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Puberty and asthma in a cohort of Swedish children

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1 Title

2 Puberty and asthma in a cohort of Swedish children

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39 The shift in asthma prevalence from male to female predominance during the pubertal
40 years is believed to result from an increased incidence amongst girls, rather than remission
41 amongst boys [1,2]. Moreover, from the pubertal years onward, airway hyperresponsiveness,
42 a classic feature of asthma, also worsens amongst girls but improves in boys [3]. Asthma
43 medication use, a proxy for asthma severity, follows a similar pattern, with females requiring
44 greater medication from puberty onward [2,4].

45 These observations support the potential involvement of sex-specific factors with
46 asthma during this period. But, all physical changes of pubertal development cannot be
47 considered equally in relation to asthma, particularly amongst girls. Menarche appears to
48 play a substantial role in asthma presence and timing of onset. Early menarche predicts
49 poorer lung function [5] and higher post-menarchal asthma incidence [6] compared to
50 average/late menarchal age.

51 To better understand the associations between puberty and asthma, we aimed to assess
52 associations between pubertal staging and asthma symptoms and treatment in a longitudinal,
53 population-based cohort of Swedish children ('BAMSE') born in 1994-96 [7]. The original
54 cohort of 4089 infants was representative of the study catchment area, except higher rates of
55 parental smoking amongst non-responders [7]. Participant characteristics did not differ
56 between those followed through Year 12 and those lost to attrition [8]. At Years 8 and 12,
57 parents completed questionnaires on wheeze frequency in the previous 12 months and asthma
58 medication. Subjects were deemed to have asthma based on parental reports of ≥ 4 episodes
59 of wheeze or ≥ 1 episode of wheeze in combination with inhaled corticosteroid use in the past
60 12 months. Pubertal incidence of asthma was defined as no asthma at Year 8, but asthma at
61 Year 12. At Year 12, children completed pubertal development questions, based on the
62 composite pubertal scoring system the Peterson index [9, unpublished information from AC
63 Peterson]. Data were collected on 3 measures for both boys and girls (skin changes, linear

64 growth spurt, pubic hair growth), 2 measures for boys (voice change, beard growth) and 2
65 measures for girls (breast development, menarche). This scoring system permits for the
66 inclusion of the multiple characteristics of pubertal development along a continuum. For
67 boys, all characteristics contributed equally. Girls reporting menarche by Year 12 were
68 considered to be in late- or post puberty, regardless of other characteristics. Participants were
69 then categorized into one of five mutually exclusive categories: pre-, early-, mid-, late- or
70 post puberty. We further considered menarche independent of pubertal staging.

71 We used binomial logistic regression to analyse these data and report odds ratios
72 (OR) and corresponding 95% confidence intervals (CI) for unadjusted analyses and models
73 adjusted for confounding by age at Year 12. Analyses were performed with STATA 11.0
74 (StatCorp LP, College Station, TX, USA). Permission for this study was obtained from the
75 Regional Ethical Review Board of the Karolinska Institutet, Stockholm, Sweden.

76 At Year 12, the response rate was 82% (3366/4089), with asthma status available for
77 99% (3339/3366). We excluded those for whom pubertal data were unavailable. This
78 yielded a sample of 2721 (67% of the original cohort), of whom 50.2% were boys.. Nearly
79 all boys (1347/1378; 97.8%) were in pre-, early- or mid-puberty. Nearly half of girls
80 (651/1368; 47.6%) were in late- or post-puberty. Thus, we created sex-specific pubertal
81 staging categories. Boys were trichotomized into pre-, early- or mid/late puberty (none
82 reported post puberty). Girls were trichotomized as pre/early-, mid- or late/post puberty.
83 Approximately half (47.6%) of girls reported menarche by Year 12. Compared to boys, girls
84 had a lower odds of asthma at each assessment (e.g. Year 8: OR 0.66; 95%CI 0.47-0.92; Year
85 12: OR 0.57; 95% CI 0.42-0.78).

86 Pubertal staging was not found to be associated with asthma presence vs. absence in
87 boys (Table). In contrast, girls being late/post puberty was inversely associated with asthma
88 at Year 12 (OR 0.35; 95% CI 0.16-0.78). Amongst girls only, the odds of pubertal incidence

89 of asthma vs. asthma at neither Year 8 nor Year 12 decreased with more advanced pubertal
90 staging (mid-puberty: OR 0.36; 95% CI 0.15-0.88; late/post puberty: OR 0.25; 95% CI 0.09-
91 0.68). Menarche and asthma presence at Year 12 (OR 0.58; 95% CI 0.33-1.02), and menarche
92 and pubertal incidence of asthma (OR 0.56; 95% CI 0.26-1.19) followed a similar trend,
93 although these results did not reach statistical significance. In neither sex was pubertal
94 staging associated with asthma medication use at Yr12.

95 The widely accepted sex shift in asthma prevalence during adolescence [1,2] was not
96 noted in BAMSE through Year 12. Rather, pubertal incidence of asthma was lower amongst
97 girls than boys (3.0% vs. 5.2%, $p < 0.01$), and indeed lower in girls in late/post puberty vs.
98 early puberty. Our results are contrary to others' findings, including a report of a null
99 association between pubertal staging and asthma remission or incidence amongst similar-
100 aged youth [10]. However, their null findings may be partly explained by the low number of
101 participants in late puberty at baseline [10].

