

Original Contribution

Body Mass Index Development and Asthma Throughout Childhood

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Initially submitted February 8, 2016; accepted for publication August 29, 2016.

Several studies have found an association between overweight and asthma, yet the temporal relationship between their onsets remains unclear. We investigated the development of body mass index (BMI) from birth to adolescence among 2,818 children with and without asthma from a Swedish birth cohort study, the BAMSE (a Swedish acronym for “children, allergy, milieu, Stockholm, epidemiology”) Project, during 1994–2013. Measured weight and height were available at 13 time points throughout childhood. Asthma phenotypes (transient, persistent, and late-onset) were defined by timing of onset and remission. Quantile regression was used to analyze percentiles of BMI, and generalized estimating equations were used to analyze the association between asthma phenotypes and the risk of high BMI. Among females, BMI development differed between children with and without asthma, with the highest BMI being seen among females with persistent asthma. The difference existed throughout childhood but increased with age. For example, females with persistent asthma had 2.33 times’ (95% confidence interval: 1.21, 4.49) greater odds of having a BMI above the 85th percentile at age ≥ 15 years than females without asthma. Among males, no clear associations between asthma and BMI were observed. In this study, persistent asthma was associated with high BMI throughout childhood among females, whereas no consistent association was observed among males.

asthma; body mass index; child

Abbreviation: BMI, body mass index.

Childhood obesity has emerged as one of the most serious public health challenges during the past few decades (1). Obesity increases the risk of several adverse health outcomes, and consistent evidence also supports an association between childhood overweight or obesity (most often defined by body mass index (BMI)) and asthma (2–4).

Overweight and obesity have been suggested to affect asthma in several ways—for example, through effects on lung function and through release of inflammatory factors from adipose tissue (3). Prenatal factors have also been shown to play important roles in the development of asthma (5–7). For example, we have previously shown that the association between maternal BMI in early pregnancy and childhood asthma persisted up to age 16 years (8). However, the association was partly mediated by the child’s own overweight.

Because most of the studies on overweight or obesity and asthma have been cross-sectional (9–11), the temporal order

of a possible association and the timing of overweight in relation to onset of asthma are not completely understood. Although a number of longitudinal studies (12–15) and 1 Mendelian randomization study (4) indicated that high BMI precedes asthma in childhood, others suggested a bidirectional association, with asthma also increasing the risk of becoming overweight (16, 17). In the BAMSE (a Swedish acronym for “children, allergy, milieu, Stockholm, epidemiology”) Project, a population-based birth cohort study, it was previously shown that having a high BMI at ages up to 4 years did not increase the risk of asthma at school age, if the child became normal-weight by age 7 years (18). Similar results from other studies (19–21) also showed that current overweight, but not early transient overweight, was associated with an increased risk for asthma.

Asthma might increase the risk of overweight through reduced physical activity due to the presence of asthma

symptoms during exercise (22). An observed association between overweight and asthma might also be explained by shared genetic factors, overdiagnosis, and comorbidity and may be confounded by lifestyle or dietary factors (23).

Altogether, these results suggest that high BMI in early childhood may not have a long-term effect on asthma and that asthma could also influence the risk of overweight. However, only a few studies have been able to investigate the association between BMI and asthma throughout the participant's entire childhood (15, 21). Our aim in the present study was to investigate BMI development and the risk of high BMI from birth to adolescence in relation to different asthma phenotypes (transient, persistent, and late-onset asthma), in comparison with no asthma.

METHODS

Study design and study population

The study population included children from the BAMSE cohort, a Swedish population-based birth cohort established in Stockholm 1994–1996 (24). In brief, 4,089 children have been followed through repeated administration of parental questionnaires collecting information on symptoms of allergic disease and environmental and lifestyle exposures. The baseline questionnaire was answered when the children were 2 months of age, on average, and follow-up questionnaires were sent out at approximately 1, 2, 4, 8, 12, and 16 years of age. At ages 12 and 16 years, the participants themselves answered an additional questionnaire. The latest follow-up (16 years) was conducted in 2010–2013, with a response rate of 78% for the parents and 76% for the adolescents.

