Early Life Growth and the Development of Preschool Wheeze, Independent from Overweight: The LucKi Birth Cohort Study

Dianne de Korte-de Boer, MSc[1], Monique Mommers, PhD[1], Carel Thijs, PhD[1], Marielle Jaminon, MD[2], Maria Jansen, PhD[3], Suhreta Mujakovic, PhD[4], Frans J. M. Feron, MD, PhD[5], and Onno C. P. van Schayck, PhD[6]

Objective To investigate whether birth weight and postnatal growth rates are independently related to the development of overweight and wheeze up to age 3 years.

Study design Children from the LucKi Birth Cohort Study with complete follow-up for repeated questionnaires (at age 0, 7, and 14 months and 3 years) and informed consent to use height and weight data (measured by trained personnel at age 0, 7, and 14 months and 2 and 3 years) were included (n = 566). Wheeze (parental-reported) and overweight (body mass index [BMI] >85th percentile) were regressed with generalized estimating equations on birth weight and relative growth rates (difference SDS for weight, height, and BMI).

Results Higher birth weight and higher weight and BMI growth rates were associated with increased risk of overweight, but not of wheeze, up to age 3 years. Higher height growth rate was associated with lower risk of wheeze up to 3 years, independent of overweight (aOR, 0.65; 95% CI, 0.53-0.79). In time-lag models, wheeze was associated with subsequently reduced height growth up to age 14 months, but not vice versa.

Conclusion Only height growth rate, and not weight and BMI growth rate, is associated with preschool wheeze, independent of overweight. Children who wheeze demonstrate a subsequent reduction in height growth up to age 14 months, but not vice versa. Because height growth rate is not associated with overweight, preschool wheeze and overweight are not associated throughout early life growth. *(J Pediatr 2015;166:343-9)*.

See editorial, p 226

The prevalence of childhood asthma has increased in many countries.[1] In parallel, rising trends in childhood overweight and obesity have been observed.[2] An association between asthma and overweight in children has been found in several prospective studies.[3] Proposed causal factors for this association include systemic inflammation, mechanical changes associated with high body weight, changes in airway hyperresponsiveness, decreased physical activity, and changes in diet,[4] but the exact pathways through which overweight may lead to asthma are currently poorly understood.[5]

Alternatively, overweight and asthma might not be causally related, but certain early life factors may play a role in the development of both asthma and overweight independently. One such factor may be growth in fetal life and early life. In parallel with somatic growth, development of the lungs starts in utero and continues after birth. After 16 weeks of gestation, the pattern of the airway branching is complete, and thereafter the airways only grow in size and not in number.[6] In contrast, the alveoli develop mainly postnatally, from 36 weeks of gestation to at least 3 years after birth, and continue to increase in volume until lung growth is completed in early adult life.[7] Thus, reduced or accelerated growth in fetal and early life may disrupt normal airway development and growth, leading to impaired function.

Birth weight, an indicator of fetal growth and maturation, and postnatal growth are associated with wheeze/asthma and overweight. Both low and high birth weight seem to predispose for asthma[8,9] and overweight,[10-12] although studies report inconsistent findings. Unfavorable conditions in utero, such as maternal smoking during pregnancy,[13] may cause impaired somatic growth and impede lung development, thus explaining the risk of asthma in low birth weight children.[9] In addition, low birth weight children often experience catch-up growth during infancy, which ultimately may lead to overweight.[14] Children with a high birth weight tend to remain overweight throughout childhood.[11] Rapid postnatal weight gain is consistently associated with overweight later in life[11,15] and also has been associated with later wheeze[16-18] or asthma,[19,20] although some studies did not identify an association between growth rate and asthma symptoms.[21,22]

To gain more insight into potential causal pathways, it is of interest to study associations in different age periods and to study height, weight, and body mass index (BMI) growth rates separately. Thus, in the present population-based

BMI	Body mass index
GEE	Generalized estimating equations

From the [1]Department of Epidemiology, School of Public Health and Primary Care, Maastricht University, Maastricht, The Netherlands; [2]Orbis Child and Youth Health Care, Orbis Medical Concern, Sittard, The Netherlands; [3]Department of Health Services Research, School of Public Health and Primary Care, Maastricht University, Maastricht, The Netherlands; [4]Department of Research and Development, South Limburg Public Health Service, Geleen, The Netherlands; and Departments of [5]Social Medicine and [6]General Practice, School of Public Health and Primary Care, Maastricht University, Maastricht, The Netherlands

The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.08.064

prospective cohort study, we examined whether birth weight and height, weight, and BMI growth rate are independently related to wheeze and overweight in children up to 3 years of age.

