

ORIGINAL ARTICLE

Impact of childhood asthma on growth trajectories in early adolescence: Findings from the Childhood Asthma Prevention Study (CAPS)

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ABSTRACT

Background and objective: Understanding the associations between childhood asthma and growth in early adolescence by accounting for the heterogeneity of growth during puberty has been largely unexplored. The objective was to identify sex-specific classes of growth trajectories during early adolescence, using a method which takes the heterogeneity of growth into account and to evaluate the association between childhood asthma and different classes of growth trajectories in adolescence.

Methods: Our longitudinal study included participants with a family history of asthma born during 1997–1999 in Sydney, Australia. Hence, all participants were at high risk for asthma. Asthma status was ascertained at 8 years of age using data from questionnaires and lung function tests. Growth trajectories between 11 and 14 years of age were classified using a latent basis growth mixture model. Multinomial regression analyses were used to evaluate the association between asthma and the categorized classes of growth trajectories.

Results: In total, 316 participants (51.6% boys), representing 51.3% of the entire cohort, were included. Sex-specific classes of growth trajectories were defined. Among boys, asthma was not associated with the classes of growth trajectories. Girls with asthma were more likely than girls without asthma to belong to a class with later growth (OR: 3.79, 95% CI: 1.33, 10.84). Excluding participants using inhaled corticosteroids or adjusting for confounders did not significantly change the results for either sex.

SUMMARY AT A GLANCE

The association between childhood asthma and heterogeneous sex-specific classes of growth trajectories during adolescence was investigated. No differences were found for boys with versus without asthma. However, girls with asthma had a higher probability of belonging to a class with later growth than those without asthma.

Conclusion: We identified sex-specific heterogeneous classes of growth using growth mixture modelling. Associations between childhood asthma and different classes of growth trajectories were found for girls only.

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Key words: adolescent, growth and development, growth charts, puberty, sex.

Abbreviations: BMI, body mass index; CAPS, Childhood Asthma Prevention Study; GMM, growth mixture modelling; HREC, Human Research Ethics Committee; ICS, inhaled corticosteroid; RPAH, Royal Prince Alfred Hospital.

INTRODUCTION

Growth patterns vary widely between individuals during adolescence.^{1,2} In addition, growth patterns may be disturbed in children with asthma during the pubertal years.^{3,4} Heterogeneity in growth patterns has not been addressed in previous studies of associations between childhood asthma and growth.^{3–11} Rather, growth of children with asthma has been compared to reference trajectories. In one prospective study of children with asthma, growth after 10 years of age deviated from reference trajectories and puberty was delayed.⁴ In another cohort of children followed up to 15 years of age, no associations between the presence

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of asthma and growth in height were identified.⁵ Unfortunately, although it is known that the timing of growth during puberty differs between boys and girls,^{1,2} neither of these studies included sex-stratified results.^{4,5} Growth standards from growth curves developed using cross-sectional data and longitudinal data approximate each other until children are 9 years of age.¹ However, from the start of puberty, growth standards from cross-sectional and longitudinal growth curves differ because the tempo of growth during puberty significantly varies between individuals.¹ Thus, growth curves based on cross-sectionally collected data may not be the most suitable references for data on growth during puberty.

The aim of this study was to identify sex-specific classes of growth trajectories during early adolescence, using growth mixture modelling (GMM), a method which takes heterogeneity of growth into account and to evaluate the association between childhood asthma and different classes of growth trajectories in adolescence.

METHODS

Participants

Participants were members of the Childhood Asthma Prevention Study (CAPS) birth cohort initially designed as a randomized controlled trial to evaluate the effect of house dust mite avoidance and/or omega-3 supplementation in reducing the risk of asthma. The interventions were implemented from birth to age 5 years and the cohort has been followed up. Details on the study design, intervention, population and results of the randomized controlled trial and of follow-ups at 8 and 11.5 years of age are published elsewhere.^{12–17} Pregnant women and their unborn children at high risk of asthma (defined as at least one parent/sibling with asthma) were recruited between January 1997 and December 1999 in the Sydney region. The sociodemographic characteristics of this cohort are similar to the general population in Sydney, aside from a higher proportion of Australian-born and tertiary educated parents amongst CAPS participants.¹⁴ The study population for this analysis includes members of the cohort who completed at least five height measurements during puberty (Fig. 1).

Ethical approval was obtained from the Sydney Local Health District (RPAH Zone) HREC Protocol Numbers X08-0277 and HREC/08/RPAH/472. CAPS was registered at Australian New Zealand Clinical Trials Registry with registration ID: ACTRN12605000042640.

