

Overweight and changes in weight status during childhood in relation to asthma symptoms at 8 years of age

Salome Scholtens, PhD,^a Alet H. Wijga, PhD,^b Jacob C. Seidell, PhD,^c Bert Brunekreef, PhD,^{a,d} Johan C. de Jongste, MD, PhD,^e Ulrike Gehring, PhD,^a Dirkje S. Postma, MD, PhD,^f Marjan Kerkhof, MD, PhD,^g and Henriette A. Smit, PhD^{b,d} *Utrecht, Bilthoven, Amsterdam, Rotterdam, and Groningen, The Netherlands*

Background: Asthma may be more prevalent in overweight children. However, how early overweight and changes in weight status during childhood affect the asthma risk is unclear.

Objectives: To investigate overweight and changes in overweight status in children age 1 to 8 years in relation to asthma symptoms in childhood.

Methods: We studied 3756 children who participated in a large birth cohort study. The parents reported their children's weight and height, and wheeze, dyspnea, and prescription of inhaled corticosteroids in yearly questionnaires. Sensitization to inhalant allergens and bronchial hyperresponsiveness (BHR) were determined at 8 years.

Results: At 8 years, 275 children (7.3%) wheezed, 361 (9.6%) had dyspnea, and 268 (7.1%) had a prescription of inhaled corticosteroids in the preceding year. Children who had a persistent high body mass index (BMI, weight/height²) during childhood or a high BMI at 6 to 7 years had a significantly increased risk of dyspnea (adjusted odds ratio, 1.68; 95% CI, 1.18-2.39, for a high BMI at 6-7 years) and measured BHR (adjusted odds ratio, 1.66; 95% CI, 1.10-2.52) at 8 years. Children with a high BMI at a young age, but who developed a normal BMI at 6 to 7 years, did not have an increased risk of dyspnea or BHR at 8 years. BMI was not associated with sensitization.

Conclusion: Children with a current high BMI are at increased risk to have dyspnea and BHR at 8 years. A high BMI at an earlier age is not related to an increased risk if the child has

become normal weight at 6 to 7 years. (J Allergy Clin Immunol 2009;123:1000-1006.)

Key words: Obesity, body mass index, asthma, child, cohort study

The risk to develop asthma may be increased in overweight children.¹⁻³ Prospective studies showed that children who had a high BMI at baseline had a higher chance to develop asthma symptoms during follow-up.⁴⁻⁷ A question that remains unanswered is whether childhood asthma is related to present overweight or also to overweight at earlier ages. Are children who were overweight early in life, but have now developed a normal weight, still at increased risk to develop asthma?

In adults, Xu et al⁸ observed that a body mass index (BMI) above the 85th percentile at 14 and at 31 years was associated with asthma at 31 years of age. However, subjects who had a BMI above the 85th percentile at 14 years but not at 31 years did not have an increased risk of asthma at 31 years of age. Studies in children that analyzed the association between asthma and change in BMI or overweight status assessed change in BMI continuously or compared children who became overweight with children who did not, and were therefore not able to study the asthma risk in overweight children who became normal weight.^{6,9,10}

Insight into the association between change in overweight status during childhood and asthma could contribute to the understanding of the association between overweight and asthma. The aim of this study was to assess the association between a high BMI and asthma symptoms at different ages during childhood, and to study changes in BMI status during childhood in relation to asthma symptoms at 8 years of age. Besides reported asthma symptoms, we studied measured bronchial hyperresponsiveness (BHR) and sensitization at 8 years of age as outcome variables because of their strong association with asthma symptoms.

METHODS

Study design and study population

The study population consisted of 3756 Dutch children born in 1996 or 1997 who participated in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study. A detailed description of the study design has previously been published.¹¹ Briefly, pregnant women were recruited from the general population by means of a validated screening questionnaire on maternal allergy,¹² distributed to the women when visiting a prenatal clinic in The Netherlands. Based on this screening, 7862 women were invited to participate in the study. Approximately 50% of the invited pregnant women (n = 4146) agreed and gave written informed consent. After birth, the baseline study population consisted of 3963 children. Children born prematurely and twins were excluded from the analyses (n = 207). Questionnaires were sent to the

From ^athe Institute for Risk Assessment Sciences, Utrecht University; ^bthe Center for Prevention and Health Services Research, National Institute for Public Health and the Environment, Bilthoven; ^cthe Institute of Health Sciences, Vrije Universiteit, Amsterdam; ^dthe Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht; ^ethe Department of Pediatrics, Division of Respiratory Medicine, Erasmus Medical Center-Sophia, Rotterdam; and ^fthe Department of Pulmonology, University Medical Centre Groningen and ^gthe Department of Epidemiology and Bioinformatics, University of Groningen.

Supported by the Netherlands Organization for Health Research and Development; the Netherlands Asthma Foundation; the Netherlands Ministry of Health, Welfare and Sport; and Numico Research, The Netherlands.

Disclosure of potential conflict of interest: J. C. de Jongste has received research support from GlaxoSmithKline, Roche, and Friso. The rest of the authors have declared that they have no conflict of interest.

Received for publication July 15, 2008; revised February 19, 2009; accepted for publication February 20, 2009.