Methods

Data were obtained from the LucKi Birth Cohort Study, a dynamic prospective cohort study conducted in the southeastern region of The Netherlands. LucKi is embedded in the Dutch Child and Youth Health Care system, in which children are followed longitudinally from birth through routine visits at child health care centers. Most Dutch parents (~90%-95%) normally visit a child health care center 12 times between birth and age 4 years. Since July 2006, all parents of newborn children who live in the study region are invited to participate in LucKi starting at 1-2 weeks after birth. Parents are asked to complete questionnaires at baseline (1-2 weeks after birth) and when their child is aged 7 months, 14 months, and 3 years. The timing of the questionnaires coincides with routine visits. Parents are also asked to provide signed informed consent for extracting additional data from the Child and Youth Health Care registry. The Lucki Birth Cohort Study was approved by the Medical Ethical Committee of Maastricht University Medical Center.

For the present study, inclusion criteria were birth between July 2006 and December 2008, availability of all 4 questionnaires, and availability of parental informed consent. Exclusion criteria were birth before 37 weeks gestation (because of associated respiratory complications in preterm infants) and multiple birth (because of associated lower gestational age at birth and lower birth weight).

Anthropometric Measures

Birth weight was reported by the mother on the baseline questionnaire and also was documented by Youth Health Care personnel in the digital registry, based on information obtained from the midwife or gynecologist present at birth. Birth weight was treated as a continuous variable.

Weight, height, and BMI growth rates were determined using data from the Child and Youth Health Care registry. Nurse assistants measured the child's height and weight at each visit to the child health center in a standardized manner. BMI was calculated by dividing weight (in kilograms) by squared length (in meters). Relative growth rates were calculated over 3 different age periods: 1-7 months, 7-14 months, and 2-3 years. For each child, the height and weight measurements recorded closest to these ages were used in the analysis. If measurements were missing for a certain age but other measurements were available, then height and/or weight were estimated by linear interpolation of surrounding measurements. SDSs were calculated for height, weight, and BMI at age 1, 7, and 14 months and 2 and 3 years using the Dutch growth reference, standardized for age at measurement and sex.[23] For each growth characteristic (weight, height, and BMI), the difference in SDS at the end and the beginning of each time period was calculated. This difference score represents the child's relative growth rate in each period and was treated as a continuous variable in the analyses.

Wheezing and Overweight

The primary outcome variable, wheeze, was determined at age 7 months, 14 months, and 3 years, based on validated International Study of Asthma and Allergies in Childhood questions[24] included in each follow-up questionnaire. Parents were asked whether their child had wheezing or whistling in the chest in the previous 7 months (questionnaires at 7 and 14 months) or the previous 12 months (questionnaire at 3 years). A child was considered to have experienced wheezing in a certain period if the parents answered 'yes' to this question.

The secondary outcome variable, overweight, was determined using BMI at age 7 months, 14 months, and 3 years. Because no cutoff values for overweight exist for children younger than 2 years old, we classified children with an age- and sex-specific BMI above the 85th percentile of the present study population as overweight.[25]

Potential Confounders

Information on potential confounders was collected by questionnaires and from the registry. Data on sex, gestational age, number of older siblings, maternal smoking during pregnancy, and parental history of atopy were available from the baseline questionnaire. Breastfeeding duration, day care attendance, and environmental tobacco smoke were reported in the follow-up questionnaires at age 7 months, 14 months, and 3 years. We cross-checked variables that were also available from the registry: sex, gestational age at birth, and smoking during pregnancy.

The variables breastfeeding duration, day care attendance, and environmental tobacco smoke were defined for each time period (0-7 months, 7-14 months, and 2-3 years). Breastfeeding duration was defined as the number of months per period that the child received breast milk, exclusively or partially. All potential confounders, except breastfeeding duration, were treated as categorical variables in the analyses. Missing values were replaced with the value of the most frequent category.

Statistical Analyses

We applied univariable and multivariable logistic generalized estimating equations (GEE) models with exchangeable correlation structure, for birth weight and weight, height, and BMI growth rates separately. The GEE approach is especially suitable for analysis of longitudinal data with repeated measurements.[26] In multivariable analyses, we adjusted for all of the aforementioned potential confounders simultaneously. Multivariable models with relative growth rates as determinants were also adjusted for birth weight. An interaction term was added to the models to explore possible differences in associations between age periods, with the interaction variable age period coded as 7, 14, or 36 (reflecting age at measurement in months).

