height and weight growth curves through age 2 years were calculated according to the modified Reed1 model (13, 14) by means of the anthropometric measurements except for those at days 3–10. In general, the Reed1 model is a four-parameter growth model as described by Berkey and Reed (15). This model is convenient to describe early childhood growth in height and weight, and it is linear in its parameters. As this model is not defined at age = 0, the modified version of the first-order Reed model (14) that also comprises birth weight and height, respectively, was used. Thereby, individual growth curves were computed separately for girls and boys using nonlinear random-effects models. The first derivatives of the growth curves depict the growth velocity curves, whereas the second derivatives characterize the acceleration curves. Peak height velocity (PHV) and peak weight velocity (PWV) were defined as the maximum of the first derivatives of the height and weight growth curves, respectively. Subjects with only one or two growth measurements and also twins were excluded from all analyses.

Definition of outcome and confounding variables

Information on asthma and wheezing was collected using self-administered questionnaires at follow-up completed by the parents. The questions for physician-diagnosed asthma, requested annually from 1 to 10 years in the GINIplus study and additionally at 18 months in the LISAplus study, were used to define time variables indicating the time interval for first onset of physician-diagnosed asthma. Therefore, we only included children with complete information until first onset of asthma. At age 1, 2, 4, 6, and 10 years in the GINIplus study and also at 6 and 18 months in the LISAplus study, parents were asked whether their child had experienced wheeze in the last 6 or 12 months. The questions referred to the past 6 and 12 months, respectively, and were used to define outcome variables for wheeze at 1, 2, 4, 6, and 10 years of age.

The set of confounders included information on gender and age of the child, study center (Munich, Leipzig, Wesel, Bad Honnef), maternal smoking during pregnancy, birth weight, number of siblings, body mass index (BMI) at age 10, exclusive breastfeeding (no exclusive breastfeeding, 1–4, >4 months), parental education level, and parental history

of atopy. The parental education levels were defined as follows: low for <10, intermediate for 10 and high for more than 10 years of school. Parental atopy was defined as ever having physician-diagnosed asthma, hay fever, allergic rhinitis, allergic conjunctivitis, or atopic eczema.

Longitudinal statistical analyses

Cox proportional hazards models for interval-censored data were used to analyze the effects of peak height and weight velocities during the first 2 years of life on the first onset of physician-diagnosed asthma up to age 10. Compared to generalized estimating equations that focus only on modelling the mean of correlated observations, the cox approach for modelling the time until an event occurs is more appropriate for our analysis. Furthermore, survival curves for asthma were computed according to the approach of Turnbull (16) for interval-censored data. The association between wheeze after 2 years of age and growth velocities was assessed by using generalized linear mixed models with logit link function and random intercepts. Thereby, the influence of peak height and weight velocities on the outcome variables was defined as change of risk per interquartile range (IQR) increase in peak growth velocities.

Three models for the considered associations between the outcome variables and growth velocities with different adjustment were calculated: the unadjusted model (Model 1); adjustment for gender, study area, parental education, parental atopy, breastfeeding, siblings and maternal smoking during pregnancy (Model 2), and adjustment as in Model 2 plus birth weight and body mass index at age 10 years (Model 3). For wheeze, we additionally adjusted for age and wheezing during the first 2 years of age in Models 2 and 3. Furthermore, an interaction term of peak height and weight velocities with age was included to test whether the association between wheeze and growth velocities changed with increasing age. Therefore, age was coded 4, 6, and 10.

For illustration purposes, the study participants were grouped in three categories based on the data on growth velocities: one group included children in the lowest quartile for peak height and weight velocities, a second group those in the highest quartile, and a third group contained children in the two intermediate quartiles.

Differences between both studies were tested using Pearson's chi-squared test or Wilcoxon rank sum test. The results are presented as hazard ratios (HR) for asthma and odds ratios (OR) for wheeze, respectively, 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 2.11.1 (17) or BayesX, version 2.0.1 (18).

Results

Study characteristics for both birth cohorts and the combined population are shown in Table 1. The prevalence of physician-diagnosed asthma increased with age, whereas the prevalence of wheeze decreased. The number of children with

wheeze in the total population at age 10 years was twice the number of children with asthma (7.94% vs 3.45%). The mean of the PWV was 13.00 kg per year (SD = 2.66), and the IQR was 3.48 kg per year. For the PHV, the mean was 44.05 cm per year (SD = 4.85), and the IQR increase was 6.39 cm per year. Furthermore, the mean age at PWV was 0.54 months (SD = 0.17), and at PHV, the mean age was 0.74 months (SD = 0.14).