Reprint requests: Salome Scholtens, PhD, National Institute for Public Health and the Environment (RIVM), Centre for Prevention and Health Services Research (pb 101), P.O. Box 1, 3720 BA Bilthoven, The Netherlands. E-mail: salome.scholtens@rivm.nl. 0091-6749/\$36.00

© 2009 American Academy of Allergy, Asthma & Immunology
doi:10.1016/j.jaci.2009.02.029

Abbreviations used

BHR: Bronchial hyperresponsiveness
 BMI: Body mass index
 OR: Odds ratio
 PIAMA: Prevention and Incidence of Asthma and Mite Allergy
 SDS: SD score (*z* score)

participating parents during pregnancy, at 3 months, and yearly from 1 to 8 years of age, around the child's birthday.

At 8 years of age, a subgroup of the study population ($n = 1554$), consisting of all children of mothers with allergy ($n = 988$) and a random sample of the children of mothers without allergy ($n = 566$), was invited for a hospital-based medical examination, where a blood sample was collected and BHR was determined. Of the invited children, 1133 participated. After exclusion of children born prematurely and twins, 1070 children were available for analysis. In this subgroup, 65.5% ($n = 701$) of the children had a mother with allergy, compared with 31% ($n = 1166$) in the total study population. The study protocol was approved by the medical ethics committees of the participating institutes, and all parents gave written informed consent.

Outcome assessment

In the yearly questionnaires, the parents reported whether the child had an attack of wheeze and/or an episode of dyspnea and/or a prescription of inhaled corticosteroids for respiratory or lung problems prescribed by a medical doctor in the preceding year. In the PIAMA study, "asthma symptoms" are defined as at least 1 attack of wheeze and/or at least 1 episode of dyspnea and/or a prescription of inhaled corticosteroids. In this study, we assessed asthma symptoms at 3, 6, and 8 years of age. "Chronic asthma symptoms" were defined as having asthma symptoms at all 3 ages. In addition, we studied "wheeze without a cold" and "dyspnea without exercise" at 8 years of age as outcome variables.

In the collected blood samples at 8 years of age, specific IgE was determined on the following common inhalant allergens: house dust mite (*Dermatophagoides pteronyssinus*), cats, dogs, grass (*Dactylis glomerata*), birch, and *Alternaria alternata*. The detection limit for specific IgE was 0.35 IU/mL. Sensitization to inhalant allergens was defined as a specific IgE concentration of at least 0.70 IU/mL on at least 1 of the inhalant allergens. The limit was set at 0.70 IU/mL, because a IgE concentration of at least 0.70 IU/mL is indicative of allergic symptoms.¹³ BHR was determined according to the protocol of the European Community Respiratory Health Survey,¹⁴ defined as a decrease of 20% in FEV₁ at a cumulative dose of 0.61 mg methacholine bromide or below.

Anthropometric measures

The child's body weight (in kilograms), height (in centimeters), and date of last measurement were reported yearly by the parents. BMI was calculated as body weight in kilograms divided by height squared in meters (kg/m^2). We calculated sex-specific standard deviation scores (SDSs) of weight for age, length for age, and BMI for age by using the reference growth curves of the Dutch Fourth Nationwide Growth Study carried out in 1997.¹⁵

Because age at the reported weight and height measurements varied between children, we created 3 new age categories: 1 to 2 years, 3 to 5 years, and 6 to 7 years of age, reflecting infant age, preschool age, and school age. The SDSs within these categories were averaged. BMI SDSs were categorized in a high BMI (a BMI SDS above the 85th percentile) and a normal BMI (a BMI SDS below or equal to the 85th percentile). Although BMI might not be a clinically relevant measure in children under 2 years of age, it is currently used in most growth monitoring studies and epidemiologic research.¹⁶ A cutoff point of the 85th percentile was chosen because this cut-off is often used in studies on childhood overweight. Only a small number of children had a BMI SDS above the 95th percentile in the PIAMA study. Because the exact age at the weight and height measurement was available, the definition of

overweight according to the sex-specific and age-specific cut-off points defined by Cole et al¹⁷ was less suitable, because these cut-off points are defined per 6 months. A low BMI SDS at 6 to 7 years was defined as a BMI below the 15th percentile.

Change in BMI status between 3 to 5 and 6 to 7 years of age was classified into 4 categories. Children who had a normal BMI at 3 to 5 and at 6 to 7 years were classified as "persistent normal BMI." Children who had a high BMI at 3 to 5 years but not at 6 to 7 years were classified as "early high BMI." Children who had a normal BMI at 3 to 5 years but who had a high BMI at 6 to 7 years were classified as "late high BMI." Children who had a high BMI at 3 to 5 and at 6 to 7 years were classified as "persistent high BMI." Change in BMI status between 1 to 2 and 6 to 7 years was defined similarly.

Assessment of other variables

Maternal and paternal allergy and/or asthma were reported during pregnancy and were defined as current allergy to house dust mite or pets, current hay fever, or ever asthma. The parents reported in the questionnaires maternal education, maternal smoking during pregnancy (any smoking by the mother during pregnancy after the fourth week of pregnancy), smoking in the house by anyone when the child was 8 years of age, sex, mode of delivery (cesarean section vs vaginal delivery), and the child's birth weight. Maternal education was measured as the highest education completed and then divided into 3 categories (low, intermediate, and high education). Breast-feeding duration (in weeks) was assessed by questions on infant feeding in the questionnaires administered at 3 months and at 1 year. Maternal BMI was calculated from reported body weight (in kilograms) and height (in centimeters) when the child was 1 year of age.