Results are presented as ORs with 95% CIs. A *P* value <.05 was considered statistically significant. Data were analyzed with SPSS version 20.0 (IBM, Armonk, New York).

Results

Between July 2006 and December 2008, a total of 2317 children were enrolled in the LucKi Birth Cohort Study shortly after birth (representing ~65% of all births in the study region). For the present study, we excluded twins (n = 36) and children born before 37 weeks gestation (n = 131, 16 of whom were twins), leaving 2166 children who met the eligibility criteria. All completed questionnaires and informed consent for the use of registry data were available for 566 of these children (26.1%). Compared with the total group of eligible children within the LucKi study, the present study population of 566 subjects included slightly more boys and slightly fewer children whose mother had smoked during pregnancy. Other characteristics were similar in the 2 cohorts (Table I).

Table I. Baseline characteristics of the present study population and the total eligible study population in the LucKi cohort

Characteristics	Total eligible study population (n = 2166)*	Present study population (n = 566)†
Male sex, n (%)	1066 (49.4)	296 (52.3)
Gestational age at birth, n (%)		
37-38 wk	488 (22.5)	118 (20.8)
39-40 wk	1123 (51.8)	288 (50.9)
41-42 wk	545 (25.2)	159 (28.1)
Missing	10 (0.5)	1 (0.2)
Birth weight, g, mean (SD)	3467 (491)	3457 (484)
Breastfeeding duration		
0-7 mo, n (%)		344 (60.8)
Mo, mean (SD)		2.6 (2.8)
7-14 mo, n (%)		114 (20.1)
Mo, mean (SD)		0.7 (1.7)
Parental history of atopy, n (%)		
No	704 (32.5)	184 (32.5)
Maternal	613 (28.3)	163 (28.8)
Paternal	382 (17.6)	90 (15.9)
Both parents	457 (21.1)	125 (22.1)
Missing	10 (0.5)	4 (0.7)
Smoking during pregnancy, n (%)	271 (12.5)	56 (9.9)
Environmental tobacco smoke, n (%)		
0-7 mo		43 (7.6)
7-14 mo		37 (6.5)
2-3 y		50 (8.8)
Missing		8 (0.1)
Day care attendance, n (%)		
0-7 mo		313 (55.3)
7-14 mo		346 (61.1)
2-3 y		496 (87.6)
Older siblings, n (%)		
None	915 (42.2)	246 (43.5)
One or more	1068 (49.3)	265 (46.8)
Unknown	183 (8.4)	55 (9.7)

*Single birth children born between July 2006 and December 2008 after more than 36 weeks of gestation.
†Selection of children with complete follow-up (questionnaires and informed consent for using data from the Youth Health Care registry).

Wheezing and Overweight

Parents of 75 of the 566 children (13.3%) reported wheeze between birth and age 7 months, of whom 4 (5.3%) had ever been diagnosed with asthma by a physician. Furthermore, 28 of the 75 children (37.3%) with reported wheezing before age 7 months had ever used medication for their symptoms, with 22 (29.3%) using a bronchodilator and 1 (1.3%) using a corticosteroid. At age 14 months, 107 of the 566 children (18.9%) had reported wheezing in the previous 7 months, of whom 39 (36.4%) also wheezed before age 7 months and 8 (7.5%) had ever been diagnosed with asthma by a physician. Furthermore, 44.9% (48 of 107) of the children with wheezing between age 7 and 14 months had ever used medication for wheeze or asthma, with 35 (32.7%) using a bronchodilator and 5 (4.7%) using a corticosteroid. At age 3 years, 75 children (13.3%) had reported wheeze in the previous year, of whom 50 (66.7%) also wheezed before age 7 months and/or before age 14 months and 13 (17.3%) had ever been diagnosed with asthma by a physician. Furthermore, 49 of 75 children (65.3%) with wheeze between age 2 and 3 years had ever used medication for wheeze or asthma, with 36 (48.0%) using a bronchodilator and 4 (5.3%) using a corticosteroid.

