

Puberty and prognosis of asthma and bronchial hyper-reactivity

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It is a commonly held view that pediatric asthma frequently abates during puberty. However, little data are available that associate the stage of puberty with the prognosis of asthma and bronchial hyper-reactivity (BHR). In this study, 155 children with active asthma at 10 years of age (60 girls [38.7%], 95 boys [61.3%]) were followed-up until they reached 14 years of age. The stage of puberty was assessed by parental questionnaire; in addition, serum 3- α -androstenediolglucuronide, as an endocrinological marker for peripheral androgen status, was measured in 107 subjects. Persistence of asthma was determined via questionnaire, lung function testing, and bronchial provocation (hyperventilation of cold, dry air). At 14 years of age, 73.3% of girls were reported to have had menarche and 40.8% of boys a voice change, and only 35.5% of the subjects had experienced acute asthma symptoms during the last 12 months, with an almost unchanged gender ratio (19 girls [34.5%], 36 boys [65.5%]) vs. that recorded at 10 years of age. The level of androstenediolglucuronide was higher in the children who reported puberty (mean $\pm$ SD): 3.03 ± 2.13 nmol/l vs. 1.89 ± 1.26 nmol/l, $p = 0.003$. No statistically significant relationship was found between the reported signs of late puberty and loss of asthma or BHR. Likewise, no significant association was found between asthma persistence and the level of androstenediolglucuronide (2.39 ± 1.75 nmol/l vs. 2.44 ± 1.82 nmol/l, $p = 0.84$), or BHR and the level of androstenediolglucuronide (3.02 ± 1.97 nmol/l vs. 2.28 ± 1.67 nmol/l, $p = 0.13$), at 14 years of age, in girls or boys. At 14 years of age, no change in the gender ratio of children with active asthma had occurred. These results may indicate that the change in gender predominance of asthma through the second decade of life is not caused by increased loss of established asthma in boys between 10 and 14 years of age.

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It is commonly found that pediatric asthma abates during the second decade of life – the time-period during which puberty occurs (1–3). Asthma may change with hormonal fluctuations (4–7), and puberty is associated with fundamental changes in the hormone levels in both sexes (8). However, no data directly relating the stage of puberty or associated hormonal changes with the prognosis of asthma and bronchial hyper-reactivity (BHR) are available (9). While asthma is more prevalent in boys than in girls during childhood, this prevalence is reversed in adults (10–14), suggesting a gender-dependent mechanism

controlling the persistence of asthma during the transition from childhood to adulthood. Girls enter puberty at a mean age of 10.5 years, reach menarche at $\approx$ 13 years, and achieve complete sexual development after a mean of 4.2 years; for boys, the development begins at age 11.5 years and ends 3.5 years later (8). Therefore, it has been proposed that cut-off points for the average age of puberty should be set at between 10 and 16 years of age (8,9).

While the reporting of asthma symptoms may be affected by the psychological and social consequences of the advent of puberty, measured

variables such as lung function or BHR should be independent of these effects. BHR is closely associated with clinical asthma and, even in asymptomatic children, BHR may be associated with subsequent development of asthma (15). The prognosis of BHR is therefore probably governed by similar mechanisms as asthma symptoms, but the relationship of BHR with signs of puberty or the associated hormonal changes is unknown.

While the measurement of testicle volume and determination of the Tanner stage would have been optimal variables for puberty assessment, this was not feasible in the context of this field study. Androstenediolglucuronide is an endocrinological marker that reflects the peripheral testosterone metabolism, which in turn is closely related to the development of sexual maturation and Tanner stages (16–18). Normative population data in healthy children and adolescents are available for this substance, and a good correlation with clinical signs of puberty (such as Tanner stages) has been documented (16). Therefore, androstenediolglucuronide could be used as an objective parameter for comparison with objective and subjective markers of asthma. To our knowledge, no such comparisons have been published to date. It was the aim of this analysis to assess the relationship between reported signs and an objective marker of puberty with the prognosis of asthma and BHR in adolescence.

Patients and methods

This study was based on a large cross-sectional survey of all fourth-grade schoolchildren in Munich (19). For the purpose of this study, this age group (9–11 years) was defined as 'childhood'. A group of subjects with asthma was identified and followed-up 3 years later ('adolescence'). The appropriate ethics committee had reviewed and accepted both studies.

