

Excess Weight in Preschool Children With a History of Severe Bronchiolitis is Associated With Asthma

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Summary. Background: The relationship between excess weight gain and asthma in childhood remains inadequately defined. The aim of this study was to evaluate, as part of a prospective post-bronchiolitis follow-up, whether there is a link between earlier or current overweight or obesity and asthma or asthma symptoms at 5–7 years of age. Methods: In all, 151 former bronchiolitis patients were followed-up until the mean age of 6.45 years. At the control visit, the weights and heights were measured, and the asthma symptoms and medications for asthma were recorded. The weight status was expressed as body mass index (BMI) z-scores (zBMI). Results: There were 10 obese and 31 overweight (zBMI over national references) children. In adjusted analyses, presence of current asthma at 6–7 years of age (aOR 3.05, 95% CI 1.02–9.93) differed between overweight and normal weight children. Further, asthma ever, asthma at age 4–5 years, asthma at age 5–6 years, use of bronchodilators ever and use of ICSs during the last 12 months were more common in currently overweight than in normal weight children. Obesity was associated only with current asthma and asthma ever. Instead, there were no significant associations between birth weight, excess weight gain in infancy, or overweight at age 1.5 years, and later asthma, asthma symptoms or use of asthma medication. Conclusion: Asthma was more common in currently overweight than in normal weight former bronchiolitis patients at preschool age and early school age. **Pediatr Pulmonol.** © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

An association between obesity and asthma during childhood has gained rising interest, since the prevalence of both has increased concomitantly during the past decades.¹ However, the studies on the association have reported varying results. Some studies have found an association between overweight or obesity and an increased asthma prevalence or reduced lung function while others have not.^{1,2} In a Japanese study, the association was suggested to be U-shaped, as it seemed that both overweight and underweight increase the prevalence of asthma.³ The link between excess weight gain and asthma may be stronger in children with non-allergic asthma.² This suggests that, like in adults,⁴ obesity-related asthma may be a separate phenotype also in children.

Despite of the inconsistent results of individual studies, recent systematic reviews and meta-analyses of epidemiological data have concluded that overweight is associated with both incipient and persistent asthma at age 6–12 years, with different risks for boys and girls.^{5,6} Only one such association study has focused on children aged less than 6 years,⁷ and the results were not consistent, being different for 2–4 and 4–6 years old boys and girls.

There is some preliminary evidence that rapid weight gain in early childhood would be a risk factor for later asthma.⁸ However, a prospective intervention study in 197 children at risk for asthma from the US concluded that accelerated weight gain in infancy was not associated

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with asthma or reduced pulmonary function at pre-school or early school age.⁹ The studies on the relationship between birth weight and asthma have reported varying results.^{10–12} Both low (<2.5 kg) and high (>4.5 kg) birth weight has been associated with later asthma.¹³ Children with low birth weight and subsequent rapid weight gain leading to overweight or obesity might have the strongest risk to develop chronic respiratory illness.¹⁴

The aim of this study was to evaluate, as part of a prospective post-bronchiolitis follow-up, whether there is a link between earlier or current overweight or obesity and wheezing or asthma at preschool and early school age, with a special focus on rapid weight gain in infancy.

SUBJECTS AND METHODS

Previously healthy, full-term infants hospitalized for bronchiolitis at less than 6 months of age between December 1st 2001 and May 31st 2002, and between October 28th 2002 and May 31st 2004, were enrolled in the study. Bronchiolitis was defined as an acute lower respiratory illness characterized by rhinorrhea, cough, and diffuse wheezes or crackles.¹⁵ During hospitalization, the weights and heights were measured in all 187 infants eligible to the study. Birth weights and heights were obtained from the registers of the hospital. The weight gain before hospitalization was calculated as weight on admission minus birth weight divided by age in weeks on admission and was expressed as gram per week.¹⁶