Mean BMI (kg/m^2) was 16.91 (range, 12.91-21.13) at age 7 months, 16.96 (range, 13.35-21.38) at age 14 months, and 15.82 (range, 12.79-20.31) at age 3 years. Cutoff points for the 85th percentile BMI were 18.75 for boys and 17.99 for girls at age 7 months, 18.58 for boys and 18.03 for girls at age 14 months, and 16.94 for boys and 16.92 for girls at age 3 years.

Using univariable logistic GEE analyses, we calculated the association between overweight (determinant) and wheeze (outcome) in our population. We found that overweight was associated with wheeze at age 7 months (crude OR, 1.84; 95% CI, 1.12-3.03), but not at 14 months (crude OR, 1.19; 95% CI, 0.82-1.74) or 3 years (crude OR, 0.77; 95% CI, 0.43-1.40).

Associations of Birth Weight and Relative Growth Rates with Overweight

Higher birth weight and higher weight and BMI growth rates were associated with increased risk of overweight up to age 3 years (aOR, 1.50 [95% CI, 1.23-1.83] for each 500-g increment in birth weight, and aOR 2.33 [95% CI, 1.98-2.75] and aOR 2.47 [95% CI, 2.11-2.90], respectively, for a 1 SDS increment), but height growth rate was not associated with overweight (Table II). There was a significant interaction of weight growth rate and age ($P_{\text{interaction}}$ < .001); the association between weight growth rate and overweight became stronger with increasing age (aOR 1.98 [95% CI, 1.66-2.38] at age 7 months, 3.21 [95% CI, 2.49-4.13] at age 14 months, and 5.17 [95% CI, 3.16-8.46] at age 3 years).

Associations of Birth Weight and Relative Growth Rates with Wheezing

Birth weight and weight and BMI growth rates were not associated with wheeze up to age 3 years (aOR, 1.02 [95% CI, 0.83-1.240 per 500 g, and aOR 0.88 [95% CI, 0.73-1.05] and aOR, 1.16 [95% CI, 0.99-1.37] per SDS, respectively).

Table II. Associations of birth weight and weight, height, and BMI growth rates with overweight, wheeze, and wheeze independent of overweight in children up to age 3 years

Determinant	Overweight	Wheeze	Wheeze independent of overweight*
Birth weight (per 500 g)			
Crude OR (95% CI)	**1.48 (1.24-1.76)**	1.09 (0.92-1.30)	
aOR (95% CI)†	**1.50 (1.23-1.83)**	1.02 (0.83-1.24)	1.00 (0.82-1.22)
Weight growth rate (per SDS)			
Crude OR (95% CI)	**1.95 (1.69-2.24)**§	0.89 (0.74-1.05)	
aOR (95% CI)‡	**2.33 (1.98-2.75)**§	0.88 (0.73-1.05)	0.85 (0.71-1.03)
Height growth rate (per SDS)			
Crude OR (95% CI)	1.05 (0.89-1.24)	**0.66 (0.55-0.80)**	
aOR (95% CI)‡	1.12 (0.94-1.33)	**0.65 (0.54-0.73)**	**0.65 (0.53-0.79)**
BMI growth rate (per SDS)			
Crude OR (95% CI)	**2.20 (1.91-2.54)**	1.16 (0.99-1.36)	
aOR (95% CI)‡	**2.47 (2.11-2.90)**	1.16 (0.99-1.37)	1.15 (0.98-1.36)

ORs with 95% CIs were calculated from GEE logistic regression analyses, with an exchangeable correlation structure. Wheeze, overweight, and growth rates have been measured repeatedly in 3 time periods (age 0-7 months, age 7-14 months, and age 2-3 years). Statistically significant associations ($P < .05$) are displayed in bold type.
*By adding overweight as determinant in the multivariable models.
†Adjusted for sex, gestational age, older siblings, parental history of atopy, smoking during pregnancy, breastfeeding duration, day care attendance, and environmental tobacco smoke.
‡Adjusted for birth weight, sex, gestational age, older siblings, parental history of atopy, smoking during pregnancy, breastfeeding duration, day care attendance, and environmental tobacco smoke.
§Interaction of determinant with age period is statistically significant ($P < .001$).

A higher height growth rate was associated with lower risk of wheeze up to age 3 years (aOR, 0.65 [95% CI, 0.54-0.73] per aSDS) (Table II). The associations of birth weight, and weight, height, or BMI growth rates with wheeze did not change much with inclusion of overweight in the models (Table II).