Statistical analyses

Data analysis was conducted using SAS software version 9.1 (SAS Institute, Inc, Cary, NC). The main outcomes were defined at 8 years of age. In addition, the combination variable "asthma symptoms" at 3 years of age was studied in relation to a high BMI at 1 to 2 years, and "asthma symptoms" at 6 years of age was studied in relation to a high BMI at 3 to 5 years. The associations were analyzed by logistic regression. The associations between BMI SDS as a continuous variable and the outcome variables were analyzed in a linear regression analysis. To study the possibility of a U-shaped association between BMI and the outcome variables, the association between a low BMI SDS compared to a normal BMI SDS and the outcome variables was studied, and the association between BMI SDS quintiles and the outcome variables was studied.

Maternal allergy, paternal allergy, maternal education, maternal smoking during pregnancy, smoking in the house at 8 years, sex, mode of delivery, the child's birth weight, and breast-feeding duration were considered as potential confounders. The associations were not routinely adjusted for maternal BMI, because maternal BMI is probably a factor in the causal pathway. However, in addition we analyzed the associations with adjustment for maternal BMI. The interaction between a high BMI and sex and between a high BMI and maternal allergy were tested because these variables were regarded as important potential effect modifiers. *P* values below .05 were considered statistically significant.

Missing data and multiple imputations

At 8 years of age, 8% (293/3756) of the children of the baseline study population were lost to follow-up. Ninety percent (3106/3463) of the children who were still participating in the PIAMA study at 8 years of age completed and returned the questionnaire. For 80% (2487/3106) of the children who returned the questionnaire at 8 years of age, data on BMI were available for each of the age periods. Another 121 children had missing data on 1 of the outcome variables ($n = 45$) or confounder variables ($n = 76$), leaving 2366 children available for the complete case analysis. Of the children with missing data, 43% missed only 1 variable. In total, less than 10% of the data of used in the analyses was missing and was thus imputed.

A complete case analysis would not make efficient use of the data and might lead to biased results.^{18,19} Missing data were multiple times imputed by

using the Multivariate Imputation by Chained Equations procedure²⁰ that runs under the statistical program R version 2.5.0. After 50 iterations, convergence was achieved, resulting in 5 imputed datasets. Each imputed dataset was analyzed by standard complete data procedures, which ignore the distinction between real and imputed values. The results of the analyses were combined by using PROC MIANALYZE in SAS. All analyses were performed on the complete case data and on the imputed data.

RESULTS

Eleven percent of the children ($n = 405$) had a high BMI (a BMI SDS above the 85th percentile) at 6 to 7 years of age (Table I), showing that in our study population, a high BMI SDS was slightly less prevalent than in the Dutch reference population. At 8 years of age, asthma symptoms were prevalent in 14.1% ($n = 529$) of the children (Table II).

A high BMI at any age was associated with an increased risk of dyspnea at 8 years of age. However, the association between a high BMI and dyspnea at 8 years was most pronounced among the children who had a high BMI at 6 to 7 years (Tables III and IV). The associations between a high BMI at 6 to 7 years and wheeze, a prescription of inhaled corticosteroids, “wheeze without a cold,” and “dyspnea without exercise” were in the same direction but not statistically significant. A high BMI at 6 to 7 years was also significantly associated with “chronic asthma symptoms” (asthma symptoms at all ages; odds ratio [OR], 1.90; 95% CI, 1.26-2.85; $P = .002$; data not shown).

A high BMI at 1 to 2 years was significantly associated with a higher prevalence of asthma symptoms at 3 years (OR, 1.40; 95% CI, 1.12-1.73; $P = .003$), and a high BMI at 3 to 5 years was significantly associated with a higher prevalence of asthma at symptoms 6 years (OR, 1.36; 95% CI, 1.03-1.79; $P = .03$; data not shown).

Children who had a persistent high BMI between 3 to 5 years and 6 to 7 years of age had a significantly increased risk of dyspnea at 8 years of age compared with children with a persistent normal BMI (see Table IV). Children who had a normal BMI at 3 to 5 years but a high BMI at 6 to 7 years of age (late high BMI) had a significantly increased risk of dyspnea as well. Children who had a high BMI at 3 to 5 years but a normal BMI at 6 to 7 years of age (early high BMI) did not have an increased risk of dyspnea at 8 years of age. The associations between a persistent, late or early high BMI defined between 1 to 2 and 6 to 7 years of age and dyspnea at 8 years were comparable to the associations between a persistent, late or early high BMI defined between 3 to 5 and 6 to 7 years of age and the outcome at 8 years. (see Table IV).

Bronchial hyperresponsiveness was present in 40.0% ($n = 428$) of the children at 8 years of age (see Table II). A high BMI at 6 to 7 years was significantly associated with an increased risk of BHR (Table V). The risk of BHR was increased in children who had a late or a persistent high BMI. No association between an “early high BMI” and BHR at 8 years was observed.

Thirty percent of the children ($n = 316$) were sensitized to inhalant allergens (see Table II). A high BMI at 6 to 7 years was not associated with sensitizations at 8 years of age, nor was change in BMI status between 3 to 5 and 6 to 7 years of age (see Table V).

All associations were adjusted for maternal allergy, maternal education, maternal smoking during pregnancy, smoking by anyone in the house at 8 years of age, mode of delivery, the child’s birth weight, and breast-feeding duration. Additional adjustment for maternal BMI attenuated the association slightly, but the associations remained.

