

Association of asthma with extra-respiratory symptoms in schoolchildren: Two cross-sectional studies 6 years apart

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Epidemiological information on symptoms affecting extra-respiratory organs and apparatuses in asthmatic children is scarce. The aim of this study therefore was to evaluate, at a population level, if and what extra-respiratory symptoms are associated with asthma. Two questionnaire-based, cross-sectional surveys were carried out on 1,262 students (651 males; mean age 9.57 years, age-range 6–14 years) in 1992 and on 1,210 students (639 males; mean age 9.02 years, age-range 6–14 years) in 1998, from two elementary and two junior high schools in Rome, Italy.

Questionnaires included queries about asthma and its risk factors and extra-respiratory symptoms (headache, restlessness, sleep disturbances, urticaria, itching, and abdominal pain). Of responders, 11.9% (279/2,342) had a history of asthma. After adjustment for gender, family history of atopic disease, low birth weight, early respiratory problems, and damp house, asthma was significantly associated with recurrent abdominal pain (odds ratio [OR] 1.90; 95% confidence interval [CI]: 1.04, 3.16), itching (OR 3.15; 95% CI: 1.75, 5.68), and urticaria (OR 2.52; 95% CI: 1.02, 6.20). Asthma was reported by 10.2% (201/1,962) of children unaffected by this triad, by 20.1% (56/279; OR 2.20) with one of the symptoms, and by 31.6% (12/38; OR 4.04) with two or more symptoms. An emerging characteristic of pediatric asthma in our setting appears to be its association with certain extra-respiratory symptoms (abdominal pain, itching, and urticaria). A global, internistic approach to asthmatic children is increasingly required both in the clinical setting and in future epidemiological studies.

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During the last four decades, we have progressively changed our understanding of asthma. In the 1960s, World Health Organization (WHO) definitions focused on bronchial spasms (1); subsequently, attention turned to the underlying bronchial hyper-reactivity (2). Now, asthma is viewed as an inflammatory condition of the airways that involves mast cells and eosinophils, thus leading to bronchial hyper-responsiveness, microvascular leakage, hyper-secretion of mucus, and variable airflow obstruction (3). Allergic reactivity to inhalants is, even more than in the past, implicated in the etiopathogenesis of this syndrome (4). Moreover, the prevalence of

childhood asthma has increased substantially in western countries (4) and this disease is now not infrequently preceded or accompanied with extra-respiratory symptoms such as behavioral changes (irritability, apathy, anxiety, and sleep disorders), gastrointestinal symptoms (abdominal pain and anorexia), itching, skin eruptions, and migraine (5). This might imply that childhood asthma, while increasing in prevalence, is becoming one component of a more complex syndrome involving other organs or apparatuses. We therefore investigated if and what extra-respiratory symptoms are associated with asthma at a population level. To achieve this, we analyzed the data of two

questionnaire-based surveys, conducted 6 years apart in the 1990s, of a large student population attending four schools in Rome. The asthma prevalence emerging from these surveys in comparison with previous investigations has been reported previously (6). Here we report data arising from questionnaire items about the known risk factors for asthma, and about extra-respiratory symptoms such as headache, excessive irritability, sleep disturbances, urticaria, itching, and abdominal pain.

Subjects and methods

Study design and population

Two cross-sectional surveys were conducted between September and November in 1992 and in 1998. In both surveys, students attending two primary (1st to 5th grade) and two junior high (6th to 8th grade) schools in Rome were screened according to a protocol described previously (6). The target population consisted of 1,435 students in 1992 and 1,309 in 1998 (age-range: 6–14 years). Self-administered questionnaires were sent via the pupils to the parents for completion and were returned by 1,262 students (651 males), in 1992, and by 1,210 students (639 males) in 1998. Seventy-six pupils aged 6–8 years in 1992 and 12–14 years in 1998 participated in both surveys; when data from both 1992 and 1998 surveys were pooled together, these 76 subjects were included only once (using 1998 data).

Questionnaire

The same questionnaire was administered in the two surveys. It included questions about socioeconomic status, smoking habits, family history of asthma and other atopic diseases, and history of respiratory and non-respiratory symptoms. The questionnaire was designed in the 1970s within the framework of an Italian National Research Council project and validated with respiratory function tests in general population samples that also included children (7).

The following questions were used to identify lifetime asthma:

- 1 Has your physician ever told you that your child has asthma or asthmatic bronchitis?
- 2 Has your child ever had asthmatic attacks (attacks characterized by shortness of breath with audible wheezing)?
- 3 When playing, does your child become breathless more easily than other children?