To explore the direction of the association between height growth and wheeze, we designed 2 time-lag models. The first model (A, height→wheeze) included wheeze in age period t [wheeze(t)] as a function of height at the end of the previous age period [height(t − 1)], while controlling for wheeze in the previous age period [wheeze(t − 1)]. The second model (B, wheeze→height) included height(t) as function of wheeze in the previous period [wheeze(t − 1)], controlling for height at the end of that period [height(t − 1)]. The results of logistic (model A) and linear (model B) GEE analyses are displayed in Figure 1 (available at www.jpeds.com). In time-lag model A, the risk of wheeze(t) was positively associated with height in the previous period (OR, 1.05 [95% CI, 1.02-1.07] per cm of body height); that is, children who were taller in the previous period had a slightly greater risk of developing wheeze, which is in contradiction to the association found in the main model. In time-lag model B, height(t) was lower after a previous period of wheeze (B, −0.30; 95% CI, −0.69 to 0.10), which is in line with the negative association between height growth rate and wheeze found in the main model.

Because the interaction term of wheeze(t − 1) with age period was statistically significant in model B ($P_{interaction} < .001$), we repeated the analyses for each age period. We found that the negative association of height with previous wheeze was strongest in the first 7 months (difference in height growth [cm] between wheezers and nonwheezers: B, −1.23; 95% CI, −2.15 to −0.31), attenuated by age 14 months (B, −0.51; 95% CI, −0.92 to −0.10), and had disappeared by age 3 years (B, 0.22; 95% CI, −0.26 to 0.70) (Figure 2).

Sensitivity Analyses

To check for a nonlinear association between birth weight and the outcome variables wheeze and overweight, we added a centralized quadratic term for birth weight to the univariable models. The quadratic term was not statistically significant in any model, and thus we dropped it from all models.

To verify the existence of nonlinear associations involving BMI (ie, parabolic or U-shaped), we performed 2 sensitivity analyses. First, we repeated all analyses after excluding children with a BMI below the 15th percentile, which resulted in similar associations. Second, instead of defining overweight as a binary variable based on the 85th percentile of the BMI distribution, we used a centralized, quadratic term

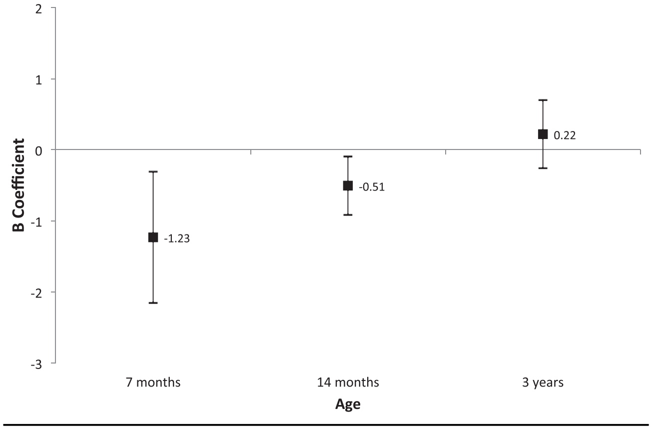


Figure 2. Associations of wheeze with subsequent height (in cm) up to age 3 years. Data are B coefficients with 95% CIs from linear time-lag GEE analyses for each age period. B coefficients represent the difference in height (in cm) between children who wheezed in the previous period compared with children who did not wheeze in that period, controlling for height at the end of the previous period.

of BMI as a continuous variable in the models with wheeze as the outcome variable. In all models, the quadratic term for BMI was not statistically significant.

The use of a cutoff point of the 85th percentile of BMI to define overweight is arbitrary, especially for children under age 2 years. Thus, we repeated the analyses using cutoff points for the 90th and 95th percentiles of BMI, but this did not change the results. We also repeated the analyses using cutoff points for 3-year-old boys and girls of a widely used international standard,[27] which were lower than the cutoff points for the 85th percentile of BMI. Instead of 85 children (15%) with a BMI in the 85th percentile, only 37 children (6.2%) in our study population were overweight according to the international standard. Nevertheless, using these different cutoff points for 3-year-old children did not change our results.

Finally, to increase comparability between our study and others, we repeated our univariable logistic GEE analyses with wheeze as the outcome and relative growth rates between 1 and 3 months as the determinant. We found associations similar to the original analyses but with slightly broader CIs, indicating that more precision in the estimates is achieved by including multiple growth rate periods in the analyses.