The initial study was conducted from September 1989 to July 1990. The response rate for the questionnaire was 88%; 5030 of the participating children were of German nationality. Active asthma was defined as a doctor's diagnosis of asthma, recurrent asthmatic bronchitis, or recurrent spastic bronchitis, each with asthma symptoms (breathlessness, asthma attacks, cough), occurring in the 12 months prior to the examination (20). Children with asthma whose parents had given consent to follow-up ($n=234$) were re-investigated 3 years later. Furthermore, a reference group of healthy children was re-tested to yield a cut-off point for the definition of BHR for both age groups.

The initial study has been described in detail previously (19,21), and the self-administered questionnaire contained items regarding a diagnosis of asthma, asthma symptom frequency and severity, and triggers of symptoms, as well as known and suspected confounders such as environmental tobacco smoke exposure, medication use, etc.

The questions of the follow-up survey were identical to those of the initial study questionnaire. Trained staff of the Children's Hospital administered the questionnaire in an interview with a parent of the child at the time of the follow-up examination. Asthma symptoms persisting in adolescence were defined using a definition identical to that used in the first study, i.e. as asthma symptoms (breathlessness, asthma attacks, and cough) occurring during the 12 months prior to follow-up. When change of voice (boys) or menarche (girls) was reported, this was interpreted as a sign of late puberty.

In the first survey, spirometry was performed in the schools by trained staff using a mobile spirometer (Pneumoskop II; Jäger, Würzburg, Germany). Cold air challenge was applied using the Respiratory Heat Exchange System (Jäger) (21). Spirometry and cold air challenge in the second survey were repeated according to the same study protocol as used in the first survey. A child was defined as being bronchial hyper-responsive at 10 years of age if the fall in forced expiratory volume over 1 s after cold air challenge ($DFEV_1$) was greater than the 95th percentile of $DFEV_1$ in an age-matched reference population. The definition of this healthy (all children without allergies or asthma) reference population has been described previously (21). As the prevalence of BHR is expected to change with age, a sub-group was randomly selected from this reference population. The 95th percentile of $DFEV_1$ in this reference sub-group was 9% in childhood (this result was identical for the whole reference group) and when the sub-group was re-challenged in adolescence, the 95th percentile was 14%. In the first survey, the sensitivity to six common aeroallergens was assessed by skin-prick testing on the forearm using a multi-test and standardized allergen extracts (house dust mite, grass, birch and hazelnut pollen, cat and dog dander; Stallergènes, Lyons, France).

In the follow-up study, blood was drawn for serum androstenediolglucuronide determination (as an endocrinological marker of puberty) from 107 subjects. Androstenediolglucuronide was measured using an established non-extraction solid-phase radioimmunoassay (RIA) employing a polyclonal anti-serum specific for 3- α -andros-

tanediolglucuronide (Diagnostic Systems Laboratories Inc., Webster, TX, USA) (16,17,22). Normative data have been generated in our laboratory (16).

Statistical analysis

Statistical analysis was performed by using the statistical software package, sas, version 6.11. Changes between the two surveys were tested for statistical significance by using Wilcoxon's signed rank test and McNemar's chi-square test. For comparison between independent groups, Wilcoxon's rank sum test was used for continuous data and a standard chi-square test was used for binary data. Data were analyzed separately for girls and boys.

In a stepwise backward logistic regression analysis, using persisting asthma symptoms in adolescence and BHR in adolescence as outcome variables, the influence of puberty and other prognostic factors on the outcome variables in adolescence was analyzed simultaneously. All previously examined prognostic factors (puberty, family history, severity of asthma in childhood, degree of BHR in childhood, allergic triggers, skin-prick score, dampness) were included in the models, and stepwise exclusion of variables was performed until all remaining prognostic factors had a statistically significant effect. Potential confounding variables were analyzed; neither passive smoking, pet ownership, nor socioeconomic status had any influence on the outcome variables in the uni-variate or multi-variate analyses. Furthermore, if one of these variables was forced into the stepwise regression model, the magnitude of the effects of the other variables remained unchanged. When reported medication was analyzed, a positive association between BHR and steroid or chromoglycate use was found in the uni-variate analysis. However, when these variables were forced into the regression model, virtually no change in the effect size of the other variables was seen. The models for both outcome variables were adjusted for gender and for the time interval between the two surveys. In all analyses, a *p*-value of less than 0.05 was considered statistically significant.

Results

The initial study had been anonymous and names were replaced by codes. Only children whose parents had signed consent for follow-up and given their addresses could be identified for follow-up. Forty of the 274 children with active asthma, who participated in the initial study,

could not be re-investigated for this reason. Of the remaining 234 children, 155 (66%) participated in the follow-up study and 153 answered the puberty question (Table 1). Spirometry and cold air challenge was performed on 90.3% of those answering the questionnaire in the first survey and on 85.8% in the second survey; 80% (124/155) completed spirometry and cold air challenge in both surveys. Measurement of androstenediolglucuronide was available in 69%. The median age of the children was 10.2 years (10.0–10.5 years, 1st to 3rd quartile) in the first survey and 13.3 years (12.9–13.8 years, 1st to 3rd quartile) in the second survey. The childhood data for the children who participated in the second survey were compared with the data for the children who were lost to follow-up (Table 2). None of the variables showed a significant difference between groups.