TABLE I. Descriptives of the study population

	Baseline population with complete data ($n = 2366$)		Baseline population with imputed data† ($n = 3756$)	
	Percent	No.	Percent	No.
Sex (girls)	48.4	1145	48.2	1811
Maternal allergy	27.8	658	31.0	1166
Maternal education (high)	37.2	881	34.8	1306
Maternal smoking during pregnancy	14.7	347	17.7	664
Smoking in the house at 8 y	15.7	372	17.9	671
Mode of delivery (cesarean section)	8.3	196	8.0	302
Breast-feeding duration (>16 wk)	36.8	871	33.0	1238
A high BMI at 1-2 y of age*	15.4	364	15.0	563
A high BMI at 3-5 y of age*	12.3	290	12.2	458
A high BMI at 6-7 y of age*	10.4	245	10.8	405
Change in BMI status between 1-2 and 6-7 y of age				
No high BMI	78.2	1851	78.3	2942
Early high BMI	11.4	270	10.9	410
Late high BMI	6.4	151	6.7	251
Persistent high BMI	4.0	94	4.1	153
Change in BMI status between 3-5 and 6-7 y of age				
No high BMI	83.2	1969	82.7	3106
Early high BMI	6.4	152	6.5	246
Late high BMI	4.5	107	5.1	192
Persistent high BMI	5.8	138	5.7	212
	Mean	SD	Mean	SD
Birth weight	3.59	(0.48)	3.56	(0.49)
Weight SDS at 6-7 y of age	0.01	(0.98)	-0.03	(1.01)
Height SDS at 6-7 y of age	0.19	(1.00)	0.14	(1.04)
BMI SDS at 6-7 y of age	-0.16	(0.98)	-0.16	(1.00)

*A high BMI was defined as BMI SDS >85th percentile; a normal BMI was defined as BMI SDS ≤85th percentile.

†Of the children with missing data, 43% missed only 1 variable. Less than 10% of the data was missing and was thus imputed.

The associations between the outcome variables and BMI SDS as a continuous variable showed similar results as the associations between the outcome variables and a high versus a normal BMI (data not shown). Per unit increase in BMI SDS at 6 to 7 years, the risk of asthma symptoms at 8 years increased by 1.19 (95% CI, 1.06-1.33; $P = .003$) in the adjusted analysis. A low BMI SDS (compared with a normal BMI SDS) was not associated with an increased risk of any of the outcome variables at 8 years. The analyses of the BMI SDS quintiles did not show a U-shaped association between BMI SDS and the outcome variables. No interaction was observed between sex and a high BMI or between maternal allergy and a high BMI.

The analyses presented in the text and tables are based on imputed data. In Table I, the descriptives of the study population are presented based on the imputed data and the complete case data. This table shows that the population with imputed data ($n = 3756$) did not differ from the complete case data ($n = 2366$) with regard the study characteristics. Most associations were more pronounced in the complete case data than in the imputed data. For example, the OR of the adjusted association between a high BMI at 6 to 7 years and asthma symptoms at 8 years of age was 1.78 (95% CI, 1.24-2.56) in the complete case

TABLE II. Prevalence of wheeze, dyspnea, and prescription of inhaled corticosteroids at 3, 6, and 8 years of age (n = 3756) and prevalence of BHR and sensitization† at 8 years of age (n = 1070)

	3 Years of age		6 Years of age		8 Years of age	
	Percent	No.	Percent	No.	Percent	No.
Wheeze	16.1	606	8.3	311	7.3	275
Dyspnea	15.6	585	10.9	409	9.6	361
Prescription of inhaled corticosteroids	8.4	315	8.2	309	7.1	268
Asthma symptoms*	23.7	889	15.2	572	14.1	529
Asthma symptoms at all 3 ages	—	—	—	—	5.8	218
Wheeze without a cold	—	—	—	—	4.3	162
Dyspnea without exercise	—	—	—	—	6.2	233
BHR	—	—	—	—	40.0	428
BHR with asthma symptoms	—	—	—	—	9.8	105
BHR without asthma symptoms	—	—	—	—	30.2	323
Sensitization†	—	—	—	—	29.6	316
Sensitization with asthma symptoms	—	—	—	—	9.8	105
Sensitization without asthma symptoms	—	—	—	—	19.8	211

*Asthma was defined as at least 1 attack of wheeze and/or 1 episode of dyspnea and/or a prescription of inhaled corticosteroids for respiratory or lung problems by a medical doctor in the preceding year.

†Sensitization was defined as a specific IgE concentration of at least 0.70 IU/mL on at least 1 of the inhalant allergens.

TABLE III. Frequencies (n) of wheeze, dyspnea, and prescription of inhaled corticosteroids at 8 years of age by BMI status* at different ages (imputed data, n = 3756)

	Wheeze		Dyspnea		Steroids		Asthma symptoms†		Wheeze without a cold		Dyspnea without exercise	
	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.
BMI status at 1-2 y of age*												
Normal BMI	7.3	234	9.7	309	7.1	227	14.0	448	4.4	140	6.4	204
High BMI	7.3	41	9.2	52	7.3	41	14.4	81	3.9	22	5.1	29
BMI status at 3-5 y of age*												
Normal BMI	7.3	239	9.3	305	6.9	228	13.7	451	4.2	139	6.1	202
High BMI	7.8	36	12.2	56	8.8	40	16.9	78	5.0	23	6.8	31
BMI status at 6-7 y of age*												
Normal BMI	7.2	241	9.1	304	6.9	232	13.4	449	4.1	138	6.0	200
High BMI	8.4	34	14.1	57	8.9	36	19.7	80	5.9	24	8.0	33
Change in BMI status between 1-2 and 6-7 y of age												
Persistent normal BMI	7.2	212	9.2	271	6.9	203	13.4	394	4.2	124	6.2	182
Early high BMI	7.1	29	8.1	33	7.0	29	13.3	55	3.5	14	4.6	19
Late high BMI	8.8	22	15.4	39	9.4	24	21.2	53	6.6	16	8.8	22
Persistent high BMI	7.8	12	12.0	18	8.1	12	17.3	27	4.9	8	6.7	10
Change in BMI status between 3-5 and 6-7 y of age												
Persistent normal BMI	7.2	223	8.9	277	6.8	212	13.3	413	4.1	127	6.0	186
Early high BMI	7.1	18	10.9	27	8.2	20	14.8	36	4.4	11	5.9	14
Late high BMI	8.2	16	14.7	28	8.2	16	20.2	39	6.1	12	8.1	16
Persistent high BMI	8.5	18	13.6	29	9.6	20	19.3	41	5.8	12	7.9	17

