

High prevalence of atopy, but not of asthma, among children in an industrialized area in North Italy: The role of familial and environmental factors – a population-based study

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The prevalence of atopy and asthma, and their association with familial and environmental factors were investigated among 13- to 14-yr-old children living in Brescia, an industrialized town in North Italy. All the 1450 children attending primary school in the town were invited to participate, and 967 of them (66.7%, 493 males) provided a valid questionnaire filled in by their parents at home. We used a modified version of the questionnaire adopted in the Italian Study of Respiratory Disorders in Childhood and Environment, which is an extended version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Six hundred and twenty-eight subjects underwent skin prick test (SPT), and 308 of them (49%) were positive for at least one of the 12 allergen extracts commonly employed. Ninety-nine children (10.2%) had a physician's diagnosis of asthma – 12.4% of the males and 8.0% of the females ($p = 0.03$). The prevalence of wheezing in the past 12 months was 6.2%. Atopy was found in 76.8% of the subjects with, and in 45.6% of those without physician's diagnosis of asthma ($p < 0.001$). Analysis by multiple logistic regression showed an inverse association between physician-diagnosed asthma and female sex (odds ratio, OR = 0.5); presence of relatives in the bedroom in initial years of life (OR = 0.6); attending day care (OR = 0.4) and infant school (OR = 0.4); a positive association with parental history of wheezing (OR = 2.5) and asthma (OR = 3.8); and the child's history of asthmatic bronchitis (OR = 31.9) and atopic eczema (OR = 3.8) in the first 2 yr of life. The strength of the associations did not change when restricting the analysis to atopic asthma. In conclusion, atopy and clinical asthma among 13- to 14-yr-old adolescents are significantly associated with some familial and environmental factors, providing further support for the hygiene hypothesis. Prevalence of atopy, but not of asthma, is high in this industrialized area. The strong association found between atopy and clinical asthma suggests that atopy may play a role in causing asthma in genetically predisposed children only.

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The prevalence of atopic disease and asthma have increased substantially worldwide in the last century, being the highest in Western countries,

especially among English-speaking populations, who are more urbanized and have a higher socioeconomic status and better medical care (1).

However, some findings suggest that the prevalence of clinical asthma among adolescents has not increased further in the last decade in Western countries (2, 3). The best known of the hypotheses put forward to explain these temporal changes in asthma prevalence is the so-called 'hygiene hypothesis', first proposed by Strachan in 1989 (4), according to which frequent infections and exposure to bacterial endotoxins in the early years of life are related to a low risk of developing asthma and atopic disease. This hypothesis has been supported by recent data showing that infection skews T helper lymphocyte differentiation toward Th1 instead of the Th2 pathway (5). Several environmental risk factors for asthma have been identified, especially family size and gestational and perinatal risk factors, as indicative of a larger exposure to infections in the first years of life (6, 7), although recent reviews show that the relations between these factors and asthma and atopy are unresolved (8, 9). The lack of standardized criteria in collecting information on the presence of asthma and of putative risk factors, and the lack of controlling for multiple risk factors when investigating the role of one of them may have contributed to these contrasting results.

The aim of this population-based study was to assess the prevalence of atopic sensitization and the prevalence and severity of asthma in adolescents, and to investigate whether infection acquired early in childhood and other familial and environmental factors are associated with asthma and atopic sensitization at the age of 13–14 yr.

Methods

Study design and population

We performed a cross-sectional study between October 2002 and June 2003 in Brescia, North Italy (200,000 inhabitants). The Brescia Province Education Office prompted teachers to collaborate in the research. The study involved all children attending the 18 primary schools in the town, with 68 classes and a total of 1450 adolescents aged 13–14 yr. The study was approved by the Ethics Committee of Spedali Civili Hospital, Brescia, and an informed consent form was signed by all the parents of the participating children.

