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Letter

Puberty and asthma in a cohort of swedish children

The shift in asthma prevalence from male to female predominance during the pubertal years is believed to result from an increased incidence among girls rather than remission among boys.^{1,2} Moreover, from the pubertal years onward, airway hyper-responsiveness, a classic feature of asthma, also worsens among girls but improves in boys.³ Asthma medication use, a proxy for asthma severity, follows a similar pattern, with females requiring greater medication from puberty onward.^{2,4}

These observations support the potential involvement of sex-specific factors with asthma during this period. However, all physical changes of pubertal development cannot be considered equally in relation to asthma, particularly among girls. Menarche appears to play a substantial role in asthma presence and timing of onset. Early menarche predicts poorer lung function⁵ and higher postmenarchal asthma incidence⁶ compared with average to late menarchal age. To better understand the associations between puberty and asthma, we aimed to assess associations between pubertal staging and asthma symptoms and treatment in a longitudinal, population-based cohort of Swedish children (Barn Allergi Milieu Stockholm Epidemiologi [BAMSE]) born in 1994–1996.⁷ The original cohort of 4089 infants was representative of the study catchment area, except for higher rates of parental smoking among nonresponders.⁷ Participant characteristics did not differ between those followed up through year 12 and those lost to attrition.⁸ At years 8 and 12, parents completed questionnaires on wheeze frequency in the previous 12 months and asthma medication. Subjects were deemed to have asthma based on parental reports of 4 or more episodes of wheeze or 1 or more episode of wheeze in combination with inhaled corticosteroid use in the past 12 months. Pubertal incidence of asthma was defined as no asthma at year 8 but asthma at year 12. At year 12, children responded to pubertal development questions based on the composite pubertal scoring system the Peterson index.⁹ Data were collected on 3 measures for both boys and girls (skin changes, linear growth spurt, and pubic hair growth), 2 measures for boys (voice change and beard growth), and 2 measures for girls (breast development and menarche). This scoring system permits the inclusion of the multiple characteristics

Table 1

Logistic regression of cross-sectional associations between pubertal staging and asthma presence at year 12

Pubertal stage	Asthma presence vs absence at year 12			
	Presence, No.	Absence, No.	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
Boys				
Prepuberty	28	321	1.00	1.00
Early puberty	59	535	1.26 (0.79–2.02)	1.16 (0.71–1.90)
Middle to late puberty	28	395	0.81 (0.47–1.40)	0.67 (0.36–1.25)
Girls				
Prepuberty to early puberty	13	148	1.00	1.00
Middle puberty	28	523	0.61 (0.31–1.21)	0.54 (0.27–1.09)
Late puberty to postpuberty	26	617	0.48 (0.24–0.96) ^b	0.35 (0.16–0.78) ^c
Menarche				
No	41	671	1.00	1.00
Yes	26	617	0.69 (0.42–1.14)	0.58 (0.33–1.02)

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted for age at year 12.

^b $P < .05$.

^c $P < .01$.

of pubertal development along a continuum. For boys, all characteristics contributed equally. Girls reporting menarche by year 12 were considered to be in late puberty or postpuberty, regardless of other characteristics. Participants were then categorized into 1 of 5 mutually exclusive categories: prepuberty, early puberty, middle puberty, late puberty, or postpuberty. We further considered menarche independent of pubertal staging.

We used binomial logistic regression to analyze these data and report odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for unadjusted analyses and models adjusted for confounding by age at year 12. Analyses were performed with STATA statistical software, version 11.0 (StatCorp LP, College Station, Texas). Permission for this study was obtained from the Regional Ethical Review Board of the Karolinska Institutet, Stockholm, Sweden.

At year 12, the response rate was 82% (3,366 of 4,089 patients), with asthma status available for 99% (3,339 of 3,366 patients). We excluded those for whom pubertal data were unavailable. This method yielded a sample of 2,721 (67% of the original cohort), of whom 50.2% were boys. Nearly all boys (1,347 of 1,378 [97.8%]) were in prepuberty, early puberty, or middle puberty. Nearly half of the girls (651 of 1,368 [47.6%]) were in late puberty or postpuberty. Thus, we created sex-specific pubertal staging categories. Boys were trichotomized into prepuberty, early puberty, or middle or late puberty (none reported postpuberty). Girls were trichotomized as prepuberty or early puberty, middle puberty, or late puberty or

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Table 2

Logistic regression of cross-sectional associations between pubertal staging and pubertal incidence at year 12

Pubertal stage	Pubertal incidence of asthma ^a			
	Incidence No.	No asthma No.	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^b
Boys				
Prepuberty	16	303	1.00	1.00
Early puberty	36	496	1.37 (0.75–2.52)	1.37 (0.73–2.57)
Middle to late puberty	12	368	0.62 (0.29–1.33)	0.61 (0.26–1.46)
Girls				
Prepuberty to early puberty	9	136	1.00	1.00
Middle puberty	14	502	0.42 (0.18–1.00)	0.36 (0.15–0.88) ^c
Late puberty to postpuberty	14	576	0.37 (0.16–0.87) ^c	0.25 (0.09–0.68) ^c
Menarche				
No	23	638	1.00	1.00
Yes	14	576	0.67 (0.34–1.32)	0.56 (0.26–1.19)

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAsthma incidence from year 8 to year 12 vs no asthma at either year 8 or year 12.