Each of these questions could be answered 'yes' or 'no'. A child was defined as 'asthmatic' if parents answered question 1, or both of questions

2 and 3, affirmatively. A family history was considered positive for atopic diseases if at least one parent or two siblings reported physician-diagnosed allergic rhinitis and/or asthma and/or atopic eczema. Current non-asthmatic symptoms were identified by asking 'is your child affected by: headache; abdominal pain; urticaria; itching; disturbed sleep; or excessive irritability?'. The answer to each of these questions could be 'never', 'rarely' or 'often'.

The questionnaire included questions on age (in years) and gender; number of siblings; father's occupation (not manual requiring a degree, others not manual, manual); birth weight (kg); breast feeding for at least 3 months (yes/no); crowding index (household/rooms); current pet ownership (cat or dog); dampness in the house; type of heating; organized sport practice; current passive smoking (households smoking cumulatively >10 cigarettes per day); and smoking during pregnancy (mother smoking ≥ 1 cigarettes/day for ≥ 1 month during pregnancy).

Statistics

Chi-square tests were used to compare prevalences between groups. We also calculated crude prevalence odds ratios (OR) with 95% confidence intervals (CI). Multivariate logistic regression analysis was used to assess whether non-asthmatic symptoms were associated with asthma after adjusting for each other and for risk factors for asthma that were associated with asthma in a univariate analysis ($p < 0.05$). SPSS software version 5.0 (SPSS Inc., Chicago, IL, USA) was used in all calculations. Bonferroni correction for multiple comparisons was utilized when appropriate.

Results

The prevalence of disorders of the upper and lower airways was similar in the two surveys. The frequency of non-asthmatic symptoms, including urticaria, itching, abdominal pain, headache, sleep disturbances, and excessive irritability, was also remarkably similar in the two surveys (Table 1).

When analysing the association of socio-demographic factors and non-asthmatic symptoms with asthma, the two sets of data (1992 and 1998) were combined. Univariate analysis showed that asthma was significantly associated with male gender, a positive family history of atopic diseases, low birth weight, respiratory problems in the first week of life, and dampness in the house, but not with other variables considered

Table 1. Prevalence of respiratory and extra-respiratory symptoms in two surveys among unselected schoolchildren 6–14 years of age

Disorder	Prevalence: % (n/total)*	
	1992 (n=1,262)	1998 (n=1,210)
Respiratory symptoms		
Stuffy nose/secretion most of the year (ever)	13.8 (173/1,204)	13.6 (164/1,206)
Stuffy nose/secretion most of the year (last 12 months)	7.2 (87/1,212)	5.7 (68/1,203)
Nocturnal cough	2.2 (27/1,254)	3.4 (41/1,206)
Shortness of breath with audible wheezing (ever)	10.6 (133/1,255)	9.5 (115/1,207)
Shortness of breath with audible wheezing (last 12 months)	4.2 (51/1,220)	3.7 (44/1,204)
Shortness of breath triggered by exercise	2.6 (32/1,252)	4.1 (50/1,206)
Bronchitis or bronchopneumonia (doctor's diagnosis)	27.0 (337/1,249)	27.6 (332/1,203)
Asthma or asthmatic bronchitis (doctor's diagnosis)	11.5 (143/1,239)	11.0 (133/1,204)
Asthma†	12.2 (149/1,224)	11.9 (142/1,193)
Extra-respiratory symptoms		
Abdominal pain		
Frequent	4.6 (56/1,213)	5.3 (64/1,200)
Rare	33.8 (410/1,213)	32.5 (390/1,200)
Urticaria		
Frequent	1.3 (16/1,204)	1.2 (14/1,200)
Rare	7.1 (85/1,204)	6.7 (80/1,200)
Itching		
Frequent	3.0 (36/1,204)	3.0 (36/1,200)
Rare	11.0 (132/1,204)	13.8 (165/1,200)
Headache		
Frequent	5.7 (70/1,229)	5.7 (69/1,199)
Rare	44.0 (541/1,229)	43.4 (520/1,199)
Sleep disturbances		
Frequent	5.6 (68/1,207)	5.4 (65/1,200)
Rare	20.0 (241/1,207)	22.5 (270/1,200)
Excessive irritability		
Frequent	7.8 (94/1,209)	7.8 (94/1,200)
Rare	22.2 (269/1,209)	24.1 (289/1,200)

*Chi-square value not significant (1998 vs. 1992) after Bonferroni's correction for multiple comparisons for any parameter in the table.

†See text for definition.

(data not shown). Asthma was significantly and positively associated with urticaria, itching, and recurrent abdominal pain, even after adjustment for potential confounders (Table 2) and when analysing, separately, data obtained in the 1992 or 1998 survey (data not shown). Hereafter, the term 'asthma-associated extra-respiratory symptoms' (AA-ERS) is used to refer to the presence of one or more of the three extra-respiratory symptoms (urticaria, itching, or recurrent abdominal pain) that were significant in this study.