The study consisted in the administration of two questionnaires, one to be filled in by the child and the other by his or her parents. The children also had to undergo a skin prick test (SPT). The survey took place in two stages. First, a medical

team held a 1-h meeting with the children at school to explain the aim and design of the study, and to distribute the informed consent forms and the questionnaires for the parents. One week later, the medical team collected the questionnaires and informed consent forms filled in by the parents, and administered the second questionnaire to the children in the classroom in the presence of their teachers, after which the children underwent the SPT under medical supervision.

Questionnaires

We used a modified version of the SIDRIA (Italian Studies on Respiratory Disorders in Childhood and the Environment) self-administered questionnaire (10), which is an extended version of the ISAAC questionnaire (11). It consisted of three sections. The first part covered general health aspects regarding atopic symptoms (wheezing and respiratory symptoms, rhinitis and cough, eczema and itching) of the child, siblings and parents. The second one contained questions on the history of acute and chronic diseases of the upper and lower respiratory tract, and of atopic diseases. The third section collected information on perinatal period, breastfeeding, vaccination, day care and infant school attendance, household crowding and respiratory infections in the initial years of life. This questionnaire was filled in by the parents. A simplified version of the questionnaire, containing questions on the child's asthma and respiratory symptoms only, was administered to the children at school. Children were considered to have asthma if their parents reported the diagnosis by a physician ('lifetime asthma'), independently of the presence of wheezing in the last 12 months.

Skin prick tests

SPT were performed with 12 allergen extracts: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, graminaceae mix, *Alternaria alternata*, cat epithelium, dog epithelium, *Betula verrucosa*, *Parietaria officinalis*, *Cladosporium herbarum*, *Olea europea*, *Artemisia vulgaris* and *Corylus avellana*. Histamine (10 mg/ml) and diluent were used as positive and negative controls, respectively. Atopy was defined as the presence of one or more positive skin reactions to allergens tested. The wheal was positive if the mean of its perpendicular diameters was at least 3-mm longer than the negative control. No adverse effects were observed.

Statistical analysis

All the analyses were performed using information taken from the questionnaires filled in by the parents, as they were found to provide more valuable information on their children's lifetime health history, particularly that of asthma, than the children themselves (12). In fact, the multicentre Italian study SIDRIA-2 derived the information about lifetime prevalence of illnesses from the parental questionnaire (10). However, we assessed the agreement between the answers provided by the children and their parents, to assess the reliability of the questionnaire data, using Cohen's kappa statistic to evaluate agreement beyond chance (13). We investigated the association between clinical asthma and various putative risk factors using common methods for comparing proportions. We also computed the prevalence odds ratio (OR) with its 95% confidence intervals (95% CI) as a measure of association between the presence of physician-diagnosed asthma and each risk factor when taking account of all the others fitting multiple logistic regression models. The prevalence OR may be regarded as an estimate of the relative risk under some assumptions (14). All the tests were two-tailed and performed using a 0.05 threshold for refusing the null hypothesis using the Stata package version 8.2 (Stata Statistical Software: Release 8.0 College Station, TX: Stata Corporation).

Results

Of the 1450 adolescents who were given questionnaires for their parents, 979 returned them, 967 (66.7%, 493 males) of which were complete and analyzed. Physician diagnosis of asthma was found in 99 of them (10.2%) – 12.4% among males (61 of 493) and 8.0% among females (38 of 473) ($p = 0.03$). Of the children with physician diagnosis of asthma, 41 received pharmacological treatment (41.4%), 22 (22.2%) had been admitted to hospital and 20 (20.2%) had been

taken to an Emergency Department owing to asthma at least once in their lives.

Table 1 shows the frequency of asthma symptoms according to physician diagnosis of the disease. Wheezing in the lifetime (86.9%), wheezing in the last 12 months (40.4%) and dry cough not associated with colds or respiratory infections (40.4%) were the most commonly reported symptoms in children with asthma. These proportions were significantly lower in children without a clinical diagnosis of asthma – wheezing in the lifetime was found in 10.9%, wheezing in the last 12 months in 2.3% and dry cough not associated with colds or respiratory infections in 13.2% of them ($p < 0.001$ for each comparison). Overall, wheezing in the last 12 months was found in 6.2% of the children.