*A high BMI was defined as BMI SDS >85th percentile; a normal BMI was defined as BMI SDS ≤85th percentile.

†Asthma was defined as at least 1 attack of wheeze and/or 1 episode of dyspnea and/or a prescription of inhaled corticosteroids by a medical doctor in the preceding year.

data and 1.62 (95% CI, 1.19-2.22) in the imputed data. In the on-line supplementary data, the results for all complete case analyses are shown (Tables E1 and E2).

DISCUSSION

Children with a high BMI at 6 to 7 years were more likely to have asthma symptoms and BHR at 8 years of age compared with children with a normal BMI. A high BMI at earlier ages was not associated with asthma symptoms and BHR at 8 years of age in

children who became normal weight. A high BMI was not associated with sensitization.

Strengths of the current study were the longitudinal study design, the follow-up until 8 years of age with repeated data collection on weight and height and on asthma symptoms, and the large study population with a low attrition rate. In addition to data on asthma symptoms, we collected data on prescription of inhaled corticosteroids and measured sensitization and BHR.

The observed associations could not be explained by confounding factors like breast-feeding and maternal education,

TABLE IV. Adjusted[†] associations between a high BMI[‡] at different ages and change in BMI status during childhood, and wheeze, dyspnea, and prescription of inhaled corticosteroids at 8 years of age (imputed data, n = 3756)

	Wheeze		Dyspnea		Steroids		Asthma symptoms [§]		Wheeze without a cold		Dyspnea without exercise	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
High BMI at 1-2 y of age [‡]	1.03	0.69-1.54	0.95	0.66-1.36	1.07	0.73-1.56	1.05	0.80-1.40	0.91	0.53-1.56	0.81	0.51-1.28
High BMI at 3-5 y of age [‡]	1.09	0.71-1.67	1.35	0.95-1.91	1.33	0.86-2.05	1.28	0.93-1.75	1.21	0.69-2.11	1.14	0.69-1.88
High BMI at 6-7 y of age [‡]	1.21	0.79-1.84	1.68	1.18-2.39*	1.34	0.88-2.03	1.62	1.19-2.22*	1.47	0.85-2.56	1.43	0.84-2.43
Change in BMI status between 1-2 and 6-7 y of age												
Persistent normal BMI	1.00		1.00		1.00		1.00		1.00		1.00	
Early high BMI	1.03	0.64-1.65	0.87	0.56-1.37	1.06	0.68-1.68	1.02	0.72-1.43	0.86	0.47-1.60	0.74	0.43-1.27
Late high BMI	1.27	0.76-2.12	1.82	1.18-2.80*	1.43	0.85-2.39	1.77	1.21-2.58*	1.60	0.79-3.26	1.54	0.84-2.83
Persistent high BMI	1.12	0.57-2.20	1.39	0.78-2.46	1.22	0.64-2.34	1.40	0.86-2.28	1.17	0.48-2.83	1.14	0.54-2.43
Change in BMI status between 3-5 and 6-7 y of age												
Persistent normal BMI	1.00		1.00		1.00		1.00		1.00		1.00	
Early high BMI	1.00	0.49-2.02	1.25	0.75-2.07	1.26	0.71-2.24	1.14	0.72-1.80	1.09	0.47-2.51	0.99	0.50-1.95
Late high BMI	1.20	0.65-2.23	1.83	1.11-3.03*	1.25	0.64-2.44	1.71	1.10-2.66*	1.55	0.71-3.41	1.48	0.72-3.04
Persistent high BMI	1.21	0.71-2.05	1.61	1.03-2.52*	1.45	0.84-2.53	1.57	1.06-2.34*	1.41	0.68-2.92	1.38	0.71-2.67

P* < .05.[†]Adjusted for maternal allergy, maternal education, smoking during pregnancy, smoking in the house at 8 years of age, mode of delivery, birth weight, and breast-feeding duration.[‡]A high BMI was defined as BMI SDS >85th percentile; a normal BMI was defined as BMI SDS ≤85th percentile.[§]Asthma was defined as at least 1 attack of wheeze and/or 1 episode of dyspnea and/or a prescription of inhaled corticosteroids by a medical doctor in the preceding year.TABLE V.** Adjusted[†] associations between a high BMI[‡] at different ages and change in BMI status during childhood, and sensitization[§] and BHR at 8 years of age in the children who participated in the medical examination (imputed data, n = 1070)