In addition to the questionnaires, the children were also invited to undergo clinical examinations at ages 4, 8, and 16 years. The numbers of children participating in the clinical examinations were 2,965 (73%) at 4 years, 2,640 (65%) at 8 years, and 2,616 (64%) at 16 years.

Assessment of height and weight and definition of BMI

At the clinical examinations carried out at ages 4, 8, and 16 years, weight was measured with light indoor clothes to the nearest 0.1 kg using an electronic scale, and height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. In addition, among 2,594 children (63% of the original cohort), measurements of weight and height were collected from school and health-care records at 10 predefined ages up to age 12 years: 6 months (± 2 weeks), 12 and 18 months (± 4 weeks), 2, 3, 4, and 5 years (± 6 months), and 7, 10, and 12 years (-6 to $+11$ months). However, the child's exact age at each measurement was unavailable. Self-reported weight and height data were collected at ages 12 and 16 years. This information was used if an individual lacked information from the health record ($n = 455$ at age 12 years) or the clinical examination ($n = 458$ at age 16 years). Self-reported height and weight have been validated at age 16 years, showing overall high agreement with measured values (25). Data on weight and length at birth were collected from the Swedish Medical Birth Register ($n = 3,959$).

BMI was calculated as body weight in kilograms divided by squared height in meters. In total, BMI was available at 13 different time points: birth; 6, 12, and 18 months; and 2, 3, 4, 5, 7, 8, 10, 12, and 16 years. The availability of data at each age is displayed in Web Table 1 (available at <https://academic.oup.com/aje>). The study was approved by the regional ethical review board in Stockholm. The parents of all participating children gave their written informed consent for the clinical investigations.

Definition of health outcomes

Asthma was defined based on parental questionnaires (6, 8). Age-specific definitions were used. At ages 1 and 2 years, asthma was defined as at least 3 episodes of wheeze after 3 months of age and in the last 12 months, respectively, in combination with treatment with inhaled glucocorticosteroids and/or signs of suspected hyperreactivity without concurrent upper respiratory infection. At ages 4, 8, 12, and 16 years, asthma was defined as at least 4 episodes of wheeze in the last 12 months or at least 1 episode of wheeze during the same time period, in combination with occasional or regular treatment with inhaled glucocorticosteroids.

Three asthma phenotypes (transient, persistent, and late-onset) were defined by timing of onset and remission. Transient asthma was defined as fulfilling the definition of asthma at age 1, 2, and/or 4 years but not at ages 8, 12, and 16 years. Persistent asthma was defined as fulfilling the definition of asthma at age 1, 2, and/or 4 years and at age 8, 12, and/or 16 years. Late-onset asthma was defined as fulfilling the definition of asthma at age 8, 12, and/or 16 years but not at ages 1, 2, and 4 years.

The definitions of overweight phenotypes are provided in the Web Appendix.

Covariates

Information on covariates was obtained from the baseline questionnaire (sex, parental allergic disease, parental occupation, and maternal smoking during pregnancy and/or in infancy), the 1-year questionnaire (breastfeeding), the 8-year questionnaire (intake of fatty fish), the 12- and 16-year questionnaires (pubertal status, physical activity), and the Swedish Medical Birth Register (maternal BMI in early pregnancy, gestational age).

Statistical analyses

Differences in the distribution of exposure characteristics in relation to asthma phenotypes were analyzed using the Kruskal-Wallis test (continuous variables) and the χ^2 test (categorical variables). BMI development was modeled at different percentiles using quantile regression (26) with splines with 5 knots (at birth, 6 months, 1 year, 2 years, and 12 years). Quantile regression provides estimates of any quantile of the dependent variable, and it can therefore offer a more complete picture of a statistical association than ordinary linear regression. Regression coefficients are interpreted as the change in the dependent variable at a certain percentile per 1-unit change in the independent variable. The number and placement of the knots were chosen in order to maximize the model fit, defined

by the pseudo- R^2 value. The difference in BMI development over time between females and males was tested by including a term for interaction between age and sex. Differences between females and males across the asthma phenotypes over time were tested by including a term for 3-way interaction between age, asthma phenotype, and sex. The interaction terms were tested for overall significance by means of the Wald test. As a sensitivity analysis, BMI measurements at ages 7, 10, and 12 years were excluded, since age varied by up to -6 to +11 months at these ages.