A total of 532 questionnaires filled in by the children were matched with those completed by their parents, to allow an analysis of agreement between the information provided by children and their parents. A very high level of agreement was found regarding physician diagnosis of asthma (94.9% of agreement with kappa of 0.76) and a fairly high agreement for asthma symptoms, ranging from 69.1% for wheezing in the past to 85.8% for wheezing in the last 12 months, the kappa statistic ranging between 0.45 and 0.66. According to the children's questionnaires, wheezing in the last 12 months was found in 8.2% of subjects.

A total of 628 subjects underwent SPT (65% of participants) and 308 (49%) of them tested positive for at least one of the allergens investigated. Considering the most common allergens, 181 subjects (28.8%) were positive for *Dermatophagoides pteronyssinus*, 171 (27.2%) for *Dermatophagoides farinae*, 221 (35.2%) for graminaceae and 93 (14.8%) for parietaria. No differences were found in the proportion of males or in the prevalence of clinical asthma or asthma symptoms between the 628 subjects undergoing SPT and the 339 who did not. The tested children

Table 1. Asthma-related symptoms among 13- to 14-yr-old subjects according to physician diagnosis of asthma

Symptom	Physician diagnosis of asthma		
	Yes (n = 99)	No (n = 868)	Total (n = 967)
Wheezing in the lifetime	86 (86.9%)	95 (10.9%)	181 (18.7%)
Wheezing in the last 12 months	40 (40.4%)	20 (2.3%)	60 (6.2%)
Sleep disturbed owing to wheezing in the last 12 months	12 (12.1%)	5 (0.6%)	17 (1.8%)
Speech limited owing to talk for wheezing in the last 12 months	6 (6.1%)	3 (0.3%)	9 (0.9%)
Wheezing during or after exercise in the last 12 months	30 (30.3%)	20 (2.3%)	50 (5.2%)
Dry cough apart from cold or chest infection in the last 12 months	40 (40.4%)	115 (13.2%)	155 (16.1%)

Percentages are computed on the column total.

were not significantly different from the untested ones as regards the prevalence of lifetime asthma (11% vs. 9%, $p = 0.3$) and of the main asthma-related symptoms, such as wheezing in the lifetime (20% vs. 16%, $p = 0.1$) and wheezing in the last 12 months (7% vs. 5%, $p = 0.4$), although the former showed a slightly higher prevalence of allergic rhinitis symptoms (30% vs. 23%, $p = 0.02$).

As shown in Table 2, atopy was found in 53 of the 69 (76.8%) subjects with and in 255 of the 559 (45.6%) without physician diagnosis of asthma ($p < 0.001$). The OR for positive SPT was 3.9 for a child with physician diagnosis of asthma. A strong association was also found between SPT positivity and each asthma-related symptom, especially wheezing in the last 12 months (OR = 8.6) and wheezing during or after exercise in the last 12 months (OR = 7.3).

As most atopic children had no physician diagnosis of asthma (255 of 308, 82.8%), we also analyzed the prevalence of allergic rhinitis symptoms to assess the proportion of atopic asymptomatic subjects. Allergic rhinitis symptoms were found in 269 adolescents (27.8%). A strong association between atopy and allergic rhinitis symptoms was evident, as 47.7% (147 of 308) children with a positive SPT compared with 13.1% (42 of 320) with a negative SPT had allergic rhinitis (prevalence OR = 6.04; 95% CI: 4.08–8.94). Therefore, 161 of 308 atopic children (52.3%) had neither lifetime asthma nor allergic rhinitis symptoms, and hence can be regarded as asymptomatic atopic subjects (25.6% of the total tested).

We investigated the association between physician diagnosis of asthma and the following list of variables: (i) parental history of wheezing, and allergic and respiratory diseases; (ii) variables

concerning the initial years of children's life, including being preterm, history of breastfeeding and being over 4 months at infant formula introduction; (iii) history of lower respiratory tract infections and atopic eczema in the first 2 yr of life; (iv) the number of siblings, the presence of relatives in the bedroom in the children's first 2 yr of life, attending day care at 0–2 yr of age and attending infant school at 3–5 yr of age.