102 We are the first to report on the association between pubertal staging and asthma
103 using a composite and validated measure of puberty classified into one of three mutually
104 exclusive categories. Others have reported on puberty [11] and timing of menarche [5,6] and
105 asthma. One other group has considered multiple pubertal characteristics in their
106 classification of pubertal staging [10]. However, they considered puberty as a binary
107 outcome: early vs. late puberty [10]. Inclusion of a third category in our establishment of
108 pubertal staging gleans further insight into the understanding of the progression through
109 puberty on asthma presence and incidence during the pubertal years. This provided the
110 opportunity to better elucidate the associations between asthma and puberty than earlier
111 studies.

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

115 **References**

- 116 1. Nicolai T, Illi S, Reinhardt D, Nicolai T. Longitudinal follow-up of the changing
117 gender ratio in asthma from childhood to adulthood: role of delayed manifestation in
118 girls. *Pediatr Allergy Immunol*. 2003 Aug;14(4):280–3.
119
- 120 2. Almqvist CA, Worm M, Leynaert B, working group of GA²LEN WP 2.5 Gender.
121 Impact of gender on asthma in childhood and adolescence: a GA²LEN review.
122 *Allergy*. 2008 Jan;63(1):47-57.
123
- 124 3. Tantisira KG, Colvin R, Tonascia J, Strunk RC, Weiss ST, Fuhlbrigge AL. Airway
125 responsiveness in mild to moderate childhood asthma: sex influences on the natural
126 history. *Am J Respir Crit Care Med*. 2008 Aug 15;178(4):325-31.
127
- 128 4. Karlstad O, Nafstad P, Tverdal A, Skurtveit S, Furu K. Prevalence, incidence and
129 persistence of anti-asthma medication use in 2- to 29-year-olds: a nationwide
130 prescription study. *Eur J Clin Epidemiol*. 2010 Apr;66(4):399-406.
131
- 132 5. Macsali F, Real FG, Plana E, et al. Early age at menarche, lung function, and adult
133 asthma. *Am J Respir Crit Care Med*. 2011 Jan 1;183(1):8-14.
134
- 135 6. Al-Sahab B, Hamadeh MJ, Ardern CI, Tamim H. Early menarche predicts incidence
136 of asthma in early adulthood. *Am J Epidemiol*. 2011 Jan 1;173(1):64-70.
137
- 138 7. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE Project: presentation of
139 a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol*. 2002;13(suppl
140 15):11-3.
141
- 142 8. Ballardini N, Kull I, Lind T, Hallner E, Almqvist C, Ostblom E, Melén E, Pershagen
143 G, Lilja G, Bergström A, Wickman M. Development and comorbidity of eczema,
144 asthma and rhinitis to age 12 – data from the BAMSE birth cohort. *Allergy*. 2012
145 Apr; 67(4):537-44.
146
- 147 9. Petersen AC, Crockett L, Richards M, Boxer A. A self-report measure of pubertal
148 status: reliability, validity, and initial norms. *J Youth Adolesc*. 1988 April;17(2):117-
149 33.
150
- 151 10. Vink NM, Postma DS, Schouten JP et al. Gender differences in asthma development
152 and remission during transition through puberty: the TRacking Adolescents'
153 Individual Lives Survey (TRAILS) study. *J Allergy Clin Immunol*. 2010
154 Sep;126(3):498-504.e1-6.
155
156

157 **Table. Logistic Regression of Cross-Sectional Associations between Pubertal Staging and Asthma Presence and Pubertal Incidence at**
 158 **Year 12**

Pubertal Stage	Asthma Presence vs. Absence at Yr12						Pubertal Incidence of Asthma*					
	Presence n	Absence n	Unadjusted		Adjusted†		Incidence n	No Asthma n	Unadjusted		Adjusted†	
			OR	95% CI	OR	95% CI			OR	95% CI	OR	95% CI
Boys												
Pre-puberty	28	321		1.00		1.00	16	303		1.00		1.00
Early puberty	59	535	1.26	0.79-2.02	1.16	0.71-1.90	36	496	1.37	0.75-2.52	1.37	0.73-2.57
Mid/late puberty	28	395	0.81	0.47-1.40	0.67	0.36-1.25	12	368	0.62	0.29-1.33	0.61	0.26-1.46
Girls												
Pre/early puberty	13	148		1.00		1.00	9	136		1.00		1.00
Mid-puberty	28	523	0.61	0.31-1.21	0.54	0.27-1.09	14	502	0.42	0.18-1.00	0.36	0.15-0.88‡
Late/post puberty	26	617	0.48	0.24-0.96‡	0.35	0.16-0.78§	14	576	0.37	0.16-0.87‡	0.25	0.09-0.68‡
Menarche												
No	41	671		1.00		1.00	23	644		1.00		1.00
Yes	26	617	0.69	0.42-1.14	0.58	0.33-1.02	15	579	0.67	0.34-1.32	0.56	0.26-1.19

*Asthma incidence from Yr8 to Yr12 vs. no asthma at either Yr8 or Yr12

†Adjusted for age at Yr12

‡p<0.05

§p<0.01