Age was thereafter combined into categories (birth, 6 months-1.9 years, 2-3.9 years, 4-7.9 years, 8-11.9 years, 12-14.9 years, and ≥ 15 years), and the association between asthma phenotypes and the risk of high BMI (defined as BMI above the 85th percentile in nonasthmatic children) was analyzed using generalized estimating equations with a binomial family, a logit link function, and an unstructured correlation matrix (27). The 85th percentile was chosen because this is a commonly used cutoff for defining overweight in children (28). In addition, the association between overweight phenotypes and asthma phenotypes was analyzed by multinomial logistic regression. Potential confounders were selected a priori from the previous literature and on the basis of their association

with asthma phenotypes (Table 1): allergic heredity, maternal smoking during pregnancy and/or the child's infancy, parental occupation, maternal BMI in early pregnancy, gestational age, and breastfeeding. These variables were included in a separate model, and thereafter potential mediators or additional confounders (pubertal status, physical activity, and intake of fatty fish) were added one by one to the a priori model. Variables that affected the estimate by $\geq 10\%$ were included in an additionally adjusted model, whereas others were excluded from further analyses.

Children were included in the present analyses if information on asthma phenotype and at least 1 BMI measurement taken from birth to age 16 years was available ($n = 1,412$ females and $n = 1,406$ males). All analyses were performed using Stata statistical software, version 13 (StataCorp LP, College Station, Texas).

RESULTS

Descriptive results of exposure and outcomes

A comparison between the study population ($n = 2,818$) and children who did not fulfill the inclusion criteria ($n = 1,271$;

Table 1. Distribution of Exposure Characteristics in Relation to Asthma Phenotypes Among Children in the BAMSE Project ($n = 2,818$), Stockholm, Sweden, 1994-2013

Exposure ^a	No Asthma ($n = 2,214$)			Transient Asthma ($n = 176$)			Late-Onset Asthma ($n = 256$)			Persistent Asthma ($n = 172$)			P Value
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	
Maternal BMI ^b in early pregnancy			22.8 (3.2)			22.9 (3.5)			23.2 (3.4)			23.6 (3.5)	0.003 ^c
Gestational age, weeks			39.6 (1.7)			39.3 (2.2)			39.4 (2.0)			39.2 (2.2)	0.09 ^c
Physical activity ^d at age 16 years, hours/week			4.9 (4.6)			5.6 (4.8)			5.2 (3.9)			5.6 (4.5)	0.007 ^c
Male sex	1,060	47.9		109	61.9		130	50.8		107	62.2		<0.001
Breastfeeding for at least 4 months	1,818	82.2		128	74.0		202	78.9		127	74.7		0.006
Parental allergic disease	619	28.2		64	37.0		105	41.5		87	51.5		<0.001
Maternal smoking ^e	250	11.3		35	19.9		29	11.3		37	21.5		<0.001
Parental professional occupation	1,881	85.8		147	87.5		206	81.4		127	74.7		<0.001
Late pubertal/postpubertal at age 16 years ^f													
Males	498	55.7		52	60.5		60	59.4		48	58.5		0.67
Females	1,005	98.3		61	100		102	100		55	100		0.72
Intake of fatty fish ≥ 1 time/week at age 8 years	260	15.1		15	11.2		30	15.4		21	14.6		0.67
Overweight at age 16 years ^g	317	14.9		36	21.8		50	21.6		43	27.0		<0.001

Abbreviations: BAMSE, Children, Allergy, Milieu, Stockholm, Epidemiology; BMI, body mass index; SD, standard deviation.

^a Data were missing for some variables.

^b Weight (kg)/height (m)².

^c Kruskal-Wallis test for continuous variables; χ^2 test for all other variables.