Assessments

Asthma at 8 years of age was defined as wheeze in the 12 months prior to assessment plus either ever-diagnosed asthma (reported at 18 months and/or 3, 5 or 8 years of age) or airway hyperresponsiveness (at 8 years of age).¹⁶

Inhaled corticosteroids (ICSs) use at 8 years of age was defined as daily or long-term ICS use in the last

12 months reported in the questionnaire during the clinic visit.

Height assessments were performed every third month starting around participants' 11th birthdays and continuing until December 2013. Height assessments were performed in families' homes using wall-mounted stadiometer (SECA206, Seca, Hamburg, Germany), which were installed in a standardized manner during a home visit by a CAPS team member. Parents were instructed how to use the stadiometer and asked to record the measurements to the nearest 0.5 cm.

Data analysis

GMM was used to identify classes of growth trajectories between 11 and 14 years of age (detailed below). Subsequently, participants were assigned to the class to which they had the highest estimated posterior probability. Unadjusted and adjusted multinomial regression analyses were performed to evaluate the association between asthma status at 8 years of age (yes/no) and assigned growth trajectory class. Potential confounders were CAPS dietary intervention group, parental obesity, ethnicity, smoking during pregnancy, parental education and breastfeeding. These confounders were included because they have been associated with growth.¹⁸ Additionally, analyses adjusting for ICS use or excluding participants using ICS at 8 years of age were performed. All analyses were stratified by sex. Results are presented as OR with 95% CIs. Regression analyses were carried out in SAS 9.3 (SAS Institute, Cary, NC, USA). *P*-values <0.05 were considered statistically significant.

Identification of classes of growth trajectories

First, a natural cubic spline model was used to smooth and interpolate all raw height measurements recorded between 9 and 16 years of age for participants with at least five height measurements. This minimum number of data points was chosen to ensure that the cubic spline smoothing procedure provided a good fit to the data. Second, these smoothed height data were used in the latent basis GMM to identify classes of growth trajectories. GMM identifies unobserved sub-populations and describes longitudinal changes in height within each sub-population. Thereby, GMM examines the differences in growth between the unobserved sub-populations.¹⁹ In contrast to most other methods in growth research, GMM does not require an assumption that all participants come from the same underlying distribution.¹⁹ The method has been previously used in developmental research to define groups with similar developmental trajectories, such as for groups of similar BMI trajectories.^{18,20} Methods for GMM model selection and determination of optimal number of classes are described in detail in Appendix S1, Supplementary Information. All GMM models were performed in Mplus version 7.1 (Muthén & Muthén, Los Angeles, CA, USA).²¹

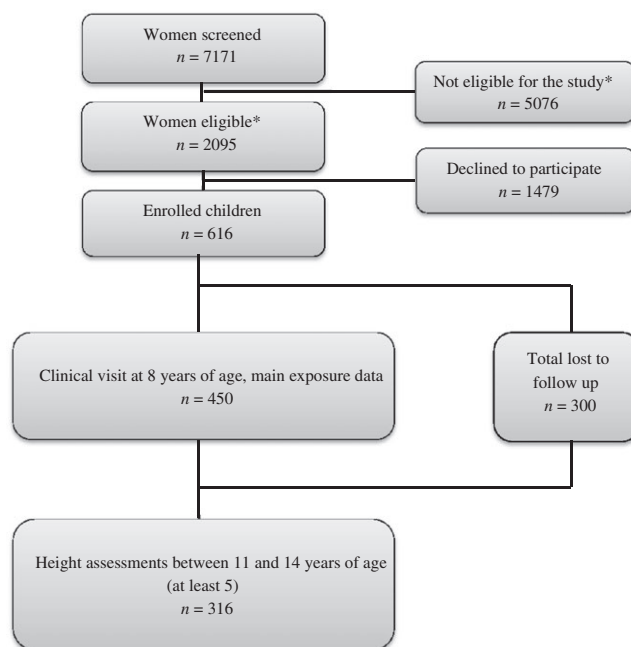


Figure 1 Flow chart for recruitment to the study as part of Childhood Asthma Prevention Study, Sydney, Australia, 1997–2013. *Inclusion criteria are described in Reference 12.

RESULTS

Of the 616 participants in the CAPS cohort, 316 (51.3% of the entire cohort; 163 of 316 (51.6%) boys) were included in this study. Those who had withdrawn before the first height assessment at around 11 years of age ($n = 216$, 35.1%) and those with less than five height assessments ($n = 84$, 13.6%) were excluded. The participants had older mothers, parents with higher education and were breastfed for a longer time than those whose data was excluded (Table S1, Supplementary Information). Asthma at 8 years of age was more common in boys than girls (29.4% vs 18.3%, $P < 0.05$) (Table 1).

