

Letter to the Editor

Sex differences in asthma during the first 8 years of life: The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study*To the Editor:*

Before puberty, the prevalence of asthma and wheeze is higher in boys than girls.¹ Because of difficulties of diagnosing asthma at early ages,² it is unknown at what age sex differences in asthma develop. Our main objective was to determine the age of onset of sex differences in asthma risk. Because the mechanisms underlying the observed sex differences in childhood asthma are not yet fully understood,³ we also evaluated the role of atopy and perinatal exposures.

In the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort, 4146 pregnant women were recruited from the general population, and their children were followed from birth (1996-1997) to age 8 years.⁴ Data were collected by questionnaires during pregnancy, at ages 3 months and 1 year, and yearly thereafter. The study population consisted of 3308 children with questionnaire-based data on asthma at age 8 years.

Asthmatic wheeze at ages 1 to 7 years was defined as parent-reported wheeze at ages 1, 2, 3, 4, 5, 6, or 7 and asthma at age 8 years. Thus, wheeze at ages 1 to 7 years was only considered to be asthmatic wheeze if children had asthma at age 8 years. Wheeze in children without asthma at age 8 years was considered as transient wheeze. The definition of asthma at age 8 years was based on questionnaire data: at least 1 attack of wheezing and/or 1 episode of dyspnea and/or 1 prescription of inhaled corticosteroids in the past 12 months.

Specific IgE was measured at age 8 years in a subgroup of 776 children in which children of mothers with allergy were oversampled.⁵ Atopy was defined as a specific IgE concentration of ≥ 0.70 IU/mL for at least 1 of the following inhalant allergens: house dust mite, cat, dog, birch, grass, and mold. Atopic asthma at age 8 years was defined as asthma with atopy at age 8 years.

The relation between sex and the prevalence of asthmatic wheeze was studied longitudinally by using general estimating equations. Sex differences in the incidence (rate of new cases) of asthmatic wheeze were studied by using a Cox proportional hazard analysis (option TIES = discrete of PHREG procedure in SAS; SAS Institute, Inc, Cary, NC).

The study population was similar to the total PIAMA population with respect to the characteristics shown in Table I; a significant sex difference was observed only for mean birth weight.

At age 8 years, 15.1% of the boys and 10.8% of the girls had asthma (odds ratio [OR], boys vs girls, 1.5; 95% CI, 1.2-1.8). The prevalence of total wheeze decreased strongly with age, in contrast with the prevalence of asthmatic wheeze, which remained fairly stable (Table II).

The prevalence of asthmatic wheeze was higher in boys than girls from the first year of life onward (Table II). The sex difference varied little with age (ORs, boys vs girls, ranging 1.6-2.0; $P < .05$). The sex difference for total wheeze was smaller, with ORs ranging from 1.3 to 1.6.

Boys had a higher incidence of asthmatic wheeze than girls in the first 3 years of life, with an overall incidence ratio for this period of 1.7 (95% CI, 1.3-2.2; Fig 1). In the 4 to 7 years age period, incidence was similar in boys and girls (incidence ratio,

TABLE I. Characteristics of the study population

	Boys n (%)	Girls n (%)
Region		
North	1698 (30.9)	1610 (32.3)
Central	1698 (43.0)	1610 (39.4)
West	1698 (28.3)	1610 (26.2)
Low maternal education	1691 (21.5)	1601 (21.7)
Allergic mother†	1698 (29.0)	1610 (28.7)
Allergic father†	1696 (29.8)	1609 (31.5)
Smoking during pregnancy‡	1678 (15.4)	1588 (16.5)
Breast-feeding§		
>16 wk	1682 (36.1)	1595 (38.2)
Older siblings	1698 (51.8)	1610 (48.8)
At 3 mo in the home		
Smoking mother or father	1693 (22.3)	1858 (23.2)
Cat	1697 (33.2)	1610 (31.5)
Dog	1696 (14.9)	1609 (14.5)
Damp/mold spots¶	1662 (9.6)	1572 (9.0)
First year		
Attending day care	1688 (25.9)	1599 (23.7)
>4 h/wk		
	Mean (SD)	Mean (SD)
Birth weight (g)	3589 (547)	3457 (514)*

* $P < .05$.

†Parents were defined as having allergy if they had hay fever, pet allergy, house dust mite allergy, or asthma ever.