^d Self-reported amount of vigorous physical activity.

^e During pregnancy and/or the child's infancy.

^f Based on a pubertal development scale (45).

^g Defined according to the International Obesity Task Force cutoffs (46).

Web Table 2) showed that parental allergic disease, parental professional occupation, and breastfeeding for at least 4 months were more common among included children, whereas maternal smoking during pregnancy and/or infancy was less common.

Among children in the study population, 27,292 BMI values were available for the 13 different time points (see Web Table 1 for more detailed information). Transient asthma was present among 6.2% of the children, late-onset asthma among 9.1%, and persistent asthma among 6.1%. Males had higher prevalence of all asthma phenotypes than females. The distribution of exposure characteristics in relation to asthma phenotypes is displayed in Table 1. In general, children with persistent asthma differed most from children without asthma. For example, maternal smoking during pregnancy and/or in infancy was more prevalent among children with persistent asthma (21.5% as compared with 11.3% among children without asthma), whereas parental professional occupation was less prevalent (74.7% as compared with 85.8% among children without asthma).

BMI development throughout childhood in relation to asthma phenotypes

The BMI data and the estimated BMI percentiles (5th, 15th, 25th, 50th, 75th, 85th, and 95th) are shown by sex in Figure 1. At all percentiles, BMI increased rapidly from birth and reached an infancy peak just before 1 year of age. After 1 year of age, BMI decreased up to around 6 years of age at the median value (usually referred to as the “adiposity rebound” (29)) and then increased throughout the rest of childhood. BMI was slightly higher among males than among females ($P < 0.01$ at the fifth percentile and $P < 0.001$ at the other percentiles). For example, at age 16 years, the 85th percentile (the commonly used cutoff for overweight) was 23.9 among females and 24.4 among males.

Figure 2 shows BMI development at the 85th percentile for the different asthma phenotypes. The association between asthma phenotypes and BMI differed between females and males ($P < 0.001$). Among females, children with persistent asthma had the highest BMI throughout childhood, whereas children without asthma had the lowest BMI throughout most of childhood. In contrast, males with and without asthma had similar BMI development, with only marginally higher BMIs being seen among males with asthma.

The difference in BMI between females with persistent asthma, compared with no asthma, seemed to increase with age from school age onward. At age 16 years, the 85th percentile BMI was 23.6 for females without asthma and 27.4 for females with persistent asthma. These differences correspond to a 10.6-kg (23.4-pound) difference in weight for a female who is 167 cm (65.8 inches) tall (the mean height at the 16-year follow-up). Among females with transient and late-onset asthma, BMI development was relatively similar, and generally slightly higher compared with nonasthmatics.

Excluding the time points 7, 10, and 12 years from the analyses led to similar results (data not shown). Modeling BMI at the median value (Web Figure 1) showed that differences in BMI between the asthma phenotypes were smaller compared with the 85th percentile among females, although