After hospitalization for bronchiolitis, the children were invited to follow-up visits on average at 18 months of age and between 5 and 7 years of age. One hundred and twenty-nine children (69%) attended the first control visit.¹⁶ The parents were interviewed by using a structured questionnaire, including data on atopy, passive smoking, and maternal and paternal asthma, and pet keeping. One hundred and twenty-seven (68%) children attended the second control visit.¹⁷ The parents completed a structured questionnaire on wheezing episodes, asthma diagnoses, use of bronchodilators and inhaled corticosteroids (ICS), separately for the preceding 12 months, and the parents of additional 39 children were interviewed by phone using the same questionnaire (Fig. 1). Current asthma was considered to be present, if the child was on continuous maintenance medication for asthma, or if the child had suffered from doctor-diagnosed episodes of wheezing or prolonged/night cough during the preceding 12 months with a diagnostic finding in exercise challenge test.¹⁷ Exercise challenge test (ECT) consisted of free running outdoors for 8 min and measurements of pre- and post-exercise airway resistance by impulse oscillometry (IOS) (Jaeger, Master Screen IOS, Höchberg, Germany). A 35% or greater increase in resistance at 5 Hz was considered as pathological.^{17,18}

At both control visits, on average at 18 months of age and between 5 and 7 years of age, the weights and heights of the children were measured using standardized techniques and calibrated scales and stadiometers. Weight and height data of the study subjects not attending the control visit were collected from the registers of the municipal well-baby centres. The sex- and age-specific height-related body mass index (BMI) values expressed as z-scores (zBMI) were calculated by using the Finnish national population-based weight and height data as reference.¹⁹ The cut-off value of the zBMI for overweight was 1.16 for girls and 0.78 for boys (corresponding BMI of >25 kg/m² in young adults) and for obesity 2.11 for girls and 1.70 for boys (corresponding BMI of >30 kg/m² in young adults), respectively. Since national sex- and age-specific height-related BMI charts are available only from the age of 24 months onwards, overweight was defined as weight-for-length (WFL) >110% and obesity as WFL >120% at the 18-month follow-up visit, as published recently.¹⁰

The Ethics Committee of the Tampere University Hospital District approved the study. Informed consent was obtained from the parents before enrolling of the children during hospitalization and at both control visits.

STATISTICAL METHODS

Data were analyzed by the SPSS package version 21 (IBM Corp., NY). Chi Square and Fisher's exact tests were used for categorized variables, and student's *t*-test for normally distributed and Mann-Whitney test for non-normally distributed continuous variables. Analysis of variance (ANOVA) and logistic regression, adjusted for sex, history of atopy, passive smoking in infancy and maternal asthma, were used in multivariate analyses. ANOVA was used to analyze the differences between the group means. The *P* value <0.05 was considered as statistically significant. The results are expressed as frequencies, proportional frequencies, medians, means and standard deviations (SD), and as crude odds ratios (OR) or as for sex, history of atopy, history of smoking at home, pets in the family and maternal asthma adjusted ORs (aOR), and their 95% confidence intervals (95% CI), when appropriate.

RESULTS

At the 5–7-year follow-up, weight and height data were available from 153/166 (92.2%) children. The mean age of the children was 6.45 years (range 5.51–7.24, SD 0.51). The mean weight of the children was 24.4 kg (range 16–47, SD 4.75) and the mean height was 120.62 cm (range 105–136 cm, SD 6.15). There were 79 (52%) boys. Overweight was present in 31 (18.7%) children and obesity in 10 (6.0%) children (zBMIs over national cut-offs for overweight or obesity, respectively). There were