The proportional course of the survival curves for the three different groups, illustrated in Fig. 1, indicates an association between peak height and weight velocities and asthma. For wheeze, Fig. 2 shows the frequencies of ever having experienced wheeze from birth to 10 years of age for the three different growth velocity categories.

Tables 2 and 3 present the results on the association between growth velocities and asthma and wheeze, respectively. Peak weight velocities (adjHR: 1.26; *P*-value: 0.003) but not peak height velocities (adjHR: 1.08; *P*-value: 0.362) were significantly associated with physician-diagnosed asthma after adjustment for gender, parental education, parental atopy, breastfeeding, number of siblings, maternal smoking during pregnancy, and study center (Model 2, Table 2). After further adjustment for birth weight and body mass index at age 10 years, the relationship between asthma and PWV remained statistically significant (adjHR: 1.22; *P*-value: 0.031). Thereby, each IQR increase in PWV increased the risk of asthma by 0.22 (Model 3, Table 2).

Sensitivity analyses where we excluded the GINI intervention group and adjusted for the intervention status, respectively, showed substantially the same relationship between peak growth velocities and asthma.

For wheeze, neither PHV (adjOR: 1.07; *P*-value: 0.802) nor PWV (adjOR: 1.11; *P*-value: 0.680) had a statistically significant effect after multiple adjusting for potential confounding factors including birth weight and BMI at the age of 10 years (Model 3, Table 3). Compared to 10 years of age, children had an increased risk of wheeze at 4 years of age (adjOR: 1.92) and at 6 years of age (adjOR: 1.28), respectively. The analyses for wheeze were repeated including an interaction term for the interaction between age and peak height velocities and peak weight velocities, respectively, but the interaction was not significant (data not shown). Therefore, the association between growth velocities and wheeze does not change over time.

Discussion

Increased weight gain during infancy (PWV) is associated with an increased risk of physician-diagnosed asthma in our study, but not with wheeze. Neither the relationship between PHV and asthma nor that between this velocity and wheeze was statistically significant.

A few previous studies have investigated the relationship between early childhood growth and atopic diseases longitudinally. Paul et al. (19) investigated the influence of infant weight gain patterns from birth to age 2 or 3 years on asthma development in children at high risk of asthma. Thereby, they differentiated between accelerated, average and

Table 1 Baseline characteristics of the study population of the two German birth cohorts GINIplus and LISAplus