All variables associated with physician diagnosis of asthma in univariate analysis were included in a multiple logistic regression model, and those with a p -value of less than 0.1 were retained. Some of these variables were closely related to each other, for instance, day care and infant school attendance, and therefore one of them became non-significant when including the other in the model. The final, most parsimonious model is set out in Table 3. An inverse association was found between physician diagnosis of asthma and female sex (OR = 0.5), presence of relatives in the bedroom (OR = 0.6), day-care attendance at 0–2 yr of age (OR = 0.4) and infant school attendance at 3–5 yr of age (OR = 0.4). On the contrary, parental history of wheezing (OR = 2.5), parental history of asthma (OR = 3.8), and child's history of asthmatic bronchitis (OR = 31.9) and atopic eczema (OR = 3.8) in the first 2 yr of life were positively associated with clinical asthma. When restricting the analysis to the 628 adolescents with SPT, the presence of asthma with positive SPT (atopic asthma) was associated with the same factors as found in the total subjects. In particular, significant associations were observed between atopic asthma and asthmatic bronchitis (OR = 15.6), atopic eczema (OR = 3.2), parental history of wheezing (OR = 3.3) and asthma (OR = 4.4) (data not shown in table). Breastfeeding was not

Table 2. Asthma-related symptoms and physician diagnosis of asthma according to the reactivity to skin prick test among 628 children tested

Physician diagnosis of asthma or symptom	Skin prick test			
	Positive* (n = 308)	Negative (n = 320)	Total (n = 628)	OR (95% CI)
Physician diagnosis of asthma				
Yes	53 (76.8%)	16	69	3.9 (2.2–7.0)
No	255 (45.6%)	304	559	–
Wheezing in the lifetime	84 (66.1%)	43	127	2.4 (1.6–3.6)
Wheezing in the last 12 months	37 (88.1%)	5	42	8.6 (3.4–21.5)
Sleep disturbed owing to wheezing in the last 12 months	11 (78.6%)	3	14	3.9 (1.2–13.2)
Speech limited owing to wheezing in the last 12 months	6 (85.7%)	1	7	6.3 (0.8–28.2)
Wheezing during or after exercise in the last 12 months	32 (86.5%)	5	37	7.3 (2.9–18.4)
Dry cough apart from cold or chest infection in the last 12 months	73 (66.4%)	37	110	2.4 (1.5–3.7)

*Percentages are computed on the row total.

OR, odds ratio for positive skin prick test having physician diagnosis of asthma or each symptom.

CI, confidence interval.

Table 3. Factors associated with physician diagnosis of asthma by multiple logistic regression

Risk factor	Physician diagnosis of asthma			
	Yes (n = 99)	No (n = 868)	OR (95% CI)	p-value
Gender (female vs. male)				
Male	61 (61.6%)	432 (49.8%)	–	–
Female	38 (38.4%)	435 (50.2%)	0.5 (0.3–0.9)	0.04
Parental history (one or both parents)				
Wheezing	38 (38.4%)	100 (11.5%)	2.5 (1.1–5.5)	0.03
Asthma	37 (37.4%)	86 (9.9%)	3.8 (1.7–8.1)	0.001
Respiratory infections and atopic eczema in the first 2 yr of life				
Asthmatic bronchitis	50 (50.5%)	30 (3.5%)	31.9 (16.5–61.7)	<0.001
Atopic eczema	28 (28.3%)	84 (9.7%)	3.8 (1.9–7.6)	<0.001
Presence of relatives in the bedroom (yes vs. no)	43 (43.4%)	339 (39.1%)	0.6 (0.3–1.1)	0.08
Day-care attendance (0–2 yr of age) (yes vs. no)	10 (10.1%)	138 (15.9%)	0.4 (0.2–1.1)	0.07
Infant school attendance (3–5 yr of age) (yes vs. no)	74 (74.8%)	780 (89.9%)	0.4 (0.2–0.8)	0.01

OR, odds ratio for physician diagnosis of asthma computed using multiple regression, including all the variables in the table and sex as independent variables. CI, confidence interval.

associated with physician diagnosis of asthma when considering all subjects together. However, a separate analysis of atopic and non-atopic children showed an inverse relation between breastfeeding and asthma among children with a positive SPT, though not statistically significant (OR = 0.43, 95% CI: 0.15–1.25, $p = 0.12$), and no relation among those with a negative SPT (OR = 0.88) (data not shown in table).