Discussion

Our findings show that in preschool children, only height growth rate is associated with wheeze, independent of overweight, and that birth weight, weight growth rate, and BMI growth rate are associated with overweight only. Thus, early life growth rates cannot explain an association between preschool wheeze and overweight. Furthermore, time-lag analyses revealed that wheeze is associated with subsequently reduced height growth up to age 14 months, but not vice versa.

Our findings are in contrast with those of other studies on the association between early life growth patterns and wheeze, which identified an association of weight growth[16-20] but no association of height growth[16-19] with later wheeze and/or asthma. In line with our findings, 2 other studies found no association between weight growth and later wheeze,[21,22] but no other study has reported an association of height growth and wheeze. Furthermore, we could not confirm an association of (high or low) birth weight with wheeze as has been found in some studies,[9] although not in others.[18,22]

Such conflicting results may derive from differences in methodological choices, such as definition of growth rates and timing of outcome measurements. In our study, growth was defined as difference scores of standardized weight, height, or BMI in 3 periods (age 1-7 months, age 7-14 months, and age 2-3 years), whereas others have categorized growth between age 0 and 2 years[21] or in several intermediate periods[16-18] into slow, normal, and rapid weight gain, or have used parameters of modeled growth curves to define growth patterns.[19,20,22] Sensitivity analyses with relative growth rates calculated over 1-3 months only as a determinant did not change our conclusions, however. Results of studies that focused solely on BMI as marker for growth may be influenced by an inverse association of height growth with wheeze as we found in the present study, by inaccurately attributing an effect to weight gain instead of reduced height growth, emphasizing the importance of studying weight and height separately.

Another difference is that we used repeatedly measured wheeze as an outcome measure, whereas in other studies the outcomes were measured only once or were combined into a single endpoint (eg, ever wheeze). Although our sample size is smaller than that of some other studies, we achieved sufficient statistical power to detect a statistically significant negative association between height growth and wheeze. In addition, some other studies measured outcomes in school-aged children. In preschool children, wheeze is more prevalent and associated mainly with viral infections, whereas in older children with persistent wheeze up to age 6 years and older, wheeze is associated mainly with atopy.[28] Thus, it is likely that not all children with wheeze symptoms in our study population will go on to develop allergic asthma as they age.

Our results indicate that most likely different mechanisms are responsible for the association of growth with overweight and for the association of growth with wheeze in preschool children. In the association with overweight (based on BMI), weight gain seems to play a key role, and in the association with wheeze, reduced height is primarily involved. Because overweight and weight gain are by definition closely related, a strong association between weight growth rate and overweight was to be expected in our study. In the absence of an association of weight growth rate and wheeze, however, our results do not confirm a causal relation between overweight and wheeze/asthma through pathways related to high body weight, such as increased visceral fat deposition, mechanical changes, and low-grade systemic inflammation. Rather, the (nonsignificant) estimates of the association between weight growth rate and wheeze point to a protective effect of weight growth rate for preschool wheeze in our study population.

From our time-lag models, we conclude that in the association of height and wheeze, reversed causation was introduced; wheeze was associated with subsequently reduced height growth, but not vice versa. This eliminates the possibility that restricted height growth affects airway growth and thereby leads to respiratory problems. Potential explanations for height growth restriction in children with wheeze include an adverse effect on growth of asthma medication, such as inhaled corticosteroids[29]; comorbidities of wheeze/asthma, such as gastroesophageal reflux disease,[30] which may hinder sufficient nutrient intake[31] and thereby lead to reduced height growth; or the presence of an underlying condition, for instance, a respiratory tract infection, that induces wheeze episodes and may as well cause temporal growth restriction. The latter explanation is supported by the fact that the association between wheeze and height growth disappears at age 3 years, because older children are less susceptible to viral infections. The use of corticosteroids was low in this young population (1.3%-5.3% of the children with reported wheeze) and thus is an unlikely explanation for our findings.

Strengths of the present study are its prospective design and the use of repeatedly measured outcome measures. Also, because trained nurse assistants measured height and weight in a standardized manner, bias associated with self-reporting of height and weight (eg, social desirability bias, recall bias) was eliminated.[32] Furthermore, the use of standardized International Study of Asthma and Allergies in Childhood questions to measure the outcome of wheezing permits comparison with other studies.