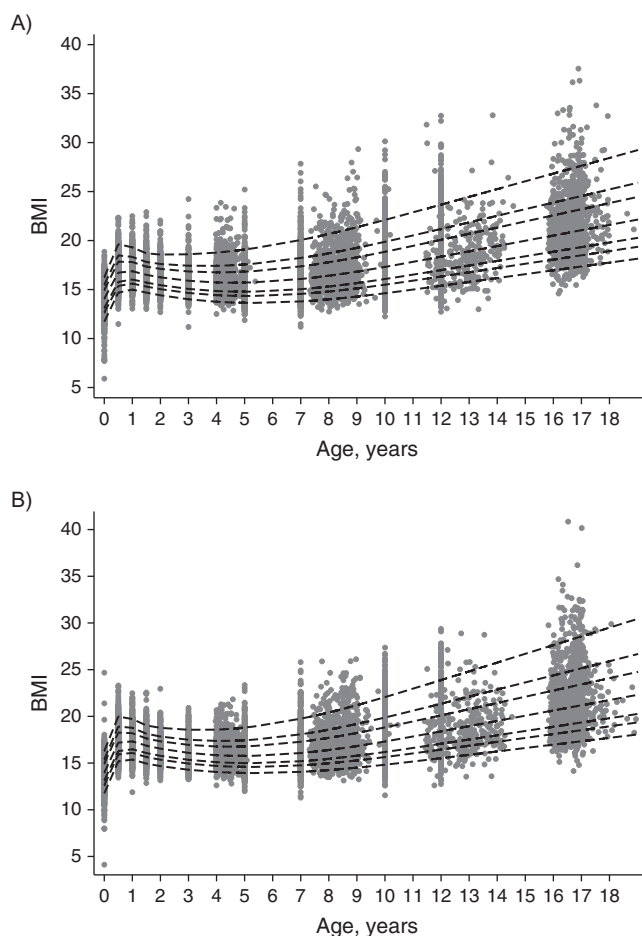


Figure 1. Body mass index (BMI) measurements (weight (kg)/height (m)²) and estimated percentiles of BMI (5th, 15th, 25th, 50th, 75th, 85th, and 95th) throughout childhood among females (A) and males (B) in the BAMSE Project, Stockholm, Sweden, 1994–2013. BMI development was modeled through quantile regression using splines with 5 knots. At ages 4, 8, 12, and 16 years, BMI from clinical investigations and questionnaires was used. At the other ages, register and health-record data without exact age at each measurement were used. (BAMSE is a Swedish acronym for “children, allergy, milieu, Stockholm, epidemiology.”)

persistent and late-onset asthma were still associated with a somewhat higher BMI compared with no asthma.

Figure 3 shows the adjusted odds ratio for having a BMI above the 85th percentile (as calculated in the nonasthmatics) for the different asthma phenotypes in combined age periods (exact values are shown in Web Table 3). Among females, persistent asthma was associated with high BMI throughout childhood, reaching statistical significance in all age periods except birth and 6 months–1.9 years (Figure 3C). For example, the adjusted odds ratio was 2.33 (95% confidence interval: 1.21, 4.49) at age ≥ 15 years. Late-onset asthma appeared to be associated with high BMI at birth and in middle and late childhood, with increasing, although nonsignificant, odds ratios towards the older ages (Figure 3B). Transient asthma was associated with high BMI at birth and in middle childhood, although the confidence

intervals were broad and the association reached statistical significance at ages 4–7.9 years only (Figure 3A).

Among males, the associations between asthma phenotypes and high BMI were less clear. Persistent asthma was associated with high BMI at some ages, reaching statistical significance at 6 months–1.9 years, and there was a tendency towards an inverse association at birth (Figure 3F). Among males with transient and late-onset asthma, the pattern was relatively similar to that seen among females, although none of the associations reached statistical significance (Figure 3D and 3E). Additional adjustment for pubertal status, physical activity, or intake of fatty fish (Web Figure 2) did not change the observed associations in females or males (data not shown).

Analyzing the association between overweight phenotypes and asthma phenotypes ($n = 880$ females and $n = 887$ males) showed that among females, late-onset overweight was associated with late-onset asthma and persistent overweight was associated with persistent asthma. Among males, transient overweight was associated with transient asthma (Web Table 4).

DISCUSSION

In the present study, we analyzed the development of BMI from birth to adolescence in relation to asthma phenotypes among 2,818 children from a population-based prospective birth cohort study, the BAMSE Project. Among females, persistent asthma was associated with high BMI throughout childhood, whereas no clear pattern was observed among males.

An association between childhood overweight and asthma or asthma symptoms has been observed in several cross-sectional (30–33) and cohort (13–15, 34) studies. However, few studies have repeatedly followed children from birth to adolescence, and the temporal order between the onsets of the two conditions is not yet fully understood. It is also still unclear how changes in BMI and BMI development are associated with asthma throughout childhood, as most studies use information on BMI at 1 point in time only. In a pooled analyses of data from 8 European birth cohorts, Rzehak et al. (12) investigated whether trajectories of BMI development were associated with asthma at ages up to 6 years and found that a rapid increase in BMI during the first 2 years of life was associated with asthma. Children with persistent rapid growth up to 6 years of age also showed a tendency toward an association, although statistical power to draw any conclusions from this group was too low. In a similar analysis carried out among 1,456 participants from the Isle of Wight birth cohort up to age 18 years, Ziyab et al. (21) found that an early persistent overweight trajectory and a delayed overweight trajectory, but not an early transient overweight trajectory, were associated with asthma at age 18 years. In a birth cohort of 9,723 children from the United Kingdom (15), it was further found that rapid weight growth in infancy and early childhood, but not after age 3 years, was associated with later asthma.