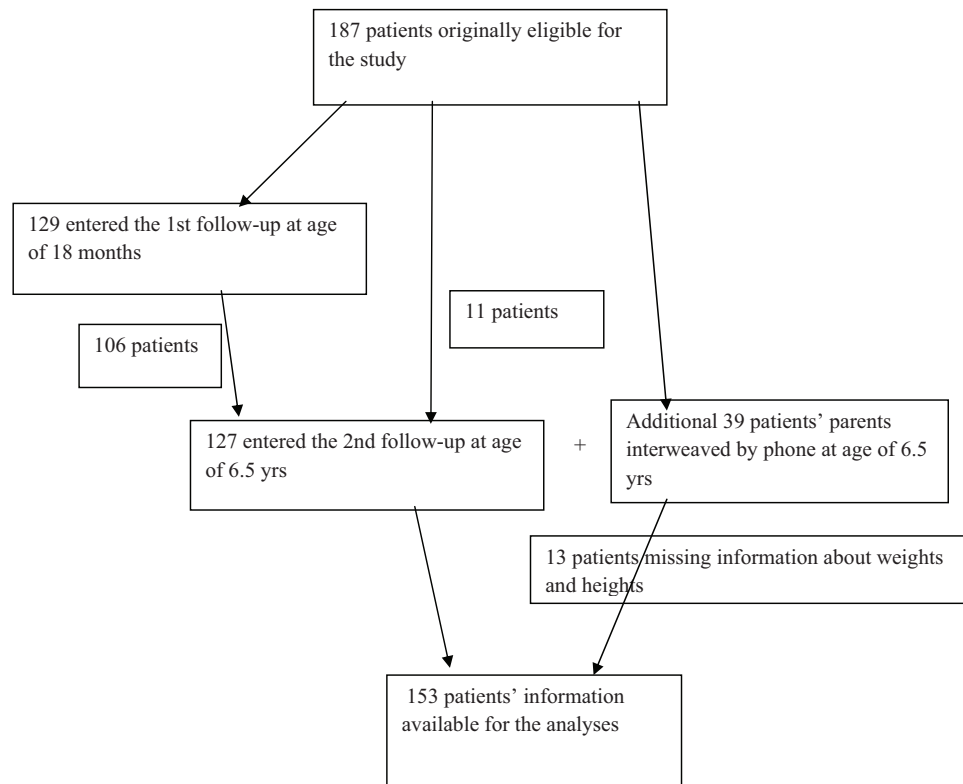


Fig. 1. Flow chart: eligible infants and children attending the control visits at 18 months and 6.5 years of age.

no significant differences between the groups of normal weight, overweight, or obese children in demographic characteristics (Table 1).

Table 2 presents asthma and medication data in relation to weight status at 6.45 (median) years of age. Current asthma was present in 19 (12.4%) children, in 12 boys (20.2% of boys), and 7 girls (9.5% of girls). In addition, there were 21 children with no current asthma who had used previously, but not during the preceding 12 months, ICSs as maintenance medication for asthma. Thus, the number of children with asthma ever in life before or during the study was 40 (26.1%). Among them, asthma was present in 16 children at 4–5 years of age, and in 21

children at 5–6 years of age. In crude analyses, asthma ever and use of bronchodilators ever were significantly more common in overweight than in normal weight children (Table 2). In adjusted analyses, current asthma, asthma ever, asthma at age 4–5 years, asthma at age 5–6 years, use of bronchodilators ever and use of ICSs during the last 12 months were all significantly more common in overweight than in normal weight children (Table 3). Instead, the difference between obese children and normal weight children was significant only for asthma at age 5–6 years and asthma ever in crude analyses (Table 2) and for current asthma, asthma at age 5–6 years and asthma ever in adjusted analyses (Table 3).

TABLE 1—Demographic Characteristics of the 153 Children

	Normal weight (N = 122)	Overweight (N = 31)	Obesity (N = 10)
Age (yrs, mean, range, SD)	6.43 (5.51–7.24, SD 0.51)	6.52 (5.68–7.21, SD 0.48)	6.79 (6.06–7.15, SD 0.35)
Males N (%)	65 (53.3)	14 (45.2)	3 (30.0)
Weight (kg, mean, range, SD)	22.94 (16–31, SD 3.20)	30.54 (24–47, SD 5.05)	35.30 (29–47, SD 5.30)
Height (cm, mean, range, SD)	120.12 (105–136, SD 6.23)	122.60 (113–135, SD 5.51)	123.83 (115–132, SD 5.17)
zBMI	−0.06 (−3.09–1.29, SD 0.09)	1.87 (1.31–2.77, SD 0.44)	2.45 (2.10–2.77, SD 0.23)
History of atopy N (%)	39 (32.0)	6 (19.4)	3 (30.0)
Maternal asthma N (%)	19 (15.6)	2 (6.5)	1 (10.0)
Pet in the family N (%)	49 (40.2)	11 (35.5)	5 (50.0)
Smoking in the family N (%)	34 (27.9)	9 (29.0)	3 (30.0)