This study is also subject to some limitations. First, selection bias may have been introduced. Our study population was largely comparable with the total group of eligible children, but with slightly more boys and slightly less children whose mother had smoked during pregnancy. Additional exploration indicated that in the group with complete follow-up, the prevalence of wheeze was slightly higher (data not shown). Because boys are more likely to wheeze than girls, and because mothers of lower socioeconomic status are more likely to smoke during pregnancy, these differences likely indicate that parents of children with respiratory symptoms and parents with higher socioeconomic status were more inclined to complete all questionnaires in the LucKi Birth Cohort Study. This has implications for the generalizability of our results, but because we adjusted for sex and smoking during pregnancy in our multivariable analyses, and because other related characteristics, such as birth weight, were comparable, the internal validity of the present study likely is not threatened. Moreover, repeating our crude analyses with children with less-complete follow-up for questionnaires yielded similar associations of relative growth rates and wheeze (data not shown). The exclusion of preterm and multiple-birth children means that the present study results cannot be generalized to these specific groups.

Second, the study's observational design leaves the possibility of residual confounding in the analyses, for example, because we lacked data on maternal height and weight. Nonetheless, we were able to control our analyses for many potential confounders, some of which were also measured repeatedly over the study period. A third limitation is the use of BMI cutoff points for overweight in children younger than 2 years. The use of BMI as a proxy for visceral fat mass is currently a topic of debate, and there is no internationally validated cutoff point for children under age 2 years. We believe that our use of BMI cutoff points for the purpose of defining (changes in) overweight in our study population is justified, supported by the fact that using different cutoff points in the sensitivity analyses did not change the results. ■

The authors wish to thank all parents and their children for participating in LucKi, and the co-workers of Orbis Jeugdgezondheidszorg for collecting the data.

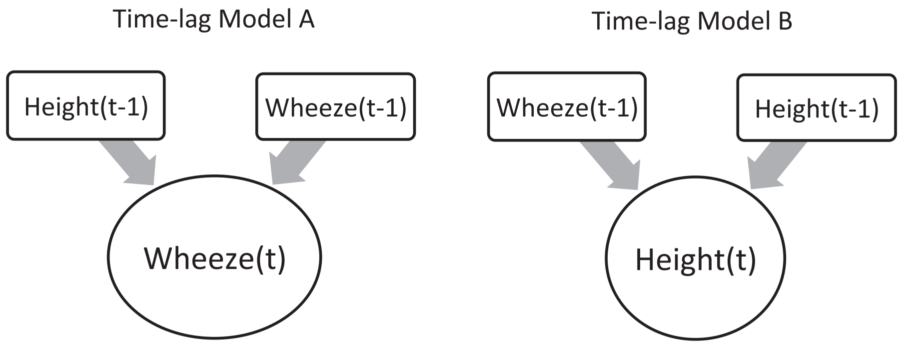
Submitted for publication Jan 20, 2014; last revision received Jul 24, 2014; accepted Aug 27, 2014.

Reprint requests: Dianne de Korte-de Boer, MSc, Department of Epidemiology, School of Public Health and Primary Care, Maastricht University, PO Box 616, 6220 MD Maastricht, The Netherlands. E-mail: dianne.dekorte@maastrichtuniversity.nl