At 14 years of age, 73.3% of girls had had menarche, 40.8% of boys a voice change, and 64.5% (100/155) of the subjects had experienced no acute asthma symptoms during the last 12 months (68.3% [41/60] girls, 60.6% [57/94] boys). BHR was found in 17.3% (23/133) of the subjects (24.0% [12/50] girls, 12.5% [10/80] boys), a significant decrease compared to the first survey (27.1% [38/140] BHR; *p* = 0.002). At 10 years of age, 61% of children with active asthma were boys and 39% girls, and this ratio was almost unchanged at 14 years of age in the children who still had asthma symptoms (65% boys, 35% girls).

No statistically significant difference was found between children with or without reported clinical late puberty and loss of asthma (69.5% vs. 57.7%) (Table 3) or BHR (78.2% vs. 87.1%) (Table 4). In boys, 68.4% (26/38) of those with a change of voice had lost asthma compared with 56.4% (31/55) of those without this sign of late puberty (NS) (Table 3). In girls, 70.4% (31/44) of those with menarche had lost their asthma symptoms compared with 62.5% (10/16) of those without menarche (NS) (Table 3).

The level of androstenediolglucuronide was higher in children with reported signs of late puberty than in those without (3.03 ± 2.13 nmol/l vs. 1.89 ± 1.26 nmol/l, *p* = 0.003), particularly in boys (Table 5).

None of the children took regular systemic steroids during the 3 months before the second study period. One child had taken oral steroids intermittently (on average once per week); however, the results from hormone measurements remained virtually unchanged when this subject was excluded from the analysis.

No significant association was observed between asthma persistence at age 14 and the level of

Table 1. Response rates in the follow-up study sample

	Survey	Response rates
Childhood	Parental questionnaire	155/155 (100.0%)
	Lung function and cold air challenge	140/155 (90.3%)
Adolescence	Parental questionnaire (including a question about puberty)	153/155 (98.7%)
	Lung function and cold air challenge	133/155 (85.8%)
	Measurement of androstandiol	107/155 (69.0%)

Table 2. Characteristics of subjects lost to follow-up and subjects who participated in the second survey

Characteristics	Lost to follow-up childhood data (n=119)	Follow-up childhood data (n=155)
Female†	50 (42.0)	60 (38.7)
BHR†	24 (23.3)	38 (27.1)
Prick score (mm)*‡	9.9 (9.2)	12.4 (10.6)
Family history of asthma†	22 (18.5)	38 (24.5)
More severe asthma†§	79 (66.4)	100 (64.5)
Allergic trigger†¶	69 (59.0)	87 (56.1)

*Values are expressed as: mean (standard deviation).

†Values are expressed as: n (%).

‡Sum of the wheal sizes of the skin-prick tests carried out using six different aeroallergens.

§More than 10 episodes during the last 12 months, episodes lasting >1 week, steroid therapy, diagnosis of bronchial asthma (as opposed to recurrent asthmatic or recurrent spastic bronchitis).

¶Allergic trigger of symptoms according to the parental questionnaire.

BHR, bronchial hyper-reactivity.

No significant differences were found.

Table 3. Asthma lost at 14 years of age

	All	Pre/early puberty	Late puberty	Significance
Boys	57/94 (60.6%)	31/55 (56.4%)	26/38 (68.4%)	NS
Girls	41/60 (68.3%)	10/16 (62.5%)	31/44 (70.4%)	NS

NS, not significant for comparisons between pre/early puberty vs. late puberty, and boys vs. girls.

androstanediolglucuronide (2.38 ± 1.75 nmol/l vs. 2.43 ± 1.82 nmol/l, $p = 0.84$), or BHR at age 14 and the level of androstanediolglucuronide (3.01 ± 1.96 nmol/l vs. 2.28 ± 1.67 nmol/l, $p = 0.13$). The same was found when boys and girls were analysed separately (Table 6). When the group was subdivided into atopic (those with positive skin-prick tests) and non-atopic children, or into those with and without reported allergic triggers, the results remained unchanged. Also, no association of respiratory symptoms at 14 years of age with reported menarche, change of voice or androstanediol levels, was found.

