

Longitudinal follow-up of the changing gender ratio in asthma from childhood to adulthood: role of delayed manifestation in girls

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Boys suffer more often from asthma than girls, while in adults the gender ratio is reversed. It is not clear when exactly this change occurs and by what mechanism. From a cohort of all 5030 German 4th grade pupils (age 10 years) in Munich, 274 children with current asthma were identified (164 males, 110 females) through a questionnaire, and skin prick tests were performed. These subjects were re-evaluated at ages 14 and 20 years with a questionnaire. A random sample ($n = 1000$) of all 3538 German children without current asthma at age 10 was also re-evaluated at age 20 (controls). At age 20, only 24.5% (21 males, eight females) of the initial asthma group still had symptoms, and their gender ratio remained male dominated. In the controls, 4.8% (48/1000) had current asthma at age 20 and these were predominantly female: 6.4% (31/485) of control girls vs. 3.3% (17/515) of boys ($p = 0.022$). Half of the new asthma cases had had no symptoms or diagnoses until age 10, and atopy at age 10 was not associated with subsequent asthma in these. Asthma at age 10 has no better prognosis in boys than in girls, and the mechanism of the changing gender ratio appears to be late incidence of asthma among girls. Because the latter constitute a considerable part of adult asthma cases, it appears important to further explore this asthma phenotype and the risk factors associated with it.

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Introduction

In childhood, boys suffer more often from asthma than girls, while this gender ratio is reversed in adults (1–3). It is not clear exactly when this change occurs or by what mechanism, and whether it is due to a better prognosis of established asthma in boys or an increased incidence of new cases in girls. Previous studies have been cross-sectional (4) or follow-ups of established asthma, or did not include measured risk factors such as sensitization. It has been recommended that prognosis of asthma is best established from population studies (5). It was the aim of this study to assess this change in a large population-based survey, from age 10 to

20 years, when most of the change in gender predominance seems to occur.

Methods

All German 4th grade pupils were surveyed in the Munich study on allergies and asthma during the 1989/90 school year. The methods of this large school-based cross-sectional study have been described in detail elsewhere (6). Current asthma was defined as a doctor's diagnosis of asthma or recurrent asthmatic bronchitis in the presence of asthma symptoms in the past 12 months. Atopy was defined as a positive skin prick test to at least one of the inhalant allergens tested. 5.4%

(274/5030) of children reported current asthma. Of those, 163 consented to follow-up and 155 individuals could be re-evaluated after 4 years (mean age 13.5 years, range 12.1–15.4 years), and 118 again 6 years later (mean age 20.1 years, 19.6–21.5 years). Re-evaluation consisted of a telephone interview and a mailed questionnaire containing ISAAC questions (7).

A pilot study and power estimate showed that approximately 1000 subjects would be needed to verify or exclude a gender difference in new cases. A random list from the 3538 German children without current asthma at age 10 with questionnaire and skin prick test data who had given consent to follow-up was generated (control group). Using 2143 consecutive subjects from this list, the required 1000 could be tracked and were interviewed via telephone. A detailed questionnaire was sent to those reporting current asthma at age 20. The study had been approved by the local ethics committee.

Statistics

All analyses were performed using the SAS 6.12 package (SAS Institute GmbH, Heidelberg, Germany). Classical chi-square and, for small samples, Fisher's exact test were used to assess associations, and $p < 0.05$ was considered significant.

Results

The subjects in the control group who could not be reached did not differ significantly from those could be re-evaluated with respect to diagnoses, reported symptoms, allergy test results at age 10 or possible confounding factors, such as socioeconomic status.

The results of the follow-up are given in Table 1. An analysis of the effect of puberty and other risk factors on the 4-year follow-up data has been reported elsewhere (8, 9).

Asthma persisting at age 14 and 20 in children with current asthma at age 10

At age 14, 35.5% (55/155) continued to have current asthma, with a gender ratio (male : female) of 1.9 : 1. At age 20, 24.5% (29/118) reported current asthma, with a gender ratio of 2.6 : 1. Of those who had outgrown their asthma symptoms by age 14, 12% (12/100) were again asthmatic at age 20. A trend for more atopy at age 10 years was seen among children with persistent asthma. Active tobacco smoking was not related to asthma at age 14 or 20 (data not shown).

Table 1. Follow-up of children with current asthma at age 10 years and a random sample of all control children from the same cohort

	1989	1994	2000
Asthma at age 10	n = 274		
Asthma		35% (55/155)	24.5% (29/118)
Male	n = 164	65.5% (36/55)	72.4% (21/29)
Female	n = 110	34.5% (19/55)	27.6% (8/29)
Gender ratio (male/female)	1.5 : 1	1.9 : 1	2.6 : 1
Atopy in persisting asthma			87.5% (21/24)
Atopy in asthma remission			70.1% (47/67)*
Control Group	n = 1000		
Asthma at age 20			4.8% (48/1000)
Male			3.3% (17/515)
Female			6.4% (31/485)**
Gender ratio (male/female)			0.55 : 1
No symptoms/ diagnosis <10 years			50.0% (24/48)
Atopy in asymptomatic group			35.0% (7/20)
No asthma at age 20			95.2% (952/1000)
Male			96.7% (498/515)
Female			93.6% (454/485)
Gender ratio (male/female)			1.1 : 1
No symptoms/ diagnosis <10 years			71.2% (677/952)†
Atopy in asymptomatic group			49.2% (205/417)

*p = 0.093 persisting vs. remitting asthma.