Unlike these previous studies, we used an alternative approach by investigating whether BMI development at different percentiles differed among nonasthmatics and children

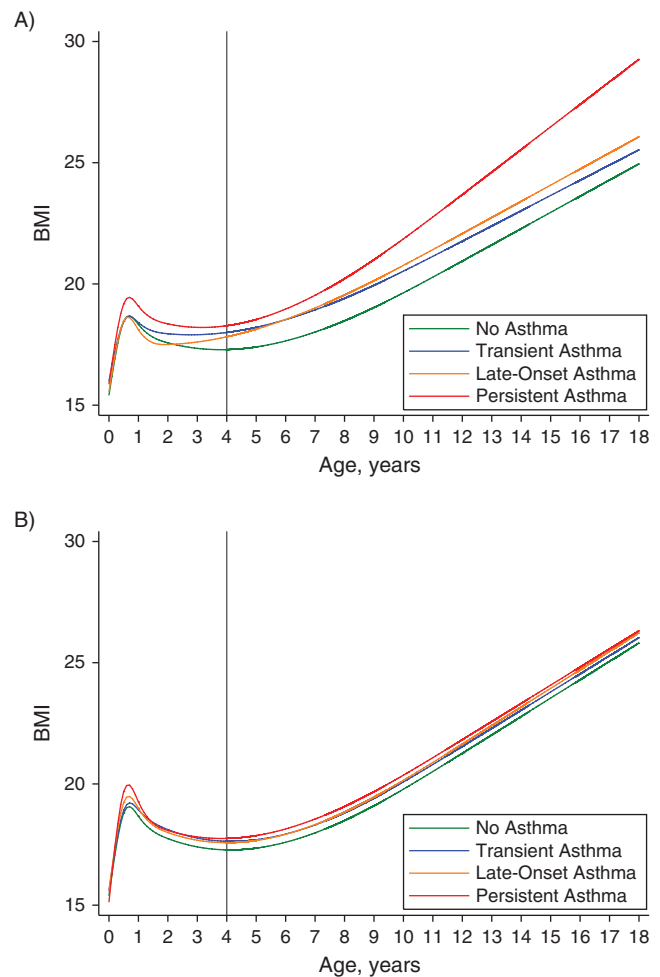


Figure 2. The 85th percentile of body mass index (BMI; weight (kg)/height (m)²) throughout childhood for different asthma phenotypes among females (A) and males (B) in the BAMSE Project, Stockholm, Sweden, 1994–2013. BMI development was modeled through quantile regression using splines with 5 knots. (BAMSE is a Swedish acronym for “children, allergy, milieu, Stockholm, epidemiology.”)

with transient, late-onset, and persistent asthma. Our results do not provide clear evidence on the temporality of an association between overweight and asthma—although, when interpreting the comparison of BMI development across asthma phenotypes, females with late-onset asthma seemed to be already starting to have an increase in BMI in early life, which indicates that BMI was slightly elevated even before the child developed asthma according to our definition. Persistent asthma was associated with high BMI throughout childhood in females, indicating that already having an elevated BMI at a young age is important for asthma development and persistence and/or that asthma and overweight share common risk factors in early life. However, the analyses of overweight phenotypes in relation to asthma phenotypes showed that transient overweight was not associated with persistent or late-onset asthma, highlighting the importance of managing overweight at an early age.