^bAdjusted for age at year 12.

^c $P < .05$.

postpuberty. Approximately half of the girls (47.6%) reported menarche by year 12. Compared with boys, girls had a lower odds of asthma at each assessment (eg, year 8: OR, 0.66; 95% CI, 0.47–0.92; year 12: OR, 0.57; 95% CI, 0.42–0.78).

Pubertal staging was not found to be associated with asthma presence vs absence in boys (Table 1). In contrast, girls being in late puberty or postpuberty was inversely associated with asthma at year 12 (OR, 0.35; 95% CI, 0.16–0.78). Among girls only, the odds of pubertal incidence of asthma vs asthma at neither year 8 nor year 12 decreased with more advanced pubertal staging (middle puberty: OR, 0.36; 95% CI, 0.15–0.88; late puberty or postpuberty: OR, 0.25; 95% CI, 0.09–0.68) (Table 2). Menarche and asthma presence at year 12 (OR, 0.58; 95% CI, 0.33–1.02) and menarche and pubertal incidence of asthma (OR, 0.56; 95% CI, 0.26–1.19) followed a similar trend, although these results did not reach statistical significance. In neither sex was pubertal staging associated with asthma medication use at year 12.

The widely accepted sex shift in asthma prevalence during adolescence^{1,2} was not noted in BAMSE through year 12. Rather, pubertal incidence of asthma was lower among girls than boys (3.0% vs 5.2%, $P < .01$) and indeed lower in girls in late puberty or postpuberty vs early puberty. Our results are contrary to others' findings, including a report of a null association between pubertal staging and asthma remission or incidence among similar-aged youth.¹⁰ However, their null findings may be partly explained by the low number of participants in late puberty at baseline.¹⁰

To our knowledge, we are the first to report on the association between pubertal staging and asthma using a composite and validated measure of puberty classified into 1 of 3 mutually exclusive categories. Others have reported on puberty¹ and timing of menarche^{5,6} and asthma. One other group has considered multiple pubertal characteristics in their classification of pubertal staging.¹⁰ However, they considered puberty as a binary outcome: early vs late puberty.¹⁰ Inclusion of a third

category in our establishment of pubertal staging gleans further insight into the understanding of the progression through puberty on asthma presence and incidence during the pubertal years. This provided the opportunity to better elucidate the associations between asthma and puberty than earlier studies.

In conclusion, we found an inverse association between puberty and asthma prevalence and incidence for girls only. Follow-up at year 16 will glean further insight into these associations as more children reach late puberty and postpuberty.

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References

- [1] Nicolai T, Pereszlenyiova-Bliznakova L, Illi S, Reinhardt D, Nicolai T, von Mutius E. Longitudinal follow-up of the changing gender ratio in asthma from childhood to adulthood: role of delayed manifestation in girls. *Pediatr Allergy Immunol*. 2003;14:280–283.
- [2] Almqvist CA, Worm M, Leynaert B, Working Group of GA²LEN WP 2.5 Gender. Impact of gender on asthma in childhood and adolescence: a GA²LEN review. *Allergy*. 2008;63:47–57.
- [3] Tantisira KG, Colvin R, Tonascia J, Strunk RC, Weiss ST, Fuhlbrigge AL. Airway responsiveness in mild to moderate childhood asthma: sex influences on the natural history. *Am J Respir Crit Care Med*. 2008;178:325–331.
- [4] Karlstad O, Nafstad P, Tverdal A, Skurtveit S, Furu K. Prevalence, incidence and persistence of anti-asthma medication use in 2- to 29-year-olds: a nationwide prescription study. *Eur J Clin Epidemiol*. 2010;66:399–406.
- [5] Macsali F, Real FG, Plana E, et al. Early age at menarche, lung function, and adult asthma. *Am J Respir Crit Care Med*. 2011;183:8–14.
- [6] Al-Sahab B, Hamadeh MJ, Ardern CI, Tamim H. Early menarche predicts incidence of asthma in early adulthood. *Am J Epidemiol*. 2011;173:64–70.
- [7] Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE Project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol*. 2002;13(suppl 15):11–13.
- [8] Ballardini N, Kull I, Lind T, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12 – data from the BAMSE birth cohort. *Allergy*. 2012;67:537–544.
- [9] Petersen AC, Crockett L, Richards M, Boxer A. A self-report measure of pubertal status: reliability, validity, and initial norms. *J Youth Adolesc*. 1988;17:117–133.
- [10] Vink NM, Postma DS, Schouten JP, et al. Gender differences in asthma development and remission during transition through puberty: the TRacking Adolescents' Individual Lives Survey (TRAILS) study. *J Allergy Clin Immunol*. 2010;126:498–504.e1–6.