	Sensitization [§]				BHR			
	Percent	No.	OR	95% CI	Percent	No.	OR	95% CI
BMI status at 1-2 y of age [‡]								
Normal BMI	30.7	273	1.00		38.9	347	1.00	
High BMI	23.9	43	0.66	0.44-1.01	45.2	81	1.28	0.89-1.85
BMI status at 3-5 y of age [‡]								
Normal BMI	29.9	278	1.00		38.8	361	1.00	
High BMI	27.5	38	0.84	0.53-1.31	48.1	67	1.43	0.97-2.12
BMI status at 6-7 y of age [‡]								
Normal BMI	29.5	280	1.00		38.5	365	1.00	
High BMI	30.0	36	0.99	0.62-1.60	52.0	63	1.66	1.10-2.52*
Change in BMI status between 1-2 and 6-7 y of age								
Persistent normal BMI	30.4	250	1.00		37.7	310	1.00	
Early high BMI	23.7	30	0.65	0.40-1.06	43.5	55	1.28	0.83-1.96
Late high BMI	34.4	24	1.15	0.65-2.03	54.0	37	1.88	1.07-3.26
Persistent high BMI	24.4	13	0.70	0.32-1.53	49.4	26	1.54	0.84-2.83
Change in BMI status between 3-5 and 6-7 y of age								
Persistent normal BMI	30.1	266	1.00		38.0	336	1.00	
Early high BMI	21.5	14	0.61	0.30-1.27	44.5	29	1.33	0.78-2.29
Late high BMI	25.7	12	0.83	0.39-1.80	52.9	25	1.82	0.95-3.50
Persistent high BMI	32.8	24	1.04	0.58-1.87	51.4	38	1.62	0.96-2.73

**P* < .05.[†]Adjusted for maternal allergy, maternal education, smoking during pregnancy, smoking in the house at 8 years of age, mode of delivery, birth weight, and breast-feeding.[‡]A high BMI is defined as BMI SDS >85th percentile; a normal BMI was defined as BMI SDS ≤85th percentile.[§]Sensitization was defined as a specific IgE concentration of at least 0.70 IU/mL on at least 1 of the inhalant allergens.

because those variables were included in all analyses. We dealt with possible selection bias caused by loss to follow-up or missing data on individual variables by multiple imputation of the missing data. This approach decreased the risk of selection bias and allowed us to make efficient use of the data.

Our asthma symptoms definition was based on wheeze, dyspnea, and prescription of inhaled corticosteroids reported by the parents. Although these factors are important indicators for asthma in children, wheeze and dyspnea are also common symptoms of respiratory infections in young children. However,

wheeze, dyspnea, and use of inhaled corticosteroids in children of 8 years of age are more suggestive of asthma than of infections. Furthermore, in support of this, we observed similar associations between a high BMI and asthma symptoms, a high BMI and chronic asthma symptoms (asthma symptoms at all 3 ages), and a high BMI and BHR at 8 years of age.

A limitation of this study was that weight and height of the children were reported by the parents. At 4 years of age, only a slight difference between measured and parental reported weight and height was observed in the children who participated in the PIAMA study.²¹ The difference between measured and reported data tended to be higher among children with a high BMI. It is possible that the associations between BMI and the outcome variables were somewhat attenuated by this phenomenon.

Furthermore, if the association between overweight and asthma in the child is mediated through increased levels of inflammatory factors, the actual risk measure of interest is total fat mass or percentage body fat, because the levels of inflammatory factors are increased by an increase in total fat mass. However, BMI is thought to be a valid proxy for fat mass in children because of its strong association with total fat mass.^{22,23} Adjustment for fat mass may result in a greater attenuation of the observed associations.

The increased asthma risk in children with a high BMI and in children who became overweight during follow-up has also been reported by others.^{3-6,9,10} A study by Carroll et al²⁴ showed that overweight children were more likely to be admitted to a hospital because of an asthma exacerbation, suggesting that the asthma exacerbation is more severe in overweight patients. The association between a change from a high BMI to a normal BMI and asthma has not been studied before in children, to our knowledge. However, the results corresponded with the results of an observational study in adults.⁸ One previous study did show an increased prevalence of BHR among children with a high BMI,²⁵ whereas another did not observe this.²⁶ The latter study assessed BHR by a hypotonic saline provocation tests, and a high BMI was defined as a BMI above the 75th percentile, which might explain the conflicting results. In both studies, a high BMI was positively associated with asthma symptoms. With regard to the association between BMI and sensitization, 2 studies observed no association between BMI and sensitization like in our study.^{25,27} One study reported a positive association between BMI and a positive skin prick test result in girls but not in boys.²⁸ We did not observe effect modification by sex in any of the outcome variables, as Mai et al²⁹ did.

A common explanation for the increased asthma risk in overweight children is the direct mechanical effect of an increased fat mass on lung function. The strong association with dyspnea and the weaker association with wheeze and inhaled corticosteroids would be in favor of such an explanation. In addition, the finding that overweight was in particular associated with asthma symptoms in children who were overweight at the time the asthma symptoms occurred lends support to this explanation. The observed increased risk of BHR in children with a high BMI might be explained by the low tidal volumes in overweight children. It has been put forward that, because of the low tidal volumes in overweight persons, airway responsiveness may be increased by changes in the airway smooth muscle.^{30,31}

Another reason for the increased asthma risk in overweight children might be the immunologic changes observed in

overweight subjects. Overweight is increasingly viewed as a chronic state of low-grade systemic inflammation.³²⁻³⁴ White adipose tissue not only is a site of energy storage but also has endocrine functions, and it secretes several immunologic active factors.³⁵ Overweight has been associated with higher levels of leptin and proinflammatory cytokines such as TNF- α , IL-6, IL-1 β , and C-reactive protein. These immunologic changes may influence airway function in both the short term and the long term.^{30,31}

In our study, we are not able to draw conclusions regarding the mechanism underlying the association between overweight and asthma in children. We hypothesize that both mechanisms work simultaneously. Studies that contain detailed repeated data on immunologic status and mechanic characteristics may give insight in the underlying mechanism of the association between overweight and asthma.