TABLE 2—Data on Current and Earlier Asthma and Asthma Medication at 5–7 Years of Age, in Relation to Weight Status, in 153 Children Hospitalized for Bronchiolitis at Less Than 6 Months of Age

	Normal weight (N = 122)	Overweight** (N = 31)	Obesity** (N = 10)
Current asthma N (%)	14 (11)	6 (19)	3 (30)
Inhaled corticosteroid last 12 months N (%)	14 (11)	7 (23)	3 (30)
Bronchodilators last 12 months N (%)	23 (19)	7 (23)	2 (20)
Asthma ever N (%)	26 (21)	14 (45)*	5 (50) [‡]
Bronchodilators ever N (%)	49 (40)	19 (61) [‡]	6 (60)
Asthma dg 4–5 years N (%)	11 (9)	5 (16)	1 (10)
Asthma dg 5–6 years N (%)	14 (11)	7 (23)	4 (40) [‡]

**P* = 0.011 versus normal weight.[‡]*P* = 0.043 versus normal weight.[†]*P* = 0.031 versus normal weight.[‡]*P* = 0.050 versus normal weight.

**zBMIs over national cut-off for overweight or obesity (19).

Complete data on birth weight, weight gain in infancy before hospitalization and weight status when entering the study were available from 119 (71.7%) children. The 24 children with birth weight >4,000 g, or the 17 children with birth weight <3,000 g, did not present with significantly more or less current or previous asthma, or did not need significantly more or less asthma medication, than children with normal birth weight (data not shown). Only children with birth weight <3,000 g had used less bronchodilator medication ever in life (aOR 0.14, 95% CI 0.03–0.67).

There were 106 (60.3%) children with complete weight and height data available from both control visits. Seven of the 10 overweight children at age 18 months were overweight also at age 6–7 years, 4 (57%) had asthma ever, and 2 (29%) had asthma at age 6–7 years. Neither overweight (WFL > 110%) nor underweight (WFL

< 90%) at age 18 months was associated with current or previous asthma (Table 4). Weight gain before hospitalization for bronchiolitis had no association with any asthma variable or any asthma medication variable; the results remained as negative when children with birth weight >4,000 or <3,000 g were analyzed separately (data not shown).

DISCUSSION

The main result of this prospective post-bronchiolitis study was that obesity and overweight at the median age of 6.5 years were associated with current asthma and with asthma ever in life until that age. In addition, overweight was associated with the variables describing asthma treatment. The results were robust to adjustments with sex, history of atopy and maternal asthma, which all associated significantly with asthma development in this same cohort.¹⁷ Instead, high birth weight and excess weight gain in infancy, which were associated with post-bronchiolitis wheezing in this same cohort (10), had no association with current or previous asthma.

In a systematic review,⁵ eight of the 10 epidemiological studies with at least 4 years follow-up showed mainly positive, though sex-dependent associations between overweight/obesity and asthma in adolescents aged >12 years. In two studies, the associations were independent of sex, in three were seen only in males and in three only in females. A most recent meta-analysis including six studies confirmed the association between overweight or obesity and an increased risk of incident asthma in 6- to 18-year-old children.⁶ A dose-responsiveness of elevated BMI on asthma incidence was observed, and boys had significantly higher risk than girls.⁶ Only one study has reported an increased asthma risk in relation to high BMI (the highest quintile) before school age, and the association was not consistent, being significant in 2–3 years old boys and in 4–5 years old girls.⁷ Thus, our observations confirming the association