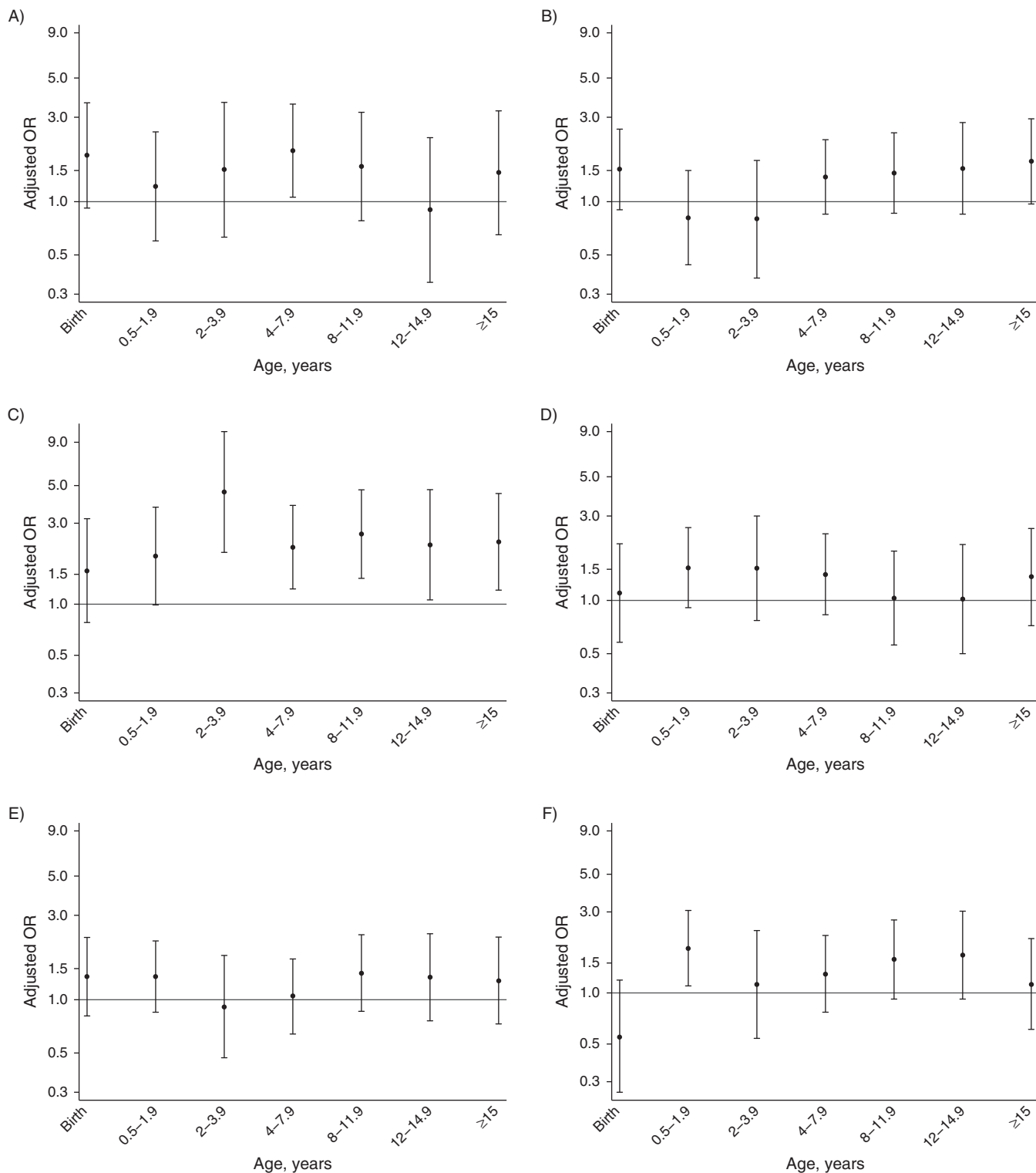


Figure 3. Adjusted odds ratio (OR) for having a body mass index (BMI; (weight (kg)/height (m)²) above the 85th percentile (as calculated in non-asthmatics) among children with different asthma phenotypes as compared with nonasthmatics in the BAMSE Project, Stockholm, Sweden, 1994–2013. Analyses were performed using generalized estimating equations models with adjustment for allergic heredity, maternal smoking during pregnancy and/or in infancy, parental occupation, maternal BMI in early pregnancy, gestational age, and breastfeeding. A) Transient asthma—females; B) late-onset asthma—females; C) persistent asthma—females; D) transient asthma—males; E) late-onset asthma—males; F) persistent asthma—males. Bars, 95% confidence intervals. (BAMSE is a Swedish acronym for “children, allergy, milieu, Stockholm, epidemiology.”)