	Mean (standard deviation) or % (n/N)		
	LISAplus (n = 3095)	GINIplus (n = 5991)	Total (n = 9086)
Peak height velocity*†, cm/year	44.57 (4.83)	43.74 (4.83)	44.05 (4.85)
Peak weight velocity*†, kg/year	12.84 (2.57)	13.09 (2.71)	13.00 (2.66)
Gender male, %	51.21 (1585/3095)	51.3 (2991/5830)	51.27 (4576/8925)
Study centre			
Munich, %	47.33 (1465/3095)	49.22 (2949/5991)	48.58 (4414/9086)
Wesel, %	11.24 (348/3095)	50.78 (3042/5991)	37.31 (3390/9086)
Leipzig, %	31.53 (976/3095)	0 (0/5991)	10.74 (976/9086)
Bad Honnef, %	9.89 (306/3095)	0 (0/5991)	3.37 (306/9086)
Exclusive breastfeeding†			
1–4 months, %	33.6 (933/2777)	29.68 (1350/4549)	31.16 (2283/7326)
>4 months, %	46.09 (1280/2777)	41.46 (1886/4549)	43.22 (3166/7326)
Parental education‡†			
Low, %	6.15 (188/3058)	12.91 (766/5932)	10.61 (954/8990)
Medium, %	29.63 (906/3058)	29.5 (1750/5932)	29.54 (2656/8990)
High, %	64.22 (1964/3058)	57.59 (3416/5932)	59.84 (5380/8990)
Parental atopy§†, %	55.42 (1580/2851)	49.81 (2935/5892)	51.64 (4515/8743)
Smoking during pregnancy, %	17.46 (519/2972)	17.97 (943/5249)	17.78 (1462/8221)
No siblings†, %	56.35 (1740/3088)	52.8 (3138/5943)	54.01 (4878/9031)
BMI at 10 years, kg/m ²	16.79 (2.31)	16.9 (2.36)	16.86 (2.34)
Birth weight, kg	3.47 (0.45)	3.47 (0.47)	3.47 (0.46)
Asthma¶			
1 year†, %	0.18 (5/2705)	1.11 (51/4611)	0.77 (56/7316)
2 years†, %	0.39 (10/2596)	1.19 (51/4292)	0.89 (61/6888)
3 years, %	0.92 (22/2388)	1.13 (47/4161)	1.05 (69/6549)
4 years, %	0.98 (23/2347)	1.31 (52/3980)	1.19 (75/6327)
5 years, %	2.21 (48/2171)	2.16 (83/3840)	2.18 (131/6011)
6 years, %	2.08 (45/2167)	2.34 (87/3722)	2.24 (132/5889)
7 years, %	2.72 (46/1694)	2.9 (93/3210)	2.83 (139/4904)
8 years, %	2.36 (40/1694)	2.83 (91/3210)	2.67 (131/4904)
9 years, %	3.19 (54/1694)	3.43 (110/3210)	3.34 (164/4904)
10 years, %	2.89 (49/1694)	3.74 (120/3210)	3.45 (169/4904)
Wheeze¶			
1 year†, %	22.72 (608/2676)	13.77 (631/4584)	17.07 (1239/7260)
2 years†, %	23.42 (611/2609)	11.02 (478/4339)	15.67 (1089/6948)
4 years, %	10.84 (262/2416)	9.76 (387/3967)	10.17 (649/6383)
6 years, %	9.55 (208/2177)	8.91 (341/3826)	9.15 (549/6003)
10 years, %	7.06 (121/1715)	8.4 (276/3284)	7.94 (397/4999)

*During first 2 years of life.

†Significant difference between GINI and LISA study.

‡Medium defined as general certificate of secondary education (GCSE); high defined as general qualification for university entrance or university degree.

§Defined as ever having physician-diagnosed asthma, hay fever, allergic rhinitis, allergic conjunctivitis, or atopic eczema.

¶Prevalences in the last 12 months.

decelerated weight gain based on established norms. Their finding was that weight gain patterns were not associated with asthma symptoms at 5 or 6 years of life, but they were related to asthma exacerbations.

Pike et al. (20) examined the influences of prenatal and postnatal growth velocities on atopy and wheeze at 3 years of age. They showed that faster abdominal circumference growth during the 11th and 19th week of gestation followed by weak growth in late gestation was associated with atopy,

but atopy was not associated with postnatal growth. On the contrary, wheeze before 3 years of age was related to conditional infant growth, especially to weight gain from 0 to 6 months and from 6 to 12 months, respectively. However, the associations between length growth and wheeze were not significant.

Another study that describes the association between postnatal weight gain, lung function, and early asthma is the study of Turner et al. (21). In their analyses, they determine an

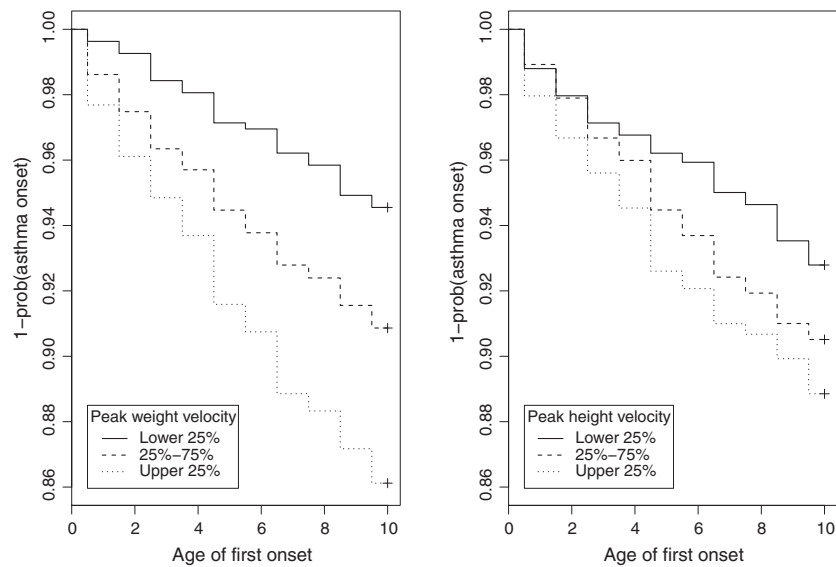


Figure 1 Survival curves for asthma, separately for peak weight and height velocities.