TABLE 3—Logistic Regression: Current and Earlier Asthma and Asthma Medication, in Relation to Current Overweight and Obesity, in 163 Children Hospitalized for Bronchiolitis in Infancy, Expressed as Adjusted Odds Ratios (aOR), and 95% Confidence Intervals (95%CI)

	Overweight** (N = 31)	Obesity** (N = 10)
	aOR* (95% CI)	aOR* (95% CI)
Current asthma	3.05 (1.02–9.93)	3.97 (0.98–7.80)
Inhaled corticosteroid last 12 months	4.47 (1.23–16.25)	4.17 (0.65–26.66)
Bronchodilators last 12 months	1.80 (0.62–5.25)	0.81 (0.12–5.28)
Asthma ever	7.01 (2.38–20.67)	6.12 (1.25–30.02)
Bronchodilators ever	2.88 (1.22–6.78)	1.96 (0.50–7.69)
Asthma dg 4–5 years	4.18 (1.02–17.13)	0.90 (0.07–10.99)
Asthma dg 5–6 years	3.65 (1.09–12.23)	8.52 (1.53–47.40)

*Adjusted for age on admission, sex, maternal asthma, and atopy and passive smoking in infancy.

**zBMIs over national cut-off for overweight or obesity (19).

TABLE 4—Logistic Regression: Current and Earlier Asthma and Asthma Medication, in Relation to Overweight and Underweight at 1.5-Year Control Visit, in 106 Children Hospitalized for Bronchiolitis in Infancy, Expressed as Adjusted Odds Ratios (aOR), and 95% Confidence Intervals (95%CI)

	WFL >110% (N = 10)	WFL <90% (N = 18)
	aOR* (95% CI)	aOR* (95% CI)
Current asthma	1.33 (0.21–8.57)	0.64 (0.13–3.31)
Inhaled corticosteroid last 12 months	1.56 (0.29–8.27)	1.26 (0.32–5.04)
Bronchodilators last 12 months	1.17 (0.23–5.95)	0.82 (0.23–2.96)
Asthma ever	2.99 (0.78–11.51)	0.42 (0.11–1.60)
Bronchodilators ever	1.26 (0.34–4.71)	0.55 (0.19–1.62)
Asthma dg 4–5 yrs	2.23 (0.41–12.22)	0.41 (0.05–3.37)
Asthma dg 5–6 yrs	2.52 (0.57–11.03)	0.60 (0.12–2.89)

*Adjusted for age on admission, sex, maternal asthma, and atopy and passive smoking in infancy.

between overweight or obesity and asthma at 6–7 years of age are novel.

In adults, obesity-related asthma exists as a distinct clinical asthma phenotype, characterized by non-eosinophilic airway inflammation and poor responses to treatment with inhaled corticosteroids.²⁰ In line, the efficacy of inhaled corticosteroids has been reduced in obese children with asthma, though lung function and bronchial reactivity have been only marginally affected.²¹ In an American clinical and lung function study including 490 children and adults with mild persistent asthma, obese 6- to 11-year-old children had the largest reduction in lung function, but 12- to 17-year-olds presented with more airflow obstruction and asthma symptoms, compared with non-obese asthmatic children.⁴ This means, that obesity-related asthma starts to develop as a separate phenotype of late-onset childhood asthma between 6 and 12 years of age.

The association between obesity and asthma exists in both atopic and non-atopic children, but the association is stronger in the absence of atopy.²² The subjects of the present study were former bronchiolitis patients hospitalized at age less than 6 months, with respiratory syncytial virus as a frequent and rhinovirus as an infrequent causative agent.^{17,23} The preschool outcome was better in the present study than in many other post-bronchiolitis studies, which have included more patients with rhinovirus-associated wheezing and more patients who are atopic or prone to atopy.^{24,25} Thus, without an enrichment of patients at high-risk for asthma, the association of overweight or obesity with asthma may be even more prominent, as seen in this present study.