We conclude that a high BMI is associated with an increased risk of asthma symptoms, in particular the risk of dyspnea, and BHR at the age the child has a high BMI. A high BMI earlier in life is not associated with asthma symptoms and BHR if the child develops a BMI within the normal range. These results suggest that the development of a normal weight may positively affect asthma in overweight children.

Key messages

- Current overweight in children is associated with dyspnea and BHR at preschool and school age.
- Overweight does not have a lasting effect on childhood dyspnea and BHR if the child develops a normal weight.

REFERENCES

1. Litonjua AA, Gold DR. Asthma and obesity: common early-life influences in the inception of disease. *J Allergy Clin Immunol* 2008;121:1075-84.
2. Chinn S. Obesity and asthma. *Paediatr Respir Rev* 2006;7:223-8.
3. Flaherman V, Rutherford GW. A meta-analysis of the effect of high weight on asthma. *Arch Dis Child* 2006;91:334-9.
4. Mannino DM, Mott J, Ferdinands JM, Camargo CA, Friedman M, Greves, et al. Boys with high body masses have an increased risk of developing asthma: findings from the National Longitudinal Survey of Youth (NLSY). *Int J Obes (Lond)* 2006;30:6-13.
5. Gilliland FD, Berhane K, Islam T, McConnell R, Gauderman WJ, Gilliland SS, et al. Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol* 2003;158:406-15.
6. Gold DR, Damokosh AI, Dockery DW, Berkey CS. Body-mass index as a predictor of incident asthma in a prospective cohort of children. *Pediatr Pulmonol* 2003;36:514-21.
7. Burgess JA, Walters EH, Byrnes GB, Giles GG, Jenkins MA, Abramson MJ, et al. Childhood adiposity predicts adult-onset current asthma in females: a 25-yr prospective study. *Eur Respir J* 2007;29:668-75.
8. Xu B, Pekkanen J, Laitinen J, Jarvelin MR. Body build from birth to adulthood and risk of asthma. *Eur J Public Health* 2002;12:166-70.
9. Mamun AA, Lawlor DA, Alati R, O'Callaghan MJ, Williams GM, Najman JM. Increasing body mass index from age 5 to 14 years predicts asthma among adolescents: evidence from a birth cohort study. *Int J Obes (Lond)* 2007;31:578-83.
10. Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmatic symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med* 2001;163:1344-9.
11. Brunekreef B, Smit J, de Jongste J, Neijens H, Gerritsen J, Postma D, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002;13(suppl 15):55-60.
12. Lakwijk N, Van Strien RT, Doekes G, Brunekreef B, Gerritsen J. Validation of a screening questionnaire for atopy with serum IgE tests in a population of pregnant Dutch women. *Clin Exp Allergy* 1998;28:454-8.

13. Kerkhof M, Schouten JP, De Monchy JG. The association of sensitization to inhalant allergens with allergy symptoms: the influence of bronchial hyperresponsiveness and blood eosinophil count. *Clin Exp Allergy* 2000;30:1387-94.
14. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954-60.
15. 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.
16. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva: World Health Organization, Department of Nutrition for Health and Development; 2006.
17. 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.
18. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley and Sons; 1987.
19. Schafer JL. Analysis of incomplete multivariate data. London: Chapman & Hall; 1997.
20. van Buuren S, Oudshoorn, K. MICE: multivariate imputation by chained equations. R package version 1.15. 2005. Available at: <http://web.inter.nl.net/users/S.van.Buuren/mi/html/mice.htm>. Accessed May 31, 2007.
21. Scholtens S, Brunekreef B, Visscher TL, Smit HA, Kerkhof M, de Jongste JC, et al. Reported versus measured body weight and height of 4-year-old children and the prevalence of overweight. *Eur J Public Health* 2007;17:369-74.
22. Pietrobelli A, Faith MS, Allison DB, Gallagher D, Chiumello G, Heymsfield SB. Body mass index as a measure of adiposity among children and adolescents: a validation study. *J Pediatr* 1998;132:204-10.
23. Guida B, Pietrobelli A, Trio R, Laccetti R, Falconi C, Perrino NR, et al. Body mass index and bioelectrical vector distribution in 8-year-old children. *Nutr Metab Cardiovasc Dis* 2008;18:133-41.
24. Carroll CL, Stoltz P, Raykov N, Smith SR, Zucker AR. Childhood overweight increases hospital admission rates for asthma. *Pediatrics* 2007;120:734-40.
25. Mai XM, Nilsson L, Axelson O, Braback L, Sandin A, Kjellman NI, et al. High body mass index, asthma and allergy in Swedish schoolchildren participating in the International Study of Asthma and Allergies in Childhood: Phase II. *Acta Paediatr* 2003;92:1144-8.
26. Huang SL, Shiao G, Chou P. Association between body mass index and allergy in teenage girls in Taiwan. *Clin Exp Allergy* 1999;29:323-9.
27. von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax* 2001;56:835-8.
28. Hancox RJ, Milne BJ, Poulton R, Taylor DR, Greene JM, McLachlan CR, et al. Sex differences in the relation between body mass index and asthma and atopy in a birth cohort. *Am J Respir Crit Care Med* 2005;171:440-5.
29. Mai XM, Becker AB, Sellers EA, Liem JJ, Kozyrskyj AL. Infrequent milk consumption plus being overweight may have great risk for asthma in girls. *Allergy* 2007;62:1295-301.
30. Tantisira KG, Weiss ST. Complex interactions in complex traits: obesity and asthma. *Thorax* 2001;56(suppl 2):ii64-73.
31. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med* 2006;174:112-9.
32. Hersoug LG, Linneberg A. The link between the epidemics of obesity and allergic diseases: does obesity induce decreased immune tolerance? *Allergy* 2007;62:1205-13.
33. Schwarzenberg SJ, Sinaiko AR. Obesity and inflammation in children. *Paediatr Respir Rev* 2006;7:239-46.
34. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Low-grade systemic inflammation in overweight children. *Pediatrics* 2001;107:E13.
35. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 2004;89:2548-56.