Daily bronchodilator use ($p = 0.001$) and prophylactic inhaled therapy (cromoglycate or steroids, $p = 0.001$) at 14 years of age were significantly related to reported clinical asthma persistence, but not to clinical puberty signs or steroid metabolism. Also, height, weight and body mass index at both study periods (and their change between measurements) were not related to the prognosis of asthma and BHR.

In the multi-variate models with persistence of asthma or with BHR as outcome variables,

neither puberty nor androstanediolglucuronide were found to be significant independent variables. The risk for persistent symptoms was increased for children with more severe asthma in the first survey and if symptoms were triggered by allergens; BHR at 14 years of age was increased significantly with initial BHR, with allergic triggers and dampness (data published in ref. 23).

Discussion

At 14 years of age, no significant association was found between menarche (girls) or a change of voice (boys) and the prognosis of asthma, lung function and BHR in adolescents who had had active asthma at 10 years of age. The initial sample was population based and therefore no selection bias is expected, in contrast to studies following up asthma patients identified from clinics. In the study group, the predominance of boys with active asthma remained essentially unchanged between 10 and 14 years of age. (The age between 10 and 16 years can be regarded as

Table 4. No bronchial hyper-reactivity at 14 years of age

	All	Pre/early puberty	Late puberty	Significance
Boys	70/80 (87.5%)	41/47 (87.2%)	29/34 (85.3%)	NS
Girls	38/50 (68.3%)	13/15 (86.7%)	25/35 (71.4%)	NS

NS, not significant for comparisons between pre/early puberty vs. late puberty, and for boys vs. girls.

Table 5. Puberty and androstanediolglucuronide

	n	Androstanediolglucuronide mean (SD)
Boys, puberty –	43	1.95 (1.37)
Boys, puberty +	25	4.10 (2.40)*
Girls, puberty –	14	1.73 (0.90)
Girls, puberty +	23	1.87 (0.83)

* $p < 0.0001$ (Wilcoxon rank sum test) between boys with and without puberty.

Table 6. Persistent asthma and bronchial hyper-reactivity (BHR) at 14 years of age, and level of androstanediolglucuronide

	Asthma lost (n=98)	Asthma (n=55)	No BHR	BHR
Boys (n=70)	2.77 (2.16)†	2.69 (1.94)†	2.57 (1.94)*	3.79 (2.13)*
Girls (n=37)	1.90 (0.87)†	1.63 (0.81)†	1.75 (0.76)*	1.85 (0.93)*

Data represent mean (SD) values, in nmol/l, of androstanediolglucuronide.

†Not significant for asthma vs. asthma lost, BHR vs. no BHR (Wilcoxon rank sum test).

the pubertal range.) This observation may indicate that the change from male to female predominance in asthma occurs very late or even beyond the pubertal phase. On the other hand, a greater number of girls may experience a recurrence of asthma, which had not been active when they were 10 years of age, or asthma may be more often newly diagnosed in females older than 10 years of age.

The androstanediol values reported in this study are in good agreement with published normal ranges for this age group (16). The increase with reported signs of late puberty was significant only in boys, reflecting the generally lower differences reported for girls (16) and the fact that almost three out of four girls had already reported menarche at follow-up.

The decreasing frequency of asthma symptoms from childhood to adolescence, found in this study, is in agreement with previous data (24) and was paralleled by a decrease in the prevalence of BHR from 27.1% to 17.3%. While the parental awareness and reporting of asthma symptoms may be influenced by the behavioral and social changes associated with puberty, this is unlikely for the measurement of BHR. The 95th percentile of $DEFV_1$ in the control group was 14% in adolescence compared with 9% at age 10, which is in contrast to the previously reported decrease of bronchial reactivity to pharmacological provocations with age (25). This decrease has been

attributed to younger children receiving relatively larger doses of the inhaled substance (26), which may not be relevant for cold air hyperventilation challenge where the thermal load is adapted to actual lung size. The specificity of cold air challenge in both parts of the study was, by definition, 95%. Using the resulting cut-off, the frequency of positive tests in children with asthma and symptoms during the previous 12 months was 27% in the first study and 28% in the follow-up, i.e. the sensitivity of cold air challenge for detecting children with active asthma was unchanged. Therefore, the decrease in BHR with age seen in this population of asthmatics appears to be real and makes it less probable that the observed decrease in asthma would only be caused by a changing perception or reporting of symptoms. Moreover, changing the cut-off value did not alter the fact that gender had no influence on the prognosis of BHR.