Discussion

This study aimed to add some information on the prevalence of asthma, allergic rhinitis and atopy, and their possible associations with various familial and environmental factors, among a large sample of children living in an industrialized town in Southern Europe, using a population-based study design. Although several investigations have already been performed on these topics, there is still no definite answer as to the role of putative risk factors for asthma. Furthermore, the rapidly changing scenario of allergic diseases in various parts of the world in the last few decades justifies further research, as shown by the new multicenter studies that have just been carried out or are in progress, such as the ISAAC-2 and SIDRIA-2.

We found that 10.2% of adolescents living in an industrialized town in North Italy have physician diagnosis of asthma. The prevalence of asthma is higher in males (12.4%) than females (8%), and the female sex is inversely associated with asthma when also taking account of other risk factors (OR = 0.5). When considering the prevalence of wheezing in the last 12 months according to the ISAAC study (11), we found a prevalence of 6.2% when using

parents' questionnaires and 8.2% when using those provided by the children themselves. These figures are consistent with the values reported by most centers taking part in the ISAAC study, including the Italian areas (15). Most adolescents with physician diagnosis of asthma were not severely affected: 20% had had one or more accesses to a hospital emergency room, 22% had been admitted to a paediatric department owing to acute asthma, 5% had experienced exercise-induced wheezing, and less than 1% had been woken up by wheezing at night or had their speech impaired by wheezing. Only 41% of the asthmatic adolescents were being treated with drugs for asthma, suggesting that, despite the current guidelines, many asthmatic children are undertreated, as confirmed by recent surveys in Italy and other Western countries (16, 17).

We also tested children for the most common allergens using SPT. About 35% of the total subjects did not undergo the test because they did not present signed parental consent. No substantial differences were found between tested and untested children with regard to gender, familial and environmental variables associated with asthma and the prevalence of lifetime asthma and asthma-related symptoms, though a slightly higher prevalence of rhinitis symptoms was found among the former.

A very high proportion of children undergoing SPT (49%) were atopic, defined as reactivity to at least one allergen. This percentage is moderately higher than the 35–45% reported in other areas in Italy (18, 19). We used 12 allergens, whereas six 'core' allergen extracts were recommended for the ISAAC II study (20). However, the type and the number of allergens used for SPT are unlikely to explain these differences. Brescia is an indus-

trialized town with a high traffic density and heavy air pollution, which may help explain the high proportion of atopic subjects. Some authors observed a higher prevalence of positive SPT among asthmatic children living in urban compared with rural areas (21), and two recent studies performed in Europe found that traffic-related air pollution was associated with allergic sensitization (22, 23), though others failed to confirm this association (6).

Of the children with positive SPT, 52.3% had neither lifetime asthma nor allergic rhinitis symptoms and they were regarded as asymptomatic atopic subjects (25.6% of the total tested) though some of them may have had modest symptoms of allergic diseases that their parents did not report. Anyway, this proportion, though seemingly rather high, is not very different from those found in some aforementioned Italian studies, in which a large number of SPT-positive children did not have symptoms of allergic respiratory disorders (18, 19).

We found that almost 77% of children with clinical asthma were reactive to some allergens, the most common being mites. This proportion is similar to that reported among 9- to 14-yr-old children in other population-based studies in the 1990s (21), and confirms the strong association between asthma and one or more environmental allergens: the OR for a positive SPT was about 3.5 among children with a physician diagnosis of asthma, compared with those without, in agreement with other studies (21).