‡Mother smoked during the first 4 weeks of pregnancy.

§Any breast-feeding (either exclusive or partial).

||Smoking in the home at least once a week.

¶In living room or child's bedroom.

1.1; 95% CI, 0.7-1.7). For total wheeze, the incidence ratio for boys versus girls was 1.3 (95% CI, 1.1-1.5) in the age period 0 to 3 years and 1.1 (95% CI, 0.8-1.4) in the age period 4 to 7 years.

Analyses in the subgroup with data on atopy ($n = 776$) showed that the prevalence of atopy at age 8 years was higher in boys than girls (36.4% vs 24.0%; OR, 1.8; 95% CI, 1.3-2.5). In this subgroup, the prevalence of asthma at age 8 years was higher than in the total study population (19.1% in boys and 14.9% in girls), but the association with sex was similar to the association in the total study population (boys vs girls, OR, 1.4; 95% CI, 0.9-2.0). Sex differences in asthma prevalence were similar in atopic and nonatopic children (no effect modification). In the subgroup, the overall OR for the prevalence of asthmatic wheeze at ages 1 to 7 years in boys versus girls was 1.6 (95% CI, 1.1-2.5). Adjustment for atopy at age 8 years reduced this OR to 1.3 (95% CI, 0.9-2.0).

The association between the perinatal risk factors shown in Table I and asthma risk at age 8 years was similar in boys and girls.

Sensitivity analyses were conducted, repeating the main analyses with a stricter definition of asthma. In these analyses, atopy was included in the definition of asthma at age 8 years. Thus, wheeze at ages 1 to 7 years was only considered to be asthmatic in children with atopic asthma at age 8 years. Results were similar to those of the main analyses (overall OR for the prevalence of asthmatic wheeze at ages 1-7 years in boys vs girls, 2.0; 95% CI, 1.2-3.2; other results not shown).

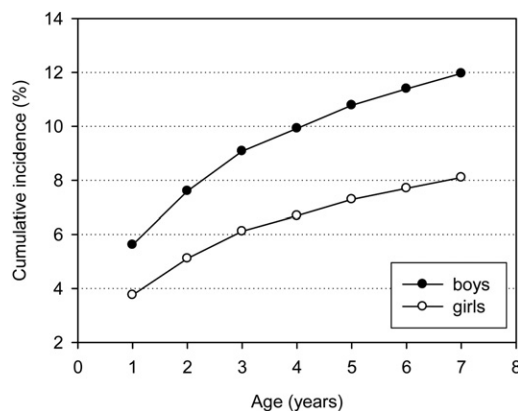
We used longitudinal data to differentiate at ages 1 to 7 years between asthmatic wheeze (if asthma was present at age 8 years) and transient wheeze (if asthma was absent at age 8 years).

TABLE II. Sex differences in the prevalence of total wheeze and asthmatic wheeze* (as opposed to transient wheeze)

Age (y)	N		Total wheeze			Asthmatic wheeze*		
	Girls	Boys	Girls %	Boys %	OR† (95% CI)	Girls %	Boys %	OR† (95% CI)
1	1543	1635	17.8	22.7	1.37 (1.15-1.63)	3.7	6.1	1.74 (1.25-2.43)
2	1582	1673	14.6	19.7	1.43 (1.19-1.72)	3.4	5.7	1.68 (1.20-2.36)
3	1587	1668	13.9	16.7	1.25 (1.04-1.52)	4.0	6.5	1.72 (1.25-2.37)
4	1567	1645	9.3	13.7	1.56 (1.25-1.94)	3.8	6.6	1.78 (1.30-2.45)
5	1562	1644	7.4	11.3	1.60 (1.25-2.03)	3.4	6.7	2.01 (1.45-2.81)
6	1571	1657	6.7	8.9	1.37 (1.06-1.77)	3.9	6.2	1.63 (1.18-2.24)
7	1528	1632	4.8	6.6	1.36 (1.01-1.83)	3.0	5.0	1.66 (1.16-2.37)

*Wheezing at ages 1 to 7 years was labeled "asthmatic wheeze" only if children had asthma at age 8 years (see Methods).

†Derived from general estimating equation analysis.