The adjusted risk of lifetime asthma increased linearly with the number of reported AA-ERS; compared with children without AA-ERS (201/1962, 10.2%), those with one AA-ERS (56/279, 20.1%) had an OR of 2.20 of having asthma, and those with two or more AA-ERS (12/38, 31.6%) had an OR of 4.04.

After stratification for gender and family history of asthma or atopy, the occurrence of one or more AA-ERS corresponded to a two-fold prevalence of asthma in each category (Fig. 1). At one extreme, females without a family history of atopic diseases and without AA-ERS had a

rather low prevalence of asthma (6.2%); by contrast, at the other extreme, males with a family history of atopic diseases and with AA-ERS had a seven-fold higher prevalence of asthma (45.0%).

Discussion

In two pediatric populations studied during the 1990s, we found that asthma was associated not only with the established risk factors of male gender and a family history of atopic diseases, but also with extra-respiratory symptoms, namely urticaria, frequent itching, and recurrent abdominal pain. This association persisted after adjustment for gender, a family history of atopic diseases, and for relevant peri-natal and post-natal risk factors. Moreover, a 'dose-response-like' relationship was observed, i.e. the OR of having asthma rose linearly with the number of AA-ERS. We also found that each of the three symptoms was independently associated with asthma with a power similar to that of male gender or of a family history of atopic diseases. By contrast, other extra-respiratory symptoms,

Table 2. Asthma in relation to extra-respiratory symptoms in schoolchildren

Disorder	Subjects (n)	With asthma*		OR	Adjusted OR (95% CI)†
		n	%		
Abdominal pain					
Frequent	114	21	18.4	1.90	1.78 (1.04; 3.03)
Rare	754	100	13.3	1.29	1.23 (0.92; 1.64)
Never	1,421	151	10.6	1	1
Urticaria					
Frequent	28	71	25.0	2.77	2.52 (1.02; 6.20)
Rare	151	38	25.2	2.79	2.56 (1.68; 3.90)
Never	2,103	226	10.7	1	1
Itching					
Frequent	69	19	27.5	3.31	3.15 (1.75; 5.68)
Rare	279	53	19.0	2.05	1.97 (1.39; 2.80)
Never	1,934	199	10.3	1	1
Headache					
Frequent	128	18	14.1	1.37	1.43 (0.82; 2.49)
Rare	1,011	133	13.2	1.27	1.23 (0.93; 1.63)
Never	1,164	124	10.7	1	1
Sleep disturbances					
Frequent	125	21	16.8	1.58	1.39 (0.83; 2.33)
Rare	486	59	12.1	1.08	0.96 (0.69; 1.34)
Never	1,675	190	11.3	1	1
Excessive irritability					
Frequent	181	29	16.0	1.64	1.41 (0.89; 2.21)
Rare	527	78	14.8	1.49	1.25 (0.92; 1.70)
Never	1,580	165	10.4	1	1

*See text for definition.

†Adjusted for: gender; family history of atopic diseases; house dampness; low birth weight; and respiratory problems in the first week of life. CI, confidence interval; OR, odds ratio.

namely headache, marked restlessness, and sleep disturbance, were not significantly associated with asthma.