TABLE E1. Adjusted[†] associations between a high BMI[‡] at different ages and change in BMI status during childhood, and wheeze, dyspnea, and prescription of inhaled corticosteroids at 8 years of age (complete case data, n = 2366)

	Wheeze		Dyspnea		Steroids		Asthma symptoms [§]		Wheeze without a cold		Dyspnea without exercise	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
High BMI at 1-2 y of age [‡]	0.98	0.61-1.58	0.95	0.63-1.44	1.01	0.63-1.61	1.03	0.73-1.45	0.80	0.41-1.58	0.82	0.48-1.42
High BMI at 3-5 y of age [‡]	1.31	0.81-2.12	1.44	0.96-2.17	1.45	0.91-2.32	1.44	1.02-2.04*	1.05	0.53-2.08	1.01	0.57-1.79
High BMI at 6-7 y of age [‡]	1.37	0.82-2.28	1.73	1.14-2.64*	1.46	0.88-2.42	1.78	1.24-2.56*	1.42	0.73-2.76	1.43	0.82-2.50
Change in BMI status												
between 1-2 and 6-7 y of age												
Persistent normal BMI	1.00		1.00		1.00		1.00		1.00		1.00	
Early high BMI	0.92	0.52-1.61	0.95	0.59-1.54	1.04	0.61-1.78	0.99	0.66-1.48	0.79	0.36-1.77	0.78	0.41-1.49
Late high BMI	1.29	0.58-2.89	1.27	0.62-2.61	1.13	0.48-2.68	1.49	0.83-2.68	0.98	0.30-3.23	1.09	0.43-2.80
Persistent high BMI	1.39	0.74-2.61	2.01	1.22-3.32*	1.68	0.92-3.05	1.97	1.27-3.04*	1.63	0.75-3.52	1.57	0.81-3.06
Change in BMI status												
between 3-5 and 6-7 y of age												
Persistent normal BMI	1.00		1.00		1.00		1.00		1.00		1.00	
Early high BMI	1.14	0.58-2.25	1.27	0.72-2.25	1.27	0.66-2.44	1.14	0.69-1.88	0.84	0.30-2.37	0.77	0.33-1.81
Late high BMI	1.52	0.80-2.88	1.77	1.03-3.04*	1.70	0.91-3.16	1.93	1.22-3.03*	1.33	0.55-3.18	1.36	0.66-2.80
Persistent high BMI	1.20	0.54-2.67	1.77	0.96-3.29	1.12	0.55-2.71	1.65	0.96-2.83	1.50	0.59-3.86	1.46	0.65-3.27

* $P < .05$.[†]Adjusted for maternal allergy, maternal education, smoking during pregnancy, smoking in the house at 8 years of age, mode of delivery, birth weight, and breast-feeding duration.[‡]A high BMI was defined as BMI SDS >85th percentile; a normal BMI was defined as BMI SDS ≤85th percentile.[§]Asthma was defined as at least 1 attack of wheeze and/or 1 episode of dyspnea and/or a prescription of inhaled corticosteroids by a medical doctor in the preceding year.

TABLE E2. Adjusted[†] associations between a high BMI[‡] at different ages and change in BMI status during childhood, and sensitization[§] and BHR at 8 years of age in the children who participated in the medical examination (complete case data, n = 574)

	Sensitization [§]		BHR	
	OR	95% CI	OR	95% CI
High BMI at 1-2 y of age [‡]	0.64	0.38-1.08	1.24	0.79-1.94
High BMI at 3-5 y of age [‡]	0.93	0.53-1.61	1.13	0.68-1.88
High BMI at 6-7 y of age [‡]	1.14	0.62-2.08	1.95	1.12-3.42*
Change in BMI status between 1-2 and 6-7 y of age				
Persistent normal BMI	1.00		1.00	
Early high BMI	0.71	0.39-1.29	1.23	0.73-2.05
Late high BMI	1.43	0.67-3.07	2.20	1.04-4.62*
Persistent high BMI	0.70	0.27-1.83	1.76	0.78-3.96
Change in BMI status between 3-5 and 6-7 y of age				
Persistent normal BMI	1.00		1.00	
Early high BMI	0.77	0.35-1.70	1.02	0.51-2.06
Late high BMI	0.95	0.35-2.58	3.42	1.34-8.77*
Persistent high BMI	1.18	0.57-2.46	1.41	0.71-2.82

* $P < .05$.[†]Adjusted for maternal allergy, maternal education, smoking during pregnancy, smoking in the house at 8 years of age, mode of delivery, birth weight, and breast-feeding.[‡]A high BMI is defined as BMI SDS >85th percentile; a normal BMI was defined as BMI SDS ≤85th percentile.[§]Sensitization was defined as a specific IgE concentration of at least 0.70 IU/mL on at least 1 of the inhalant allergens.