**FIG 1.** Sex differences in the cumulative incidence of asthmatic wheeze. Wheeze at ages 1 to 7 years was labeled "asthmatic wheeze" only if children had asthma at age 8 years. The curves shown are based on survivor function estimates derived from a discrete time hazard model.

Strengths of this longitudinal study are the availability of annual data on wheeze and of data on atopy in a substantial subgroup at age 8 years. There is no gold standard to define asthma, and every questionnaire-based asthma definition, including the PIAMA definition, may result in some misclassification. Potential misclassification is, however, unlikely to differ by sex. Also, sensitivity analyses, using a stricter definition of asthma, showed sex differences very similar to those observed in the main analyses. Atopy was assessed at the age of 8 years, and the directionality of the association between atopy and asthmatic wheeze therefore needs to be interpreted with caution. The follow-up rate was high in the PIAMA study and similar in boys and girls. Stratification showed that oversampling of allergic mothers in the subgroup did not affect sex differences in asthmatic wheeze. The observed sex differences therefore apply to the total study population. The PIAMA population is relatively highly educated compared with the general population, but parental education did not affect the sex differences reported here. We assume therefore that the observed sex differences in the development of asthmatic wheeze are generalizable to the general population.

The prevalence of asthmatic wheeze was significantly higher in boys than girls already at the age of 1 year, and this higher prevalence persisted during the first 7 years of life. The incidence of asthmatic wheeze was higher in boys than girls in the first 3 years of life, but not thereafter. The observed sex differences were larger for asthmatic wheeze than for total wheeze, suggesting that sex differences are stronger for asthma than for transient symptoms.

Young boys are thought to have smaller airway diameters in proportion to their total lung volume than girls, predisposing them to airway obstruction and wheeze.^{1,6} Our results suggest that sex differences in asthma may partly be explained by the higher prevalence of atopy in boys and cannot be explained by a stronger effect of perinatal risk factors in boys.

Alet Wijga, PhD^a

Cora Tabak, PhD^a

Dirkje S. Postma, MD, PhD^b

Marjan Kerkhof, MD, PhD^c

Marjan H. Wieringa, PhD^d

Maarten O. Hoekstra, MD, PhD^e

Bert Brunekreef, PhD^{g,h}

Johan C. de Jongste, MD, PhD^e

Henriette A. Smit, PhD^h

From ^athe Center for Prevention and Health Services Research, National Institute of Public Health and the Environment, Bilthoven; the Departments of ^bPulmonology and ^cEpidemiology, University Medical Center Groningen, University of Groningen; ^dthe Department of Otorhinolaryngology, Head and Neck Surgery, Erasmus University Medical Center, and ^ethe Department of Pediatrics/Respiratory Medicine, Erasmus University Medical Center—Sophia Children's Hospital, Rotterdam; ^fthe Department of Pediatrics, University Medical Center St Radboud, Nijmegen; ^gthe Institute for Risk Assessment Sciences, University of Utrecht; and ^hthe Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands. E-mail: alet.wijga@rivm.nl.

The PIAMA study is supported by The Netherlands Organization for Health Research and Development; The Netherlands Organization for Scientific Research; The Netherlands Asthma Fund; The Netherlands Ministry of Spatial Planning, Housing, and the Environment; and The Netherlands Ministry of Health, Welfare, and Sport.

Disclosure of potential conflict of interest: D. S. Postma is a consultant for Nycomed and receives research support from Top Institute Pharma and AstraZeneca. The rest of the authors have declared that they have no conflict of interest.

REFERENCES

- Almqvist C, 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.
- Martinez FD, Godfrey S. Wheezing disorders in the preschool child: pathophysiology and management. London and New York: Martin Dunitz; 2003.
- Postma DS. Gender differences in asthma development and progression. *Genet Med* 2007;4(suppl B):S133-46.
- Brunekreef B, Smit J, de Jongste J, Neijens H, Gerritsen J, Postma D, et al. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002;13(suppl 15):55-60.
- Scholtens S, Wijga AH, Seidell JC, Brunekreef B, de Jongste JC, Gehring U, et al. Overweight and changes in weight status during childhood in relation to asthma symptoms at 8 years of age. *J Allergy Clin Immunol* 2009;123:1312-8, e2.
- Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. *Thorax* 1999;54:1119-38.

doi:10.1016/j.jaci.2010.09.022