Previous studies have shown mixed results regarding sex differences in children; some studies have found a stronger association between overweight and asthma in girls (35–37) and others in boys (34, 38). Possible explanations for a potentially stronger association in females, particularly among adults, have been discussed and involve influences of sex hormones (39) and differences in the reporting or diagnosis of asthma (40). Not all studies have formally tested for interaction between the sexes, however (35, 37), and when this was done, differences were not always significant (34). In the present study, an association among females but not among males ($P < 0.001$ for interaction) was mainly observed for persistent asthma, where differences in BMI seemed to increase in middle-to-late childhood. In general, girls enter puberty earlier than boys and have a greater increase in body fat percentage during puberty than boys (41). Therefore, sex differences in the association between BMI and asthma could be explained by differences in pubertal development, if asthma is also associated with pubertal status. However, in a previous study from the BAMSE Project, Protudjer et al. (42) did not find an association between persistent asthma (defined as asthma at age 1, 2, or 4 years and at age 8 years) and pubertal status at age 12 years among girls. In addition, adjusting for pubertal status in the present study did not affect the association between asthma and high BMI in late childhood.

Another potential explanation for sex differences across asthma phenotypes might be differences in physical activity. Boys with asthma might be more active and engage more in sports than girls with asthma.

Many plausible mechanisms exist for an association between obesity and asthma, and several review papers have discussed these mechanisms in detail (3, 23, 43). Obesity might affect lung function or affect the immune system through inflammation. Prenatal factors, epigenetics, and shared genetics might also play an important role (44). Asthma may also be associated with obesity through reduced physical activity (22), although in the present study, children with asthma reported more physical activity than children without asthma.

The strengths of the present study include the population-based prospective birth cohort design, a large study size, a high response rate, and an extensive number of BMI and asthma measurements taken from birth to age 16 years. BMI was further based on measured weight and height at all ages, except for a subsample of participants at ages 12 and 16 years. The high quality of the BMI assessments over time provided the possibility to study BMI longitudinally throughout childhood. Using quantile regression provided additional information about the statistical association with the whole BMI distribution, especially the high BMI percentiles.

Some potential limitations require attention. Asthma was defined according to parental reports, and some misclassification might have been present, since different parents may perceive asthma symptoms differently. Such a bias might be differential if parents of overweight children are more observant about wheezing in their child than parents of normal-weight children. In addition, although the participants were from a population-based cohort, selection bias cannot be ruled out, as there were some differences between children who were included in the analyses and those who were not included. Parents of overweight children might, for example,

be less willing to give access to their child's height and weight data from records. However, this would affect the observed association only if it were also related to the child's asthma status. Finally, although we took several previously identified confounders into account, the associations might have been influenced by residual or unmeasured confounding, as is virtually always the case in observational studies.

In summary, BMI development throughout childhood differed between children with and without asthma among females, with the highest BMI being seen among females with persistent asthma. This study highlights the importance of monitoring weight status among children with asthma.

ACKNOWLEDGMENTS

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This work was supported by the Swedish Research Council, the Stockholm County Council, the Swedish Heart and Lung Foundation, the Swedish Research Council for Health, Working Life and Welfare, the Swedish Asthma and Allergy Foundation, the European Commission's Seventh Framework Programme (29 Program MeDALL (Mechanisms of the Development of Allergy), grant agreement 261357), and the Strategic Research Program in Epidemiology at the Karolinska Institutet.

We thank the staff of the BAMSE Project, especially Eva Hallner and Sara Nilsson. We also thank Dr. Ralf Kujala for statistical support.

Conflict of interest: none declared.

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