**p = 0.022 male vs. female.

†p = 0.0018 asthma at age 20: symptoms vs. no symptoms < age 10 (within the control -group).

Atopy = at least one positive skin prick test to a panel of aeroallergens (6) at age 10; not all children had a skin prick test available.

Incidence of asthma

In the control group, 4.8% (48/1000) reported current asthma at age 20, and these were predominantly female: 6.4% (31/485) of all women and 3.3% (17/515) of all men in the control group ($p = 0.022$). Neither weight, height nor body mass index at age 10 predicted the incidence of asthma.

By definition, the control group contained all children without current asthma at age 10, i.e. also children with reported wheeze but no diagnosis of asthma at age 10 years (18.9% (189/1000)), and a former diagnosis of asthma but no current symptoms at age 10 (11.0% (110/1000)), respectively. Asthma at age 20 was reported by 6.3% (12/89) of those with early wheeze without a diagnosis of asthma before age 10, and 11% (12/110) of those control children with former asthma. Recurrence of asthma at age 20 among children with wheeze or asthma before the age of 10 years ($n = 299$) occurred in 12.0% (16/133) of all females and 4.8% (8/66) of all males.

Half of all cases with asthma at age 20 years (24/48) were incident cases reporting no wheeze or asthma diagnosis before age 10. These

subjects were predominantly female (15/24, gender ratio 0.6 : 1) and atopy at age 10 was not associated with incident asthma in this group.

We calculated an estimate of the gender ratio of current asthma at age 20 for the initial total cohort from the control and follow-up arms of the study, taking response rates and sample size into account. This estimated gender ratio was 0.77 : 1 (male/female), and was dominated by women with late (recurrent or incident) asthma.

Discussion

As a result of methodological limitations, the results of this study must to some extent be considered preliminary. Because of monetary and personnel constraints, only a random sample of the initial control cohort could be re-evaluated at age 20. Also, the follow-up of the controls consisted of a telephone interview, and a full questionnaire was only sent to subjects reporting current asthma at age 20. Therefore, not all possible confounding factors operative at age 20 are known for asymptomatic control persons. Also, no second skin prick test at age 20 was possible with this study design. Still, we feel that for the question of gender ratio change, the available data are sufficient. The advantage of the present study is that it follows a population-based cohort including controls from 10 to 20 years, and atopy was measured at the beginning of the follow-up.

In this study we found, as have others (2, 9), a good prognosis for children with current asthma at age 10 over the following decade. However, at the end of the study period, the male predominance in current asthma cases was preserved, indicating no better prognosis in boys than girls. Late asthma cases were twice as likely in girls than in boys in the control group.

Previously reported population-based studies have been either retrospective or cross-sectional, or have used reported eczema or hay fever as markers of atopy instead of measuring sensitization. A cross-sectional questionnaire-based study from the Nottingham area found a reversal of the gender ratio around 12 years of age (4). An Australian study used a cohort consisting mostly of asthma patients (10). The gender ratio remained male dominated: 2.1 : 1 at age 14, 1.5 : 1 at age 21 and 1.2 : 1 at 28 years, and fits well with our data from the asthma follow-up arm. In the population-based British National Child Development Study (1, 2), the asthma gender ratio changed from 1.23 : 1 at age 7 to

1.31 : 1 at age 11, to 1.47 : 1 at age 16 and then to 0.59 : 1 at age 23. Reported atopy at the time of presentation but not in childhood was a risk factor in this study. However, the authors have not reported repeated individual follow-ups. A similar cohort study from Tasmania found that 10% of children without symptoms at age 7 had developed asthma at age 30, and female gender represented a risk factor (11). Similarly, a Swedish retrospective study found a high incidence in girls age 16–20 with reported atopy as risk factor (12). It appears that boys often express an early atopy-associated type of asthma with a good prognosis. The 50% of children with asthma at age 20 who had had symptoms and/or asthma before age 10 (but no current asthma at 10) were mostly girls and seemed to run an intermittent or more delayed course of a similar asthma phenotype.

However, 50% of the new cases had had neither symptoms nor diagnoses before age 10. These subjects were mostly female, and atopy at age 10 was not associated with late asthma. Current research is mainly directed at finding risk factors for the inception and exploration of possible interventions for early-onset, atopy-associated asthma in children. Because these women constitute a considerable number of the adult asthma cases, it appears important to further explore this asthma phenotype and the risk factors associated with it as well.

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