We found that many factors were independently associated with the presence of asthma, when also restricting the analysis to subjects with atopic asthma. First of all, parental history of wheezing, and especially of asthma, was significantly associated with child asthma, in agreement with others (9). It has been argued, in fact, that asthma may be associated with genes regulating certain pulmonary features and functions, such as allergic sensitization, inflammation and tissue damage, or bronchial hyper-reactivity (9). Second, various environmental factors, which may be seen as proxies of exposure to infectious agents in early childhood, such as the presence of older siblings, the sharing of the child's bedroom by relatives and day care or infant school attendance were associated with a reduced risk of asthma, though some of them were no longer statistically significant at the 0.05 level by multivariate analysis. However, the strong association between these variables (multicollinearity) does not allow the effect of each of them to be disentangled: for instance, children who had attended day care at 0–2 yr of age were

also more likely to attend an infant school at 3–5 yr.

Twenty years after the first formulation of the 'hygiene hypothesis', our findings confirm that family size, day-care attendance and other factors are associated with a reduced risk of asthma and allergic sensitization, as found in various studies (5). This hypothesis maintains that a crowded, highly promiscuous environment may favour children's exposure to 'polymicrobial' aerosols, causing recurrent mild or asymptomatic upper respiratory tract infections, which in turn lower the risk of developing atopy, shifting Th0 cells toward the Th1 phenotype or stimulating T cells with regulatory function (Thr) (24, 25). A prospective study found, in fact, that repeated viral infections, such as runny nose, or chronic infections, such as herpes virus infection and measles, early in life, reduce the risk for the development of asthma up to school age, whereas no effects were observed for other types of infection (26). Bacterial endotoxins may also play a role, as they are proinflammatory substances of gram-negative bacteria cell wall, and they are abundant in an environment where animals, carpets and dust are present. Children exposed to high amount of endotoxins may be protected from developing asthma, as these substances are Th1 stimulating, as supported by recent studies showing an inverse relationship between endotoxin burden in the environment and subsequent development of atopic asthma and allergic sensitization (27, 28).

We found a strong association between clinical asthma and history of asthmatic bronchitis in the first 2 yr of life (OR = 32), owing to the fact that about half of the asthmatic children had asthmatic bronchitis reported by their parents. On the contrary, no association was observed between asthma and the history of other respiratory infections in the same period, such as pneumonia, bronchiolitis, sinusitis and laryngitis. These results did not vary when only considering children with atopic asthma. The association between asthma at age 13 and asthmatic bronchitis in the first 2 yr of life must be interpreted with caution, owing to the retrospective design of the study. On the one hand, the parents of asthmatic children may have misinterpreted the early manifestation of a wheezing tendency as episodes of chest infection, or may have confused bronchiolitis with wheezing bronchitis. On the other hand, our finding is in agreement with other studies showing that lower respiratory tract infections early in life may increase the risk of wheeze in the initial years of life (wheezing bronchitis), and cause alterations in lung growth

and differentiation, which ultimately lead to persistent wheeze and allergic asthma (25, 29, 30).

Finally, some of the strengths and weaknesses of the study should be mentioned. The study was population based, and included the majority of the children living in the area. A fair number of them also underwent the prick test, and the tested subjects did not differ from the untested ones with regard to the prevalence of asthma and the other variables investigated, so selection bias seems unlikely to have occurred. We used questionnaires similar to those adopted in international research, which have been validated and administered to thousands of children of the same age as those included in this survey. The high agreement found between children's and parents' questionnaires concerning asthma symptoms and history of physician-diagnosed asthma suggest a fairly high internal consistency of the data collected by questionnaire. Although our study was retrospective, it should be noted that a large amount of research on asthma aetiology has been performed using cross-sectional studies with prevalence cases, which have proved highly valuable (1).

In conclusion, this study confirmed that both genetic and environmental factors are associated with clinical asthma, especially with atopic asthma at 13–14 yr of age. The inverse association of environmental factors with allergic asthma adds further support to the hypothesis that early exposure to microbial load in the environment may effectively modulate the immune response and protect the child from developing asthma later in life. Atopic sensitization was found in 49% of the total and 45% of children without asthma, suggesting that asthma only develops in a small number of genetically predisposed children who are exposed to specific environmental factors.

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