A total of 3492 smoothed three-monthly height measurements between 11 and 14 years of age were used to define classes of growth trajectories. Participants had, on average, 6.4 smoothed height measurements between 11 and 14 years of age.

For both boys and girls, a GMM model with three classes was identified as optimal (Appendix S1 and Table S2, Supplementary Information). The three classes of growth trajectories for boys are presented in Figure 2A. There was no significant difference between the three classes according to height at starting point ($P = 0.12$). The class *Later growth* ($n = 100$, 61.3%) was characterized by the lowest height at end point (166 cm) and the lowest maximum growth rate (12.8 cm/year) at the latest age (12.9 years of age). The class *Intermediate growth* ($n = 48$, 29.4%) was characterized by the tallest height at end point (170 cm) and intermediate age at maximum growth rate (12.5 years of age). The classes *Intermediate growth* and *Earlier growth* ($n = 15$, 9.2%) had similar maximum growth rates (14.8 cm/year). *Earlier growth* was additionally characterized by intermediate height at end point

(168 cm) and the earliest age at maximum growth rate (12.0 years of age).

The three classes of growth trajectories for girls are shown in Figure 2B. There was no difference between the three classes by height at end point ($P = 0.21$) or maximum growth rate ($P = 0.86$). The class *Earlier growth* ($n = 71$, 46.4%) was characterized by the tallest starting height (150 cm) and the earliest age at maximum growth rate (11.8 years of age). The class

Table 1 Clinical characteristics of the study participants ($n = 316$) from the Childhood Asthma Prevention Study, Sydney, Australia, 1997–2013

Characteristics	Boys <i>n</i> (%)	Girls <i>n</i> (%)
Gender	163 (51.6)	153 (48.4)
Asthma status at 8 years		
Asthma		
No	110 (67.5)	118 (77.1)
Yes	48 (29.4)	28 (18.3)
Missing	5 (3.1)	7 (4.6)
ICS use [†]		
No	148 (90.8)	136 (88.9)
Yes	10 (6.1)	10 (6.5)
Missing	5 (3.1)	7 (4.6)
Growth characteristics [‡]	Mean (SD)	Mean (SD)
Height at 11 years (cm)	146 (6.52)	147 (7.27)
Height at 14 years (cm)	167 (8.52)	161 (6.24)

[†]Daily or long-term ICS use in the last 12 months at 8 years of age.

[‡]Height measurements from smoothed data after natural cubic spline process.

ICS, inhaled corticosteroid; SD, standard deviation.

Intermediate growth ($n = 52$, 34.0%) was characterized by an intermediate starting height (145 cm) and an intermediate age at maximum growth rate (12.1 years of age). The class *Later growth* ($n = 30$, 19.6%) was characterized by the shortest starting height (139 cm) and the latest age at maximum growth rate (12.9 years of age).

Earlier growth was selected as reference groups in the regression analyses for both boys and girls.

In boys, asthma at 8 years of age was not significantly associated with classes of growth trajectories (Table 2, boys). In contrast, amongst girls, asthma at 8 years of age was associated with classes of growth trajectories (Table 2, girls). Compared to girls without asthma, girls with asthma at 8 years of age were more likely to be assigned to *Later growth* than to *Earlier growth* (OR: 3.79; 95% CI: 1.33, 10.84). *Intermediate growth* compared with *Earlier growth* did not differ between girls with asthma versus girls without asthma

(OR: 1.35; 95% CI: 0.49, 3.68). Adjusting for potential confounders, adjusting for ICS use or excluding participants who reported using ICS did not significantly change the results.

DISCUSSION

In a cohort of children at high risk for asthma, we defined three classes of growth trajectories for boys and for girls between 11 and 14 years of age. Asthma was not associated with growth trajectory classes in boys. In contrast, girls with asthma were more likely to belong to a class of growth trajectories with late growth compared to girls without asthma. This association was still significant when adjusting for potential confounding factors or excluding participants using ICS.

As we used a novel approach to assess growth differences, our results are not readily comparable to earlier studies. In some previous studies, no associations between asthma and growth during early adolescence were found.^{5,8–10,23} In other studies, a relationship was identified between asthma and slow growth during adolescence using reference growth charts.^{3,4} The difference between our findings and others may be attributable to differences in the ages of study participants, study design or stratification by sex.