The likelihood of loss of asthma symptoms is indeed high over the period in adolescence when sexual development takes place. However, this appears not to be closely related to hormonal changes, as reflected by a marker of peripheral testosterone metabolism or events such as the change of voice in boys and menarche in girls (irrespective of atopic status). One limitation of this study that needs to be considered when interpreting the results is that hormone levels and asthma symptoms were not measured repeatedly

over the intervening 4-year period. If this had been performed, a better intra-individual assessment of the timing of hormonal changes and decreasing asthma symptoms might have been obtained. However, the hormone levels measured were not higher in children who lost their asthma symptoms. It remains possible that the overall hormonal changes occurring during this age period drive anatomic development, with growth of airway size, changes in airway geometry or determinants of bronchial reactivity, and is thereby indirectly responsible for the decrease in asthma prevalence observed. These mechanisms may have developed to a similar degree in all children in our sample, independently of the clinical or endocrinological markers of puberty.

One limitation of this study is that an established staging system of pubertal development, such as testicle volume and Tanner stages, was not determined. This would have allowed a better characterization of the sexual development. However, this was not practically feasible within the limitations of our epidemiological study. A blood sample was drawn by the study nurse for other laboratory determinations, and we therefore chose to measure an endocrinological marker (3- α -androstenediol) in the serum. The levels of other hormones associated with sexual development, such as estradiol and testosterone, show considerable overlap between pubertal stages. A good correlation with Tanner stages and other signs of sexual development has been described for 3- α -androstenediol (16). Nevertheless, this marker will obviously not fully describe the complex hormonal changes occurring during puberty. One could argue that most girls had reached menarche, and the very similar androstenediol levels in those who had not suggest that all girls already had a pubertal hormonal status, in contrast to most of the boys. This might predict that a greater number of boys would lose their asthma when they reached late puberty, while girls had already attained their maximal decline in prevalence. This, however, appears unlikely because the loss of asthma or BHR was no more prevalent in boys who had already reached late puberty compared with those who had not. Another explanation for the similar hormone levels may be the small number of girls without menarche at age 14, or that 3- α -androstenediol is not a good marker for late puberty in girls. In addition, blood was available from only 69% of participants, which further limits the power of detecting differences between groups.

Owing to these limitations, the hormone measurement results can only be seen as an indication supporting the notion that sexual development per se is not the crucial driving force behind the change in gender prevalence of asthma in the second decade of life, at least not in children with active asthma at 10 years of age.

The puberty age range is spread over 10–16 years of age (8), and puberty is closely associated with hormone levels and metabolism. As only $\approx 50\%$ of our study sample had experienced menarche or a voice change (both signs of late puberty) at age 14, at least some differences might be expected if the sex hormone effects were crucial for the loss of asthma during adolescence. At age 14, 64.1% of the children with active asthma at age 10 had experienced no asthma symptoms during the previous 12 months. While adolescents with reported signs of late puberty had lost active asthma slightly more often than those without those signs, this difference was not statistically significant. However, as a reported change of voice or menarche was assessed by using a parental questionnaire, mis-classification could have occurred as parents might have been unable to judge their children's status correctly. Although it is unlikely that these errors would have been linked to the presence of persisting asthma symptoms, this potential mis-classification would have reduced the ability to detect existing differences between the groups. Furthermore, some pubertal developments will have been present in all adolescents, and the presence or absence of voice change or menarche as signs of late puberty may not be the most relevant markers for possible hormonal influences on asthma persistence.

In our whole study cohort, the proportion of boys and girls with active asthma showed an almost unchanged male predominance between 10 and 14 years of age. Even if the measured hormone levels might be considered insufficient to characterize pubertal stage, and if reported menarche or change of voice may be flawed owing to parental errors, all three observations point in the same direction. It appears unlikely that the change from pediatric male to adult female predominance of asthma is the result of an increased loss of symptoms in boys during the age period when most of the pubertal changes occur. On the other hand, the incidence of new cases of asthma in individuals without a previous doctor's diagnosis of asthma might be different in females compared to males after puberty, and may contribute to the changed gender ratio. The

design of the present study does not allow us to answer this question.

While the results of this study are preliminary because they are limited by methodological constraints, the findings are in good agreement with a recent meta-analysis of studies describing the changes in asthma prevalence during the transition from childhood to adulthood (9). This review concluded that there was indirect evidence that puberty itself had no influence on the gender-specific change in prevalence, while no studies using direct measurements of the hormonal or physiological changes associated with puberty were available. Published data show a decline in asthma prevalence with age that is no more prominent during puberty than during the previous years. In many studies the switch between male and female preponderance occurs towards the end of the second decade. It has been proposed that gender-specific differences – other than the hormonal changes directly associated with puberty – and age are the main factors governing this transition (9).

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