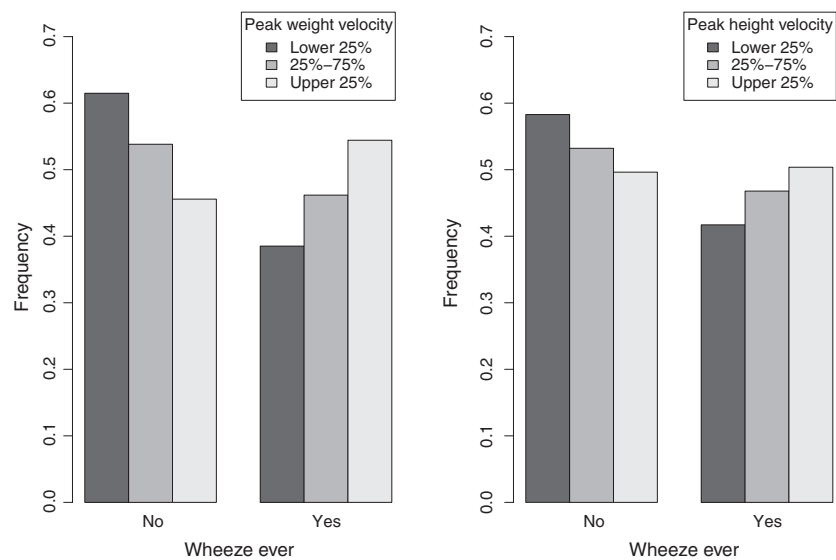


Figure 2 Barplots for ever wheezing, separately for peak weight and height velocities.

Table 2 Hazard ratios (HR) for the association between peak height and weight velocities per interquartile range (IQR) increase and onset of asthma

	Peak weight velocity (PWV)*				Peak height velocity (PHV)*			
	<i>n</i>	HR	95% CI	<i>P</i> -value	<i>n</i>	HR	95% CI	<i>P</i> -value
Model 1†	4059	1.50	1.33, 1.70	<0.001	4060	1.32	1.16, 1.50	<0.001
Model 2‡	3524	1.26	1.08, 1.47	0.003	3525	1.08	0.92, 1.26	0.362
Model 3§	3033	1.22	1.02, 1.47	0.031	3034	1.08	0.88, 1.31	0.466

*Per IQR increase.

†Unadjusted model.

‡Adjusted for gender, parental education, breastfeeding, parental atopy, number of siblings, maternal smoking during pregnancy, and study center.

§Adjusted for all variables in model 2 plus birth weight and body mass index at age 10 years.

Table 3 Odds ratios (OR) for the association between peak height and weight velocities per interquartile range (IQR) increase and wheeze

	Model 1*				Model 2†				Model 3‡			
	<i>n</i>	OR	95% CI	<i>P</i> -value	<i>n</i>	OR	95% CI	<i>P</i> -value	<i>n</i>	OR	95% CI	<i>P</i> -value
Peak weight velocity (PWV)	6228				5193				3445			
PWV IQR increase		1.23	0.81, 1.88	0.336		1.09	0.71, 1.68	0.681		1.11	0.68, 1.79	0.680
Age												
4 years						2.04	1.63, 2.56	<0.001		1.92	1.49, 2.46	<0.001
6 years						1.40	1.11, 1.76	0.004		1.28	0.99, 1.65	0.058
10 years						1.00				1.00		
Peak height velocity (PHV)	6229				5194				3446			
PHV IQR increase		1.13	0.73, 1.75	0.580		1.00	0.64, 1.57	0.985		1.07	0.64, 1.77	0.802
Age												
4 years						2.04	1.63, 2.56	<0.001		1.92	1.49, 2.46	<0.001
6 years						1.40	1.11, 1.76	0.004		1.28	0.99, 1.65	0.058
10 years						1.00				1.00		

*Unadjusted model.

†Adjusted for age, gender, parental education, breastfeeding, parental atopy, siblings, maternal smoking during pregnancy, wheeze in the first 2 years, and study center.