Recent studies on childhood asthma and growth have predominantly focused on the effect of treatment with ICS on growth. Interestingly, studies of children with asthma but in absence of ICS use also describe growth retardation,^{7,11,23} indicating that asthma alone may affect growth. Since our results did not significantly change when excluding participants with ICS or adjusting for ICS, our study contributes to this discussion.

Growth in adolescence can be seen as a proxy for pubertal development since one of the most pronounced events is the adolescent growth spurt.² Boys experience the adolescent growth spurt at mean 14 years of age,²⁴ and girls at a mean of 12 years of age.²⁵ At 11 years of age, more girls than boys have commenced puberty,^{24,25} thereby partly explaining why the classes of growth trajectories for girls differed more in starting point compared with boys. At 14 years of age, nearly all girls, but not all boys, have completed their adolescent growth spurt.^{2,24,25} This could explain why the classes of growth trajectories were more homogenous in height at end point for girls compared with boys. Future follow-up will permit us to examine whether the growth acceleration in boys with asthma is delayed. In some,^{9,26} but not all^{23,27} previous studies, childhood asthma is associated with puberty and pubertal staging. Notably, later pubertal staging may be inversely associated to asthma and asthma incidence in girls only.²⁸ Given these collectively inconclusive results, further investigations into asthma and puberty are warranted.

Strengths of this study include the longitudinal design with regular follow-ups. Height assessments every 3 months allowed a detailed examination of the change in height over time. Additionally, asthma assessments including both standardized questionnaires and clinical tests increased the accuracy with

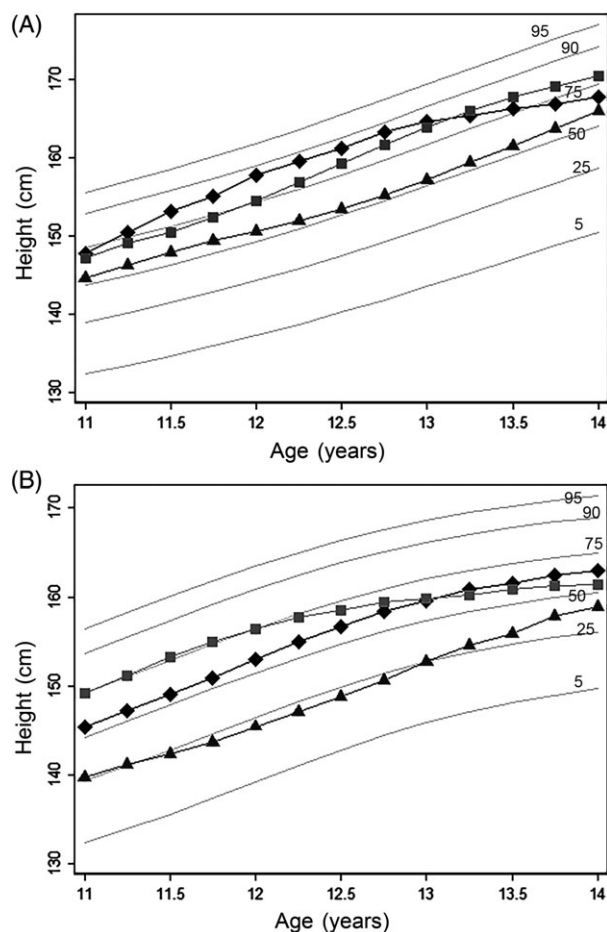


Figure 2 Classes of growth trajectories for boys (A: ◆, earlier growth (9%); ■, intermediate growth (29%); ▲, later growth (61%)) and girls (B: ◆, intermediate growth (34%); ■, earlier growth (46%); ▲, later growth (20%)) between 11 and 14 years of age, Sydney, Australia, 1997–2013. The light grey lines in the background are the Centers for Disease Control and Prevention growth trajectories for boys and girls for percentiles 5, 25, 50, 75, 90 and 95.²² The black lines represent the estimated mean values, calculated from growth mixture models, of height each time point for each class of growth trajectories.