We were not able to confirm the earlier observations that a rapid or excess weight gain in infancy increases the risk of later asthma.⁸ In this same cohort, the birth weight

over 4,000 g and an excess weight gain in that subgroup before 6 months of age were associated with more post-bronchiolitis wheezing until 1.5 years of age,¹⁰ but this was not anymore to be seen at the median age of 6.5 years. In a study of 197 American children at high risk for asthma, the early-life weight gain pattern was not associated with daily asthma symptoms or lung function at 5- to 6-years of age, but decelerated weight gain was associated with fewer emergency doctor visits and less rescue treatments with corticosteroids.⁹ In a Dutch study in 5,125 children, rapid weight gain during the first 3 months of life was associated, independently from birth weight, with subsequent wheezing illnesses.²⁶ In a large birth cohort study of 12,050 European children (Global Allergy and Asthma European Network) a rapid rise in BMI during the first 2 years of life increased the risk of asthma up to age 6 years.²⁷ In the present study, an association was found between birth weight <3,000 g and less use of bronchodilators in early childhood. This may mean less bronchial reactivity in children born as term with low birth weight.

Overweight temporarily fastens the height growth and the growth of the lungs. In line, high weight at age of 1 year was associated with a decreased risk of asthma and better lung function at the ages of 6 and 8 years in high-risk children.²⁸ In the Netherlands,²⁹ the late onset of overweight at 6–7 years was associated with increased risk of asthma symptoms at age 8 years. As seen in the present and many other studies,^{2,3,5} overweight and obesity are strongly tracked in children, and the effects of previous and current weight gains are difficult to study separately. The same tracking concerns also asthma from 3 to 6 years of age.³⁰ In the present study, 18.7% of children were overweight and 6.0% were obese at 6.5 years of age. In 2006, when older, stricter national weight references were in use, the prevalence of overweight and obesity was lower in Finnish 5-year-old children: 9.8% and 2.5% in boys, and 17.7% and 4.3% in girls, respectively.³¹ The question if bronchiolitis is a risk factor for both asthma and obesity remained without an answer, and needs a study with population-based controls.

There are several theories concerning the mechanisms between overweight or obesity and asthma in children. High body weight causes systemic inflammation, which may further lead to airway inflammation and subsequent asthma.² Other explanations have been a common genetic background between overweight and asthma, mechanical changes associated with body adiposity, decreased physical activity, and dietary factors and increased insulin resistance.² The present study was primarily planned to assess the role of viruses and host immunity in bronchiolitis and subsequent wheezing,¹⁶ and therefore, the mechanisms such as common immunology between overweight, wheezing, and asthma³² were not studied.

The strength of the present post-bronchiolitis study is the prospective and longitudinal design. In addition, studies on the association between overweight and asthma at this age are lacking. The weights and heights were measured by experienced nurses at the study visits using standard methods. Although, the standardized ISAAC questionnaire was not in use, identical questions on symptoms of asthma, wheezing, eczema, and rhinitis were asked. The limitations of this study are the relatively small number of the children who were obese at the control visit and the number of dropouts, since in only 60% of the cases, clinical data including weight and height data were available from both control visits. The analyses were adjusted for sex, history of atopy, passive smoking in infancy, and maternal asthma, which have been significant confounders in this cohort.¹⁷ However, data were not available for further adjustment with maternal body mass index, maternal educational level, or with children's feeding habits, which are potential confounders in pediatric obesity studies.^{2,8,27} In addition, the study subjects were highly selected that is children who were hospitalized for bronchiolitis at age <6 months. On the other hand, just they form a risk group for later pulmonary and lung function disorders, and based on the present results, should avoid the development of overweight.

The results of this study confirm the association between excess weight gain and asthma in childhood but whether this association is causal still remains unclear. Future studies are needed to investigate the mechanisms behind this relationship and also whether obesity-related asthma among children really should be considered and treated as a separate phenotype.

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