‡Adjusted for all variables in model 2 plus birth weight and body mass index at age 10 years.

inverse relationship between changes in lung function from age 1 to 12 months and weight gain in infancy. As infants with a small change in pulmonary function related to a reduced lung function at 1 month have an increased risk of early asthma symptoms, Turner et al. (21) assume an indirect association between weight gain and asthma in early childhood.

A limitation of these three studies (19–21) is the small sample size of 197, 154, and 1548 study participants, respectively. In addition, these studies did not include longitudinal analyses of the relationship between weight gain and atopic outcomes.

Data from the larger PIAMA birth cohort study (sample size of 3756 children) showed an association between BMI changes from 1 to 2 and 6 to 7 years and BMI changes from 3 to 5 and 6 to 7 years, respectively, and the prevalence of asthma symptoms like dyspnea and bronchial hyperresponsiveness at 8 years (22). This association was only statistically significant if the children had a persistent or current high BMI. An early high BMI was not associated with asthma symptoms at 8 years if the child again has a normal BMI before 8 years of age (22). Furthermore, Rona et al. (23) pointed out that rapid weight gain and growth in length during the first year are related to an increased risk of wheeze during this period.

Summarizing the results of the few epidemiological studies with longitudinal data, there is neither a consistent association between BMI early in life and asthma onset in school age nor for BMI and wheeze. No study has attempted to use peak growth velocities in prospective cohorts of children so far.

There are several potential biological mechanisms for the association between obesity and asthma (24). For instance, the reduced lung and tidal volume in obese individuals can

encourage a shortening of the airway smooth muscle, which results in airway narrowing. Furthermore, as adiposity is a state of low-grade systemic inflammation (24), this inflammation can affect the lung and lead to asthma exacerbations. Further mechanisms that cause or worsen asthma are changes in hormones like leptin and adiponectin and comorbidities like dyslipidemia, sleep-disordered breathing, type 2 diabetes, hypertension, and gastroesophageal reflux (24). For example, Scott et al. (25) found a significant increase in leptin levels in obese asthmatics compared to non-obese asthmatics and non-asthmatics.

To the best of our knowledge, there is no specific mechanism for the association between weight gain and the development of asthma in childhood so far. However, one might speculate that experience of illness in early childhood might have an effect on delayed growth and rapid growth after recovery. Consequently, peak velocities of growth might be also considered as proxy of severe diseases in childhood.

Indeed, we tested the effect of onset of diseases such as pneumonia, otitis media, varicella, or diarrhoea during the first 6 months of life on peak weight velocities in the LISA-plus study, but found no association (data not shown).

One of the strengths of the current study was the longitudinal study design and longitudinal data analysis. Since children were followed up until 10 years of age, information on asthma was prospectively collected for each year of age. For the outcome variable wheeze in the last 12 months, information was available for 1, 2, 4, 6, and 10 years of life. Furthermore, growth was measured from birth to 2 years of age at seven time points. The height and weight measurements were taken from the baby check-up books ('U-Untersuchungen').

A limitation of the current study was that the information on wheeze was not requested on a yearly base. However, we believe that a retrospective exploration of wheezing symptoms beyond a period of last 12 months is well justified. Moreover, as we considered only the appearance of wheezing after infancy growth, there remained only three measurements (at age 4, 6, and 10).

One reason why PWV is associated with asthma but not wheeze may be that asthma-like symptoms such as wheeze are less specific than parental-reported doctor diagnosis. Considering the low 'true' asthma prevalence, the wheezy children are mainly children with respiratory infectious episodes.

As the Reed model smoothes the growth curves over the first 2 years of life, this model might miss extreme growth changes over a short period. This is important when Reed model results will be compared with the results of catchup growth effects in very short periods.

Furthermore, as different growth patterns and velocities may lead to the same weight change between two measurements, one reason for the opposite study findings may be the difference between the Reed model and the weight change concept based on two time points used in other studies.

In conclusion, the results of our study demonstrate that higher peak weight velocities during infancy increased the risk of physician-diagnosed asthma in childhood. For PHV, we found no association with asthma and wheeze, as well as for PWV and wheeze.

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Authors contributions

CF carried out the statistical analyses and wrote the manuscript. ET, JH and UM were involved in development of the statistical analysis plan and interpreting the results. SK, CPB, HEW, AvB, DB, UK, BS, IL, OH, IB, and JH designed and/or conducted the study and revised the manuscript. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Conflict of interest

None declared.

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