Table 2 Multinomial logistic regression analysis on the association between asthma and classes of growth trajectories in boys and girls, Sydney, Australia, 1997–2013

Exposures	N	Earlier growth			Intermediate growth			Later growth		
		<i>n</i>	OR	95% CI	<i>n</i>	OR	95% CI	<i>n</i>	OR	95% CI
<i>Boys</i>										
Asthma at 8 years	158 [†]	15			47			96		
No	110	10	1.00	—	30	1.00	—	70	1.00	—
Yes	48	5	1.00	—	17	1.14	0.33, 3.87	26	0.74	0.23, 2.38
Adjusted analyses										
Asthma at 8 years [‡]	158 [†]	15			47			96		
No	110	10	1.00	—	30	1.00	—	70	1.00	—
Yes	48	5	1.00	—	17	0.93	0.27, 3.23	26	0.62	0.19, 2.02
Asthma at 8 years [§]	146 [¶]	12			45			89		
No	100	7	1.00	—	29	1.00	—	64	1.00	—
Yes	46	5	1.00	—	16	0.49	0.09, 2.56	25	0.35	0.07, 1.74
<i>Girls</i>										
Asthma at 8 years	146 ^{††}	67			52			27		
No	118	58	1.00	—	43	1.00	—	17	1.00	—
Yes	28	9	1.00	—	9	1.35	0.49, 3.68	10	3.79	1.33, 10.84
Adjusted analyses										
Asthma at 8 years, adjusted for ICS use [‡]	146 ^{††}	67			52			27		
No	118	58	1.00	—	43	1.00	—	17	1.00	—
Yes	28	9	1.00	—	9	2.30	0.71, 7.43	10	5.19	1.51, 17.93
Asthma at 8 years, adjusted for confounding factors [§]	140 ^{‡‡}	64			50			26		
No	114	56	1.00	—	41	1.00	—	17	1.00	—
Yes	26	8	1.00	—	9	1.46	0.46, 4.66	9	3.96	1.14, 13.78

Bold text indicates statistical significance (P -value < 0.05).

^{*}Missing value on asthma status, boys = 5.

[‡]Adjusted for ICS use the last 12 months reported at 8 years.

[§]Adjusted for confounding factors: CAPS dietary intervention group (active/control), any breastfeeding ≥ 6 months (yes/no), parental obesity (both parents overweight, only mother overweight, only father overweight and normal weight), ethnicity (Caucasian, European, Middle Eastern, Indian, Asian, Pacific Islander, South American and other), smoking during pregnancy (yes/no) and father's education status (tertiary level/less than tertiary level).

[¶]Missing value on confounding factors or asthma status, boys = 17.

^{††}Missing value on asthma status, girls = 7.

^{‡‡}Missing value on confounding factors or asthma status, girls = 13.

CAPS, Childhood Asthma Prevention Study; CI, confidence interval; ICS, inhaled corticosteroid; N, total number of participants; *n*, number of participants in the group; OR, odds ratio.

which asthma status was determined. The use of latent basis GMM to define height trajectories is a novel and powerful method, which permitted identification of data-derived heterogeneous growth patterns in early adolescence. GMM allowed us to take advantage of the longitudinal nature of the data by providing a useful summary of available height measurements between 11 and 14 years of age without assuming that the underlying population follow the same overall growth pattern. To the best of our knowledge, we are the first to apply this method in order to identify the association between childhood asthma and classes of growth trajectories in adolescence. Our result shows that growth trajectories are heterogeneous, rather than following a single common pattern. Methods accounting for this heterogeneity add an important dimension to the investigation of growth during puberty compared with methods built upon the assumption that growth is homogenous.

One major limitation to the study is attrition of the study population, particularly as it relates to socio-

economic status. As socio-economic status is associated with adult height,²⁹ selection bias cannot be ruled out. Height measurements were performed by the participants' parents with a standardized stadiometer after instructions by a study team member. However, we anticipate that there will be more measurement error than would have been the case if technical staff had performed the measurements. Nevertheless, it is likely that this will be non-differential with respect to the risk factors of interest (asthma status). The small sample size contributes to the wide CIs in the regression analyses. In addition, the small sample size may have contributed to problems in achieving convergence of the GMM and in identifying more than three classes. The model fit statistics and other measures, such as entropy, can be used as a guide to deciding the optimal number of classes. But when these measures do not agree, as in some instances in this analysis, the decision on the number of classes is based on interpretability and parsimony. For these reasons and also because

all participants were recruited from the same city and were at high risk for asthma, some caution is warranted when generalizing our findings.

In conclusions, we identified sex-specific heterogeneous classes of growth using GMM and showed that girls with asthma are more likely to have slow growth during puberty compared to girls without asthma. Importantly, there was no difference in height at end point between the classes of growth trajectories in girls. From a clinical perspective, this is a particularly valuable finding since it could be used to reassure adolescent girls with asthma who experience later growth.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1 Model selection and determination of optimal number of classes in growth mixture modelling.

Table S1 Growth mixture model fit statistics for 1–5 classes in boys and girls.

Table S2 Comparison of characteristics amongst Childhood Asthma Prevention Study participants with at least five height measurements and those lost to attrition.