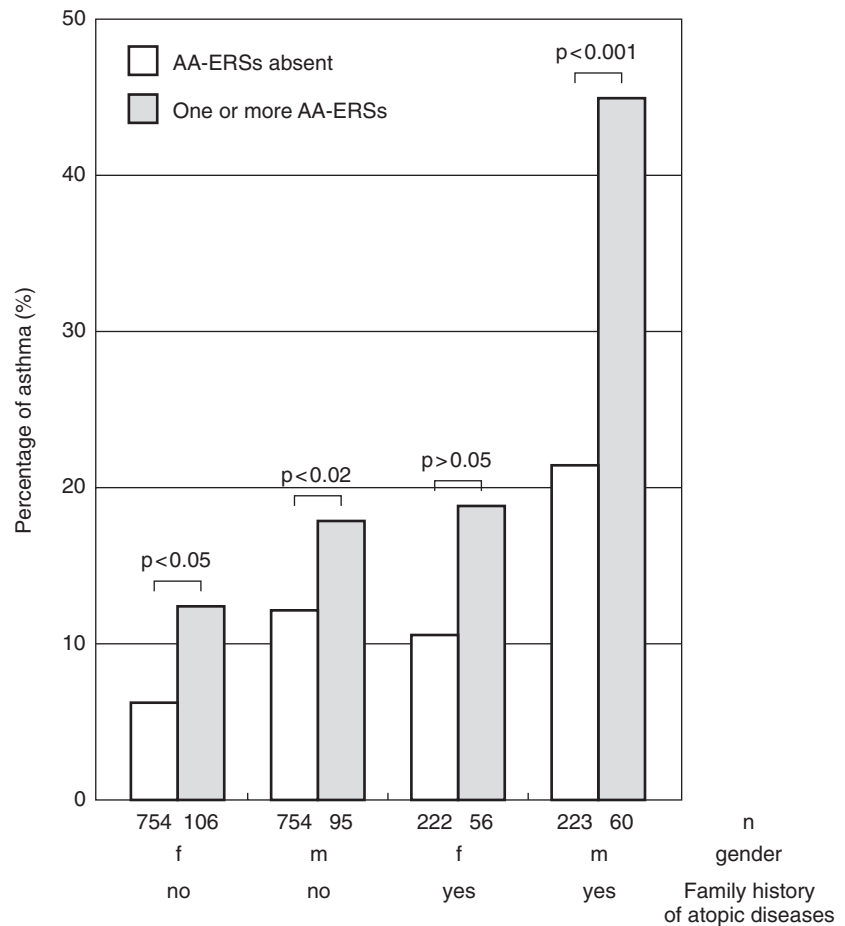
It is not easy to account for the associations observed in this study. With regard to cutaneous AA-ERS, the most simple hypothesis is that both urticaria and itching are associated with asthma because all three situations may have a common 'atopic background'. However, in our population, urticaria and itching were only weakly associated with each other (data not shown), and moreover there was no interaction between the two symptoms in the multivariate analysis. These findings suggest that the pathogenetic mechanisms of urticaria and itching are not identical and that the association between urticaria and asthma, or between itching and asthma, cannot be explained completely on 'a common atopic background'. In addition, these associations were unrelated to the presence or absence of a family history of atopic diseases, suggesting that the mechanism underlying the link between urticaria or itching and asthma differs from that underlying the link between atopic eczema and asthma. However, caution should be exerted in drawing any conclusion as to the role of atopy in the associations reported here, because our study populations did not undergo an objective test for

immunoglobulin E (IgE) sensitization and no items on lifetime diagnosis of atopic eczema were included in the questionnaire.

The association of asthma with recurrent abdominal pain was unrelated to the presence or absence of a family history of asthma or of other atopic diseases, which suggests that an atopic predisposition is also not relevant for the association itself. Similarly, Peckham et al. (8) identified in a British cohort study a strong association of abdominal pain with doctor-diagnosed 'wheezy bronchitis', and a very much weaker association with 'asthma'. In the same population, Strachan et al. (9) reported higher frequencies of asthma and/or wheezy bronchitis in subjects with recurrent abdominal pain, but only among individuals with no other atopic manifestations (atopic eczema or allergic rhinitis). The conclusions of the two British studies are consistent with our finding that abdominal pain is associated with asthma, irrespective of predisposition to atopic diseases. By contrast, Caffarelli et al. (10) recently found that abdominal pain (and some other gastrointestinal symptoms) was more frequently reported by asthmatic children with positive skin prick tests to food allergens.

The intriguing finding that extra-respiratory symptoms such as urticaria, itching, and abdom-

Fig. 1. Prevalence of asthma by gender and family history of atopic diseases and by the occurrence of any of the following asthma-associated extra-respiratory symptoms (AA-ERS): urticaria, itching, recurrent abdominal pain (alone or in combination).



inal pain are associated with asthma, independently of gender and a family history of atopic diseases, has yet to be explained. Both asthma and AA-ERS may be linked to an unknown frequent genetic predisposition which is partially unrelated to atopy; or AA-ERS and specific components of asthma (e.g. bronchial hyper-reactivity) may be triggered by exposure to the same environmental factors. Thus, a general increase in 'hyper-reactivity' (both allergen-specific and non-allergen specific) and of the mucosae of the digestive and respiratory tract and of the skin, could explain the associations reported in the present study. Indeed, asthma-like inflammatory reactions have been detected in the gut of asthmatic patients (11,12). The nature of the AA-ERS can provide a clue as to the causative environmental factors: it seems unlikely that inhalant allergens cause itching, urticaria or abdominal pain, and the most plausible candidates are manipulated food or beverages.

In conclusion, further epidemiological studies are needed to investigate the occurrence of extra-respiratory symptoms in asthma and their risk factors. A global internistic approach to the

asthmatic child may disclose that asthma is not infrequently the expression, at the bronchial level, of a disorder that also affects other organs and tissues.

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