References

1. Anandan C, Nurmatov U, van Schayck OC, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. Allergy 2010;65:152-67.
2. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. Int J Pediatr Obes 2006;1:11-25.
3. Papoutsakis C, Priftis KN, Drakouli M, Prifti S, Konstantaki E, Chondronikola M, et al. Childhood overweight/obesity and asthma: is there a link? A systematic review of recent epidemiologic evidence. J Acad Nutr Diet 2013;113:77-105.
4. Beuther DA. Recent insight into obesity and asthma. Curr Opin Pulm Med 2010;16:64-70.
5. Sin DD, Sutherland ER. Obesity and the lung, 4: obesity and asthma. Thorax 2008;63:1018-23.
6. Jeffery P. The development of the large and small airways. Am J Respir Crit Care Med 1998;157:s174-80.
7. Stick S. Pediatric origins of adult lung disease, 1: the contribution of airway development to paediatric and adult lung disease. Thorax 2000;55:587-94.
8. Remes ST, Patel SP, Hartikainen AL, Jarvelin MR, Pekkanen J. High birth weight, asthma and atopy at the age of 16 yr. Pediatr Allergy Immunol 2008;19:541-3.
9. Tedner SG, Ortqvist AK, Almqvist C. Fetal growth and risk of childhood asthma and allergic disease. Clin Exp Allergy 2012;42:1430-47.
10. Yu ZB, Han SP, Zhu GZ, Zhu C, Wang XJ, Cao XG, et al. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. Obes Rev 2011;12:525-42.
11. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ 2005;331:929.
12. Oldroyd J, Renzaho A, Skouteris H. Low and high birth weight as risk factors for obesity among 4 to 5-year-old Australian children: does gender matter? Eur J Pediatr 2011;170:899-906.
13. Bjerg A, Hedman L, Perzanowski M, Lundback B, Ronmark E. A strong synergism of low birth weight and prenatal smoking on asthma in schoolchildren. Pediatrics 2011;127:e905-12.
14. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ 2000;320:967-71.
15. Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. Acta Paediatr 2006;95:904-8.
16. Sonnenschein van der Voort AM, Jaddoe VW, Raat H, Moll HA, Hofman A, de Jongste JC, et al. Fetal and infant growth and asthma symptoms in preschool children: the Generation R Study. Am J Respir Crit Care Med 2012;185:731-7.
17. van der Gugten AC, Koopman M, Evelein AM, Verheij TJ, Uiterwaal CS, van der Ent CK. Rapid early weight gain is associated with wheeze and reduced lung function in childhood. Eur Respir J 2012;39:403-10.
18. Pike KC, Crozier SR, Lucas JS, Inskip HM, Robinson S, Roberts G, et al. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. Thorax 2010;65:1099-106.
19. Flexeder C, Thiering E, Bruske I, Koletzko S, Bauer CP, Wichmann HE, et al. Growth velocity during infancy and onset of asthma in school-aged children. Allergy 2012;67:257-64.

20. Rzehak P, Wijga AH, Keil T, Eller E, Bindslev Jensen C, Smit HA, et al. Body mass index trajectory classes and incident asthma in childhood: results from 8 European birth cohorts. A Global Allergy and Asthma European Network initiative. J Allergy Clin Immunol 2013;131:1528-36.
21. Paul IM, Camera L, Zeiger RS, Guilbert TW, Bacharier LB, Taussig LM, et al. Relationship between infant weight gain and later asthma. Pediatr Allergy Immunol 2010;21:82-9.
22. Anderson EL, Fraser A, Martin RM, Kramer MS, Oken E, Patel R, et al. Associations of postnatal growth with asthma and atopy: the PROBIT Study. Pediatr Allergy Immunol 2013;24:122-30.
23. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, et al. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47:316-23.
24. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 1995;8:483-91.
25. Spear BA, Barlow SE, Ervin C, Ludwig DS, Saelens BE, Schetzina KE, et al. Recommendations for treatment of child and adolescent overweight and obesity. Pediatrics 2007;120(Suppl 4):S254-88.
26. Twisk J. Applied longitudinal data analysis for epidemiology: A practical guide. Cambridge, UK: Cambridge University Press; 2003.
27. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240-3.
28. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. N Engl J Med 1995;332:133-8.
29. de Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. Am J Respir Crit Care Med 2012;185:12-23.
30. de Groot EP, Duiverman EJ, Brand PL. Comorbidities of asthma during childhood: possibly important, yet poorly studied. Eur Respir J 2010;36:671-8.
31. Mathisen B, Worrall L, Masel J, Wall C, Shepherd RW. Feeding problems in infants with gastro-oesophageal reflux disease: a controlled study. J Paediatr Child Health 1999;35:163-9.
32. Connor Gorber S, Tremblay M, Moher D, Gorber B. A comparison of direct vs self-report measures for assessing height, weight and body mass index: a systematic review. Obes Rev 2007;8:307-26.



	Wheeze(t) *OR (95% CI)*		Height(t) *B (95% CI)*
Height(t-1)	**1.05 (1.02-1.07)**	Wheeze(t-1)	-0.30 (-0.69; 0.10)*
Wheeze(t-1)	**2.21 (1.30-3.17)**	Height(t-1)	**0.58 (0.54; 0.61)**

Figure 1. Associations of height(t − 1) (in cm) with wheeze(t) (time-lag model A) and of wheeze(t − 1) with height(t) in cm (time-lag model B) in children up to age 3 years. Data are ORs and beta values (B) with 95% CIs from logistic and linear GEE models, respectively. Statistically significant associations ($P < .05$) are in bold type. *Interaction of determinant with age period is statistically significant ($P < .001$).